Jeremy M.D. Nightingale
Editor

Intestinal Failure

Second Edition

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A Doctor and or Health Worker's Oath

I promise to treat all patients equally, with humanity, respect and to the best of my ability.

I shall listen to their story, keep their confidences and be honest at all times.

I shall strive to bring hope, however small.

I shall endeavour to improve my knowledge, and to be aware of new treatments.

I shall admit that which I do not know and shall not be afraid to seek help from those who do.

I shall promote freedom of thought and its expression.

I shall willingly teach my skills to others.

In memory of my father, Jon Nightingale, who died in August 1997 of motor neurone disease.

Foreword to Second Edition

Do we really need another textbook of intestinal failure, especially one following a very successful first edition from Dr Jeremy M.D. Nightingale, a pioneering leader in the field? With this second edition Jeremy delivers a resounding yes!

Intestinal failure is a devastating disease. In the five decades or so since the development of parenteral nutrition, the present era more than any other has seen incredible improvements in outcomes for patients with intestinal failure. Very significant improvements have stemmed simply from the widespread recognition of the value of multidisciplinary intestinal rehabilitation, approaches to prevent complications related to parenteral nutrition through better catheter care or lipid management and incremental improvements in outcomes for intestinal transplantation. There have been remarkable advancements in the characterization and approval of intestinotrophic peptides with more along the way.

It is in this context that Dr Nightingale's updated second edition of *Intestinal Failure* could not be more timely. The book represents a herculean effort spanning five years and brings together an international authorship of experts collectively representing several decades of experience in intestinal failure. The current edition adds 27 new chapters! Of particular interest and relevance are new or updated chapters covering mesenteric ischemia, radiology in intestinal failure, encapsulating peritoneal sclerosis, pro-adaptive hormones, drug absorption, etc. To give just a few examples, the chapter on mesenteric ischemia written by the experienced team from Paris describes best practices from a multidisciplinary acute intestinal stroke unit. There is a comprehensive description and approach to managing encapsulated peritoneal sclerosis, a vexing and poorly understood condition that appears to be increasing in incidence. For the first time, there is a very thorough chapter on management of impaired drug absorption in patients with short bowel syndrome. I am especially pleased to see well-written chapters describing psychological aspects of intestinal failure, quality of life, patient perspectives, and ethical and legal aspects of nutritional support.

In his foreword to the first edition, Sir Miles Irving wrote that "Jeremey Nightingale has performed an outstanding service …the book will act as a standard text for those who need to know how to deal with patients afflicted by this difficult condition." I will go further—with this authoritative textbook, Jeremy has put together the most comprehensive text one could hope for in intestinal failure. Far from being standard text, this book will be essential reading for established experts in intestinal failure and all who aspire to have sound basic understanding to manage this challenging condition well. I anticipate that my own autographed copy will see much use!

May, 2023

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Foreword to First Edition: 2001

To have been party to the recognition of a new specialty, encourage its development, see it acknowledged as a specialty in its own right and then bring it to a maturity and set it on its future path, all within the space of 30 years, must be regarded as both an awe inspiring experience and a privilege.

Such has been the experience of the team of authors that have contributed to this unique volume. It is remarkable that it is only 30 years since Dudrick, Wilmore, Vars and Rhoads showed that children could grow and mature normally when sustained by parenteral nutrition alone. From this classic study has developed the whole field of intestinal failure and its treatment.

This book brings together those who were the pioneers, those who refined the techniques that enabled patients to receive safe enteral and parenteral nutrition outside the hospital and those who now have the task of taking the management of intestinal failure to the next stages. The assembled chapters reveal a remarkable record of international interdisciplinary collaboration between scientists and clinicians, doctors and nurses, health economists and those with expertise in the relatively new discipline of the measurement of quality of life. What is most gratifying, however, is the inclusion of an authoritative and scientifically rigorous expression of the patient perspective. The management of intestinal failure was arguably the trailblazer in demonstrating that successful outcomes could only be obtained if the patient was incorporated as an integral part of the therapeutic team.

Jeremy M.D. Nightingale has performed an outstanding service to gastroenterology by bringing together a group of authors who provide not only an authoritative, current statement on the total management of patients with intestinal failure but also a record of the development of this specialty which will act as a reliable reference for many years to come.

This book sets the seal on Intestinal Failure as a distinct specialty and will act as a standard text for those who need to know how to deal with patients afflicted with this difficult but fascinating condition.

Sir Miles Irving

Emeritus Professor at the University of Manchester,
Newcastle Upon Tyne, Tyne and Wear, England
May, 2001

Preface

This new edition of an international multi-author textbook brings the broad subject of intestinal failure in adults and children to a wide readership. A simple, easy to remember definition of intestinal failure is presented "reduced intestinal absorption causing malnutrition and/or dehydration". It encompasses patients with many underlying diagnoses who need nutritional and/or fluid support by oral, enteral or parenteral routes due to an impairment/failure of intestinal absorption. Many of these patients will be managed in non-specialist hospitals and often without the need for parenteral support.

The second edition (62 chapters) includes updated versions of the original 34 chapters. In addition there are new chapters that cover many other aspects of intestinal failure/nutritional support including psychology, drug absorption, pancreatitis and critical care. Each chapter starts with practical key points and a summary, then follows clinical guidance and information based on the recent literature.

Doctors, nurses, dietitians, pharmacists, research workers and patients have written the chapters to give different viewpoints that relate to nutritional support in hospitals and in the community. This edition should provide an essential source of reference to all members of a nutrition support team and to specialist workers/researchers in the field.

Please send any comments, corrections, additional information or suggestions for inclusion in a future edition to the editor.

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Jeremy M.D. Nightingale

Acknowledgements

I wish to thank my main trainers/mentors. These include Peter Willoughby, Rodney Burnham, Michael Kamm, Michael Farthing, John Mayberry, Tony Wicks, Barrie Rathbone and especially John Lennard-Jones (JLJ). JLJ was an inspirational "can do" person whose research followed from the clinical problems he managed. Following a ward round at St Mark's Hospital in 1987, when it was situated on City Road in London, he asked me which patients/problems I had found most interesting. Put on the spot, I replied that it was those with a short gut and receiving parenteral support. Thus began my research/special interest in nutritional support which along with inflammatory bowel disease has been a major part of my professional life.

Thanks go to two committees that I have been fortunate to chair; the British Intestinal Failure Alliance (BIFA) committee and the Nightingale Trust for Nutritional support. They have helped develop logical ways to manage patients needing nutritional support and are referred to when appropriate in the chapters.

I would like to thank all the authors of the first edition (published in 2001) whose contributions helped formulate many of the chapters in this new updated version.

I am grateful to the associate editors Simon Lal, Mattias Soop and Ahash Mehta who will be responsible for future editions.

I thank Nicola Burch and the nutrition support team in Coventry for helping me maintain a broad experience of all aspects of nutritional support while working on this book.

I thank all the many brave patients who have given me the knowledge, awareness and many skills that I have tried to incorporate into this book.

I particularly thank my wife (Sally) and our sons (James and Peter) for tolerating the many hours this textbook has taken to complete.

Contents

Part III Chronic (Long-Term) Intestinal Failure

Part IV Consequences of Intestinal Failure

Part V Assessment and Treatment of Intestinal Failure

Abbreviations

A&E	Accident and emergency
AA	Amino acid
AABF	Amino acid-based formula
AANH	Artificially assisted nutrition and hydration
ABD	Acid-base disturbance
ACR	Acute cellular rejection
ACS	American College of Surgeons
ACT	Acceptance and commitment therapy
ADA	Adalimumab
ADP	Adenosine diphosphate
ADP	Air displacement plethysmography
AGI	Acute gastrointestinal injury
AgRP	Agouti-related peptide
AIDS	Acquired immunodeficiency syndrome
AIO	All-in-one
AIR	Autologous intestinal reconstruction
ALP	Alkaline phosphatase
AMI	Acute mesenteric ischaemia
ANC	Acute necrotic collection
ANTT	Aseptic non-touch technique
AP	Acute pancreatitis
Apo AIV	Apolipoprotein AIV
ART	Anti-retroviral therapy
ASPEN	American Society for Parenteral and Enteral Nutrition
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AuSPEN	Australian Society of Parenteral and Enteral Nutrition
AVF	Arteriovenous fistula
AWR	Abdominal wall repair
AXR	Abdominal radiograph
BANS	British Artificial Nutrition Survey
BAPEN	British Association for Parenteral and Enteral Nutrition
BCS	Biopharmaceutical classification system
BDA	British Dietetic Association
BDP	Beclomethasone dipropionate
BFT	Barium follow through
BIA	Bioelectrical impedance analysis
BIFA	British Intestinal Failure Alliance
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BMR	Basal metabolic rate

BMS	Bare metal stents
BNF	British National Formulary
BO	Bowel obstruction
BP	Blood pressure
BPD	Bilio-pancreatic diversion
BPNG	British Pharmaceutical Nutrition Group
BSG	British Society of Gastroenterology
Ca	Calcium
CA	Coeliac artery
cAMP	Cyclic adenosine monophosphate
CANH	Clinically assisted nutrition and hydration
CBD	Common bile duct
CBT	Cognitive behavioural therapy
CCN2	Cellular communication network factor 2
CDED	Congenital diseases of enterocyte development
CDT	Catheter-directed thrombolysis
CE	Conforormité européenne. European conformity mark indicating a product meets the essential requirements of the relevant EU directives and standards for that product
CFTR	Cystic fibrosis transmembrane conductance regulator
CHG	Chlorhexidine gluconate
CHI	Creatinine height index
CHO	Carbohydrate
CIF	Chronic intestinal failure
CIPO	Chronic intestinal pseudo-obstruction
Cl	Chloride
CLABSI	Central line-associated bloodstream infection
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CNS	Central nervous system
COVID	Coronavirus disease
CPPD	Calcium pyrophosphate dihydrate
Cr	Chromium
CR	Chyme reinfusion
CRBSI	Catheter-related blood stream infection
CRF	Chronic renal failure
CRP	C-reactive protein
CSD	Congenital sodium diarrhoea
CT	Computerised tomography
CTCAE	Common terminology criteria for adverse events
CTE	Computerised tomography enterography
CTE	Congenital tufting enteropathy
CTZ	Chemoreceptor trigger zone
Cu	Copper
CVC	Central venous catheter
CVID	Common variable immunodeficiency
CVT	Central vein thrombosis
DAMP	Danger-associated molecular patterns
DBD	Donation after brain death
DC	Dendritic cell
DCH	Delayed cutaneous hypersensitivity
DEXA	Dual-energy x-ray absorptiometry
DFH	Distal feeding and/or hydration

DIT	Diet-induced thermogenesis
DJ	Duodeno-jejunal
DJBL	Duodenal-jejunal bypass liner
DNA	Deoxyribonucleic acid
DNI	Drug-nutrient interactions
DPEG	Direct percutaneous endoscopic jejunostomy
DPP	Dipeptidyl peptidase
DR	Digital radiography
DTP	Differential time to positivity
EA	Enteropathic arthritis
EAA	Essential amino acids
EAF	Entero-atmospheric fistula
EATL	Enteropathy-associated T-cell lymphoma
EBV	Epstein-Barr virus
ECCO	European Crohn´s and Colitis Organisation
ECF	Enterocutaneous fistula
ECG	Electrocardiogram
ECL	Enterochromaffin-like cells
ECMO	Extracorporeal membrane oxygenation
EDS	Ehlers-Danlos syndrome
EDTA	Ethylenediaminetetraacetic acid
EEN	Early enteral nutrition
EF	Enteral feed
EFA	Essential fatty acid
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EHF	Extensively hydrolysed formulae
EI	Energy intake
EMA	Endomysial antibody
EMA	European Medicines Agency
EMDR	Eye movement desensitisation and reprocessing
EPS	Encapsulating peritonitis
ERAS	Enhanced recovery after surgery
ERCP	Endoscopic retrograde pancreatography
ESG	Endoscopic sleeve gastroplasty
ESICM	European Society of Intensive Care Medicine
ESPEN	European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism)
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
ESWL	Extracorporeal shockwave lithotripsy
ETEC	Enterotoxigenic
ETF	Enteral tube feeding
EUS	Endoscopic ultrasound
FABP	Fatty acid binding protein
FDA	Food and Drug Administration (USA)
FGF	Fibroblast growth factor
FISH	Fluorescence in-situ hybridisation
FMT	Faecal microbiota transplantation
FODMAP	Fermentable oligosaccharides, disaccharides, monosaccharides and polyols
Fr	French gauge (same as CH =Charrière) circumference of a tube in millimetres (Fr =diameter x π)
FU	Fluorouracil
fURS	Flexible ureteroscopy

FXR	Farnesoid X receptor
GALT	Gut-associated lymphoid tissue
GCSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GH	Growth hormone (hGH: human growth hormone)
GHR	Growth hormone receptor
GHRH	Growth hormone releasing hormone
GI	Gastrointestinal
GIP	Gastric inhibitory peptide or polypeptide, or glucose-dependent insulinotropic polypeptide
GIT	Gastrointestinal tract
GLIM	Global leadership initiative on malnutrition
GLP-1 and 2	Glucagon-like peptide-1 and -2
GLP-2R	Glucagon-like peptide-2 receptor
GORD	Gastro-oesophageal reflux
GPS	Glasgow prognostic score
GRS	Glucose rehydration solution
GSV	Great saphenous vein
GVHD	Graft versus host disease (acute or chronic)
HAART	Highly active antiretroviral therapy
HACCP	Hazard analysis critical control point
HB-EGF	Heparin-binding growth factor
HCO_3	Bicarbonate
HD	Haemodialysis
HES	Hospital episode statistics
HETF	Home enteral tube feeding
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HOS	High output stoma
HPAC	High amplitude propagated contractions
HPN	Home parenteral nutrition
HPS	Home parenteral support (includes fluid and nutrition)
HSC	Haematopoietic stem cell
HSCT	Haemopoietic stem cell transplantation
HVM	Hollow visceral myopathy
I	Iodine
IAP	Intra-abdominal pressure
IASP	International Association for the Study of Pain
IBD	Inflammatory bowel disease
ICAM	Intercellular adhesion molecule
ICER	Incremental cost effectiveness ratio
ICPI	Immune checkpoint inhibitor
ICU	Intensive care unit
ICV	Ileocaecal valve
IDA	Iron deficiency anaemia
IDSA	Infectious Disease Society of America
IF	Intestinal failure
IFALD	Intestinal failure-associated liver disease
IFRD1	Interferon-related developmental regulator
IFU	Intestinal failure unit
IFX	Infliximab
IGF	Insulin-like growth factor

IHD	Intermittent haemodialysis
IJV	Internal jugular vein
Il	Interleukin
ILE	Intravenous lopid emulsion
IMA	Inferior mesenteric artery
iNOS	Inducible NO synthase
INS	Intestinal insufficiency
IPA	Isopropyl alcohol
IRU	Intestinal rehabilitation unit
ITX	Intestinal transplantation
IVC	Inferior vena cava
IVF	Intravenous fluids
IVS	Intravenous saline
JCB	Jejuno-colic bypass
JIB	End-to-end jejuno-ileal bypass
K	Potassium
KGF	Keratinocyte growth factor
LAMS	Lumen apposing metal stents
LCFA	Long-chain fatty acids
LCT	Long-chain triglycerides (14–24 carbon atoms)
LFA	Lymphocyte function antigen
LFT	Liver function test.
LILT	Longitudinal intestinal lengthening and tailoring
LITRE	Looking into the requirements for equipment
LOS	Length of stay
LSB	Liver small bowel transplant
MAHA	Microangiopathic haemolytic anaemia
MAMC	Mid-arm muscle circumference
MAMP	Microbial-associated molecular patterns
MARSI	Medical adhesive-related skin injury
MARSIPAN	Management of Really Sick Patients with Anorexia Nervosa
MBD	Metabolic bone disease
MCT	Medium-chain triglycerides (6–12 carbon atoms)
MDT	Multidisciplinary team
MEED	Medical emergencies in eating disorders
MEF	Minimal enteral feeding
MELD	Model for end-stage liver disease
Mg	Magnesium
mGIF	Modified gastrointestinal failure
MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency
MIN	Minimally invasive necrosectomy
MMC	Migrating motor complex or interdigestive migrating complex
Mn	Manganese
MNA	Mini nutritional assessment
MNGIE	Mitochondrial neurogastrointestinal encephalomyopathy
Mo	Molybdenum
MODS	Multiple organ dysfunction syndrome
MPC	Myeloid progenitor cells
MR	Magnetic resonance
MRCP	Magnetic resonance cholangio-pancreatography
MRE	Magnetic resonance enterography
MRI	Magnetic resonance imaging

MRP	Multidrug resistance-associated protein
MTBT	Mixed triglyceride breath test
MUAC	Mid-upper arm circumference
MUFA	Monounsaturated fatty acid
MUST	Malnutrition universal screening tool
MVID	Microvillus inclusion disease
MVT	Multi-visceral transplant
N	Nitrogen
Na	Sodium
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NASIT	National Adult Small Intestinal Transplantation forum
ND	Nasoduodenal
NEC	Necrotizing enterocolitis
NFC	Needle-free connector
NF-KB	Nuclear factor kappa light chain enhancer of activated B cells
NG	Nasogastric
NGT	Nasogastric tube
NHS	National Health Service (in United Kingdom)
NICE	The National Institute for Health and Care Excellence (formerly the National Institute for Clinical Excellence)
NIOSH	National Institute for Occupational Safety and Health
NIS	National inpatient sample
NJ	Nasojejunal
NJT	Nasojejunal tube
NK	Natural killer cell
NLR	NOD-like receptors
NOD	Nucleotide-binding oligomerization domain
NOMI	Non-occlusive mesenteric ischaemia
npRQ	Non-protein respiratory quotient
NPSA	National Patient Safety Agency
NPY	Neuropeptide Y
NSAID	Non-steroidal anti-inflammatory drugs
NSQIP	National Surgical Quality Improvement Program
NST	Nutrition support team
OAGB	One anastomosis gastric bypass
OGD	Oesophago-gastro-duodenoscopy
OGS	Oral glucose saline solution
ORS	Oral rehydration solution
OSFED	Other specific feeding and eating disorder
OSHA	Occupational Safety and Health Administration
OXM	Oxyntomodulin
P	Phosphate
PABA	Para-aminobenzoate test
PAI	Peritoneal adhesion index
PAL	Physical activity level
PAU	Peri-anastomotic ulcerations
PBSC	Peripheral blood stem cells
PCDT	Percutaneous catheter-directed thrombolysis
PCNL	Percutaneous nephrolithotomy
PD	Peritoneal dialysis
PEEL	Peritonectomy and enterolysis
PEG	Percutaneous endoscopic gastrostomy

PEGJ	Percutaneous endoscopic gastro-jejunostomy
PEJ	Percutaneous endoscopic jejunostomy
PERT	Pancreatic enzyme replacement therapy
PET-CT	Positron emission tomography and computed tomography
PFG	Percutaneous fluoroscopic gastrostomy
PFGJ	Percutaneous fluoroscopic gastro-jejunostomy
pH	Potential hydrogen
PICC	peripherally inserted central catheter
PINNT	Patients on Intravenous and Nasogastric Nutrition Therapy
PIPOS	Paediatric intestinal pseudo-obstruction syndromes
PIT	Psychodynamic interpersonal therapy
PLAG	Percutaneous laparoscopically assisted gastrostomy
PMT	Percutaneous mechanical thrombectomy
PMU	Psychological medicine unit
PN	Parenteral nutrition
PNALD	Parenteral nutrition-associated liver disease
PNIQ	Parenteral nutrition impact questionnaire
PPI	Proton pump inhibitor
PPOI	Prolonged postoperative ileus
PRES	Posterior reversible encephalopathy syndrome
PRG	Percutaneous radiological gastrostomy
PRGJ	Percutaneous radiologically inserted gastro-jejunostomy
PRR	Pattern recognition receptors
PS	Parenteral support (includes fluid and nutrition)
PTA	Percutaneous transluminal angioplasty
PTFE	Polytetrafluoroethylene
PTLD	Post-transplant lymphoproliferative disorder
PUFA	Polyunsaturated fatty acid
PVC	Polyvinyl chloride
PVT	Porto-mesenteric and splenic vein thrombosis
PWO	Persistent withdrawal occlusion
PYY	Peptide YY
QoL	Quality of life
RA	Rheumatoid arthritis
RBC	Red blood cell
RCD	Refractory coeliac disease
RCT	Randomised clinical trial
REE	Resting energy expenditure
RFS	Refeeding syndrome
RIG	Radiologically inserted gastrostomy
RIGJ	Radiologically inserted gastro-jejunostomy
RIRS	Retrograde intrarenal surgery
RIV	Reference intake value
RNA	Ribonucleic acid
RNI	Reference nutrient intake
ROMS	Retrograde open superior mesenteric artery stenting
RRT	Renal replacement therapy
RT	Radiotherapy
rURS	Rigid ureteroscopy
RYGB	Roux en y gastric bypass
SACT	Systemic anti-cancer treatment
SARC	Simple questionnaire of sarcopenia
SBS	Short bowel syndrome

SC	Subclavian vein
SCFA	Short chain fatty acids
SCT	Secretin cerulean test
Se	Selenium
SEP	Sclerosing encapsulating peritonitis
SGA	Subjective global assessment
SGLT	Sodium-glucose co-transporter
SIBO	Small intestinal bacterial overgrowth
SILT	Spiral intestinal lengthening and tailoring
SIRS	Systemic inflammation response syndrome
SLE	Systemic lupus erythematosus
SMA	Superior mesenteric artery
SMV	Superior mesenteric vein
SNAP	Sepsis-nutrition-anatomy-plan
SPT	Secretin pancreozymin test
SRSB	Segmental reversal of the small bowel
SSTR	Somatostatin receptor
STEP	Serial transverse enteroplasty
SUSS	Sit up-squat-stand test
SVC	Superior vena cava
T2D/T2DM	Type 2 diabetes mellitus
TAR	Transversus abdominis release
TA-TMA	Transplant-associated thrombotic microangiopathy
TBI	Total body irradiation
TEE	Total energy expenditure
TGF	Transforming growth factor (alpha and beta)
TLR	Toll-like receptor
TNF	Tumour necrosis factor
TRM	Transplant-related mortality
TST	Triceps skinfold thickness
tTG	Tissue transglutaminase
UDCA	Ursodeoxycholic acid
UFED	Unspecified feeding or eating disorder
UHT	Ultra-high temperatures
UK	United Kingdom
UKELD	United Kingdom model for end-stage liver disease
US	Ultrasound
USA	United States of America
USTE	Ustekinumab
UV	Ultraviolet
VBG	Vertical banded gastrostomy
VCAM	Vascular cell adhesion molecule
VEDO	Vedolizumab
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal peptide
VOD	Veno-occlusive disease of the liver
VTE	Venous thromboembolism
WBC	White blood cell
WHO	World Health Organisation
WON	Walled-off-necrosis
WTP	Willingness to pay
Zn	Zinc

Part I

Introduction

Historical Overview of Intestinal Failure

John E. Lennard-Jones, Gil Hardy,
and Khursheed N. Jeejeebhoy

Key Points

1. The first resection of more than 200 cm small bowel was described in 1880 and in 1980 the term intestinal failure was first coined.
2. The first attempt at parenteral nutrition (PN) was with milk infusions in 1873 and 100 years later the first patient was reported receiving PN at home (in 1973).
3. An everted mucosal ileostomy and the development of satisfactory appliances that adhered to the skin in 1952 helped the management of many patients after a bowel resection.
4. The reasons for intestinal failure have widened from massive resections due to volvulus/strangulated hernia, Crohn's disease and mesenteric infarction to include surgical complications and dysmotility.
5. The composition of PN nutrition and the bags has been changing since the 1960s with improvements in amino acid and micronutrient formulations, the development of lipid emulsions and recently the multi-chamber bags.
6. Venous access for PN started with arteriovenous fistulas, then with safe aseptic placement catheters with their tips at the vena caval/atrial junction were used. With careful aseptic care the incidence of catheter related blood stream infection has reduced.

J. E. Lennard-Jones has died before the publication of this book.

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Introduction

The term 'intestinal failure' was used by Irving and colleagues in the title of a paper published in 1980 [1]. In the following year, a book chapter by Fleming and Remington gave the first definition as a 'reduction in functioning gut mass below the minimal amount necessary for adequate digestion and absorption of nutrients' [2]. Irving and his colleagues popularized the term when they described their work in a specially designated 'Intestinal Failure Unit' for the treatment of complex intestinal disorders [3]. A key feature of this unit was the ability to provide safe, effective, long-term parenteral nutrition. The phrase 'intestinal failure' began in surgical practice as a unifying concept for apparently different conditions all of which have the common feature that the normal absorptive function of the small intestine is impaired, usually to such an extent that parenteral feeding is needed [3]. It is now recognized that some patients can also be treated by giving extra or special nutrients via the intestine. The definition of intestinal failure in the first edition of this book is of 'a reduction of intestinal absorption that, without treatment or compensatory mechanisms, results in malnutrition and/or dehydration'. This includes the need for enteral or parenteral supplements (nutrition and fluid) to maintain a normal nutritional/hydration state. Malabsorption of a single nutrient, such as Vitamin B_{12}, or the need for a special diet to exclude a damaging component such as gluten, is not included within this definition.

Loss of intestinal absorptive function can be complete or partial. Intestinal failure may be described as *acute* when it is reversible in the short term or *chronic* if long-term treatment over weeks, months, or longer is required especially if continued treatment is needed at home. The conditions leading

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to intestinal failure are such surgical conditions as intra-abdominal sepsis and ileus, a high volume entero-cutaneous fistula, intestinal obstruction or temporary severe malabsorption after extensive small bowel resection or it can be due to chemotherapy.

Parallel Developments

Developments in different disciplines since the middle years of last century have led to our current understanding and treatment of intestinal failure. First, the application to both normal subjects and those with intestinal resection of new laboratory techniques, has advanced understanding of small intestinal function. Second, the scope of surgical treatment has extended to include more complex operations on the intestine so that intestinal failure occurs more frequently, and is often more severe, than hitherto. During the same time period medical causes of intestinal failure have been recognized. Third, clinical necessity has stimulated the application of innovative techniques to treat the condition in the short- or long-term. These parallel developments in time will be described sequentially in the following review.

Advances in Knowledge

Sites of Nutrient Absorption and Effect of Resection

Many of the laboratory measurements, now regarded as routine, were developed at the beginning of the second half of the twentieth century. For example, a widely used method for measurement of fat in faeces was first reported in 1949 and microbiological techniques for the measurement of folic acid or vitamin B_{12} in blood were devised in 1956 and 1961 respectively. Radio-isotope methods for measuring vitamin B_{12} absorption were developed in the late 1950s.

In 1957 the first direct measurements of nutrients in human intestine was made by Borgstrom et al. [4] who fed a liquid meal with an unabsorbed marker and using intubation sampled the intestinal contents at various distances to determine the absorption of nutrients as the bolus fed progressed down the small bowel. They found that over 90% of all macronutrients namely carbohydrate, protein and fat were absorbed within 100 cm of jejunum [4]. Although in intact human subjects fat absorption was complete in the jejunum, Intestinal resection studies showed that after jejunal resection feeding increasing amounts of fat did not increase loss in stool indicating that the remaining ileum could maintain normal fat absorption despite the absence of the jejunum which is the normal site of fat absorption. In contrast when the ileum was resected fat malabsorption increased with increasing amounts of fed fat [5–7]. Based on intubations studies of Borgstrom et al. [4] ileal resection should have no effect on fat absorption. This paradox was solved in the 1960s by the observation that bile salts necessary for fat absorption are recycled through the ileum and during a meal, calculations by Borgstrom et al. suggest that the bile salt pool is recycled twice. Hence loss of the ileum depletes the bile salt pool in the jejunum and reduces fat absorption. Intestinal resection studies also showed another unique function of the ileum namely vitamin B_{12} absorption [5].

The need of patients with distal ileal resection for parenteral supplements of vitamin B_{12} is now well recognised.

Fluid and Electrolyte Fluxes

In addition to macronutrient absorption the small bowel was shown to be the site of massive fluid and electrolyte fluxes. The intubation studies by Borgstrom et al. [4] indicated that the ingested meal is diluted three to five times as it passes the duodenum. Seminal studies showed that the jejunum had large pores and absorption was mainly by solvent drag leaving the luminal electrolyte concentration similar to plasma. While there was coupled sodium and glucose active transport throughout the small bowel [8–10], osmotic gradient was not maintained in the jejunum. Hence a hyperosmotic meal of milk and doughnuts caused a greater dilution in the proximal bowel than a steak meal of lower osmolality. In contrast there was an osmotic gradient between plasma and lumen in the ileum where there were smaller pores and especially in the colon [11–13].

Effect of Malabsorption on the Colon

Malabsorption of bile salts results in these salts entering the colon where they promote water secretion and thus diarrhea. Bile acid malabsorption caused by ileal resection causes fat malabsorption. After resection of the ileum the entry of bile salts and fatty acids into the colon stimulated colonic peristaltic motor activity and inhibited water and electrolyte absorption by long-chain fatty acids entering the colon was shown in the 1970s and 1980s to be a potential factor in causing diarrhoea in patients with a short small intestine anastomosed to colon [14, 15]. The mechanism of increased oxalate absorption by the colon in patients with a short gut, leading to hyperoxaluria and oxalate renal stones, was unraveled in the 1970s as due to a combination of colonic calcium binding by long-chain fatty acids and the effect of a higher than normal concentration of bile salts on the colonic mucosa [16].

Adaptation of the Residual Small Intestine After a Partial Resection

Experiments in animals, dating from the early years of the century, but particularly from the late 1960s onwards, have shown that when a length of small intestine is resected, with anastomosis of the proximal jejunal and distal ileal segments, marked hypertrophy with increased absorptive function of the distal ileum occurs [17]. It seems that the distal ileum which plays little part in normal nutrient absorption has a capacity for increasing its absorptive role when nutrients reach it due to proximal resection of intestine. Functional investigation in man has shown increased absorption of water, sodium, glucose and calcium in the jejunum [18–20], but villous hyperplasia has not been demonstrated in man when distal intestine is resected with formation of a terminal jejunostomy [21]. These findings were explained in the 1990s by the findings that isolated glucagon- like peptide 2 (GLP2) produced by L cells of the ileum and colon increased intestinal epithelium proliferation [22].

Development of Surgical Practice

Extensive Resection

The first resection in humans of more than 200 cm of small intestine has been attributed to Koberle in 1880, and 55 of such operations were reported up to 1912 [23]. Most such operations until the middle years of the century were performed as an emergency for removal of non-viable intestine infarcted due to strangulation or volvulus. Thus, in a 1935 review of 257 cases the commonest reasons for resection were volvulus in 76 and strangulated hernia in 45 (Table 1) [24]. Mesenteric artery or vein occlusion constituted only 13% of the cases at that time, whereas by 1969 the proportion had risen to 48% [25]. This change may reflect a decreased incidence of hernial strangulation, increasing age of the population and the fact that surgeons became willing to resect a long length of infarcted intestine in the knowledge that treatment was now available to compensate for the resulting malabsorption.

Extensive small bowel resection for vascular insufficiency of the central portion of the small bowel usually spares the proximal and distal ends. Such operations lead to removal of mid-small bowel with jejuno-ileal anastomosis and retention of the colon. The distal ileum has considerable potential for adaptation and the colon, with its capacity for avid absorption of sodium and water, prevents severe fluid and sodium depletion. These cases, with a reasonable good prognosis, still occur but the knowledge that parenteral therapy is available (see below) now allows surgeons to resect even the whole small bowel for a condition such as desmoid tumour of the mesentery. There are now also many people in whom the residual intestine is limited to a relatively short length of residual jejunum ending in a stoma.

Table 1 Reasons for 'extensive' and 'massive' intestinal resections in adults in 1912 and 1935

Flint 1912: 'Extensive' intestinal resection [23]	
Strangulated hernia	19
Tumour	10
Gangrene	4
Adhesions/bands	4
Tuberculosis	3
Uterine perforation	3
Other	6
Unknown	6
Total	**55**
Haymond 1935: 'Massive' intestinal resection [24]	
Volvulus	76
Strangulated hernia	45
Mesenteric thrombosis	34
Tuberculosis	16
Mesenteric tumours	14
Uterine perforation	11
Adhesions/bands	7
Other	54
Total	**257**

Construction of a Stoma

The surgery of ulcerative colitis was greatly facilitated by the development and introduction of an everted mucosal ileostomy in 1952 and the development of satisfactory appliances adherent to the skin during the same period [26]. From time to time colectomy for ulcerative colitis is complicated by a vascular accident which leads to loss not only of the colon but also a large part of the small bowel with creation of a terminal jejunostomy.

This operation may be needed electively for the treatment of Crohn's disease when there is extensive involvement of both small and large bowel. Thus in a series reported in 1992 of 86 patients each with less than 200 cm of small bowel remaining, 38 had a jejunostomy as the result of surgical treatment for Crohn's disease or ulcerative colitis [27].

Entero-Cutaneous Fistula

A high volume entero-cutaneous fistula is similar in its effluent to a high jejunostomy, but is often complicated by sepsis. While maintaining nutrition parenterally, surgeons can now delay definitive operation for a high-volume entero-cutaneous fistula until sepsis is dealt with, the anatomical

situation is defined and the patient's general condition is optimal. Treatment in this way has greatly reduced the mortality of this condition.

Characterization of the Resection

The term 'extensive' small bowel resection was reserved in the earlier literature to describe removal of at least 200 cm. This length was chosen because it was believed to represent about one-third of the small intestinal length and experimental work suggested that up to this proportion can be removed without detriment to weight and strength. These observations failed to take account of the variable length of the human small intestine. In 1935, Haymond [24] drew attention to this variability and observed correctly that 'a resection of a large amount in one individual would constitute a different percentage of the total length in another'. Before closing the abdomen after a resection, surgeons should thus measure the length of residual intestine along the anti-mesenteric border, and define the proportions of proximal and distal intestine.

Follow-up observations have shown the prognostic importance of these records. Patients with less than 200 cm of small bowel remaining fall into three groups: those with an anastomosis between residual jejunum and ileum proximal to an intact colon; those with anastomosis of small bowel to colon; and those with a terminal small intestinal stoma [27]. The prognosis as regards the need for long-term parenteral nutrition (PN) therapy depends in each group on the length of residual small bowel [28] but those with a colon can tolerate shorter lengths of small bowel than those with a jejunostomy. The role of residual ileum and colon to allow the bowel to adapt and permit patients to return to oral nutrition after resection and initial dependence on home parenteral nutrition (HPN) was demonstrated in the 1990s. The findings showed that the presence of ileum and colon allowed very short bowels to become independent of PN followed by the presence of colon alone joined to jejunum and those least likely to become independent of PN were those with a jejunostomy [29].

Surgical Treatment of Intestinal Failure

Although procedures [30, 31] have been performed with some success to lengthen a short residual intestine or delay passage of its contents to allow absorption to occur, the main hope of surgical advance centres on intestinal transplantation [32]. Rejection of the graft remains a problem but the successful result when an identical twin was the donor pointeds to the success of the surgical technique; the problems to be overcome remain mainly immunological [33].

Recognition of Medical Causes of Intestinal Failure

A number of congenital disorders associated with intestinal failure were described during the 1970s and 1980s. For example, a rare congenital defect of intestinal villus formation in babies [34] and a number of different familial types of pseudo-obstruction have been identified [35]. The latter may present as a myopathy in which the intestine becomes wide, atonic and subject to bacterial overgrowth or as a disorder of the myenteric nerve plexus which leads to obstructive episodes without mechanical cause. Chronic pseudo-obstruction has also been recognized later in life secondary to a systemic disorder such as scleroderma or as a sporadic condition of unknown cause.

Development of Treatment

Enteral Nutrition (Table 2)

The earliest enteral feeds were given rectally by enema. The ancient Egyptians gave wine, whey, milk and/or barley broth nutrient enemas [36]. John Hunter gave one of the earliest orogastric feeds documented in 1790 to a patient who had had a stroke. He used a pig bladder as a reservoir for an egg, water, sugar, milk or wine feed and this was squeezed into the stomach through a feeding tube, made by a watchmaker, consisting of a whale bone and eel skin [36]. Feeding tubes were at first large and made of rubber, gradually these have been refined to radio-opaque fine-bore tubes initially made of polyvinyl chloride but now largely replaced by silicone or polyurethane [37]. While the first gastrostomies and jejunostomies were fashioned at laparotomy, they are now mostly placed using endoscopic and radiological techniques [38–42].

In 1943 milk protein was used to make casein hydrolysates as the protein component of a feed, subsequently some feeds have been based on soya bean or egg white. Carbohydrate was first given as glucose or sucrose, but in

Table 2 Key developments in enteral nutrition

BC	Nutrient enemas used by Ancient Egyptians [36]
1790	Oro-gastric feeding tube [36]
1867	Soft rubber tubing for gastric lavage [37]
1876	Surgical gastrostomy [38]
1885	Surgical feeding jejunostomy [39]
1910	Oro-duodenal feeding [40]
1943	Casein hydrolysates [36]
1952	Surgically placed needle jejunostomy [41]
1963	Chemically defined (elemental) diet for space travel [36]
1980	Endoscopic gastrostomy [41]
1981	Radiological gastrostomy [42]
1990s	Immunomodulation (glutamine, arginine and MCTs)

order to keep the osmolality low, glucose-polymer mixtures derived from the hydrolysis of corn starch were used [36, 43]. Lipid as long-chain triglyceride was derived from soya, corn or safflower oils, and lipid as medium-chain triglyceride from coconut oil.

Parenteral Nutrition (Table 3)

Fluid and electrolyte balance has been maintained in patients with intestinal failure since the earliest days of intravenous fluid administration. One of the earliest reports of giving intravenous nutrition was when three patients who had cholera and were considered about to die, were given intravenous fresh (still warm) cow's milk, two of these patients survived [44]. Isotonic, or slightly hypertonic, solutions of glucose were given by peripheral infusion but not enough to provide an adequate energy source because higher concentrations caused thrombosis of the vein. The problems to be solved before intravenous feeding could become a reality, were to devise solutions which provide a non-irritant form of amino-nitrogen for synthesis of protein and an adequate energy source.

Intact protein, other than human plasma or albumin, tends to be allergenic. These whole proteins were used in the first half of the twentieth century for temporary nutritional support but expansion of the circulating plasma volume and slow turnover of the protein were limiting factors. Early workers suggested that amino acid solutions might be effective but it was not until 1937 that an amino acid solution produced by hydrolysis of casein was first shown to be a practicable method of treatment [45]. By 1943, a review recorded treatment of at least 500 patients with this product and included a reference to combined treatment with an intravenous lipid emulsion (ILE) [46]. A casein enzymatic hydrolysate, in which amino acids and small peptides were separated from residual large peptides by dialysis, was widely used in Europe during the 1950s and 1960s, and a fibrin hydrolysate was used in America. Intensive work defined the optimal amino acid composition, including the ratio of essential to nonessential amino acids and the need to provide the amino acids in an L-form. It was recognized that a mixture of crystalline amino acids would have the advantage of providing flexible solutions of known composition and such a solution was first used clinically in 1940 for intravenous nutrition in children [47]. However, the initial technical difficulty, and thus high commercial cost, of such solutions delayed their introduction for routine use until the 1960s and early 1970s, since when they have superseded the use of protein hydrolysates.

Table 3 Key developments in parenteral nutrition

1873	Milk infusions to treat cholera [44]
1937	Protein hydrolysates (amino acids) infusions [45]
1952	Subclavian vein catheterization using infraclavicular approach [48]
1961	Lipid emulsion [50]
1965	Complete Parenteral Nutrition using central catheter [50]
1968	Hypertonic glucose infused into a large vein [56]
1970	Long-term parenteral nutrition ('the artificial gut') using arterio-venous shunt [57]
1973	All-in-One system for ambulatory PN [60]
1973	Home PN using a tunneled catheter [67]
1973	Teflon-cuffed tunnelled silicone rubber catheter [68]
2000	Multi Chamber Bags for PN [71]

An ILE offered the possibility of a rich caloric source which would not be osmotically active. However, there were many initial difficulties. Low molecular weight triglycerides were found to be acutely toxic. Cotton seed oil and soya bean oil emulsions had low acute toxicity and between 1948 and 1972 Meng and colleagues in Nashville USA studied the former in animal and human models [49], but unfortunately a minor impurity gave rise to toxic effects. Consequently the product was withdrawn and ILE were not approved for use by the United States Food and Drug Administration (FDA) until 1972.

Meanwhile development of the soya bean oil ILE, emulsified with egg yolk phosphatides, continued in Sweden. The product, which mimicked the structure of chylomicrons, proved non-toxic in animals and was used successfully in humans for the first time during the early 1960s [50]. During a 1963 conference in London, organized and chaired by Meng, the Swedish group, led by Wretlind and Schuberth described their research on the experimental and clinical development of this preparation, which was approved for use in UK and many other European countries in 1962 and is still in use today. This was a major advance and, there was an immediate surge of interest in the use of ILE as a high energy source of essential fatty acids.

In 1965 Lawson [51] was able to provide PN using protein hydrolysate, glucose and lipid, separately through a central venous catheter and Sherwood Jones and Peaston reported that in the ICU at Whiston hospital, Liverpool, "*intravenous feeding is routinely instituted if either oral or tube feeding is contraindicated or complicated by side-effects*" [52]. Fructose, sorbitol, xylitol and ethanol were all popular as alternative energy sources in Australia, Germany and the UK in the 1970's/'80's [53–55] but all have metabolic disadvantages compared to glucose. Which is metabolically the most suitable energy substrate. However, at only 4 kcal/g the quantity needed was limited by the need to keep the volume of infusate physiological and avoid thrombosis of peripheral veins. Dudrick and colleagues overcame the high osmolality problem in 1968 by infusing hypertonic glucose into a large central vein where the blood flow is adequate to dilute the solution and thus avoid local phlebitis and thrombosis [56]. This technique was widely adopted in America where ILE were unavailable, and administration of

PN through a central vein has been standard practice, particularly for long-term parenteral feeding. Some patients with chronic intestinal failure require prolonged, even lifelong, parenteral feeding. There was excitement when the concept of an 'artificial gut' based on the experience of prolonged renal dialysis was introduced by Scribner and colleagues in 1970 [57]. The original technique based on intermittent infusion via an arterio-venous fistula was successfully adopted in Australia, New Zealand and The Netherlands where there are still some long-term PN patients managing this technique at home [58, 59]. In 1973, the Broviac silicone rubber catheter with a Dacron cuff to seal and fix it within a skin tunnel, proved satisfactory and nine patients were treated at home in USA [60, 61]. This remains a long-term catheter of choice.

Solassol and Joyeux in the 1970's, pioneered the first 'All-in One' (AIO) admixtures, in a single re-usable silicone rubber container, that could be prepared aseptically in their hospital pharmacy [62]. The novel French PN system was administered to cancer and bowel disease patients, in Montpellier, via a small portable pump. This innovative system reduced the number of manipulations and daily infusion time to 8 hrs, allowing the patient to become ambulatory and eventually to manage their PN at home (HPN). However, because of stability and microbiological concerns at that time, AIO admixtures were not immediately popular outside of France and mixing any other solutions with ILE was discouraged by Wretlind [63]. In Canada, Jeejeebhoy and colleagues described an alternative system for HPN using a tunneled silicone for short bowel patients and published details of 13 patients treated at home for up to 23 months [64]. At the same time Jarnum reported on Danish experiences with long term HPN patients in Copenhagen since 1967 [65, 66]. In UK, the use of the tunnelling technique was first mentioned in 1978 and 25 patients treated at different centres were described in 1980 at a conference held for the purpose [67, 68]. HPN is now a standard technique in many countries for patients with long-standing intestinal failure who cannot be treated successfully using an enteral regimen.

During the 1970s and 1980s much R&D was conducted on nutrient solutions to ensure optimal ratio of energy to protein, relative proportions of different amino acids, and content of vitamins and trace elements. The safety of the technique of fluid administration both in hospital and at home was improved. For example, the original need for multiple bottle changes and additions was simplified in the 1970's by adopting the French approach but aseptically mixing the ingredients in a single disposable 3 litre bag [68, 69]. Sophisticated pumps have been developed to control the rate of flow and warn of air bubbles or line blockage. Air bubbles in the solution have been minimized, and stability enhanced by manufacturing the bag from oxygen impermeable plastics [70]. The need for expensive hospital-based Aseptic Units (ASU) for compounding PN has now diminished, with industry manufacturing a range of 'ready-to-use' multi chamber bags (MCB) with the nutrients sterilized in separate chambers, that can be stored at room temperature, resulting in long shelf lives prior to mixing. MCB, introduced in Europe during the 1990's, significantly improve pharmacy workload, can be more cost effective and may reduce risk of bloodstream infections [71, 72].

Most important of all, protocols and educational programs, that cover PN prescription, compounding and administration, have been developed to minimize infection and venous thrombosis so that the risk of these complications is now low when care is provided by an experienced team [73].

Resection and Anastomosis

Metabolic studies of patients after resection date back at least to 1938. An example of an investigation aimed at improving management is a report in 1949 of giving a patient with short gut a liquid feed made up of protein hydrolysate, milk, cream and glucose compared with a normal diet [74]. The patient retained only 15 cm of jejunum anastomosed to transverse colon. She had lost weight from 64 kg to 42 kg, complained of weakness and dizziness (blood pressure 80/60), abdominal pain and bloating, and passed 3–6 stools daily. This is a vivid description of the chronic poor health of a patient at that time with a major resection of small intestine. The synthetic diet did not help her but it is interesting to note that she was taking only 1345 kcal daily in her normal diet which contained 48 g of fat.

It gradually became apparent that patients with a short small intestine in continuity with colon benefit from a low fat, high carbohydrate diet. Such patients need to eat more energy-giving foods than normal to compensate for malabsorption. A child reported in 1961 who had lost the whole of his jejunum and retained only 39 cm of ileum showed immediate improvement on a low fat, high protein, high carbohydrate diet. Weight loss was reversed, a growth spurt commenced and diarrhoea diminished [75]. Similarly, an adolescent who retained only 13 cm of jejunum and 5 cm of terminal ileum did well when dietary carbohydrate and protein were increased and part of the fat intake was replaced by medium-chain triglycerides [76].

The work of Booth et al. [6] and Andersson et al. [77] during the 1960s and 1970s showed that a low fat diet decreases diarrhoea, loss of divalent cations (calcium and magnesium) and urinary oxalate. It is only in recent years that a further benefit of increased dietary carbohydrate has been demonstrated; unabsorbed carbohydrate entering the colon is fermented by colonic bacteria yielding short-chain fatty acids which are absorbed as a source of energy [78, 79].

Terminal Jejunostomy

A patient who underwent an extensive small bowel resection in 1958 which left 120 cm of small bowel ending in a jejunostomy was troubled mainly by profuse drainage from the stoma [80]. When investigated in 1973, the jejunostomy effluent at times exceeded the volume of nutrients taken by mouth. Such profuse losses, with incipient sodium and magnesium deficiency, are a common problem in patients with a short gut and a jejunostomy.

Developments in treatment to minimize sodium losses from the jejunostomy have been threefold. First, it was shown that when such a patient drinks water, or a dilute sodium solution, there is a net sodium loss from the jejunostomy [81, 82]. When a normal person drinks water, sodium enters the upper intestine from the blood but this sodium is re-absorbed by the ileum or colon; in these patients it is lost from the body via the stoma. Second, the same research showed that the coupling of sodium and glucose absorption can be utilized to promote sodium absorption [81, 82]. Thus such patients should restrict their water intake and substitute a glucose-electrolyte solution. Animal and human experiments showed that the concentration of sodium in this solution should be at least 90 mmol/L to promote sodium absorption in the upper gut [83]. Third, opiate drugs, such as codeine phosphate or loperamide and octreotide can make a small contribution to reducing losses [84, 85]. Lastly, drugs which reduce gastric [86, 87], or all digestive secretions [88, 89] can benefit patients in whom the diluting effect of these digestive juices leads to a greater fluid output than taken by mouth.

Comparisons of oral intake and jejunostomy loss have shown that many patients absorb 60% or less of energy in their diet [90]. Thus, they need to eat more than normal or, if absorption is only about 30%, receive a parenteral supplement. In certain patients total jejunostomy loss exceeds the volume of food and fluid taken by mouth. Such patients cannot survive without parenteral supplements [91]. Unlike patients with an intact colon, fat is not deleterious to patients with a jejunostomy and is a valuable source of energy [92–94].

Pharmacological Treatment of Short Bowel

The observation that GLP2 will allow proliferation of small bowel epithelium [22] and increase small bowel function could not be applied in clinical practice because this hormone was rapidly hydrolysed by dipeptidyl-peptidase and after injection has a very short existence in circulation. In 1999 an analogue (teduglutide) with prolonged action biosynthesized by NPS Allelix [95] .as shown by subsequent controlled trials by Jeppeson et al. showed that it was capable of improving intestinal function in patients on HPN so as to reduce the need for Parenteral Nutrition [96].

Conclusion

The concept of intestinal failure, the reasons for it, physiological understanding of impaired intestinal absorption and the development of treatments have largely occurred during the last 50 years. It is perhaps because this concept is relatively new that the term is not yet part of core medical teaching, as is the case with cardiac, respiratory, hepatic or renal failure. The following chapters do much to establish intestinal malabsorption, severe enough to require replacement therapy, as another universally recognized type of system failure.

References

1. Milewski PJ, Gross E, Holbrook I, Clarke C, Turnberg LA, Irving MH. Parenteral nutrition at home in management of intestinal failure. Br Med J. 1980;1:1356–7.
2. Fleming CR, Remington M. Intestinal failure. In: Hill GL, editor. Nutrition and the Surgical Patient. Edinburgh: Churchill Livingstone; 1981. p. 219–35.
3. Irving M, White R, Tresadern J. Three years' experience with an intestinal failure unit. Ann R Coll Surg Engl. 1985;67:1–5.
4. Borgstrom B, Daalq A, Lundh G, Sjovall J. Studies of intestinal digestion and absorption in the human. J Clin Invest. 1957;36:1521–36.
5. Booth CC. The metabolic effects of intestinal resection in man. Postgrad Med J. 1961;37:725–39.
6. Booth CC, Macintyre L, Mollin DL. Nutritional problems associated with extensive lesions of the distal small intestine in man. Quart J Med. 1964;33:401–20.
7. Booth CC, Alldis D, Read AE. Studies on the site of fat absorption: 2. Fat balances after resection of varying amounts of the small intestine in man. Gut. 1961;2:168–74.
8. Schedl HP, Clifton JA. Solute and water absorption by the human small intestine. Nature. 1963;199:1264–26.
9. Fordtran JS, Rector FC Jr, Carter NW. The mechanisms of sodium absorption in the human small intestine. J Clin Invest. 1968;47:884–900.
10. Fordtran JS. Stimulation of active and passive sodium absorption by sugars in the human jejunum. J Clin Invest. 1975;55:728–37.
11. Fordtran JS, Locklear TW. Ionic constituents and osmolality of gastric and small intestinal fluids after eating. Am J Dig Dis. 1966;11:503–21.
12. Fordtran JS, Rector FC Jr, Ewton MF, Soter N, Kinney J. Permeability characteristics of the human small intestine. J Clin Invest. 1965;44:1935–44.
13. Davis GR, Santa Ana CA, Morawski SG, Fordtran JS. Permeability characteristics of human jejunum, ileum, proximal colon and distal colon: results of potential difference measurements and unidirectional fluxes. Gastroenterology. 1982;83:844–50.
14. Ammon HV, Phillips SF. Inhibition of colonic water and electrolyte absorption by fatty acids in man. Gastroenterology. 1973;65:744–9.

15. Spiller RC, Brown ML, Phillips SF. Decreased fluid tolerance, accelerated transit, and abnormal motility of the human colon induced by oleic acid. Gastroenterology. 1986;91:100–7.
16. Dobbins JW, Binder HJ. Importance of the colon in enteric hyperoxaluria. N Engl J Med. 1977;296:298–301.
17. Bristol JB, Williamson RCN. Nutrition, operations, and intestinal adaptation. J Parenter Enter Nutr. 1988;12:299–309.
18. Weinstein DL, Shoemaker CP, Hersh T, Wright HK. Enhanced intestinal absorption after small bowel resection in man. Arch Surg. 1969;99:560–2.
19. Dowling RH, Booth CC. Functional compensation after small-bowel resection in man. Lancet. 1966;1:146–7.
20. Gouttebel MC, Saint Aubert B, Colette C, Astre C, Monnier LH, Joyeux H. Intestinal adaptation in patients with short bowel syndrome. Dig Dis Sci. 1989;34:709–15.
21. O'Keefe SJD, Shorter RG, Bennet WM, Haymond MW. Villous hyperplasia is uncommon in patients with massive intestinal resection. Gastroenterology. 1992;102:A231.
22. Drucker DJ. Biological actions and therapeutic potential of the glucagon-like peptides. Gastroenterology. 2002;122:531–44.
23. Flint JM. The effect of extensive resections of the small intestine. Bull Johns Hopkins Hosp. 1912;23:127–44.
24. Haymond HE. Massive resection of the small intestine. An analysis of 257 collected cases. Surg Gynec Obstet. 1935;693:705.
25. Simons BE, Jordan GL. Massive bowel resection. Am J Surg. 1969;118:953–9.
26. Brooke BN. The management of an ileostomy including its complications. Lancet. 1952;2:102–4.
27. Nightingale JMD, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces need for parenteral therapy, increases incidence of renal stones but does not change high prevalence of gallstones in patients with short bowel. Gut. 1992;33:1493–7.
28. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud J-C, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology. 1999;117:1043–50.
29. Crenn P, Morin MC, Joly F, Penven S, Thuillier F, Messing B. Net digestive absorption and adaptive hyperphagia in adult Short bowel patients. Gut. 2004;53:1279–86.
30. Mitchell A, Watkins RM, Collin J. Surgical treatment of the short bowel syndrome. Br J Surg. 1984;71:329–33.
31. Bianchi A. Longitudinal intestinal lengthening and tailoring: results in 20 children. J R Soc Med. 1997;90:429–32.
32. Grant D. Current results of intestinal transplantation. Lancet. 1996;347:1801–3.
33. Calne RY, Friend PJ, Middleton S, Jamieson NV, Watson CJE, Soin A, Chavez-Cartaya R. Intestinal transplant between two of identical triplets. Lancet. 1997;350:1077–8.
34. Philips AD, Jenkins P, Raafat F, Walker-Smith JA. Congenital microvillous atrophy. Arch Dis Child. 1985;60:135–40.
35. Anuras S, Christensen J. Recurrent or chronic intestinal pseudo-obstruction. Clin Gastroenterol. 1981;10:177–90.
36. Randall HT. Enteral nutrition: tube feeding in acute and chronic illness. J Parenter Enter Nutr. 1984;8:113–36.
37. Marks S. Enteral Feeding devices: what's old, what's new? World Small Animal Association World Congress Proceedings 2001. (www.vin.com).
38. Cunha F. Gastrostomy its inception and evolution. Am J Surg. 1946;72:610–34.
39. Torosian MH, Rombeau JL. Feeding by tube enterostomy. Surg Gynecol Obstet. 1980;150:918–27.
40. McDonald HA. Intrajejunal drip in gastric surgery. Lancet. 1954;I:1007.
41. Gauderer MWL, Ponsky JL, Izant RJ. Gastrostomy without laparotomy: a percutaneous endoscopic technique. J Pediatr Surg. 1980;15:872–5.
42. Preshaw RM. A percutaneous method for inserting a feeding gastrostomy tube. Surg Gynecol Obstet. 1981;152:658–60.
43. Silk DBA. Towards the optimization of enteral nutrition. Clin Nutr. 1987;6:61–74.
44. Hodder EM. Transfusion of milk in cholera. Practitioner. 1873;10:14–6.
45. Elman R. Amino-acid content of the blood following intravenous injection of hydrolysed casein. Proc Soc Exp Biol Med. 1937;37:437–40.
46. Editorial. Intravenous alimentation. Br Med J. 1943;1:416–7.
47. Shohi AT, Blackfan KD. The intravenous administration of crystalline amino acids to infants. J Nutr. 1940;20:305–16.
48. Aubaniac R. L'injection intraveineuse sous-claviculaire; avantages et technique. Presse Méd. 1952;60:1456.
49. Meng HC, Freeman S. Experimental studies on intravenous injection of fat emulsion into dogs. JLabClin Med. 1948;33:1503.
50. Wretlind A. Fat emulsions. In: Lee HA, editor. Parenteral nutrition in acute metabolic illness. Academic Press: London; 1974. p. 77–92.
51. Lawson LJ. Parenteral nutrition in surgery. Brit J Surg. 1965;52:795–800.
52. Sherwood-Jones E, Peaston M. Metabolic care during acute illness. Practitioner. 1966;196:271–5.
53. Coates DA. The place of ethanol in parenteral nutrition. In: Wilkinson AW, editor. Parenteral Nutrition. Churchill Livingstone Edinburgh; 1972. p. 152–9.
54. Bickel H, Halmagi M. Requirements and utilization of carbohydrates and alcohol. In: Ahnefeld FW, et al., editors. Parenteral Nutrition, Springer-Verlag. Berlin; 1976. p. 66–79.
55. Lee HA, et al. Sorbitol: some aspects of its metabolism and its role as an intravenous nutrient. In: Wilkinson AW, editor. Parenteral Nutrition. Edinburgh: Churchill Livingstone; 1972. p. 121–37.
56. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development and positive nitrogen balance. Surgery. 1968;64:134–42.
57. Scribner BH, Cole JJ, Christopher TG. Long-term parenteral nutrition; the concept of an artificial gut. JAMA. 1970;212:457–63.
58. Gillanders L et al. HPN via arterio-venous fistula access. AuSPEN HPN register 2008 at www.auspen.org.au
59. Versleijen M, et al. Excellent quality of life after 31 years of PN via an arteriovenous fistula. Eur J Clin Nutr. 2008;62:1253–4.
60. Langer B, McHattie JD, Zohrab WJ, Jeejeebhoy KN. Prolonged survival after complete small bowel resection using intravenous alimentation at home. J Surg Res. 1973;15(3):226–33.
61. Broviac JW, Cole JJ, Scribner BH. A silicone rubber atrial catheter for prolonged parenteral alimentation. Surg Gynec Obstet. 1973;136:602–6.
62. Solassol C, Joyeux H, Etco L, Pujol H, Romieu C. New techniques for long term intravenous feeding: an artificial gut in 75 patients. Ann Surg. 1974;179:519–22.
63. Wretlind A. In: Greep JM, et al., editors. Lipid emulsions and technique of peripheral administration in parenteral nutrition in Current Concepts in Parenteral Nutrition. The Hague: Martinus Nijhoff; 1977. p. 273–94.
64. Jeejeebhoy KN, Zohrab WJ, Langer B, Phillips MJ, Kuksis A, Anderson GH. Total parenteral nutrition at home for 23 months, without complication, and with good rehabilitation. Gastroenterology. 1973;65:811–20.

65. Jarnum S. Parenteral nutrition in the short bowel syndrome. Infusionstherapie Sonderheft. 1973;2:53–8.
66. Ladefoged K. Jarnum S Long-Term Parenteral Nutrition. Br Med J. 1978;2:262–6.
67. Report. Home parenteral nutrition in England and Wales. Br Med J. 1980;281:1407–9.
68. Powell-Tuck J, Farwell JA, Nielsen T, Lennard-Jones JE. Team approach to long-term intravenous feeding in patients with gastrointestinal disorders. Lancet. 1978;2:825–8.
69. Hardy G. Ten years TPN with 3 litre bags. Pharm J. 1987:H526–8.
70. Hardy G. Pharmaceutical aspects of parenteral nutrition. Nutrition. 1995;18:767–8.
71. Pichard C, Schwarz G, Frei A, et al. Economic investigation of the use of three-compartment total parenteral nutrition bag: prospective randomized unblinded controlled study. Clin Nutr. 2000;19(4):245–51.
72. Jianchun Y, et al. Efficacy, Safety, and Preparation of Standardized Parenteral Nutrition Regimens: Three-Chamber Bags vs Compounded Monobags—A Prospective, Multicenter, Randomized, Single-Blind Clinical Trial. Nutr Clin Pract. 2017;32:545–51.
73. Ayers P, et al. ASPEN Parenteral nutrition safety consensus recommendations. JPEN. 2014;38:296–333.
74. Althausen TL, Uyeyama K, Simpson RG. Digestion and absorption after massive resection of the small intestine. 1. Utilization of food from a 'natural' versus a 'synthetic' diet and a comparison of intestinal absorption tests with nutritional balance studies in a patient with only 45 cm of small intestine. Gastroenterology. 1949;12:795–808.
75. Clayton BE, Cotton DA. A study of malabsorption after resection of the entire jejunum and the proximal half of the ileum. Gut. 1961;2:18–22.
76. Winawer SJ, Broitman SA, Wolochow DA, Osborne MP, Zamcheck N. Successful management of massive small-bowel resection based on assessment of absorption defects and nutritional needs. N Engl J Med. 1966;274:72–8.
77. Andersson H, Jagenburg R. Fat-reduced diet in the treatment of hyperoxaluria in patients with ileopathy. Gut. 1974;15:360–6.
78. Royall D, Wolever TM, Jeejeebhoy KN. Evidence for colonic conservation of malabsorbed carbohydrate in short bowel syndrome. Am J Gastroenterol. 1992;87(6):751–6.
79. Nordgaard I, Hansen BS, Mortensen PB. Colon as a digestive organ in patients with short bowel. Lancet. 1994;343:373–6.
80. Simko V, Linscheer WG. Absorption of different elemental diets in a short-bowel syndrome lasting 15 years. Dig Dis. 1976;21:419–25.
81. Griffin GE, Fagan EF, Hodgson HJ, Chadwick VS. Enteral therapy in the management of massive gut resection complicated by chronic fluid and electrolyte depletion. Dig Dis Sci. 1982;27:902–8.
82. Newton CR, Gonvers JJ, McIntyre PB, Preston DM, Lennard-Jones JE. Effect of different drinks on fluid and electrolyte losses from a jejunostomy. J R Soc Med. 1985;78:27–34.
83. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJG. What is the ideal sodium concentration of oral rehydration solutions for short bowel patients? Clin Sci. 1988;74(Suppl 18):69.
84. Newton CR. Effect of codeine phosphate, Lomotil and isogel on ileostomy function. Gut. 1978;19:377–83.
85. Rodrigues CA, Lennard-Jones JE, Walker ER, Thompson DG, Farthing MJG. The effects of octreotide, soy polysaccharide, codeine and loperamide on nutrient, fluid and electrolyte absorption in the short bowel syndrome. Aliment Pharmacol Ther. 1989;3:159–69.
86. Jacobsen O, Ladefoged K, Stage JG, Jarnum S. Effects of cimetidine on jejunostomy effluents in patients with severe short-bowel syndrome. Scand J Gastroenterol. 1986;21:824–8.
87. Nightingale JMD, Walker ER, Farthing MJG, Lennard-Jones JE. Effect of omeprazole on intestinal output in the short bowel syndrome. Aliment Pharmacol Ther. 1991;5:405–12.
88. Ladefoged K, Christensen KC, Hegnhoj J, Jarnum S. Effect of a long acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome. Gut. 1989;30:943–9.
89. Nightingale JMD, Walker ER, Burnham WR, Farthing MJG, Lennard-Jones JE. Octreotide (a somatostatin analogue) improves the quality of life in some patients with a short intestine. Aliment Pharmacol Ther. 1989;3:367–73.
90. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJG. Energy absorption as a measure of intestinal failure in the short bowel syndrome. Gut. 1989;30:176–83.
91. Nightingale JMD, Lennard-Jones JE, Walker ER, Farthing MJG. Jejunal efflux in short bowel syndrome. Lancet. 1990;336:765–8.
92. Woolf GM, Miller C, Kurian R, Jeejeebhoy KN. Diet for patients with a short bowel: high fat or high carbohydrate? Gastroenterology. 1983;84:823–8.
93. Simko V, McCarroll AM, Goodman S, Weesner RE, Kelley RE. High-fat diet in a short bowel syndrome. Intestinal absorption and gastroenteropancreatic hormone responses. Dig Dis Sci. 1980;25:333–9.
94. McIntyre PB, Fitchew M, Lennard-Jones JE. Patients with a jejunostomy do not need a special diet. Gastroenterology. 1986;91:25–33.
95. Sigalet D. ALX-0600 (NPS Allelix Corp). Curr Opin Investig Drugs. 2001;2:505–9.
96. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B. O'Keefe SJ Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011;60:902–14.

Normal Intestinal Anatomy and Physiology

Jeremy M.D. Nightingale and Robin Spiller

Key Points

1. The components of the gut all function as one with all parts communicating (by nerves or hormones) with each other (intestinal orchestra).
2. Endogenous gut secretions while consuming a normal diet (about 2 kg) amount to about 4 L/24 h.
3. Small intestinal length is very variable at 160–1510 cm while colon length is 100–330 cm.
4. Jejunal mucosa has leaky intracellular junctions so its contents are near to iso-osmolar with plasma.
5. Macronutrients are broken down to small molecules (e.g peptides and oligosaccharides) by pancreatic enzymes and only to small hyperosmolar ones as they are absorbed by the intestinal mucosa.
6. Lipids are absorbed along the whole small intestine.
7. Colonic peptide hormones slow gastric emptying and gut transit (e.g. peptide YY) and increase upper gut mucosal growth (e.g. GLP2).
8. Humans are hind gut fermenters. Healthy adults have more than 1000 species of bacteria most belonging to the phyla with *Bacteroidetes* and *Firmicutes*. The bacteria are increasingly recognised not only for producing short chain fatty acids, vitamins and amino acids but for their role in diseases.
9. Luminal content is constantly being sampled by M cells and dendritic cells as part of immunological surveillance.

Introduction

The gastrointestinal tract extends from the mouth to the anus and includes many vital organs that secrete, mix and gradually break down food into molecules that can be absorbed. (Fig. 1).

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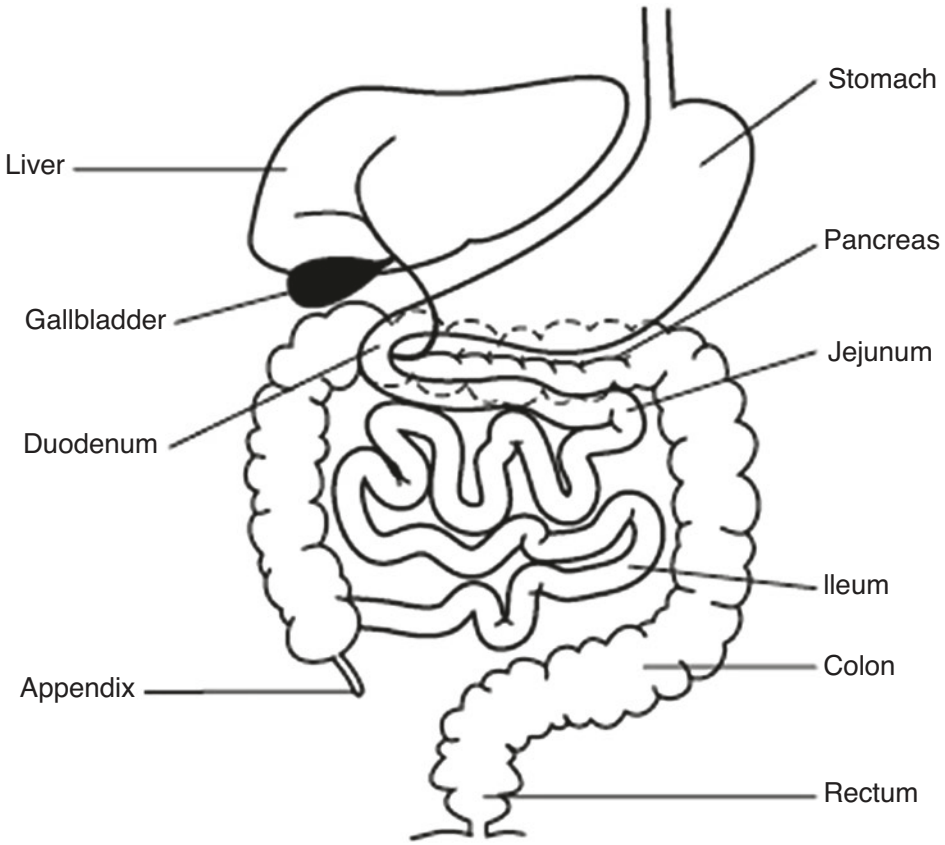

Fig. 1 Normal gastrointestinal anatomy

Oesophagus

The oesophagus is a muscular tube about 25 cm long; its function is to propel the food bolus from the pharynx to the gastric cardia. It is lined with a tough squamous epithelium. The upper two-thirds has striated voluntary skeletal muscle and the lower one-third involuntary smooth muscle [1]. About 2 kg of food and drink pass down it each day, diluted and lubricated by about 500 ml of saliva from lingual, sublingual, sub-mandibular and parotid salivary glands. Food viscosity is reduced by the acts of chewing, dilution and swallowing which stimulate a tenfold increase in salivary flow.

Stomach

The adult stomach is an acidic storage area that can hold up to 1.5 [1]. It starts digestion and delivers partly processed food at a controlled rate into the duodenum. It consists of two functionally different parts: the fundus and the antrum.

The fundus is mainly a storage area in which gastric juice is secreted and mixed with food to begin digestion. In addition to the many mucus-secreting cells found throughout the stomach, the fundal parietal cells secrete 0.1 M hydrochloric acid and intrinsic factor. During fasting the gastric pH ranges from 1.8 to 2.0; addition of food buffers this, raising the luminal gastric pH to 4–5. It should be noted that mixing is not perfect and a rim of secreted acid with pH 1 exists can form an "acid pocket" just below the lower eosophageal sphincter, which may be important in reflux oesophagitis. Acid kills most micro-organisms, denatures protein, making it more susceptible to hydrolysis, and converts inactive pepsinogen to pepsin, which is the active form of the enzyme. Intrinsic factor, a mucoprotein with a molecular weight of 55,000, binds B_{12} and this complex is absorbed in the distal 60 cm of ileum [2]. Fundal chief cells secrete pepsinogen and rennin. Pepsin is important in the breakdown of collagen, as it cleaves protein at the site of aromatic amino acids. Rennin (chymosin), which coagulates milk, may be produced by infants only.

Partly digested food from the fundus enters the antrum. The antrum has less of a secretory role and is responsible for mixing food and grinding it into small particles. Repetitive antral contractions occurring at 3 per minute propel chyme towards the pylorus, whose closure causes frequent retrograde flow. This to-and-fro flow produces shearing that reduces most food particles to less than 2 mm in diameter, a size at which they can pass through the pylorus into the duodenum. These shearing forces are weak (65 N) compared to those in the mouth (masticatory force 150 N) and so if food is not adequately, chewed chunks of material like meat will

empty as indigestible residue and will only empty with the MMC at the end of gastric emptying and thus may enter the small bowel as large chunks which will be less efficiently digested.

Thus the pylorus acts as a sieve [3]. Endocrine G cells in the antrum release gastrin, which stimulates the fundal parietal cells to secrete acid. The mixture of food, drink and secretion leaving the stomach is called chyme. Although the surface area of the stomach is small and the epithelium relatively impermeable, some molecules (e.g. alcohol and aspirin) can be absorbed from the stomach.

Duodenum

The duodenum is the widest part of the small bowel. It is 20–25 cm long and extends from the pylorus to the duodenojejunal flexure. In its structure it is essentially the same as the jejunum in that a villus structure starts absorption, but it contains submucosal bicarbonate-secreting glands of Brunner. The alkaline secretion from these glands helps to neutralize the gastric acid and provide a pH closer to the optimum for pancreatic enzymes to work. In the second part of the duodenum, alkaline pancreatico-biliary secretions are added to the chyme. The pancreatic enzymes are responsible for breaking macronutrients (protein, carbohydrate, lipid and nucleic acids) into smaller molecules (peptides, oligo/disaccharides, fatty acids/glycerol and nucleotides). Bile contains bile salts that aid lipid digestion and absorption; it also contains some end products of metabolism such as haemoglobin, cholesterol and some drugs. Bile is concentrated by the 7–10 cm long gallbladder which can hold 30–50 ml of fluid [1]. When lipid-containing chyme is within the duodenum, the gallbladder contracts and the sphincter of Oddi relaxes so that concentrated gallbladder bile is secreted into the duodenum.

Volume of Gastrointestinal Secretions

The work of Borgström et al. [4] and Fordtran and Locklear [5] provides an estimate for the daily volume of intestinal secretions when a normal diet is consumed. They have shown, using non-absorbed markers in healthy subjects, that about 4.0 L of endogenous secretions pass the duodenojejunal flexure daily. This quantity is made up of about 0.5 L saliva, 1–2 L gastric juice [6] and 1.5 L of pancreatico-biliary secretions (0.6 L is pancreatic juice [7]). Thus, each day about 6 L of chyme pass the duodeno-jejunal flexure. The process of digestion usually adds further secretions in the upper jejunum, increasing the flow still further until the mid jejunum when absorption comes to predominate and flow decreases progressively until only 1–2 L enter the colon (Table 1).

Table 1 Approximate daily volume and composition of intestinal secretions produced in response to food

	Volume (litres)	pH	Na	K	Cl (mmol/L)	HCO_3	Mg	Ca
Saliva	0.5	7	45	20	44	60	0.7	1.3
Gastric juice	2.0	2	10	10	130	0	0.5	2.0
Pancreatic juice	0.6	8	140	10	30	110	0.2	0.3
Hepatic bile	0.9	7	145	5	100	28	0.6	2.5
Small bowel secretion	1.8[a]	7	138	6	141	<5	<0.1	2.5
Serum		7.4	140	4	100	24	1.0	2.4

[a]This fluid is released and absorbed on the mucosa and rarely needs to be taken into account in calculating fluid losses. Estimates of its electrolyte composition are unreliable [8]

Jejunum and Ileum

The proximal two-fifths of the small bowel is called the jejunum, and the distal three-fifths the ileum. The jejunum diameter is 4 cm, and that of the ileum 3.5 cm. The small intestinal absorptive area is vastly increased by the villi, there being 20–40 per mm of small bowel [1]; villi are longer and more numerous in the jejunum than in the ileum (Fig. 2). The endothelial cells that line the villus are made in the crypts and migrate to the villus tip from where they are shed; these cells have a life span of only 2–5 days. The jejunum has many circular folds and is thicker, more vascular and muscular than the ileum but it has few lymphatics. The ileum has few circular folds and it contains many lymphoid follicles [1].

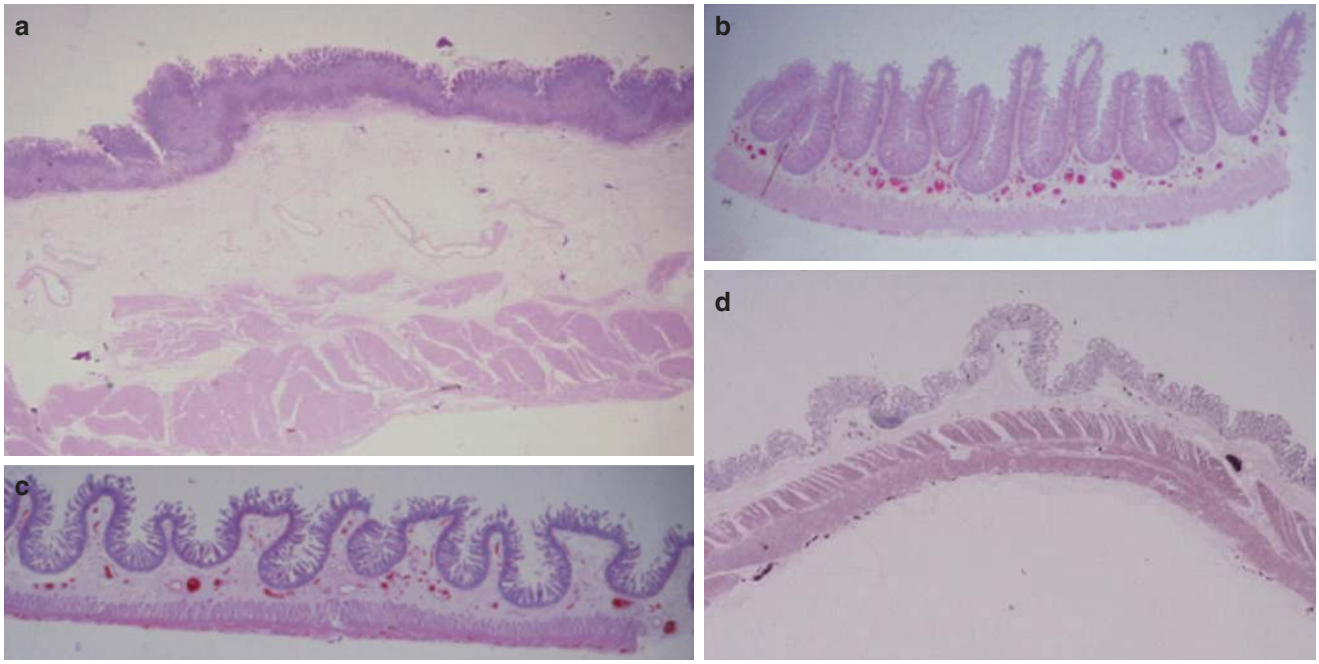

Fig. 2 Histological full-thickness sections of (**a**) stomach, (**b**) jejunum, (**c**) ileum and (**d**) colon. Kindly provided by P Domizio

Length of the Small Intestine

The normal human small intestinal length from the duodenojejunal flexure to the ileocaecal valve as measured at autopsy, by a small bowel enema or at surgery varies from 160–1510 cm (Table 2) [9–22] and is shorter in women and in most studies correlates with height. The full intestinal length is achieved by 10 years of age [9]. Congenital cases of patients having problems due to a short length of intestine have been reported [23]. Radiological measurements of small bowel length give shorter results than those obtained at autopsy or surgery, partly because radiographs are only in two dimensions. A small bowel enema [21, 22] causes bowel distension leading to overall shortening. The bowel may also be apparently shortened when measurements are made after passing a small flexible polyvinyl plastic tube through the nose to the caecum [20] as this causes the bowel to concertina around the tube [24]. The differences in length between fully stretched small bowel and non-stretched small bowel and between fully stretched small bowel and laparoscopic bowel was 137 ± 19 cm and 32.4 ± 11.4 cm, respectively [19].

An appreciation of the wide range of normal small intestinal length is important and emphasizes the need, after a bowel resection, to refer to the remaining length of small intestine rather than to the amount resected.

Table 2 Measured lengths of small intestine from the duodeno-jejunal flexure in subjects without bowel disease except Ref. 12

Author	Date	Sex	Number	Small intestinal length	
				Mean	Range (cm)
Autopsy					
Bryant [9][a]	1924	Both	160	620	300–850
		M	27	650	460–810
		F	17	590	410–760
Underhill [10][a]	1955	Both	100	620	340–790
		M	65	640	490–790
		F	35	590	340–720
Hounnou [11]	2002	Both	200	609	280–1000
		M	100	644	365–1000
		F	100	574	280–840
Hosseinpour [12]	2008	Both	30	633	+/− 90
Surgery					
Backman and Hallberg [13]	1974	Both	42	660	400–850
		M	12	700	500–850
		F	20	620	400–780
Guzman [14]	1977		121	525	SD 91
		M	83	530	SD 85
		F	38	507	SD 102
Slater and Aufses[b] [15]	1991	Both	38	500	300–780
		M	14	540	330–780
		F	24	480	300–640
Nordgren [16]	1997	Both	77	564	360–1090
		M	37	534	360–740
		F	40	591	380–1090
Hosseinpour [12]	2008	Both	100	460	285–620
		M	54	452	+/− 79
		F	46	468	+/− 80
Teitelbaum [17]	2013	Both	240	506	285–845
		M	113	533	+/−105
		F	127	482	+/− 99
Tacchino [18]	2015	Both	443	690	350–1049
		M	101	729	+/−85
		F	342	678	+/−92
Raines [19]	2015	Both	91 (51 M)	999	630–1510
Radiological					
Intubation					
Hirsch et al. [20]	1956	Both	10	260	210–320
		M	6	260	220–320
		F	4	260	210–320
Small bowel enema					
Fanucci et al. [22]	1984	M	5	310	260–370
		F	5	260	230–280
Fanucci et al. [21]	1988	Both	158	291	160–430

[a]Autopsy measurements from pylorus, all others from the duodeno-jejunal flexure (duodenum = 25 cm)
[b]21 of these patients had small bowel and 4 others colonic Crohn's disease but their small intestinal lengths were not different from 13 patients without Crohn's disease

Digestion and Absorption in the Small Intestine

Water, Sodium and Chloride

Although some water and sodium may be absorbed before chyme reaches the jejunum in most normal subjects, a meal continues to be diluted by secretions at a distance of 100 cm distal to the duodeno-jejunal flexure [4, 5]. This distance is clinically important: if a patient has a stoma situated in the upper 100 cm of jejunum, the volume that emerges from the stoma is likely to be greater than the volume taken by mouth. Such a patient will be in negative fluid and sodium balance after any food or drink [25]. Most meals have a low sodium content (10–40 mmol/L), generating a steep concentration gradient between the lumen and plasma. Sodium-rich salivary and pancreatico-biliary secretions raise the luminal level, as do intestinal secretions, so that the sodium concentration at the duodeno-jejunal flexure reaches about 90 mmol/L and increases further towards 140 mmol/L in the terminal ileum [5].

Jejunal mucosa is more permeable to water, sodium and chloride than ileal mucosa. It allows back diffusion through leaky intracellular junctions so the jejunal contents become iso-osmolar. Thus water movements in response to an osmotic gradient in the jejunum are nine times as great [26] and sodium fluxes twice as great [27] as in the ileum. Sodium absorption in the jejunum can occur only against a small concentration gradient, depends upon water movement, and is coupled to the absorption of glucose and some amino acids [28]. When the small bowel is intubated and perfused with solutions containing different amounts of sodium, absorption of sodium from the perfusate occurs if its sodium concentration is 90 mmol/L or more, while secretion of sodium into the lumen occurs if the concentration is less. Several studies have shown that maximal jejunal absorption of sodium from a perfused solution occurs at a concentration of around 120 mmol/L [29–31]. In contrast, the ileum can absorb sodium against a concentration gradient, and movement of sodium is not coupled with glucose or other nutrients. The ileum is important in conserving sodium and water when the body becomes depleted since, unlike the jejunum, the ileal mucosa can increase its sodium absorption in response to aldosterone [32]. Some chloride is actively absorbed in the ileum in exchange for bicarbonate.

Macronutrients

The salivary, gastric and pancreatico-biliary secretions reduce large molecules (e.g. polypeptides, polysaccharides, nucleotides) into medium-sized ones (e.g. oligopeptides, oligosaccharides and nucleosides) within the gut lumen. They are not designed to create small molecules (e.g. amino acids, glucose or nucleic acids) as these would be hyperosmolar and thus cause water secretion and an osmotic diarrhoea. The final breakdown to small molecules occurs at the mucosal brush border immediately before absorption (Table 3). Intubation studies in healthy subjects have shown that most polysaccharides, proteins and fats are digested and absorbed within the upper 200 cm of the small intestine [4]. The site of absorption of a meal depends upon its nature. Fibre may trap water and impede access to the mucosa and/or bind digestive enzymes reducing their efficacy. In general meat and salad are absorbed high in the jejunum, while milk and doughnuts are absorbed more distally, after a large amount of water has been secreted.

Table 3 Content and function of most upper gastrointestinal secretions

Secretion	Content	Functions/released/activated by
Saliva	α-Amylase	Converts starch to oligosaccharides, maltose, maltotriose and α limit dextrins. Needs pH 7, inactive in gastric acid
	Lipase	From lingual glands, cleaves MCTG to MCFA/glycerol, active at pH 2.5–6. Irreversibly inactivated at pH < 2.4 [33]
Gastric juice	HCl	Denatures protein, kills micro-organisms, activates pepsinogen released by gastrin, food, cholinergic agents and hypoglycaemia
	Pepsin(ogen)	Hydrolyses bonds by aromatic amino acids (tyrosine and phenylalanine) and leucine (collagen) at pH 2–3. Activated by acid
	Lipase	Cleaves MCTG to MCFA/glycerol, acid stable
	Intrinsic factor	Binds B_{12} and the complex is absorbed in the terminal ileum
	Gelatinase	Liquefies gelatine
Pancreatic juice	Bicarbonate	To neutralize acid and provide optimum pH for pancreatic enzymes, released by secretin
	α-Amylase	Starch to oligosaccharides, maltose, maltotriose and α limit dextrins
	Lipase	1 and 3 glycerol/fatty acid bonds hydrolysed, inhibited by acid
Endopeptidases	Trypsin(ogen)	Cleaves bonds next to arginine and lysine. It is activated by enterokinase an enzyme produced by duodenal mucosa and by itself. It activates all other pancreatic proteolytic enzymes
	Chymotrypsin(ogen)	Cleaves bonds by tyrosine, tryptophan, phenylalanine, methionine and leucine. Activated by trypsin
	(pro)Elastase	Cleaves bonds by alanine, glycine and serine, activated by trypsin
Exopeptidases	(pro) Carboxypolypeptidase A	Cleaves bonds by valine, leucine, isoleucine and alanine (contains zinc), activated by trypsin
	(pro) Carboxypolypeptidase B	Cleaves bonds by arginine and lysine
	DNA/RNAases	Nucleotides to nucleosides
	Esterase	Cleaves cholesterol esters
	(pro)Phospholipase A	Cleaves lecithin to lysolecithin
Bile	Bile salts (primary/ secondary)	Bind fat to form globules; then, after lipase has acted, form small micelles which transport the lipid to the brush border
Mucosa[a]	Bicarbonate	Neutralizes acid generated in process of digestion
	Enterokinase	Activates trypsin
Disaccharidases		Disaccharides to monosaccharides
	Maltase	Maltose to glucose
	Isomaltase	Isomaltose to glucose
	Sucrase	Sucrose to glucose and fructose
	Lactase	Lactose to glucose and galactose
	Trehalase	Trehalose to glucose
	α-Dextrinase	α Limit dextrins to glucose
Exopeptidases		
	Aminopeptidase	Peptides to amino acids hydrolysis starting at amino end
	Dipeptidases	Dipeptides to amino acids
Nucleosidases		Cleave nucleoside to nucleic acid and hexose/pentose

(): the name of the enzyme in its inactive secreted form

[a]Mucosal brush border (secretion of glycoprotein enzymes)

Carbohydrate and Protein

Saliva and gastric and pancreaticobiliary secretions break down carbohydrate and protein to oligosaccharides and oligopeptides. The final stage of carbohydrate and protein digestion therefore occurs on the mucosal brush border where oligosaccharides are broken down to monosaccharides and oligopeptides are broken down to amino acids immediately before absorption. In the jejunum, glucose and galactose absorption is partly coupled with that of sodium; fructose absorption occurs largely via the facilitative transporter GLUT5.

Protein is digested by enzymes that cleave protein either at specific points in the middle of proteins, endopeptidases (pepsin, trypsin, chymotrypsin and elastase), or work systematically from the ends, exopeptidases. Carboxypeptidases from pancreatic juice start at the carboxyl end while aminopeptidases on the brush border start at the amino end.

Lipid

Triglycerides and fatty acids separate into a lipid phase and do not contribute to the osmotic forces that dominate fluid flux across the small intestinal mucosa. Salivary and gastric lipase are active in the gastric juice and start digestion by splitting monoglycerides from triacylglycerol. Monoglycerides combine with bile salts to generate micelles. Shearing forces around the pylorus are believed to contribute to emulsification, the process that generates fatty droplets in the duodenum. This requires agents such as bile salts and lecithin to lower surface tension, thereby acting like soap and keeping the droplets in solution. The increased surface area of lipid is acted upon by co-lipase and lipase which cleave fatty acids from triglyceride mainly at the 1 and 3 positions. This enzymatic reaction continues as the products (free fatty acids and 2 monoglycerides) are immediately bound by bile salts to form micelles, allowing them to diffuse to the mucosal brush border for active absorption. There, fatty acid binding proteins allow removal of fatty acids from the micelles, which then diffuse back into the lumen to solubilize more lipid. The micelles protect the brush border from the damaging effects of free fatty acids.

The liver makes two bile acids, cholic and chenodeoxycholic acid. These are conjugated with glycine or taurine in the ratio 3:1. The taurine conjugates are more soluble and are present in a greater amount in people who eat meat than in vegetarians. Each day, one-third to one-quarter of the primary bile acids undergo anaerobic bacterial dehydroxylation within the terminal ileum and colon. This dehydroxylation takes place at position 7 and results in the formation of the secondary bile acids, deoxycholic acid and a little relatively insoluble lithocholic acid respectively. Most lithocholic acid is sulphated and amidated and lost in the stool. Normal human bile therefore consists of 50% cholic acid, 39% chenodeoxycholic acid, 15% deoxycholic acid and 5% lithocholic acid. The individual bile salt pool amounts to 3–5 g that circulates through the entero-hepatic circulation 5–14 times daily. This circulation is important for the action of some drugs, such as loperamide, that enter it; if the entero-hepatic circulation is disrupted (e.g. by an ileal resection) higher than normal doses of loperamide are needed for the same effect. Cholesterol also undergoes secretion in the bile and reabsorption in the small intestine, the balance of which has an important effect on serum levels. Reabsorption can be reduced by poorly absorbed plant phytosterols such as sitosterol, which competitively inhibit cholesterol uptake into micelles [34]. Fibre supplementation reduces reabsorption of bile salts by increasing ileal contents' viscosity. Ispaghula and pectin are particularly effective, while bran is ineffective. This is important because bile salt excretion stimulates bile acid synthesis from cholesterol and hence lowers serum cholesterol [35].

Long-chain fatty acids (C14–20) are absorbed and formed into chylomicrons which pass via the thoracic duct to the systemic circulation. Medium-chain fatty acids (C6–12) are absorbed in the small and large bowel and pass directly into the portal venous system; they are readily oxidized in the liver via a carnitine independent pathway.

Nucleotides

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are broken down to nucleosides by pancreatic DNA/RNA endonucleases and exonucleases, which cleave from either the middle or the end of the molecules respectively. Phosphodiesterase hydrolyses nucleotides from the 3′ end. The resulting nucleosides are split into nucleic acids and pentoses by nucleosidases at the brush border immediately before absorption.

Micronutrients

Vitamins

Water-soluble vitamins are actively absorbed from the upper intestine, with the exception of vitamin B_{12} which is selectively absorbed from the distal 60 cm of ileum [2]. The fat-soluble vitamins A, D, E and K, essential fatty acids and cholesterol do not have specific active uptake mechanisms but dissolve in the lipophilic centre of the micelles; this allows these hydrophobic molecules to diffuse through the

aqueous chyme to reach the lipid outer membrane of the brush border into which these lipophilic substances readily diffuse.

Minerals

Magnesium

Magnesium is an important cation that is a cofactor for many intracellular enzymatic reactions while its extracellular concentration modulates neuromuscular excitability; 50% is in bone. Each day, about 10–20 mmol of magnesium are consumed, of which about one-third is absorbed, principally by a gradient-driven saturable process occurring mainly in the distal small intestine and colon [36]. The proportion absorbed varies according to the amount of magnesium in the diet. When the total dietary magnesium is increased to 24 mmol in a healthy person only 24% is absorbed, while if the dietary intake is reduced to 1 mmol 76% is absorbed [37]. The jejunal absorption of magnesium, like that of calcium, is increased by 1,25-dihydroxycholecalciferol [38]. Magnesium in the circulation is 30% bound to albumin. The serum levels, however, are an unreliable index of magnesium status, and severe deficiency can occur when the serum levels are normal [39]. Under conditions of magnesium deprivation the kidney can reduce magnesium excretion to less than 0.5 mmol/day [40]. Aldosterone increases [41] and parathormone reduces renal magnesium excretion [42]. Very little magnesium is found in the intestinal secretions (Table 1).

Calcium

Of the calcium ingested, 30–80% is normally absorbed, mainly by active transport in the upper small intestine. The transport is facilitated by 1,25-dihydroxycholecalciferol, lactose and protein. Phosphates, phytates and oxalate form insoluble complexes with calcium and thus inhibit calcium absorption.

Iron

Normally, only 3–6% of the iron ingested is absorbed; this is sufficient to replace losses of 0.6 mg/day in men and 1.2 mg/day in women. Gastric acid dissolves insoluble iron salts and facilitates the reduction of ferric iron (Fe^{3+}) present in most food to ferrous iron (Fe^{2+}) which can be actively absorbed in the upper small bowel. This reduction depends on ascorbic acid, which is actively secreted in gastric juice, and other reducing agents in the diet. The amount of iron entering the circulation via the iron export protein ferroportin 1 is carefully controlled by the liver-derived regulator, hepcidin. Only a small amount is allowed to enter the circulation, while the rest is bound to apoferritin to form ferritin within a mucosal cell. This poorly absorbable complex enters the gut lumen when the mucosal cell is shed and is thus lost from the body.

Zinc

Like iron and calcium, zinc is mainly absorbed in the upper small intestine; blood levels peak 2–3 h after ingestion. Endogenous, particularly pancreatic, secretions contain substantial amounts of zinc. Intestinal luminal levels of zinc fall distally as it is actively absorbed, a process facilitated by the absorption of dipeptides. Once absorbed, it is bound to albumin and circulating macroglobulin. Excretion is via sweat and in urine and faeces. Zinc absorption is, like that of calcium, impaired by dietary phytate and oxalate [43]. Geophagia (ingestion of clay) is associated with severe zinc deficiency characterized by hypopituitarism and dwarfism [44]. Zinc deficiency is frequent in patients with Crohn's disease as there are excessive faecal losses together with a poor intake [45].

Copper

This potentially toxic metal is rapidly absorbed and loosely bound to albumin. It is rapidly taken up by the liver and avidly secreted into the circulation bound to caeruloplasmin. Deficiency is extremely rare; it can cause a microcytic anaemia and twisted abdominal hair. The main clinical problem in copper metabolism is failure to excrete it adequately. Urine excretion is normally low and the main route of excretion is via bile where copper forms a complex with a fragment of caeruloplasmin which prevents its reabsorption. Defective excretion is seen in Wilson's disease, an autosomal recessive trait characterized by caeruloplasmin deficiency and hence an accumulation of copper in the liver with resulting fibrosis.

Ileocaecal Valve

The ileocaecal valve consists of two semilunar flaps projecting into the lumen of the large bowel at the junction of the caecum and colon. Two main functions are classically attributed to the ileocaecal valve: (1) to control the passage of ileal contents into the caecum, so allowing adequate time for digestion and absorption; and (2), more importantly, to prevent the regurgitation of caecal contents into the small bowel [46]. These functions are questionable: in patients

who had had a right hemicolectomy for localized colon cancer, transit of a scrambled egg meal from the small to large bowel was qualitatively and quantitatively the same as in healthy subjects [47]. The mean anaerobic bacterial count in the distal ileum is 10^4/ml compared with 10^8/ml in the caecum; the mean coliform content is 10^3/ml in the ileum and 10^6/ml in the caecum [48]. No major episodes of colo-ileal reflux occur when the ileocaecal valve has been removed [47], thus the bacterial population in the ileum is unlikely to be changed. Ileal peristalsis is probably the main factor that keeps the number of bacteria in the small bowel so much lower than in the colon. The ileum can differentiate between liquid and solid but the ileocaecal junction cannot [49].

Colon

The average length of the colon at autopsy is about 1.6 m (range 0.8–3.3) [8, 9, 11], being longer in men than in women. The unstretched colon at colonoscopy is much shorter at about 0.9 m and its undisturbed volume averages 551 ml [50]. The colon has many haustra and its longitudinal muscle is reduced to three longitudinal bands (taeniae coli) [1]. It has the functions of absorbing water (up to 6 l/day) [51], sodium, minerals (e.g. magnesium and calcium), some vitamins and fermenting unabsorbed non-starch carbohydrate to short-chain fatty acids (acetate, propionate and butyrate). The appendix and terminal ileum may secrete antimicrobial substances to regulate the colonic bacterial flora. The functions of the right and left sides of the colon are different. The right side is mainly involved with water and sodium absorption and with fermentation (to produce short chain fatty acids and amino acids); the left colon is largely a storage and propulsive organ. The colon avidly absorbs sodium and chloride against a high concentration gradient and so normal stool contains very little sodium and chloride.

Evidence that the colon can absorb nutrients and minerals comes from reports dating as far back as ancient Egypt of various mixed enema solutions containing such ingredients as milk, egg, beef broth, wine or brandy being used to give nutrition support [51], and from the fact that magnesium poisoning can occur from magnesium sulphate enemas [52].

Gastrointestinal Motility

The gut is innervated by the vagus nerve (parasympathetic) which contains 90% sensory (afferent) and 10% efferent neurones. Information travels from the gut lumen to the brain via mucosal free nerve endings and entero-endocrine cells. These cells, whose microvilli extend into the gut lumen, respond to a range of stimuli including bacteria toxins, pH, osmolality and lipid, as well as direct contact. Stretch of the gut wall may also activate tension receptors in the muscle layers. The gut is additionally innervated from the spinal (sympathetic) nerves. There is a complex interchange of information between the submucosal and myenteric plexus and the brain. The pattern of gastrointestinal motility depends upon whether an individual is in a fasted or fed state. The electrical activity recorded from the gut does not always correspond to the pressure activity.

Stomach and Small Intestine

Fasting

During fasting, three phases of pressure activity can be identified: during phase I there is no activity; irregular activity occurs during phase II; phase III is characterized by strong rhythmic contractions starting in the stomach and spreading distally. Phase III, also called the interdigestive migrating complex or migrating motor complex (MMC), occurs every 90 min (range 50–140) and lasts for 5–10 min in any one area; it takes about 90 min to reach the terminal ileum. Although the MMC shows great regularity in a trained laboratory dog, in man its frequency and form varies both between and within an individual [53]. Some MMCs start in the stomach while the majority commence in the mid-jejunum, many petering out before reaching the terminal ileum. The MMC is strongly propulsive and is thought to be responsible for clearing the last part of a meal from the stomach and small intestine, thus having a 'housekeeper' function [54]. Loss of the MMC is associated with small bowel bacterial overgrowth [55].

Just before the MMC, there is an increase in the concentration of gastric acid and pepsinogen secreted, followed by an increase in the concentration of secreted pancreatic enzymes and bicarbonate [56]. These secretions may be the reason why, even in the fasting state, there is some output from a high jejunostomy.

Fed

In the fed stomach, a wave of depolarization (gastric slow wave or basic electrical rhythm) is associated with a peristaltic wave that starts in the mid-stomach and spreads to the pylorus every 20 s (3/min). Liquid from a mixed liquid and solid meal starts to empty as soon as it reaches the stomach, and 50% of 200 ml orange juice consumed with a pancake has left the stomach at 98 min. If the liquid is taken alone, the rate of gastric emptying is much faster. The solid emptying usually occurs in a linear fashion after a variable lag phase (usually 20–30 min) during which the meal remains in the

fundus undergoing digestion and dilution by gastric secretions. Thus the time taken for 50% of a solid pancake to leave the stomach is 150 min [57].

The frequency of the slow wave, which is now thought to originate in the interstitial cell of Cahal, varies from 12/min in the jejunum to 8/min in the ileum. Small bowel contractions can be segmental or peristaltic (rate 2–25 cm/s), peristalsis predominating in the duodenum while segmenting contractions predominate further distally. Peristalsis can cause very rapid transit if there is no inhibitory feedback from nutrients; thus water can reach the caecum in 15 min. Even with nutrients, the first part of a liquid meal can travel very rapidly, reaching the caecum in just 14 min for liquid and 24 min for solid [57]. This first sample then excites inhibitory feedback responses which slow gastric emptying to allow time for digestion and absorption. After the bulk of a meal has been emptied from the stomach, 'fasting' activity resumes.

Colon

Most of the time there is segmental contracting non-propulsive activity within the colon which allows mixing of the colonic contents and time for absorption. Several times a day, high-pressure propulsive peristaltic waves propel some of the colonic contents to the rectum ('mass movement'). Isotope studies have shown that the first part of a meal remains in the colon for a median of 31 h (range 24–48). In normal subjects most of a meal will have left the bowel within 3 days of being eaten. Colonic transit is slower in women [58]. On a Western diet, stool weight is about 200 g/day.

Controlling Mechanisms

Appetite

Body weight is a result of the balance between food intake and energy expenditure/losses. There are many factors that control appetite (regulated in the hypothalamus) and thus food intake (hunger and satiety). They include the hormone ghrelin which is the only known orexigenic gut hormone that promotes appetite while many anorexigenic gut hormones, including cholecystokinin (CCK), pancreatic polypeptide (PP), peptide YY (PYY), glucagon-like peptide (GLP)-1, and oxyntomodulin reduce appetite. Leptin is another hormone that is secreted exclusively by white adipose tissue adipocytes and reduces food intake and body weight [59]. Some bacterial metabolites (e.g. SCFAs which inhibit gastric emptying) reduce appetite.

Gastrointestinal Tract

The rate of gastric emptying is normally controlled by both neural and hormonal mechanisms so that chyme is delivered into the intestine at a rate optimal for digestion and absorption. There are at least four gastrointestinal sites which, depending on their luminal contents, may affect gastric emptying: the stomach itself, the proximal small bowel, the distal small bowel, and the colon and rectum. Large volume [60], high nutrient density (e.g. lipid-based) [61], hyper- or hypo-osmolar solutions [62] or acid [63] meals all slow gastric emptying. A painful stimulus applied outside the gut will also delay gastric emptying [64], as do various inflammatory cytokines released during infections. The upper small intestine regulates the rate of gastric emptying: studies in dogs have shown that the longer the length of duodenum and jejunum exposed to glucose [65], acid [66] or lipid (sodium oleate) [67], the greater the delay in gastric emptying. An infusion into the human ileum of lipid [68–70], protein hydrolysate [71] or carbohydrate [72, 73] delays proximal small bowel transit, and lipid [69, 74, 75] and carbohydrate [76] also delay gastric emptying. The effect of nutrients in the ileum in delaying gastric emptying and small bowel transit is referred to as the 'ileal brake'.

Evidence for two mechanisms, one delaying gastric emptying and the other delaying small bowel transit, comes from experiments which show that intravenous naloxone prevents intralipid infused into the ileum from slowing small bowel transit but does not prevent it from slowing gastric emptying [77, 78].

Events within the colon affect the rate of gastric emptying. Balloon distension in the colon or rectum of animals [79–82] and man [83] causes a rapid inhibition of gastric and intestinal contractions and tone, so delaying gastric emptying and intestinal transit. This is probably the result of a neural mechanism as the effect in animals can be abolished by splanchnic nerve excision [80, 81]. However, there is also a hormonal component as balloon inflation of the rectum causes delayed inhibition of motility in denervated jejunal loops [82]. When unabsorbed nutrients reach the colon in patients with jejunum anastomosed to colon, there is rapid slowing of gastric emptying [57]; this is probably caused by raised peptide YY levels [84] and is referred to as the 'colonic brake'.

Gastrointestinal Hormones

A hormone is a blood-borne chemical messenger that has an identifiable structure, is released in one part of the body and, after passing in the blood stream, has a physiological action in another part, even when all neural connections between

the two parts have been severed. It should also be possible to inject the hormone and induce its physiological effects.

The various gastrointestinal hormones are described here in some detail not only because they are important in controlling the activity of the gut but because they are used and may be increasingly used in the future to treat some patients with intestinal failure. Most of the hormones fall into one of two families according to their molecular structure: the gastrin family (gastrin and cholecystokinin) or the secretin family (gastric inhibitory peptide, glucagons, secretin and vasoactive intestinal peptide). The hormones (Table 4), which all are produced in response to luminal stimuli, have four main areas of action: (1) to control gastric emptying or secretion (gastrin and somatostatin); (2) to regulate the rate of digestion (cholecystokinin, secretin, gastric inhibitory peptide and motilin); (3) to slow the rate of gastrointestinal transit (GLP-1, neurotensin and peptide YY); or (4) to promote intestinal growth (GLP-2, enteroglucagon and neurotensin). Only five—gastrin, secretin, CCK, GIP and motilin—are true hormones, the others being better regarded as neuromodulators with a principally local or paracrine action. The link with the nervous system is important and many hormones are released after vagal stimulation (e.g. gastrin, somatostatin, pancreatic polypeptide and VIP).

Ghrelin

Ghrelin is a 28–amino acid peptide hormone, produced mainly in the stomach and is the only known orexigenic gut hormone (increases appetite/hunger and reduces satiety). It binds to the growth hormone secretagogue receptor (GHSR) 1a which is highly expressed in the hypothalamus and brain stem. It has been shown to stimulate appetite in both lean and obese humans, and intravenous infusions given to healthy volunteers, at a concentration similar to that observed after a 24 h fast, increase appetite and food intake by almost 30%. There is animal evidence that blocking its signaling results in a reduced body weight [85]. Ghrelin levels rise pre-prandially and decrease to baseline levels within the first hour after a meal.

Gastrin

Gastrin exists as two forms produced by the G cells situated in the gastric antrum, duodenum and jejunum. Big gastrin, G34, is found mainly in the duodenum; it has plasma half-life ($t^{1/2}$) of 42 min and is the most abundant form in the circulation in the fasting state. Little gastrin, G17, which is mainly found in the gastric antrum, has a $t^{1/2}$ of 5 min and is a more powerful stimulus in causing gastric acid secretion. Gastrin release is caused by amino acids and peptides in the stomach and by vagal nerve stimulation as occurs with hypoglycaemia or hypercalcaemia. Both forms of gastrin are inactivated in the small bowel and kidney, which may in part explain the hypergastrinaemia seen after an extensive small bowel resection or in patients with renal failure. Gastrin stimulates gastric acid and pepsin secretion in the stomach partly by causing histamine release from enterochromaffin-like (ECL) cells. Gastrin increases antral smooth muscle activity and may have a trophic effect. Excess gastrin gives rise to the Zollinger–Ellison syndrome which is characterized by duodenal and jejunal ulcers [86] and diarrhoea; the diarrhoea is the result of malabsorption caused by the excess gastric acid inhibiting pancreatic enzyme function and micelle formation.

Somatostatin

Somatostatin has been referred to as ‘endocrine cyanide’ as it reduces the circulating levels of all known gastrointestinal peptide hormones, most anterior pituitary hormones, and many others (e.g. calcitonin and renin). By endocrine, paracrine and neurotransmitter actions, it inhibits most gastrointestinal functions. It reduces gastric, pancreatic and biliary secretions [87] and reduces pentagastrin-stimulated salivary flow [88]. It slows small bowel transit, may delay gastric emptying, reduces gastrointestinal blood flow and reduces the absorption of carbohydrate, lipid and amino acids. Tumours that produce excess somatostatin (somatostatinomas) may give rise to a triad of diabetes, gallstones and malabsorption [89].

Cholecystokinin

Cholecystokinin (CCK), which was shown to be the same as pancreozymin in 1966, is rapidly metabolized by the liver. It acts as a primary regulator of upper gastrointestinal function as it balances lipid and protein digestion with the rate at which they are delivered to the small intestine. It reduces the amount of chyme reaching the upper small intestine by causing satiety [90–92] and reducing gastric emptying, while at the same time promoting digestion by causing gallbladder contraction and pancreatic secretion [93]. There are two types of CCK receptors: CCK-A in the gallbladder, pancreas

Table 4 Gastrointestinal hormones

Hormone	Amino acids	$t^{1/2}$ min	Main site	Released by	Main functions
Ghrelin	28	*35*	Parietal cells of the gastric fundus	Fasting (inhibited by food esp. protein/CHO)	Increase appetite
Gastrin	17/34	5/42	Antral G cells	Protein	Gastric acid secretion
				High serum calcium	
				Pepsinogen secretion	
Somatostatin	14/28	3	Antral/pancreatic D cells	Food (especially lipid) or acid in duodenum	Reduces salivary, gastric and pancreatico-biliary secretions
					Slows gastric emptying
					Slows small bowel transit
					Reduces portal blood flow
					'Endocrine cyanide'
Cholecystokinin (CCK)	8/33	2/5	Duodenum/jejunum I cells	Lipid and protein	Pancreatic secretion (B)
					Gallbladder contraction (A)
					Inhibits gastric emptying
					Pancreatic growth
					Satiety and memory
Secretin	27	3	Duodenum/jejunum S cells	Acid	Pancreatic bicarbonate secretion
				Starvation	Pancreatic growth
					Pepsinogen secretion
Gastric inhibitory peptide (GIP)	42	20	Duodenum/jejunum K cells	Lipid and carbohydrate	Inhibits gastric secretion
					Inhibits gastric motility
					'Incretin'[a]
Motilin	22	4.5	Duodenum/jejunum M cells	High-fat meal Alkali	Increases gastric and small intestinal motility
					Causes MMC
Pancreatic polypeptide	36	7	Pancreas	Hypoglycaemia	Gallbladder relaxation
					Reduces pancreatico-biliary secretions (not HCO_3)
Vasoactive intestinal peptide (VIP)	28	<1	Upper small intestine, colon	Intraduodenal acid	Relaxes smooth muscle
					Increases blood flow, pancreatic
					HCO_3 secretion, intestinal secretions
					Inhibits gastric secretion
Neurotensin	13	1.5	Ileum N cells	Fatty meal in upper gut	Inhibits gastric secretion, pancreatic bicarbonate secretion
					Relaxes gallbladder
					Villus/crypt growth
					Glycogenolysis
Peptide YY (PYY)	36	9	Ileum/colon L cells	Lipid or bile salts in ileum/colon	Slows gastric emptying, small bowel transit
					'Ileal and colonic brakes'
					Reduces gastric secretion, small bowel water/electrolyte absorption
Pancreatic glucagon	29	10	Pancreas A cells	Amino acids in duodenum	Inhibits pancreatic secretion
				Hypoglycaemia	Relaxes smooth muscle
					Increases blood glucose
Glucagon-like peptide-1 (GLP-1)	31	4.5	Ileum/pancreas	Rapid gastric emptying	Inhibits gastric secretion
				Lipid and carbohydrate	Inhibits gastric emptying
					'Incretin'[a]
Glucagon-like peptide-2 (GLP-2)	33	2.5	Ileum/colon L cells	Nutrients in ileum/colon	Small and large bowel villus/crypt growth
					Reduces gastric antral motility
Glicentin ("Enteroglucagon")	69	NK	Ileum/colon L cells	Nutrients	Villus growth
					Slows gut transit

(continued)

Table 4 (continued)

Hormone	Amino acids	$t^{1/2}$ min	Main site	Released by	Main functions
Oxyntomodulin	37	12	Ileum/colon L cells	Nutrients	Reduces gastric and pancreatic secretion Reduces gastric emptying Reduce appetite Incretin[a]

NK not known
[a]An 'incretin' augments the rise in plasma insulin level after oral glucose

and intestine, while CCK-B predominates in the stomach and brain. Only the first eight amino acids are needed for potency at these receptors.

Secretin

Secretin was the first of all hormones to be discovered in 1902 by Baylis and Starling who observed bicarbonate and pancreatic secretions to occur from a denervated pancreas after acid was instilled into the duodenum, and after injections of small bowel extracts [94]. It is released by duodenal and jejunal mucosa in response to acid (pH <4.5) [95], starvation and alcohol. It is metabolized in the vascular system and kidneys.

Gastric Inhibitory Polypeptide

Gastric inhibitory polypeptide (GIP) was originally thought to be an 'enterogastrone' (a substance from the bowel that inhibits gastric activity) as it is released by fat, especially long-chain fatty acids derived from triglyceride hydrolysis [96], glucose in the duodenum and to a lesser extent by amino acids. While it inhibits gastric acid secretion (also pepsin and gastrin secretion) [97] and gastric motility, these effects may not be of physiological importance in man [98]. Its main action is probably as an 'incretin' for, if GIP is infused together with glucose, a greater rise in plasma insulin occurs than if glucose alone is infused [99]. It is inactivated and cleared by the kidney.

Pancreatic Polypeptide

Pancreatic polypeptide has actions directly opposite to those of CCK. It is released rapidly after a meal but its levels remain raised long after the other hormone levels have returned to normal and its role may be to promote the storage of bile and pancreatic enzymes before the next meal [100]. It is metabolized by the liver and excreted by the kidneys. Fasting levels of pancreatic polypeptide increase with age [101] and this could contribute to the increased incidence of gallstones with age.

Motilin

Motilin release from the duodenum and proximal jejunum is stimulated by a high-fat meal and suppressed by a carbohydrate or protein meal [102]. Mixed meals thus have little overall effect on circulating motilin levels [102]. In man, unlike dogs, acid in the duodenum (not alkali) causes its release [103]. Motilin may inhibit gastric emptying at a high but physiological plasma level and promote it at a low level [104]. Motilin probably plays only a minor role in the control of normal gastric emptying; for acid infused into the duodenum or fat ingestion both delay gastric emptying yet cause motilin release [102, 103]. Motilin, however, is the only gastrointestinal hormone that has been shown to increase the rate of gastric emptying.

Motilin may be responsible for inducing the MMC, as there is a cyclical rise in plasma levels before the complex occurs and an infusion of motilin causes them to occur with increased frequency [105]. Motilin analogues such as macrolide antibiotics (e.g. erythromycin) cause premature phase III-like intense contractions of the gastric antrum and small bowel. These contractions accelerate gastric emptying and may be used to treat gastroparesis; however, the intense cramps from the small bowel contractions and diarrhoea may cause the course of antibiotics to be aborted.

Vasoactive Intestinal Peptide

Vasoactive intestinal peptide (VIP) acts mainly as a neurotransmitter but has some hormonal actions. It is metabolized locally. It is a powerful smooth muscle relaxant, and thus systemically causes hypotension, flushing and tachycardia. Its main role may be to increase the blood flow to the gut following a meal. At high levels it inhibits gastric acid secretion while stimulating pancreatic bicarbonate and intestinal fluid secretion. Tumours producing VIP (vipomas) were first reported in 1958 and are an extremely rare cause of profuse watery diarrhoea with stool volumes of 2–11 l/24 h associated with hypokalaemia and achlorhydria [106]. Symptoms may respond to injections of a long-acting synthetic somatostatin analogue, which will inhibit VIP secretion.

Neurotensin

Neurotensin is so named because it caused vasodilatation and hypotension in the rat; it also increased vascular permeability [107]. It is rapidly broken down into two fragments, each having a long half-life and being biologically active [108]. Neurotensin is found in N cells which are located mainly in the ileal mucosa; few are found in the jejunum and almost none in the colon [109]. The mechanism of neurotensin release is complex: lipid in any form taken orally or administered into the proximal jejunum causes a high and rapid rise in neurotensin levels, more so than if administered distally into the ileum [110]. It is probable that fat in the upper small intestine primes the ileal N cells by a neural or hormonal mechanism so that they can release neurotensin when exposed to this fat [110]. Neurotensin promotes small bowel growth [111].

Peptide YY

Peptide YY has structural similarities to pancreatic polypeptide. It consists of 36 amino acids with a tyrosine at each end and hence was called peptide YY [112]. It is distributed throughout the small and large intestine from duodenum to rectum (there is none in the stomach) and increases in amount from the ileum to the rectum (concentrations: jejunum 5 pmol/g, terminal ileum 84 pmol/g, ascending colon 82 pmol/g, sigmoid 196 pmol/g and rectum 480 pmol/g [113]). It coexists in the L cells with GLP-2/enteroglucagon [114, 115] and has a 70% sequence homology with the neurotransmitter neuropeptide Y. High levels of peptide YY are observed in situations in which unabsorbed nutrients reach the colon, such as tropical sprue or chronic pancreatitis [116], dumping syndrome [117] and after an ileal resection which leaves the colon in situ [84, 118]. Low levels occur in jejunostomy and ileostomy patients as their colons have been removed [84, 118].

Peptide YY may be the major hormone responsible for the ileal and colonic brakes [70, 84, 119] which slow gastric emptying and small bowel transit when unabsorbed nutrients reach the ileum or colon. Although peptide YY is stored in the same cells as GLP-2/enteroglucagon, it is unlikely to exert a major trophic effect on the gastrointestinal tract [120].

An infusion of peptide YY at a level that reproduces post-prandial concentrations causes a sustained natriuresis, probably by reducing plasma renin and aldosterone [121]. Peptide YY abolished the flushing associated with a vipoma [122].

Glucagon-Like Peptides

The existence of a bowel source of a glucagon was first realized in 1961 when the non-specific antisera for glucagon detected immunoreactive material in the gut as well as the pancreas [123, 124]. The plasma levels of this ‘enteroglucagon’ were determined by measuring total glucagon-like immunoreactivity using antisera to the middle and N-terminal portion of the glucagon sequence. Pancreatic glucagon was measured with specific C-terminal directed antisera. The enteroglucagon levels were derived by subtracting the pancreatic glucagon level from the total glucagon-like immunoreactivity [125]; This value is higher than the pancreatic glucagon level.

Enteroglucagon, as first described, consists of several different molecules all derived within the L-cells in the jejunum, ileum, and colon, often with PYY (especially in the distal gut) [114, 115] these include GLP-1, GLP-2, glicentin, and oxyntomodulin. Glicentin is probably the main molecule detected as “enteroglucagon”. The greatest concentration of enteroglucagon activity is found in the ileum and colon (duodenum 15 pmol/g, jejunum 58 pmol/g, ileum 275 pmol/g, colon 179 pmol/g and rectum 96 pmol/g) [125]; there is none in the gastric fundus and antrum. High levels may occur if there is a loss of small bowel absorptive surface area, such as in patients who have undergone small intestinal resection or jejuno-ileal bypass surgery for obesity [126].

Much information about the role of enteroglucagon in man come from the study of a single patient with a tumour that secreted enteroglucagon; it caused villus hypertrophy and increased intestinal transit time [127, 128].

The structure of human proglucagon (160 amino acids), the common precursor from which all glucagon-like molecules are post-synthetically modified, was determined in 1983 [129]. The processing of the molecule is different in the pancreas and intestine. In the pancreas it is cleaved to produce glicentin-related pancreatic polypeptide (GRPP), pancreatic glucagon and a large fragment called the major proglucagon-derived fragment (MPGF). MPGF contains GLP-1 and GLP-2. In the intestine proglucagon is cleaved to produce glicentin (69 amino acids), oxyntomodulin, both of which have glucagon activity and the glucagon-like peptides (GLP-1 and GLP-2) [130, 131]. It appears that the different molecules are produced preferentially in different sites of the intestine (e.g. GLP-1and oxyntomodulin in the small bowel and GLP-2 and glicentin in the more distal ileum/colon).

Pancreatic Glucagon

Pancreatic glucagon consists of 14 amino acids which are in the same position as in secretin, thus it can inhibit the pan-

creatic secretory response to secretin. It increases blood glucose by stimulating hepatic glycogenolysis. It is metabolized in the liver. Pancreatic glucagon is used therapeutically to relax the stomach for a barium study, and is used as a positive inotrope to treat β-blocker overdoses. Glucagonomas produce a mixture of products and are characterized by necrolytic migratory erythema, weight loss and diabetes.

Glucagon-Like Peptide-1 (GLP-1)

GLP-1 immunoactivity is co-localized with glucagon in the pancreas α-cells and enteroglucagon in the L cells in the ileum [131]. GLP-1 is secreted at the same time as pancreatic glucagon and enteroglucagon [132]. GLP-1 plasma levels rise most when gastric emptying is fast [133]. GLP-1 levels peaked 15 min after a solid meal and 15 min before insulin [133]. GLP-1 has been shown to stimulate insulin release [134, 135] and it is a more powerful 'incretin' than GIP [134]. Agonists are used to treat diabetes. It slows gastric emptying and reduces gastric secretions and there may be an effect in promoting mucosal growth so it is used in patients with a short bowel (see Chapter "Pro-adaptive hormones in the rehabilitation of adult patients with a short bowel").

Glucagon-Like Peptide-2 (GLP-2)

GLP-2 has been synthesized and its receptor characterized [136]. Its structure is highly conserved throughout all mammalian species (only 1 amino acid different in the rat). It is an enterocyte-specific growth hormone that in mice causes small and large bowel villus/crypt growth and increases small and large bowel length and weight. In mice, it also reduces body weight loss and restores mucosal integrity after colitis has been induced with dextran. In pigs, it reduces gastric antral motility [137].

As GLP-2 stimulates mucosal growth, analogues (e.g. teduglutide) have been made and given therapeutically to patients with a short bowel to promote adaptation (see Chapter "Intestinal Adaptation").

Oxyntomodulin (OXM)

OXM is named after its inhibitory action on the oxyntic glands of the stomach, it is a naturally occurring 37-amino acid peptide hormone found in the the L-cells in the small and large bowel, together with GLP-1 and it decreases gastric and pancreatic acid secretion, reduces gastric emptying, and is an incretin, suppressing appetite and causing weight loss. OXM binds to both the glucagon-like peptide-1 (GLP-1) receptor and the glucagon receptor. OXM and GLP-1 are 5–30 min after food ingestion and in proportion to meal energy content. It has a plasma half-life of approximately 12 min.

Glicentin

Glicentin was named "gli-" for "glucagon-like imunoreactivity" and "-cent-" because it was thought to be composed of 100 amino acid residues. Later it was found to consist of only 69 amino acids. Residues 33 to 61 corresponded exactly to the sequence of pancreatic glucagon. While this may be mainly what was detected as "enteroglucagon", it may not have a major role in slowing gastrointestinal transit and increasing mucosal growth.

Kinetic Architecture of the Gut

The proliferative zone is restricted to the basal two-thirds of the crypt in the small bowel and most of the colon, and to the neck region in the stomach (Fig. 3). A small number of cells at the base of this proliferative zone give rise to all the other epithelial cells [138] and can be regarded as the 'stem' cells [139]. These stem cells are of great significance as they may be the prime sites for growth control (and the main target for carcinogenesis) since they do not migrate, whereas their daughter cells are transitory and disposable. Stem cells may divide slowly and be extremely radio-sensitive; they may also be pre-programmed to self-destruct if their DNA template is badly damaged [140]. The daughter cells produced in the stem cell zone migrate up the crypt and undergo three or four 'transit' divisions before they leave the cell division cycle and differentiate to take on their functional role for their last few days before being lost. Cell death can either be a passive process, as in cell necrosis, or it can be the energy-requiring, active, gene-directed, endonuclease-activating process known as apoptosis [141]. Cell loss from the villus tip was once thought to be a passive sloughing of cells, but now is considered an active apoptotic process.

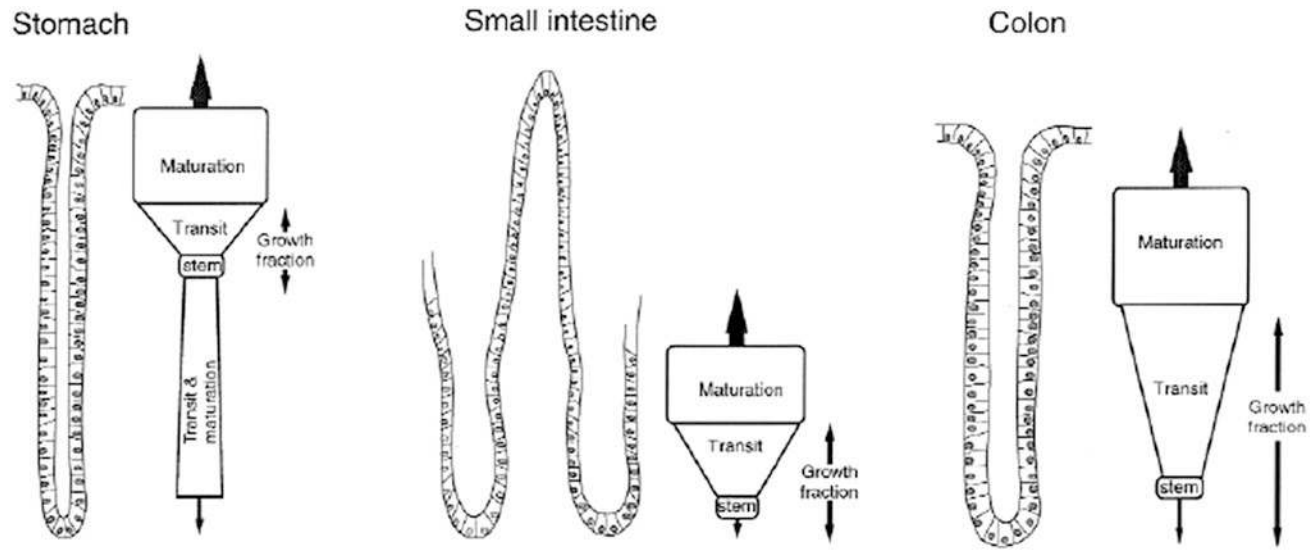

Fig. 3 Kinetic architecture of the main regions of the gastrointestinal tract. Kindly provided by RA Goodlad and RJ Playford

Crypt Proliferation

Cell division can be divided into four phases, which make up the cell cycle. Chromosomes can readily be seen separating at mitosis, which is called the M phase. The daughter cells then enter the first portion of interphase, the post-mitotic, pre-synthetic gap called G_1. Cells can either remain in G_1 or go on to the next phase of the cell cycle, the S phase, in which DNA synthesis occurs. There is then a short, second gap phase, known as G_2, in which the cell prepares for mitosis and assembles the spindle proteins. The output of cells from the crypt depends on three main factors: (i) the duration of the cell cycle; (ii) the proportion of the crypt involved in proliferation, known as the growth fraction; and (iii) the size of the crypt. Proliferative activity is not constant: there are marked circadian rhythms in proliferative activity in the gut. Some of these may be inherent but others appear to be coupled to the food intake pattern several hours previously and may be more pronounced in the colon [142].

In addition to control of cell production in the crypts, the gut can also increase its cellularity by a process of crypt division or fission, in which a crypt can be seen to develop a septum at its end; the septum then enlarges until two new crypts are created. This process is known as the crypt cycle [143]. Increased crypt fission is seen in the adult after intestinal damage [144] and after intestinal resection [145].

Immunological Functions

The huge surface area necessary for absorption renders the gut vulnerable to invasion and necessitates a complex series of defences to exclude pathogens while allowing absorption and oral tolerance of dietary antigens. The importance of this function is underlined by the fact that diarrhoeal diseases in infancy remain the commonest cause of premature death world-wide. Further evidence of the importance of adequate mucosal immunity is seen in AIDS patients who frequently suffer debilitating wasting and diarrhoea from viral, bacterial and protozoal infections. Non-immune defences are also important; these include salivary lysozyme which attacks bacterial cell walls, lactoferrin which chelates iron, thereby preventing the growth of organisms that need it, destruction of ingested organisms by gastric acid and digestive proteases, together with exclusion of pathogens by the mucus barrier and effective clearing of gut contents by propulsive motility patterns. Bile salts and antibacterial peptides secreted from Paneth cells in the base of the crypts, known as 'defensins' are also important, as are antibiotics secreted by the normal colonic flora.

Organization of the Mucosal Immune System

The mucosal immune system is provided by the gut-associated lymphoid tissue (GALT), which contains 10^{10} cells/m and accounts for 80% of the total body immunocytes. This tissue can be divided into organized and diffuse compartments. The organized GALT comprises isolated lymphoid follicles and Peyer's patches, which are collections of follicles containing precursors of T- and B-cells, commonest in the terminal ileum and proximal colon. These respond to antigenic stimulation, increasing rapidly on exposure to bacteria following birth, peaking in adolescence, and declining gradually thereafter. The diffuse GALT includes immunologically committed T- and B-cells (plasma cells producing

predominantly IgA immunoglobulin) found diffusely throughout the lamina propria and acting as the effector limb of the immune response.

Antigen Sampling

Ingested bacteria, viruses and other dietary antigens are absorbed by specialized M cells that overlie the aggregates of ileal lymphoid tissue (Peyer's patches). These cells, which account for about 10% of epithelial cells overlying the follicles, are flattened and specially adapted to rapidly pinocytose bacteria and other dietary antigens and pass them to macrophages and lymphoid cells that lie within intraepithelial 'pockets' in the M cell. Some bacteria, such as Shigella, have taken advantage of this process and use the M cell to breach the gut barrier and subsequently spread from enterocyte to enterocyte [146]. Macrophages are the main but not the sole [147] antigen-presenting cells; they take up antigens and, after processing them, present them to T-cells bound to class II major histocompatibility complex (MHC) antigens on the macrophage surface. The T-cells have receptors, structurally similar to immunoglobulins, which recognize specific antigens. They are composed of two subunits, most commonly of α and β type or less commonly of γ and δ type. These bind to the antigen–MHC complex and are thereby activated, a process facilitated by CD8 or CD4 adhesion molecules which bind to a constant region of either the class I or II MHC molecules respectively. Class II MHC molecules are expressed on antigen-presenting cells (mainly macrophages but also some epithelial cells), but class I MHC may be expressed by almost any cell in the body. These bind 'foreign' or 'neo' antigens derived from the cytosol of infected or altered cells such as viral antigens or tumour products. This process of antigen presentation takes place mainly in the dome of the lymphoid follicle, after which antigen-specific T- and B-cell precursors migrate along the lymphatics to the mesenteric lymph nodes where they mature and clonally expand. Further migration via the thoracic duct allows distribution to the entire gut lymphoid tissue. This homing back to the gut depends on the expression of adhesion molecules, such as lymphocyte function antigen (LFA-1) on the lymphocyte and up-regulation of adhesion molecules known as 'addressins' such as VCAM-1 (vascular cell adhesion molecules) and ICAM-1 or 2 (intercellular adhesion molecules), on the endothelial cells in the lymphoid follicle [148]. There B-cells differentiate into plasma cells producing immunoglobulin, mostly IgA, while activated T-cells act as cytotoxic lymphocytes as well as T-helper cells facilitating immune response to further antigenic exposure.

Intraepithelial T-cells are predominantly CD8+ (cytotoxic phenotype) with only 10% being CD4+ (helper T-cells). Their role is unclear but they are markedly raised in coeliac disease, a condition in which the T-cell receptors are predominantly of the γδ type rather than the more usual αβ type. The significance of this finding is as yet unclear but it appears to be a marker of disease susceptibility, being found in asymptomatic relatives [149].

Dendritic Cells

Dendritic cells (DCs) are antigen-presenting cells derived from bone marrow precursors and form a widely distributed cellular system throughout the body and are especially important throughout the intestine. Similarly to the M cells, they sample gut luminal content, capturing (phagocytosing), processing, and presenting antigens to naive T lymphocytes to activate them so triggering adaptive immunity.

Gut Microbiome

The composition of gut microbiota (bacteria, viruses, protozoa and fungi) is commonly quantified using DNA sequencing based methods, which may also allow analysis of metabolic potential (using metagenetic analysis). Healthy adult humans each typically harbor more than 1000 species of bacteria belonging to relatively few known bacterial phyla with *Bacteroidetes* and *Firmicutes* being the dominant phyla, followed by *Actinobacteria*, and *Proteobacteria*. An individual's microbiome changes rapidly after birth, acquiring microbiota from mother and immediate close contacts and thereafter steadily acquiring adult characteristics during adolescence, becoming quite stable over time in adulthood with later changes with ageing, at all times showing considerable inter-individual variation. Diet and other environmental factors also affect the composition of the microbiome. The gut microbe–host interactions have effects on metabolism, immune, and neuroendocrine responses. The gut microbiota plays a role in nutrient and mineral absorption, synthesis of enzymes, vitamins (e.g. vitamin K) and amino acids, and the production of short-chain fatty acids (SCFAs). The fermentation by-products acetate, propionate, and butyrate are important for gut health and provide energy for epithelial cells, enhancing epithelial barrier integrity, and provide immunomodulation and protection against pathogens. Urea can be secreted into the colon and there is converted into essential and non-essential amino acids according to the individuals need [150]. Changes in microbiome may relate to many diseases including IBD, rheumatoid arthritis, ankylosing spondylitis, type 1 diabetes and obesity.

Probiotics are live bacteria and yeasts that, when administrated in a viable form and in adequate amounts, are beneficial to human health. Prebiotics (microbiota accessible

carbohydrates or fermentable dietary fibre) are a substrate that is selectively used by host micro-organisms to confer a health benefit. Synbiotics contain a mixture of prebiotics and probiotics.

Faecal microbiota transplantation (FMT) has become a well-accepted treatment for recurrent relapsing *Clostridium difficile* infection which can be extremely difficult to cure with antibiotics as they aggravate the underlying depletion of the microbiota [151, 152].

Comparative Anatomy

Plant-eating animals digest complex carbohydrate (e.g. cellulose) either in the upper gut or in the caecal/colonic area. Ruminants have an expanded lower end of the oesophagus that forms most of the four-chamber stomach (e.g. sheep and cattle); in plant-eating birds the mid-oesophagus expands to form the crop [153]. Non-ruminants (e.g. horses, rabbits and plant-eating birds) have a long blind-ending caecum. Protozoa, both in the rumen and caecum, assist bacteria in the fermentation of plant material. Animals that digest roots, nuts and wood (e.g. pigs and elephants) have long small and large intestines. Largely carnivorous animals such as dogs and cats have a relatively short small intestine, a very small caecum and a short muscular colon [154]. Man, as an omnivore, is similar to the pig, having a colon intermediate in size between that of herbivores and carnivores.

References

1. Standring S. Grays Anatomy. The Anatomical basis of clinical practice. 42nd ed. Amsterdam: Elsevier; 2021.
2. Thompson WG, Wrathell E. The relation between ileal resection and vitamin B12 absorption. Can J Surg. 1977;20:461–4.
3. Meyer JH, Thomson JB, Cole MB. Sieving solid food by the canine stomach and sieving after gastric surgery. Gastroenterology. 1979;76:804–13.
4. Borgström B, Dahlqvist A, Lundh G, Sjövall J. Studies of intestinal digestion and absorption in the human. J Clin Invest. 1957;36:1521–36.
5. Fordtran JS, Locklear TW. Ionic constituents and osmolality of gastric and small intestinal fluids after eating. Am J Dig Dis. 1966;11:503–21.
6. Carlson AJ. The control of hunger in health and disease. Chicago, Illinois: University of Chicago Press; 1916. p. 232–47.
7. McCaughan JM, Sinner BL, Sullivan CJ. The external secretory function of the human pancreas. Physiologic observations. Arch Intern Med. 1938;61:739–54.
8. Emonts P, Vidon N, Bernier JJ, Rambaud JC. Twenty-four hour intestinal water and electrolyte flow rates in normal man: assessment by the slow marker perfusion technique (author's translation). Gastroenterol Clin Biol. 1979;3:139–46.
9. Bryant J. Observations upon the growth and length of the human intestine. Am J Med Sci. 1924;167:499–520.
10. Underhill BML. Intestinal length in man. Br Med J. 1955;2:1243–6.
11. Hounnou G, Destrieux C, Desmé J, Bertrand P, Velut S. Anatomical study of the length of the human intestine. Surg Radiol Anat. 2002;24(5):290–4.
12. Hosseinpour M, Behdad A. Evaluation of small bowel measurement in alive patients. Surg Radiol Anat. 2008;30(8):653–5.
13. Backman L, Hallberg D, Small intestinal length. An intraoperative study in obesity. Acta Chir Scand. 1974;140:57–63.
14. Guzman IJ, Fitch LL, Varco RL, Buchwald H. Small bowel length in hyperlipidemia and massive obesity. Am J Clin Nutr. 1977;30(7):1006–8.
15. Slater G, Aufses AH Jr. Small bowel length in Crohn's disease. Am J Gastroenterol. 1991;8:1037–40.
16. Nordgren S, McPheeters G, Svaninger G, Oresland T, Hultén L. Small bowel length in inflammatory bowel disease. Int J Color Dis. 1997;12(4):230–4.
17. Teitelbaum EN, Vaziri K, Zettervall S, Amdur RL, Orkin BA. Intraoperative small bowel length measurements and analysis of demographic predictors of increased length. Clin Anat. 2013;26(7):827–32.
18. Tacchino RM. Bowel length: measurement, predictors, and impact on bariatric and metabolic surgery. Surg Obes Relat Dis. 2015;11(2):328–34.
19. Hirsch J, Ahrens EH, Blankenhorn DH. Measurement of the human intestinal length in vivo and some causes of variation. Gastroenterology. 1956;31:274–84.
20. Fannucci A, Cerro P, Fannucci E. Normal small-bowel measurements by enteroclysis. Scand J Gastroenterol. 1988;23:574–6.
21. Fanucci A, Cerro P, Fraracci L, Ietto F. Small bowel length measured by radiology. Gastrointest Radiol. 1984;9:349–51.
22. Schalamon J, Schober PH, Gallippi P, Matthyssens L, Hollwarth ME. Congenital short bowel; a case study and review of the literature. Eur J Pediatr Surg. 1999;9:248–50.
23. Raines D, Arbour A, Thompson HW, Figueroa-Bodine J, Joseph S. Variation in small bowel length: factor in achieving total enteroscopy? Dig Endosc. 2015;27(1):67–72.
24. Nightingale JMD, Lennard-Jones JE, Walker ER, Farthing MJG. Jejunal efflux in short bowel syndrome. Lancet. 1990;336:765–8.
25. Fordtran JS, Rector FC Jr, Ewton MF, Soter N, Kinney J. Permeability characteristics of the human small intestine. J Clin Invest. 1965;44:1935–44.
26. Davis GR, Santa Aria CA, Morawski SG, Fordtran JS. Permeability characteristics of human jejunum, ileum, proximal colon and distal colon: results of potential difference measurements and unidirectional fluxes. Gastroenterology. 1982;83:844–50.
27. Fordtran JS, Rector FC Jr, Carter NW. The mechanisms of sodium absorption in the human small intestine. J Clin Invest. 1968;47:884–900.
28. Spiller RC, Jones BJM, Silk DB. A jejunal water and electrolyte absorption from two proprietary enteral feeds in man: importance of sodium content. Gut. 1987;28:681–7.
29. Sladen GE, Dawson AM. Inter-relationships between the absorptions of glucose, sodium and water by the normal human jejunum. Clin Sci. 1969;36:119–32.
30. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJG. What is the ideal sodium concentration of oral rehydration solutions for short bowel patients? Clin Sci. 1988;74(suppl 18):69.
31. Levitan R, Goulston K. Water and electrolyte content of human fluid after d-aldosterone administration. Gastroenterology. 1967;52:510–2.
32. Fink CS, Hamosh P, Hamosh M. Fat Digestion in the Stomach: Stability of Lingual Lipase in the Gastric Environment. Pediatr Res. 1984;18:248–54.
33. Heinemann T, KullakUblick GA, Pietruck B, Von Bergmann K. Mechanisms of action of plant sterols on inhibition of choles-

terol absorption. Comparison of sitosterol and sitostanol. Eur J Clin Pharmacol. 1991;40:S59–63.
34. Spiller RC. Cholesterol, fibre, and bile acids. Lancet. 1996;347:415–6.
35. Kayne LH, Lee DBN. Intestinal magnesium absorption. Miner Electrolyte Metab. 1993;19:210–7.
36. Graham LA, Caesar JJ, Burgen ASV. Gastrointestinal absorption and excretion of magnesium in man. Metabolism. 1960;9:646–59.
37. Krejs GJ, Nicar MJ, Zerwekh JE, Norman DA, Kane MG, Pak CYC. Effect of 1,25-dihydroxyvitamin D3 on calcium and magnesium absorption in the healthy human jejunum and ileum. Am J Med. 1983;75:973–6.
38. Lim P, Jacob E. Magnesium status of alcoholic patients. Metabolism. 1972;21:1045–51.
39. Shils ME. Experimental human magnesium depletion. I. Clinical observations and blood chemistry alterations. Am J Clin Nutr. 1964;15:133–43.
40. Horton R, Biglieri EG. Effect of aldosterone on the metabolism of magnesium. J Clin Endocrinol Metab. 1962;22:1187–92.
41. Zofkova I, Kancheva RL. The relationship between magnesium and calciotropic hormones. Magnes Res. 1995;8:77–84.
42. Reinhold JG, Parsa A, Karimian N, Hammick JW, Ismail-Beigi F. Availability of zinc in leavened and unleavened wholemeal wheaten breads as measured by solubility and uptake by rat intestine in vitro. J Nutr. 1974;104:976–82.
43. Prasad AS, Halsted JA, Nadimi M. Syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism and geophagia. Am J Med. 1961;31:532–46.
44. Nakamura T, Higashi A, Takano S, Akagi M, Matsuda I. Zinc clearance correlates with clinical severity of Crohn's disease. A kinetic study. Dig Dis Sci. 1988;33:1520–4.
45. Phillips SF, Quigley EMM, Kumar D, Kamath PS. Motility of the ileocolonic junction. Gut. 1988;29:390–406.
46. Fich A, Steadman CJ, Phillips SF, Camilleri M, Brown ML, Haddad AC, Thomforde GM. Ileocolonic transit does not change after right hemicolectomy. Gastroenterology. 1992;103:794–9.
47. Bentley DW, Nichols RL, Condon RE, Gorbach SL. The microflora of the human ileum and intra-abdominal colon: Results of direct needle aspiration at surgery and evaluation of the technique. J Lab Clin Med. 1972;79:421–9.
48. Hammer J, Camilleri M, Phillips SF, Aggarwal A, Haddad AM. Does the ileocolonic junction differentiate between solids and liquids? Gut. 1993;34:222–6.
49. Pritchard SE, Marciani L, Garsed KC, Hoad CL, Thongborisute W, Roberts WE, Gowland PA, Spiller RC. Fasting and postprandial volumes of the undisturbed colon: normal values and changes in diarrhea-predominant irritable bowel syndrome measured using serial MRI. Neurogastroenterol Motil. 2014;26:124–30.
50. Debongnie JC, Phillips SF. Capacity of the colon to absorb fluid. Gastroenterology. 1978;74:698–703.
51. Randall HT. Enteral nutrition: Tube feeding in acute and chronic illness. J Parenter Enter Nutr. 1984;8:113–36.
52. Fawcett SL, Cousins RJ. Magnesium poisoning following enema of epsom salt solution. JAMA. 1943;123:1028–9.
53. Kellow JE, Borody TJ, Phillips SF, Tucker RL, Haddad AM. Human interdigestive motility: Variations in patterns from esophagus to colon. Gastroenterology. 1986;91:386–95.
54. Itoh Z, Aizawa I, Sekiguchi T. The interdigestive migrating complex and its significance in man. Clin Gastroenterol. 1982;11:497–521.
55. Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. N Engl J Med. 1991;325:1461–7.
56. Vantrappen GR, Peeters TL, Janssens J. The secretory component of the interdigestive migrating motor complexes in man. Scand J Gastroenterol. 1979;14:663–7.
57. Nightingale JMD, Kamm MA, van der Sijp JRM, et al. Disturbed gastric emptying in the short bowel syndrome. Evidence for a 'colonic brake'. Gut. 1993;34:1171–6.
58. Kamm MA. The small intestine and colon: scintigraphic quantitation of motility in health and disease. Eur J Nucl Med. 1992;19:902–12.
59. Perry B, Wang Y. Appetite regulation and weight control: the role of gut hormones. Nutr Diabetes. 2012;2:e26.
60. Hunt JN, MacDonald I. The influence of volume on gastric emptying. J Physiol. 1954;126:459–74.
61. Hunt JN, Stubbs DF. The volume and energy content of meals as determinants of gastric emptying. J Physiol. 1975;245:209–25.
62. Hunt JN. Some properties of an alimentary osmo-receptor mechanism. J Physiol. 1956;132:267–88.
63. Hunt JN, Pathak JD. The osmotic effects of some simple molecules and ions on gastric emptying. J Physiol. 1960;154:254–69.
64. Thompson DG, Richelson E, Malagelada J-R. Perturbation of upper gastrointestinal function by cold stress. Gut. 1983;24:277–83.
65. Lin HC, Doty JE, Reedy TJ, Meyer JH. Inhibition of gastric emptying by glucose depends on length of intestine exposed to nutrient. Am J Physiol. 1989;256:G404–11.
66. Lin HC, Doty JE, Reedy TJ, Meyer JH. Inhibition of gastric emptying by acids depends on pH, titratable acidity, and length of intestine exposed to acid. Am J Physiol. 1990;259:G1025–30.
67. Lin HC, Doty JE, Reedy TJ, Meyer JH. Inhibition of gastric emptying by sodium oleate depends on length of intestine exposed to nutrient. Am J Physiol. 1990;259:G1031–6.
68. Spiller RC, Trotman IF, Higgins BE, et al. The ileal brake—inhibition of jejunal motility after ileal fat perfusion in man. Gut. 1984;25:365–74.
69. Holgate AM, Read NW. Effect of ileal infusion of intralipid on gastrointestinal transit, ileal flow rate, and carbohydrate absorption in humans after ingestion of a liquid meal. Gastroenterology. 1985;88:1005–11.
70. Spiller RC, Trotman IF, Adrian TE, Bloom SR, Misiewicz JJ, Silk DBA. Further characterisation of the 'ileal brake' reflex in man—effect of ileal infusion of partial digests of fat, protein, and starch on jejunal motility and release of neurotensin, enteroglucagon, and peptide YY. Gut. 1988;29:1042–51.
71. Read NW, McFarlane A, Kinsman RI, et al. Effect of infusion of nutrient solutions into the ileum on gastrointestinal transit and plasma levels of neurotensin and enteroglucagon. Gastroenterology. 1984;86:274–80.
72. Spiller RC, Trotman IF, Silk DBA, Lee YC, Ghatei MA, Bloom SR, Misiewicz JJ. Control of jejunal motility by ileal contents and hormones in man. Gastroenterology. 1983;84:1319.
73. Jain NK, Boivin M, Zinsmeister AR, Brown ML, Malagelada J-R, DiMagno EP. Effect of ileal perfusion of carbohydrates and amylase inhibitor on gastrointestinal hormones and emptying. Gastroenterology. 1989;96:377–87.
74. Fone DR, Horowitz M, Read NW, Dent J, Maddox A. The effect of terminal ileal triglyceride infusion on gastroduodenal motility and the intragastric distribution of a solid meal. Gastroenterology. 1990;98:568–75.
75. McL WI, Cunningham KM, Read NW. Regulation of gastric emptying by ileal nutrients in humans. Gastroenterology. 1988;94:401–4.
76. Layer P, Zinsmeister AR, DiMagno EP. Effects of decreasing intraluminal amylase activity on starch digestion and postprandial gastrointestinal function in humans. Gastroenterology. 1986;91:41–8.
77. Read NW, McL WI. Naloxone prevents the effect of ileal lipid on small bowel transit but not on gastric emptying. Gut. 1984;25:A1326.
78. Kinsman RI, Read NW. Effect of naloxone on feedback regulation of small bowel transit by fat. Gastroenterology. 1984;87:335–7.

79. Pearcy JF, Van Liere EJ. Studies on the visceral nervous system. Am J Phys. 1926;78:64–73.
80. Youmans WB, Meek WJ. Reflex and humeral inhibition in unanaesthetised dogs during rectal stimulation. Am J Phys. 1937;120:750–7.
81. Morin G, Vial J. Champ de l'inhibition reflexe provoque de par la distension de l'intestin. C R Soc Biol. 1934;113:1540–1.
82. Lalich J, Meek WJ, Herrin RC. Reflex pathways concerned in inhibition of hunger contractions by intestinal distension. Am J Phys. 1936;115:410–4.
83. Youle MS, Read NW. Effect of painless rectal distention on gastrointestinal transit of solid meal. Dig Dis Sci. 1984;29:902–6.
84. Nightingale JMD, Kamm MA, van der Sijp JRM, Walker ER, Ghatei MA, Bloom SR, Lennard-Jones JE. Gastrointestinal hormones in the short bowel syndrome. PYY may be the 'colonic brake' to gastric emptying. Gut. 1996;39:267–72.
85. Müller TD, Nogueiras R, Andermann ML, Andrews ZB, Anker SD, Argente J, Broglio F. Ghrelin. Mol Metab. 2015;4(6):437–60.
86. Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumours of the pancreas. Ann Surg. 1955;142:709–28.
87. Somatostatin RS. N Engl J Med. 1983;309(1495–1501):1556–63.
88. Loguercio C, de Sio I, Romano M, del Vecchio BC, Coltorti M. Effect of somatostatin on salivary secretion in man. Digestion. 1987;36:91–5.
89. Ganda OP, Weir GC, Soelderner JS, et al. Somatostatinoma – a somatostatin containing tumour of the endocrine pancreas. N Engl J Med. 1977;297:1352–7.
90. Sturdevant RAL, Goetz H. Cholecystokinin both stimulates and inhibits human food intake. Nature. 1976;261:713–5.
91. Muurahainen N, Kissileff HR, Derogatis AJ, Pi-Sunyer FX. Effects of cholecystokinin-octapeptide (CCK-8) on food intake and gastric emptying in man. Physiol Behav. 1988;44:645–9.
92. Lieverse RJ, Jansen JBMJ, Masclee AAM, Lamers CBHW. Satiety effects of cholecystokinin in humans. Gastroenterology. 1994;106:1451–4.
93. Schmidt WE, Creutzfeldt W, Schleser A, et al. Role of CCK in regulation of pancreaticobiliary functions and GI motility in humans: effects of loxiglumide. Am J Phys. 1991;23:G197–206.
94. Baylis WM, Starling EH. The mechanism of pancreatic secretion. J Physiol. 1902;28:325–35.
95. Meyer JH, Grossman MI. Pancreatic bicarbonate response to various acids in the duodenum of dogs. Am J Phys. 1970;219:964–70.
96. Ross SA, Shaffer EA. The importance of triglyceride hydrolysis for the release of gastric inhibitory polypeptide. Gastroenterology. 1981;80:108–11.
97. Pederson RA, Brown JC. Inhibition of histamine, pentagastrin and insulin-stimulated canine gastrin secretion by pure 'gastric inhibitory polypeptide'. Gastroenterology. 1972;62:393–9.
98. Maxwell V, Shulkes A, Brown JC, Solomon TE, Walsh JH, Grossman MI. The effect of gastric inhibitory polypeptide on pentagastrin-stimulated acid secretion in man. Dig Dis Sci. 1980;25:113–6.
99. Dupre J, Ross SA, Watson D, Brown JC. Stimulation of insulin secretion by gastric inhibitory polypeptide in man. J Clin Endocrinol Metab. 1973;37:826–8.
100. Adrian TE, Greenberg GR, Bloom SR. Actions of pancreatic polypeptide in man. In: Bloom SR, Polak JM, editors. Gut hormones. 2nd ed. Edinburgh: Churchill Livingstone; 1981. p. 206–12.
101. Adrian TE, Bloom SR, Bryant MG, Polak JM, Heitz PH, Barnes AJ. Distribution and release of human pancreatic polypeptide. Gut. 1976;17:940–4.
102. Christofides ND, Bloom SR, Besterman HS, Adrian TE, Ghatei MA. Release of motilin by oral and intravenous nutrients in man. Gut. 1978;20:102–6.
103. Mitznegg P, Bloom SR, Domschke W, Domschke S, Wunsch E, Demling L. Release of motilin after duodenal acidification. Lancet. 1976;i:888–9.
104. Christofides ND, Long RG, Fitzpatrick ML, McGregor GP, Bloom SR. Effect of motilin on gastric emptying of glucose and fat in humans. Gastroenterology. 1981;80:456–60.
105. Vantrappen G, Janssens J, Peeters TL, Bloom SR, Christofides ND, Hellemans J. Motilin and the interdigestive migrating motor complex in man. Dig Dis Sci. 1979;24:497–500.
106. Verner JV, Morrison AB. Endocrine pancreatic islet disease with diarrhoea: report of a case due to diffuse hyperplasia of non-beta islet tissue with a review of 54 additional cases. Arch Intern Med. 1974;133:492–500.
107. Carraway R, Leeman SE. The isolation of a new hypotensive peptide, neurotensin, from bovine hypothalami. J Biol Chem. 1973;248:6854–61.
108. Hammer RA, Carraway RE, Leeman SE. Elevation of plasma neurotensin immunoreactivity after a meal. Characterization of the elevated components. J Clin Invest. 1982;70:74–81.
109. Polak JM, Sullivan SN, Bloom SR, Buchan AMJ, Facer P, Brown MR, Pearse AGE. Neurotensin in human intestine: Radioimmunoassay and specific localisation in the N cell. Nature. 1977;270:183–5.
110. Wiklund B, Liljeqvist L, Rokaeus A. Studies in man on the mechanism by which fat increases the plasma concentration of neurotensin-like immunoreactivity. Acta Chir Scand. 1986;152(suppl 530):9–14.
111. Wood JG, Hoang HD, Bussjaeger LJ, Solomon TE. Neurotensin stimulates growth of small intestine in rats. Am J Phys. 1988;255:G813–7.
112. Tatemoto K. Isolation and characterization of peptide YY (PYY), a candidate gut hormone that inhibits pancreatic exocrine secretion. Proc Natl Acad Sci U S A. 1982;79:2514–8.
113. Adrian TE, Ferri G-L, Bacarese-Hamilton FHS, Polak JM, Bloom SR. Human distribution and release of a putative new gut hormone, Peptide YY. Gastroenterology. 1985;89:1070–7.
114. Ali-Rachedi A, Varndell IM, Adrian TE, Gapp DA, Van Noorden S, Bloom SR, Polak JM. Peptide YY (PYY) immunoreactivity is co-stored with glucagon-related immunoreactants in endocrine cells of the gut and pancreas. Histochemistry. 1984;80:487–91.
115. Bottcher G, Sjolund K, Ekblad E, Hakanson R, Schwartz TW, Sundler F. Co-existence of peptide YY and glicentin immunoreactivity in endocrine cells of the gut. Regul Pept. 1984;8:261–6.
116. Adrian TE, Savage AP, Bacarese-Hamilton AJ, Wolfe K, Besterman HS, Bloom SR. Peptide YY abnormalities in gastrointestinal diseases. Gastroenterology. 1986;90:379–84.
117. Adrian TE, Long RG, Fuessl HS, Bloom SR. Plasma peptide YY (PYY) in dumping syndrome. Dig Dis Sci. 1985;30:1145–8.
118. Adrian TE, Savage AP, Fuessl HS, Wolfe K, Besterman HS, Bloom SR. Release of peptide YY (PYY) after resection of small bowel, colon or pancreas in man. Surgery. 1987;101:715–9.
119. Pironi L, Stanghellini V, Miglioli M, et al. Fat-induced ileal brake in humans: a dose-dependent phenomenon correlated to plasma levels of peptide YY. Gastroenterology. 1993;105:733–9.
120. Savage AP, Gornacz GE, Adrian TE, Ghatei MA, Goodlad RA, Wright NA, Bloom SR. Is raised plasma peptide YY after intestinal resection in the rat responsible for the trophic response? Gut. 1985;26:1353–8.
121. Playford RJ, Mehta S, Upton P, et al. Effect of peptide YY on human renal function. Am J Phys. 1995;268:F754–9.
122. Mehta S, Upton P, Rentch R, et al. Preliminary report: role of peptide YY in defence against diarrhoea. Lancet. 1990;335:1555–7.
123. Unger RH, Eisentraut AM, Sims K, McCall MS, Madison LL. Sites of origin of glucagon in dogs and humans (abstract). Clin Res. 1961;9:53.

124. Ungar RH, Ketterer H, Eisentraut AM. Distribution of immunoassayable glucagon in gastrointestinal tissues. Metabolism. 1966;15:865–7.
125. Ghatei MA, Bloom SR. Enteroglucagon in man. In: Bloom SR, Polak JM, editors. Gut hormones. 2nd ed. Edinburgh: Churchill Livingstone; 1981. p. 332–8.
126. Bloom SR, Polak JM. Plasma hormone concentrations in gastrointestinal disease. Clin Gastroenterol. 1980;93:785–98.
127. Gleeson MH, Bloom SR, Polak JM, Henry K, Dowling RH. Endocrine tumour in kidney affecting small bowel structure, motility, and absorptive function. Gut. 1971;12:773–82.
128. Bloom SR. An enteroglucagon tumour. Gut. 1972;13:520–3.
129. Bell GI, Sanchez-Pescador R, Laybourn PJ, Najarian RC. Exon duplication and divergence in the human preproglucagon gene. Nature. 1983;304:368–71.
130. Orscov C, Holst JJ, Poulsen SS, Kirkegaard P. Pancreatic and intestinal processing of proglucagon in man. Diabetologia. 1987;30:874–81.
131. Dunphy JL, Fuller PJ. Enteroglucagon, bowel growth and GLP-2. Mol Cell Endocrinol. 1997;132:7–11.
132. Orskov C, Holst JJ, Knuhtsen S, Baldissera FGA, Poulsen SS, Nielsen OV. Glucagon-like peptides GLP-1 and GLP-2, predicted products of the glucagon gene, are secreted separately from pig small intestine but not pancreas. Endocrinology. 1986;119:1467–75.
133. Miholic J, Orskov C, Holst JJ, Kotzerke J, Meyer HJ. Emptying of the gastric substitute, glucagon-like peptide-1 (GLP-1), and reactive hypoglycaemia after total gastrectomy. Dig Dis Sci. 1991;36:1361–70.
134. Kreymann B, Ghatei MA, Williams G, Bloom SR. Glucagon-like peptide-17-36: A physiological incretin in man. Lancet. 1987;2:1300–4.
135. Druker DJ. Glucagon-like peptide 2. Trends Endocrinol Metab. 1999;10:153–6.
136. Brubaker PL. Glucagon-like Peptide-2 and the Regulation of Intestinal Growth and Function. Compr Physiol. 2018;8(3):1185–210.
137. Wojdemann M, Wettergren A, Hartmann B, Holst JJ. Glucagon-like peptide-2 inhibits centrally induced antral motility in pigs. Scand J Gastroenterol. 1998;33:828–32.
138. Cheng H, Leblond CP. Origin, differentiation and renewal of the four main epithelial cell types of the mouse small intestine.V. Unitarian theory of the origin of the four epithelial cell types. Am J Anat. 1974;144:537–62.
139. Potten CS, Loeffler M. A comprehensive model of the crypts of the small intestine of the mouse provides insight into the mechanisms of cell migration and the proliferative hierarchy. J Theor Biol. 1987;127:381–91.
140. Hall PA, Watt FM. Stem cells: the generation and maintenance of cellular diversity. Development. 1989;106:619–33.
141. Alison MR, Sarraf CE. Apoptosis: a gene-directed programme of cell death. J R Coll Physicians Lond. 1992;26:25–35.
142. Goodlad RA, Wright NA. The effects of starvation and refeeding on intestinal cell proliferation in the mouse. Virch Arch Cell Pathol. 1984;45:63–73.
143. Totafumo J, Bjerknes M, Cheng H. The crypt cycle: Crypt and villus production in adult intestinal epithelium. Biophys J. 1987;52:279–94.
144. Cairnie AB, Millen BH. Fission of crypts in the small intestine of the irradiated mouse. Cell Tissue Kinet. 1975;8:189–96.
145. Cheng H, McCulloch C, Bjerknes M. Effects of 30% intestinal resection on whole population cell kinetics of mouse intestinal epithelium. Anat Record. 1986;215:35–41.
146. Wassef JS, Keren DF, Mailloux JL. Role of M cells in initial antigen uptake and in ulcer formation in the rabbit intestinal loop model of shigellosis. Infect Immun. 1989;57:858–63.
147. Geppert TD, Lipsky PE. Antigen presentation by cells that are not of bone marrow origin. Reg Immunol. 1989;2:60–71.
148. Salmi M, Jalkanen S. Regulation of lymphocyte traffic to mucosa-associated lymphatic tissues. Gastroenterol Clin N Am. 1991;20:495–510.
149. Holm K, Maki M, Savilahti E, Lipsanen V, Laippala P, Koskimies S. Intraepithelial gamma delta T-cell-receptor lymphocytes and genetic susceptibility to coeliac disease. Lancet. 1992;339:1500–3.
150. Jackson AA. Salvage of urea-nitrogen and protein requirements. Proced Nutr Soc. 1995;54:535–47.
151. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ. 2018;361:k2179. https://doi.org/10.1136/bmj.k2179.
152. Ianiro G, Eusebi LH, Black CJ, Gasbarrini A, Cammarota G, Ford AC. Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. Aliment Pharmacol Ther. 2019;50:240–8.
153. Duke GE. Gastrointestinal physiology and nutrition in wild birds. Proc Nutr Soc. 1997;56:1049–56.
154. Wrong OM, Edmonds CJ, Chadwick VS. The large intestine: Its role in mammalian nutrition and homeostasis. Wellington: MTP Press; 1981.

Definitions, Classification and Severity of Intestinal Failure

Jeremy M.D. Nightingale

Key Points

1. Intestinal failure (IF) may be defined as reduced intestinal absorption causing malnutrition and/or dehydration.
2. IF may be classified according to predicted duration as short (type I-acute), medium (type II-prolonged acute) or long term (type III-chronic).
3. Further classification is based upon the disease processes, residual anatomy and pathophysiology. This gives five groups: extensive small bowel mucosal disease, intestinal dysmotility, mechanical obstruction, fistula(s) and short bowel/bypass.
4. The severity of IF can be graded according to the type of nutritional/fluid support given.
5. The severity of IF is a continuum and intestinal rehabilitation aims to maximize gut function while using the least invasive route for nutrition/and or fluid support.

Introduction

Patients needing clinically assisted nutrition and hydration (CANH) (previously termed artificial nutritional support) are likely to have one (or more) of three problems: Inadequate oral intake, digestive failure, or absorptive (intestinal) failure that results in them being referred to a nutritional support team (NST) (Fig. 1).

Intake (oral) failure is most commonly due to a failure to swallow or anorexia with associated malnutrition. A swallowing disorder is most commonly due to neurological problems (e.g. stroke, motor neurone disease, multiple sclerosis, cerebral palsy, trauma, persistent vegetative state, dementia or Parkinson's disease) or due to cancer of the head and neck. These patients often have a functional

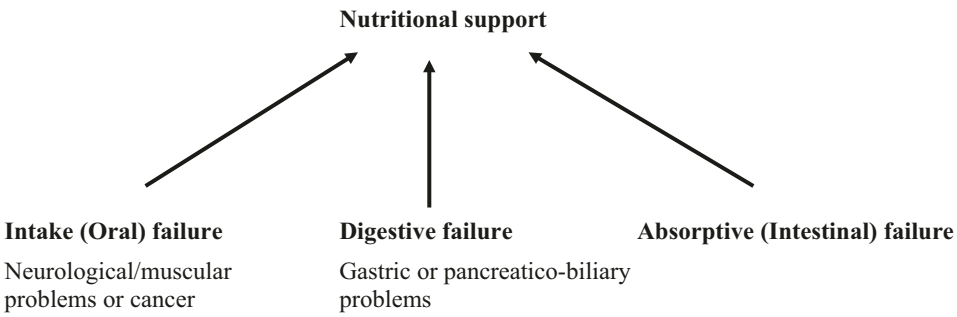

Fig. 1 Reasons for nutritional support

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gastrointestinal tract (distal to the oesophagus) so are appropriate for feeding into the gut (enteral nutrition). Some have an eating disorder (e.g. anorexia nervosa) and some are unable to consume sufficient nutrition/fluid from eating and drinking for other reasons.

Digestive failure may result from the stomach being removed or bypassed or due to a failure of pancreatico-biliary secretions (e.g. pancreatitis, cystic fibrosis or pancreatic resection/bypass). These patients may benefit from pancreatic enzyme replacement in addition to oral/enteral feeding.

Absorptive (intestinal) failure has multiple underlying aetiologies. Its definition, classification and severity are discussed below.

Definition of Intestinal failure

In 1981, Fleming CR and Remington M proposed the first definition of intestinal failure as a "reduction in functioning gut mass below the minimum amount necessary for adequate digestion and absorption of nutrients" [1].

In the first edition of this book (2001), intestinal failure was defined as" reduced intestinal absorption so that macronutrient and / or water and electrolyte supplements are needed to maintain health and/or growth. Undernutrition and/or dehydration result if no treatment is given or if compensatory mechanisms do not occur. IF was also classified as mild, moderate or severe, according to the method by which nutritional supplementation was given; orally, enterally (by tube) or parenterally [2, 3].

In 2005, Jeejeebhoy KN considered IF as when gastrointestinal function is inadequate to maintain the nutrition and hydration of the individual without supplements being given orally or intravenously [4]. In his lectures he likens the gut to an "intestinal orchestra" such that if any one part fails (e.g. stomach liquidizing, pancreas digesting or small intestine absorbing) then the overall function (absorbing nutrition and/or fluid) fails.

In 2015, the European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) (ESPEN) devised recommendations on definition and classification of IF. IF was defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is required to maintain health and/or growth [5]. ESPEN defined "intestinal insufficiency" (or "deficiency" in those languages where "insufficiency" and "failure" have the same meaning) (II/D), as the reduction of gut absorptive function that doesn't require IVS supplementation to maintain health and/or growth [5]. Therefore, the ESPEN definition of IF coincides with severe IF, whereas the ESPEN definition of II/D comprises both the moderate and mild IF, as defined and classified in the first edition of this book.

In 2019/20, the England NHS specification used the term severe IF for those patients needing PS [6].

In 2021, the ESPEN definition of IF has been included in the 11th revision of the International Classification of Diseases (ICD-11: DA96.05 Intestinal failure), which is the global standard for diagnostic health information [7].

For many diseases reference is made to a system failure, though sometimes the phrase "failure" is thought to be negative. Hence other terms including impairment, insufficiency, inadequacy, injury, deficiency and disease, have all been used and currently the phrase intestinal rehabilitation is used when possible (e.g. in naming an IF unit). This book keeps the term IF but considers that it may change in the future.

Classification of IF

Expected Duration

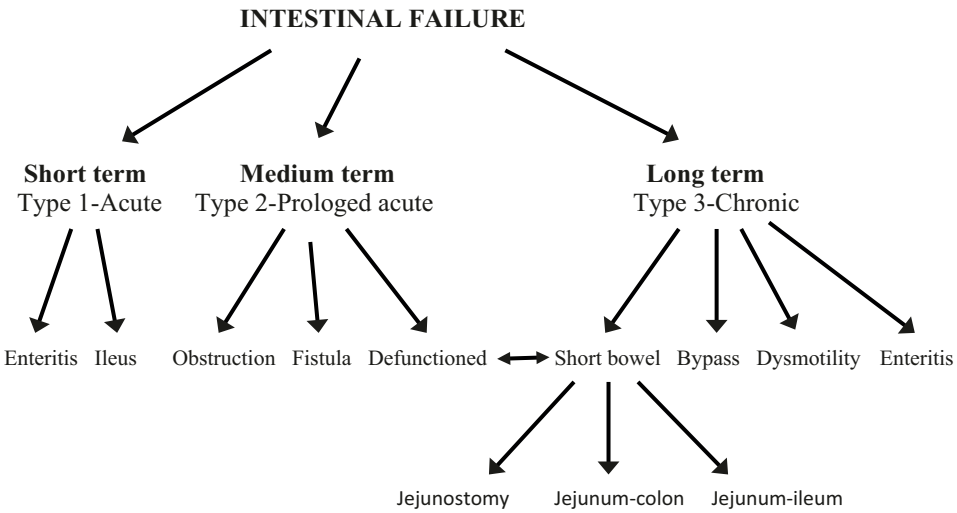
Most diseases are first classified based upon expected duration of illness as acute (short term illness that resolves) or chronic (long term illness that may be progressive). While this is still true for IF, there are 3 accepted groups: short (type 1-acute), medium (type 2-prolongedacute) and long term (type 3-chronic). Together short and medium term make up the acute group of previous classifications [2, 5].

Short term (Type I or acute IF) is usually a self-limiting condition (e.g. post-operative ileus, enteritis – infective or from chemotherapy). It lasts for less than 28 days.

Medium term (type II ot prolonged acute) is a prolonged and often more severe condition that is potentially reversible. The patients may be metabolically unstable, requiring complex multi-disciplinary care often in a high dependency unit for weeks or months. These patients usually have abdominal sepsis (often due to perforation/fistulisation), ischaemia or intestinal obstruction. This state usually lasts less than 6 months or until reconstructive surgery is performed. This group also includes those who have a resection (e.g. for ischaemia or Crohn's disease), a temporary short bowel (usually a jejunostomy) so need nutritional support before electively having bowel continuity restored [3].

Long-term (type III or chronic IF) can be due to gastrointestinal resection(s) short bowel (or gastrectomy), gut bypass (as in the surgery for obesity) or small bowel dysfunction or a chronic enteritis. The patients are metabolically stable, requiring nutritional and/or fluid support for more than 6 months and often for many years. It is most commonly irreversible unless a small bowel transplant is performed.

Fig. 2 Classification of IF



Disease Process, Residual Anatomy and Physiology

The second part of the classification is based upon the disease process (also referred to as the patho-physiological process), residual anatomy and physiology. This results in five major groups: extensive small bowel mucosal disease, intestinal dysmotility, mechanical obstruction, fistula(s), and short bowel/gut bypass (Fig. 2). A postoperative ileus is the most common reason for short term IF while a leaking gut/fistula is the most common reason for medium term IF. A short bowel is the most common reason for long-term IF and divides mainly into those with a jejunostomy and those with a colon in continuity.

Notes on Fig. 2**.**

Extensive small bowel mucosal disease is referred to as enteritis and can be a short or a long-term situation.

Dysmotility is represented in the short term by an ileus and in the long term by an enteric myopathy or neuropathy.

Any medium term condition can become long-term. For example if defunctioned bowel if not brought into circuit then the patient will be classified as having a short bowel (long-term IF).

Underlying Disease

The third part of classification is naming the specific diseases which can be included in one or more of the disease process/anatomical/physiolocical groups (Table 1) [2, 5].

Table 1 Common underlying diseases causing IF

Short term	
Mucosal disease	Gastroenteritis (includes HIV), chemo or radiotherapy
Dysmotility	Post-operative ileus (increased bowel handling, saline excess, medication and sepsis), pancreatitis and metabolic (e.g. low K)
Medium term	
Obstruction	Adhesions, neoplasia (includes desmoid) and hernias
Fistula	Post-operative complications, Crohn's disease, irradiation damage
Defunctioned	
Long term	
Short bowel	Crohn's disease, ischaemia (arterial/venous), surgical complications,trauma, volvulus, neoplasia (e.g. desmoid), atresia, gastroschisis or necrotizing enterocolitis
Bypass	Bariatric surgery, tumor and adhesions
Dysmotility	Myopathy (e.g. chronic intestinal pseudo-obstruction (CIPO)), neuropathy or idiopathic
Mucosal disease	Crohn's disease, coeliac disease, chronic ischaemia, irradiation damage, congenital (e.g. microvillus atrophy) or autoimmune enteropathy

Severity of IF

In other diseases the severity is graded upon a simple measure (e.g. ejection fraction in cardiac failure, blood gases in respiratory failure or glomerular filtration rate/creatinine in renal failure). There are measures of gut function that include xylose absorption, fasting plasma citrulline, non-fasting plasma apolipoprotein A-IV, or percentage energy absorption after a test meal (or with a normal diet). The results are

variable and balance studies are laborious and not performed in most units.

As no one test has been accepted to grade the severity of IF, the type/amount of nutritional support is used as a proxy indicator of gut function (Fig. 3).

In the previous edition of this book, the severity of IF was graded according to the type of nutritional support given *severe IF:* parenteral nutrition (PN) and/or parenteral saline are required because health cannot be sustained by exposing the small bowel mucosa to more, continuous or altered nutrients and/or electrolytes; *moderate IF:* an enteral tube is used for the administration of macronutrients and/or a glucose/saline solution; *mild IF:* dietary adjustments, oral nutrients and/or a glucose/saline solution (or sodium chloride supplements) are needed. Patient with mild IF are the most common group and are often unrecognized.

An ESPEN one-year prospective study in adults, categorized the IF into 5 groups of severity according to the type and the volume of the required PS, (PN volumes of <1, 1–2, 2–3 and >3 L/day or fluid and electrolyte alone), to be used in clinical practice and research. Clinically an aim for rehabilitating a patients having PS is to reduce the time over which an infusion given, then permit days off the PS before it is stopped [8, 9] (Fig. 3).

The use of the type of the nutritional support required as a proxy of gut function is helpful to define cost, economic impact, and severity of the disease. However, a grey zone of overlapping occurs between the categories, severe, moderate and mild IF (or IF and II/D according to ESPEN). Only 60–80% of patients admitted initially to a UK IF unit for PN ultimately go home receiving PS [9]. This may be due to factors more related to the management expertise of the professions caring for the patients and to the patient compliance with treatment than to the severity of the condition. In some cases, patients with mild/moderate IF may be categorized as severe IF (or II/D categorized as IF), because PS is prescribed instead of an otherwise effective oral/enteral support [7]. The same may occur when a patient doesn't comply with the prescribed drug and/or the dietary advice aimed to improve the intestinal absorption or to reduce the intestinal losses of fluid, so that PS is required. Indeed, the conversion of a patient from PS to oral/enteral nutrition/fluid may vary between units and also may depend upon the expertise of a unit in maximizing residual gut function. For example, giving a mucosal growth factor, establishing complete distal feeding by enteroclysis or restricting oral hypotonic fluids in patients with a jejunostomy or jejunally feeding a patient with dysmotility may alleviate the need for PS. Also, the opposite may occur, when units with low expertise in giving PS treat patients with severe IF (or IF) by a scarcely effective oral/enteral nutrition, so that they are classified as moderate/mild IF (or II/D). Furthermore, some patients may frequently change their diagnosis and classification depending upon whether they are given PS or if it is stopped. Finally, a patient may change with time, due to compensatory mechanisms, treatment (including growth factors or distal feeding) and patient compliance, from having severe IF to mild/moderate IF (or IF to II/D). For example, a patient who has had a massive small intestinal resection, and in whom intestinal adaptation has occurred, with careful dietary advice and appropriate drug therapy may be able to stop PN over 6 months to 3 years.

Research is required for a simple and objective indicator to measure the degree of intestinal dysfunction as a continuum [10].

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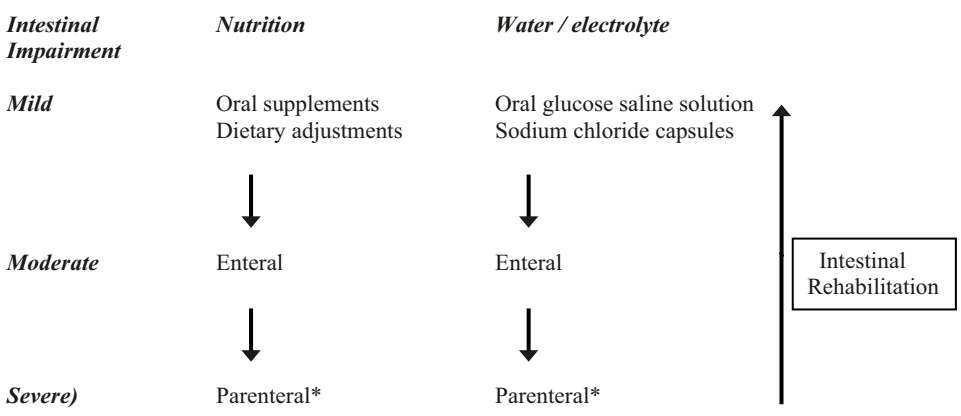

Fig. 3 Diagram to show the progression of intestinal impairment according to the route of nutritional support. Intestinal rehabilitation improves the intestinal function

*: 5 groups of severity for PS (PN volumes of <1, 1-2, 2-3 and >3 L/day or fluid and electrolyte alone)

References

1. Fleming CR, Remington M. Intestinal failure. In: Hill GL, editor. Nutrition and the surgical patient. New York: Churchill Livingstone; 1981. p. 219–35.
2. Nightingale J. Definition and classification of intestinal failure. In: Nightingale J, editor. Intestinal failure. London: Greenwich Medical Media Limited; 2001. p. xix–xx.3.
3. Nightingale JMD, Woodward J, Small bowel/Nutrition Committee of BSG. Guidelines for the management of patients with a short bowel. Gut. 2006;55(suppl IV):iv1–iv12.
4. Jeejeebhoy KN. The etiology and mechanisms of intestinal failure. In: Matarese LE, Steiger E, Seidner DL, editors. Intestinal failure and rehabilitation: a clinical guide. New York: CRC Press; 2005. p. 25–37.
5. Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C, Forbes A, Gabe S, Gillanders L, Holst M, Jeppesen PB, Joly F, Kelly D, Klek S, Irtun Ø, Olde Damink SW, Panisic M, Rasmussen HH, Staun M, Szczepanek K, Van Gossum A, Wanten G, Schneider SM, Shaffer J, Home Artificial Nutrition & Chronic Intestinal Failure, Acute Intestinal Failure Special Interest Groups of ESPEN. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34(2):171–80.
6. Intestinal failure service specification (A08/S/a). www.england.nhs.uk/wp-content/uploads/2019/07/170077S-Intestinal-Failure-Service-Specification.pdf.
7. ICD-11 for mortality and morbidity statistics: DA96.05 Intestinal failure. https://icd.who.int/dev11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f778202494.
8. Pironi L, Steiger E, Joly F, Wanten GJA, Chambrier C, Aimasso U, Sasdelli AS, Szczepanek K, Jukes A, Theilla M, Kunecki M, Daniels J, Serlie MJ, Cooper SC, Poullenot F, Rasmussen HH, Compher CW, Crivelli A, Hughes SJ, Santarpia L, Guglielmi FW, Rotovnik Kozjek N, Ellegard L, Schneider SM, Matras P, Forbes A, Wyer N, Zmarzly A, Taus M, O'Callaghan M, Osland E, Thibault R, Cuerda C, Jones L, Chapman B, Sahin P, Virgili NM, Lee ADW, Orlandoni P, Matysiak K, Di Caro S, Doitchinova-Simeonova M, Masconale L, Spaggiari C, Garde C, Serralde-Zúñiga AE, Olveira G, Krznaric Z, Petrina Jáuregui E, Zugasti Murillo A, Suárez-Llanos JP, Nardi E, Van Gossum A, Lal S. Intravenous supplementation type and volume are associated with 1-year outcome and major complications in patients with chronic intestinal failure. Gut. 2020;69(10):1787–95.
9. Pironi L, Konrad D, Brandt C, Joly F, Wanten G, Agostini F, Chambrier C, Aimasso U, Zeraschi S, Kelly D, Szczepanek K, Jukes A, Di Caro S, Theilla M, Kunecki M, Daniels J, Serlie M, Poullenot F, Wu J, Cooper SC, Rasmussen HH, Compher C, Seguy D, Crivelli A, Pagano MC, Hughes SJ, Guglielmi FW, Kozjek NR, Schneider SM, Gillanders L, Ellegard L, Thibault R, Matras P, Zmarzly A, Matysiak K, Van Gossum A, Forbes A, Wyer N, Taus M, Virgili NM, O'Callaghan M, Chapman B, Osland E, Cuerda C, Sahin P, Jones L, Lee ADW, Bertasi V, Orlandoni P, Izbéki F, Spaggiari C, Díez MB, Doitchinova-Simeonova M, Garde C, Serralde-Zúñiga AE, Olveira G, Krznaric Z, Czako L, Kekstas G, Sanz-Paris A, Jáuregui EP, Murillo AZ, Schafer E, Arends J, Suárez-Llanos JP, Shaffer J, Lal S. Clinical classification of adult patients with chronic intestinal failure due to benign disease: an international multicenter cross-sectional survey. Clin Nutr. 2018;37(2):728–38.
10. Nightingale JMD, Small M, Jeejeebhoy K. Intestinal failure definition and classification comments: Good in parts but could be better. Clin Nutr. 2016;35(2):536.

Part II

Acute (Short and Medium Term Reversible) Intestinal Failure

Postoperative Ileus

Ian Bissett and Dileep N. Lobo

Key Points

1. Avoid perioperative fluid overload.
2. Employ a standard enhanced recovery after surgery (ERAS) protocol.
3. Minimise the use of opioids.
4. Utilise minimal access techniques.
5. Prevent blood loss.
6. Don't re-operate for postoperative ileus.

Introduction

In this chapter we will consider the definition and incidence of this condition, explore the burden of prolonged postoperative ileus (PPOI) on both the patient and the health system, describe of the pathophysiology of PPOI and the main risk factors for its occurrence, list interventions that may prevent or reduce the occurrence of PPOI and present the evidence for the treatment of established PPOI. The chapter concludes with a proposed management strategy.

Definition and Incidence of Ileus

Postoperative ileus is an abnormality of the motility of the gastrointestinal tract that prevents the normal ingestion and absorption of food and elimination of waste products. Symptoms depend on the site of dysfunction. Involvement of the stomach and proximal small bowel is characterised by nausea and vomiting while more distal dysfunction results in lack of passage of flatus or stool and abdominal distension from the bowel dilatation. This dilatation of the bowel can be identified on abdominal X-ray or CT scan as bowel distension with air-fluid levels in the absence of a clear transition point to collapsed bowel on CT (Fig. 1). It is generally accepted that there is a period of 'normal' or physiological gut dysfunction following major abdominal surgery that should resolve spontaneously after a day or two. Prolongation of this period or the reoccurrence of it after return of normal function postoperatively have been recognised as Prolonged or Recurrent Postoperative Ileus.

Various definitions of PPOI have been proposed in the past including the necessity to insert a nasogastric tube after surgery, nausea and vomiting, inability to tolerate oral diet and failure to pass stool or flatus.

A novel study from the Netherlands included patients undergoing elective surgery for colonic cancer and compared scintigraphic studies of gastric emptying on day 1 and colonic scintigraphy on days 2 and 3 with specific symptoms associated with return of gut function [1]. They showed that the best measure of return on GI function was the combined measure of tolerance of solid food and defaecation. This also correlated inversely with length of hospital stay. They did not, however, provide a definition of PPOI but rather considered that all patients had postoperative ileus until both defaecation and tolerance of oral food had been achieved.

In an attempt to clarify the definition of PPOI, Vather et al. carried out a systematic review and global survey amongst those who had recently published in this area [2]. This study differentiated between normal physiological bowel dysfunction that follows surgery and when this becomes pathological as PPOI. Based on this survey they defined PPOI as the presence of any 2 of the five cardinal symptoms on or after day 4 post operatively. These are nausea or vomiting, inability to tolerate an oral diet, failure to pass flatus or stool, abdominal distension, and radiological signs of PPOI. Each of these were carefully defined. This definition provides not only the essential elements to be included but also a timeline for the commencement of

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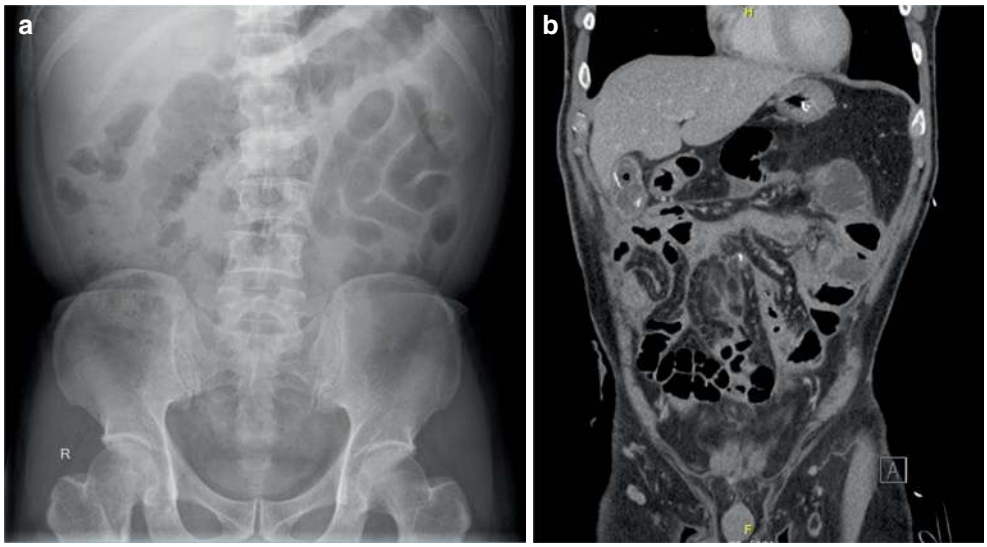

Fig. 1 A 57 year old man seven days following proctectomy and ileoanal pouch. (**a**) A plain abdominal film demonstrating distension of the small bowel and stomach. (**b**) A coronal abdominal CT demonstrating distention of the entire small bowel with a nasogastric tube visible in the stomach

PPOI. Subsequent studies have utilised this definition in their randomised clinical trials [3–5].

The incidence of PPOI varies greatly between studies from 3% to greater than 30% [3, 6]. This variation is likely to be explained by the difference in populations included in the studies, whether the data were collected prospectively and most importantly the definitions used. A recent systematic review that included 54 studies reported a pooled rate of 10% for PPOI. Unfortunately the definition of PPOI differed across the studies with the commonest definition being the reinsertion of a nasogastric tube. They showed that the rates varied depending on the definition used [7]. A snapshot study over six weeks in 10 hospitals in United Kingdom reported that 22.5% of the patients having a left or right-sided colonic resection required nasogastric tube insertion [8]. A very large study out of United States using American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) data for patients undergoing colectomy identified prolonged postoperative ileus as the most common complication, occurring in 10% of the patients [9]. Recent prospective studies using the definition proposed by Vather et al. have identified that more than one patient in four is likely to develop PPOI following a colorectal resection [3, 10].

Burden of Ileus (Effect on Morbidity and Cost of Stay)

Prolonged postoperative ileus has major negative impacts on the patient. The patient may initially appear to be progressing well but then develops nausea and abdominal distension. Vomiting follows and the bowels cease functioning. This often requires insertion of a nasogastric tube and if it does not resolve quickly intravenous feeding is required. For patients it is frightening, unpleasant and extremely disheartening. PPOI is associated with an increase in hospital stay, prolonged intravenous fluid administration and several major complications. The most serious and sometimes fatal complication is aspiration pneumonia but bronchopneumonia, thromboembolic events, electrolyte imbalance and psychological distress are also frequently associated. Recent studies have identified it as the commonest postoperative complication after colorectal surgery [9]. This complication along with anastomotic leak caused the greatest increase in hospital stay and total treatment cost following colectomy [9].

This increased cost associated with PPOI has been estimated by Goldstein et al. to be greater than $1.5 Billion annually in USA alone [11]. A study utilising the Premier Perspective Database in USA assessed nearly 20,000 patients with colectomy. Postoperative ileus was associated with a 29% increase in length of stay and a 15% increase in cost after adjusting for the influence of all other factors [12].

Pathophysiology

The aetiology of PPOI is multifactorial. Its initiation is associated with activation of inflammatory cells, autonomic dysfunction, opioid stimulation of gut opioid receptors, electrolyte abnormalities, direct injury to the intestine and derangement of gastrointestinal hormones. These interactions, triggered by both a somatic and a visceral insult and resulting in the final gut dysmotility of PPOI, are summarised in Fig. 2.

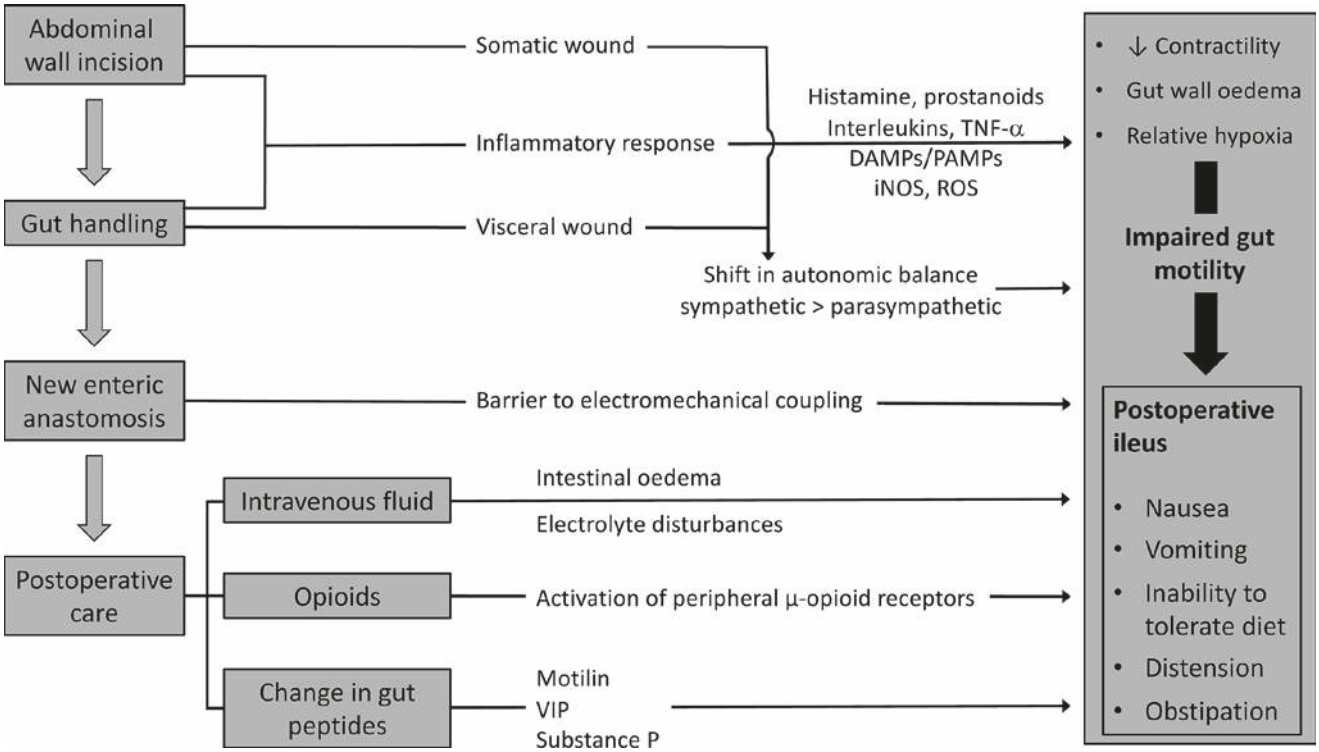

Fig. 2 Pathophysiological basis for the development of a postoperative ileus. DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; VIP, vasoactive intestinal peptide, TNF-α, tumour necrosis factor alpha, iNOS, inducible nitric oxide synthetase, ROS, reactive oxygen species [13, 19] with permission [13].

Risk Factors

Multiple risk factors for PPOI have been identified in retrospective analysis of data including; increasing age, male gender, pre-existing chronic airway disease, increasing perioperative opioid consumption, increasing intra-operative blood loss and the formation of an ileostomy [6, 14–16]. These are summarised in Table 1. In a prospective study in colorectal surgery patients using a precise definition of PPOI the factors that were independently identified out of 92 different variables were; male gender, decreasing preoperative albumin, open or converted technique (vs laparoscopic), increasing wound size, operative difficulty, operative bowel handling, red cell transfusion, intravenous crystalloid administration over postoperative day 0–3, and delayed first mobilization. These factors were then combined to create an I-Score that differentiated between those with a low, intermediate and high risk of developing PPOI [17].

Table 1 Risk factors and possible mechanisms for postoperative ileus [6, 14, 16, 18–25]. Adapted from Bragg, et al. [19], with permission

Risk factor	Possible mechanisms
Increasing age [6, 24]	Reduced overall capacity to recover from surgical insult [24]
Male gender [16]	Greater inflammatory response to surgery [21] Increased pain threshold in males, [18] resulting in higher catecholamine release [22]
Low preoperative albumin concentration [16]	Increased oedema and intestinal stretch
Acute and chronic opioid use [6, 14]	μ-opioid receptor stimulation reduces peristalsis [20, 24]
Previous abdominal surgery [6]	Increased need for adhesiolysis, increased bowel handling
Pre-existing airways/ peripheral vascular disease [16]	Reduced physiological reserve
Long duration of surgery [14, 16]	Increased bowel handling [23] and opioid use
Emergency surgery [18, 21]	Increased inflammatory and catecholamine response; secondary causes of POI
Blood loss and need for transfusion [6, 14, 16]	Increased crystalloid administration resulting in oedema [25]
Procedures requiring stomas [21]	Oedema in abdominal wall muscle and cut bowel

Prevention of PPOI

An understanding of the pathophysiology of and risk factors for PPOI as described above provides a foundation for the possible interventions that may reduce the risk of developing this condition. Many of the advances in the perioperative management of patients undergoing major elective abdominal surgery potentially impact on the trigger factors for PPOI. The advent of Enhanced Recovery after Surgery (ERAS) protocols has seen a much greater emphasis on optimising the patient's physiology in the perioperative setting. Recent evidence suggests that the ERAS protocol may actually have an anti-inflammatory effect at both the gut wall and mucosal level [26]. Systematic reviews of ERAS have consistently demonstrated reduced complications and earlier discharge from hospital [27, 28]. Increased volume of crystalloids in the perioperative setting was an independent risk factor for development of PPOI in Vather's study and those of VandeHei et al. and Lobo et al., [17, 29, 30] but this finding has not been confirmed in other randomised studies [31–33]. A possible mechanism relating the association of fluid overload with PPOI is summarised in Fig. 3 [25].

A recent systematic review of preventive measures for PPOI has summarised the different interventions [34]. These include early feeding, chewing gum, epidural anaesthetic, laparoscopy, peripheral μ-opioid receptor antagonists, prokinetic agents, non-steroidal anti-inflammatories, and coffee.

Early Enteral Feeding

Early feeding has become a central plank of the ERAS pathway, RCT evidence of its efficacy in reducing PPOI is inconsistent. In the eleven RCTs that were reviewed by Chapman et al. six showed a significant reduction in time to flatus, stool or oral tolerance, two of which also showed a reduction in length of hospital stay [34]. Early enteral feeding is widely accepted as beneficial and safe in postoperative management

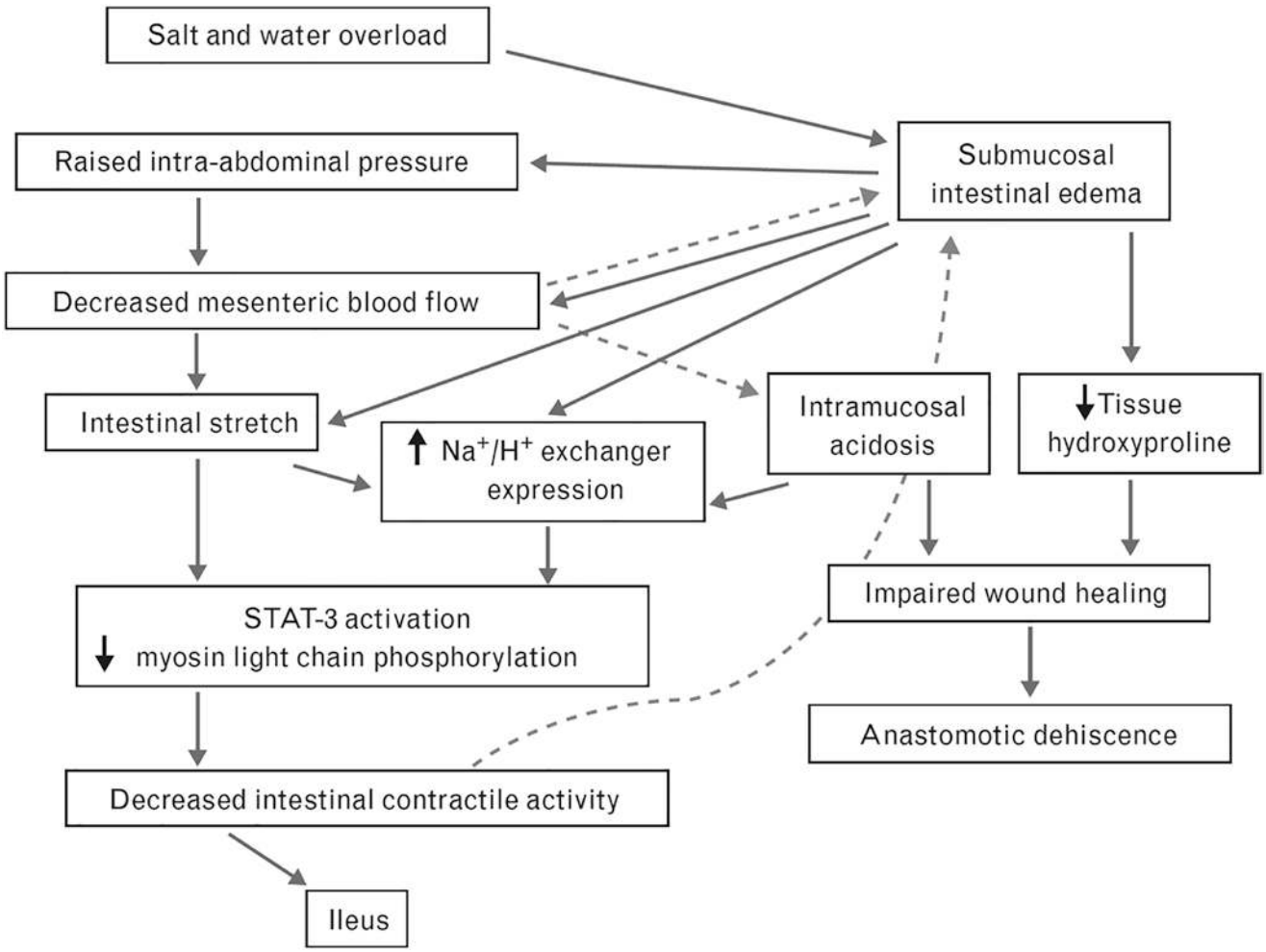

Fig. 3 Mechanisms for adverse effects of salt and water overload on gastrointestinal function, summarising data from human and animal studies. (From Chowdhury and Lobo [25], with permission)

of elective abdominal surgery with a likely benefit in hastening the return of normal intestinal function.

Chewing Gum

Chewing gum in the immediate postoperative period has the potential to stimulate salivation, swallowing and gastrointestinal hormones. A systematic review of eleven randomised studies has assessed this intervention in promoting intestinal recovery after surgery. There was no significant reduction in time to normal oral intake or time to flatus or stool in the high-quality studies but five other studies that were prone to bias did have significant reductions in time to pass flatus and/or stool. A Cochrane review that included 81 randomised studies and 9702 participants did demonstrate a reduction in time to flatus and stool but no other benefit in terms of tolerating food or shortening length of stay [35]. The reviewers state that most of the included studies had a high risk of bias. Chewing gum has little risk of causing harm and may be beneficial in reducing the time to return of normal intestinal function.

Epidural Anaesthetic

There is robust evidence provided in a Cochrane review including more than 20 studies and over 100 patients that epidural anaesthesia leads to a decrease of time to passage of stool and flatus in patients undergoing open surgery, but that there is no decrease in nausea and vomiting in the first postoperative day [36]. The evidence for a benefit in laparoscopic surgery is however much less clear. A large retrospective case matched study of US data found that in laparoscopic colorectal surgery epidural is associated with longer hospital stays, higher expense and a greater risk of urinary tract infections [37]. The benefits of epidural anaesthesia are probably limited to those undergoing open surgery.

Laparoscopy

The laparoscopic approach to surgery has repeatedly been demonstrated to result in a more rapid return of gastrointestinal function and reduction of PPOI [17, 38]. Randomised studies that have specifically addressed this issue, using gastrointestinal transit studies as the outcome, have shown laparoscopy was associated with improved gastrointestinal motility [39–41].

Alvimopan

Alvimopan is a peripheral μ-opioid receptor antagonist without central effects. It has been compared with placebo in 5 randomised clinical trials, four of which demonstrated an improvement in gastrointestinal function using a combined upper and lower GI function measure [42–45]. At present it is only available in USA in restricted centres but it has the potential to mitigate the opioid-related gut dysmotility that so often impairs postoperative recovery.

Prokinetic Agents

Multiple prokinetic agents, although theoretically promising, in practice have mostly been disappointing. However, the serotonin 4 receptor agonists, cisapride and mosapride have demonstrated enhanced gastrointestinal recovery [46, 47]. Cisapride has been withdrawn because of its significant cardiac side-effects, but other Serotonin 4 receptor antagonists, such as prucalopride are under investigation.

Non-steroidal Anti-Inflammatory Drugs

A systematic review that identified 10 RCTs comparing non-steroidal anti-inflammatory drugs (NSAIDs) with placebo in the perioperative setting found that those receiving NSAID passed both flatus and stool earlier, and tolerated a diet sooner than those receiving placebo [48]. The possible role of NSAIDs in anastomotic leak needs to be considered when deciding on the use of these agents. The studies addressing this are conflicting, but to date the selective COX-2 inhibitors have not been implicated in increasing the risk of this complication [49].

Coffee

Coffee has been proposed as an agent to reduce postoperative gut dysmotility. A randomised clinical trial comparing decaffeinated coffee, caffeinated coffee and water in the postoperative period demonstrated accelerated passage of stool and tolerance of solid diet in the decaffeinated group compared with both of the other groups. This suggests that some component of coffee rather than caffeine may stimulate earlier return of normal GI function [50].

Treatment of Prolonged Postoperative Ileus

Although the interventions above have been associated with prevention of PPOI, the treatment of an established PPOI is more problematic. At the outset a precipitating intra-abdominal complication such as anastomotic leak, intra-abdominal abscess or mechanical obstruction should be sought (usually with a contrast enhanced CT scan) and

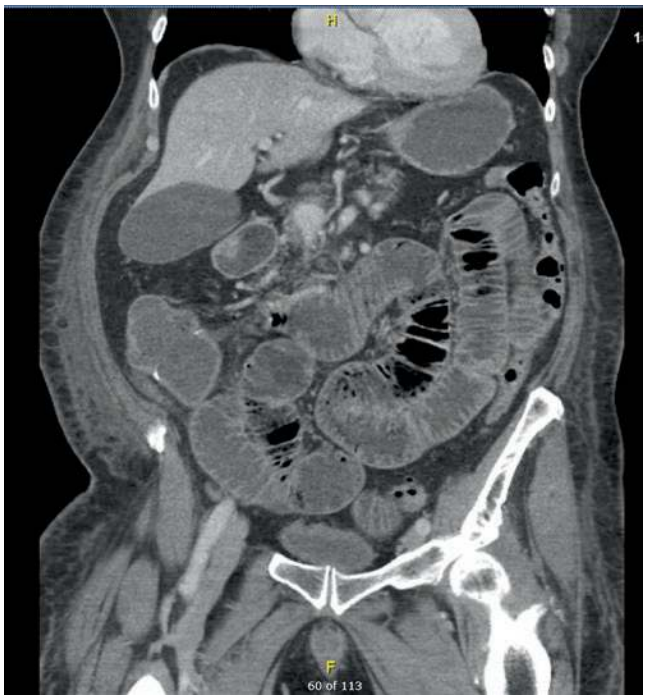

Fig. 4 A coronal CT of a 77 Year old male following right hemicolectomy demonstrating distended small bowel with the distension bowel distension also involving the anastomosis.

treated appropriately if identified (Fig. 4). The foundation of treatment of PPOI, however, is conservative and involves optimising the patient's physiology. The main features of this are: correction of fluid and electrolyte balance, reduction of opioid administration, decompression of a distended gastrointestinal tract and ensuring ongoing nutritional requirements are met.

The specific electrolytes associated with PPOI that have been reported are hypokalaemia, hyponatraemia, and hypocalcaemia [51]. Regular monitoring of these electrolytes with appropriate correction of abnormalities is required. Often patients will also have a burden of extra fluid leading to oedema of multiple tissues including the intestinal wall. Overzealous replacement of fluids must be avoided and this can be achieved by providing maintenance as isotonic dextrose-saline at a rate of 1–1.25 ml/kg/h and replacing gastric losses with an equivalent volume of balanced isotonic crystalloid solution including supplemental potassium.

Patients in the postoperative setting with PPOI may have both postoperative wound pain and discomfort associated with intestinal distension. The management of this requires a careful balance to ensure that the analgesia is adequate to control the pain without producing opioid-induced intestinal dysmotility. This can often be achieved using regular paracetamol, NSAID medication and tramadol while keeping the amount of opioid analgesia to a minimum. Alvimopan may also be used if it is available and opioids cannot be avoided.

Most patients with PPOI will require a nasogastric tube and this should be inserted if there is recurrent vomiting even if this is low volume as it may represent an overflow of a very distended stomach. Distressing abdominal distension may also be markedly relieved by insertion of a nasogastric tube. Aspiration with subsequent pneumonitis is perhaps the commonest cause of death in those with PPOI and adequate emptying of the stomach is likely to reduce the chance of this serious complication.

A combined analysis of two placebo controlled, randomised clinical trials of the use of Gastrografin in an established postoperative ileus has demonstrated an earlier onset of oral intake in those receiving Gastrografin [52]. However, the study of only 108 patients was not able to demonstrate either a shorter hospital stay or duration of the composite PPOI definition used in the studies. A potential risk associated with Gastrografin is the severe, often fatal, pneumonitis associated with its aspiration and therefore it should only be used when the stomach is known to be empty.

Patients' nutritional requirements need to be considered as oral intake is not feasible in the context of PPOI. Parenteral feeding should be initiated by 7 days postoperatively and earlier for those presenting with malnutrition to ensure that the patient does not suffer serious nutritional decline during management of PPOI [53]. Prolonged under-nutrition in the postoperative setting is associated with increased complications and mortality [54]. Provision of 25 kcal/kg and1.5 g/kg protein (based on ideal body weight) in the administered PN is likely to lead to an improvement in nitrogen balance [53]. The patient should be transitioned back to enteral nutrition as soon as tolerated.

Summary

Prolonged postoperative ileus is the commonest postoperative complication following colorectal surgery and is associated with a large burden of expense. Perioperative measures to reduce its incidence include careful avoidance of fluid overload, minimally invasive surgical approaches, adherence with ERAS principles, avoidance of postoperative opioids, early feeding and mobilisation postoperatively, non-steroidal anti-inflammatories and possibly gum chewing and coffee. Interventions once PPOI is established are primarily conservative aimed at optimising nutrition and physiology. See Table 2 prevention and Table 3 treatment below.

Table 2 Prevention

Intervention	Strength of evidence	Summary of evidence	Patient group
Early feeding	++ SR	Early feeding is safe and may reduce time to postoperative gut recovery	All
Early mobilisation	+ OS	Delayed mobilisation is a risk factor for prolonged postoperative ileus. No consensus regarding optimal mobilisation interventions	All
Avoidance of opioids	+ Large OS	Increased use of postoperative opioid analgesia impairs recovery of gut motility and prolongs length of stay. Minimise opioid analgesia postoperatively	All
Minimally invasive surgery	++ SR	Laparoscopic surgery leads to clinically significant reductions in time to gut recovery and reduces postoperative ileus compared to open surgery	All
Avoidance of fluid overload	+ RCTs, large OS	Perioperative fluid overload may impair gut motility postoperatively. Restrict IV fluid where possible, using a chloride-restricted crystalloid	All
NSAIDs	+ SR	Use of perioperative NSAIDs reduces time to passage of flatus, stool and tolerance of diet in patients undergoing open bowel resection. Role in laparoscopic resection is unclear	All
Alvimopan	++ SR	Alvimopan improves time to gut recovery and reduces ileus after open surgery. It may reduce ileus after laparoscopic surgery. The cost effectiveness of Alvimopan in an enhanced recovery setting is unclear	Open surgery
Thoracic Epidural	++ SR	Thoracic epidural reduces time to passage of flatus and stool after abdominal surgery. Unproven benefit in laparoscopic surgery	Open surgery
Prokinetics	++ SR	Currently used prokinetics (erythromycin, metoclopramide) are unlikely to improve postoperative gut recovery and to reduce postoperative ileus	NR
Chewing gum	+/– SR	Chewing gum is safe postoperatively and leads to small improvements in time to gut recovery. Clinical relevance is unclear	NR
Coffee	+/– Small RCTs	Coffee may improve postoperative gut recovery but the evidence is of low quality	NR
Novel agents (Prucalopride)	+/– RCTs	Serotonin-4 receptor agonists, such as Prucalopride, may reduce postoperative ileus and improve time to pass flatus and stool after colorectal surgery	Await further studies

SR Systematic Review, *RCT* Randomised Clinical Trial, *OS* Observational Studies, *NR* Not recommended

Table 3 Treatment

Correct electrolytes	+ OS	Electrolyte disturbances (sodium, potassium, calcium and magnesium) impair gut motility and may prolong postoperative ileus	All
Balance IV fluids with losses	+ OS	Maintenance fluid with a balanced crystalloid solution, instead of 0.9% saline, based on patient hydration status. Replacement of gastric losses with an equivalent volume of potassium-rich crystalloid	All
NG placement if required	+ OS	Selective use of nasogastric tube for patients with postoperative nausea and vomiting for symptomatic relief. Not all patients with prolonged postoperative ileus require NGT insertion	Selective use as required
Optimize analgesia	++ OS	Opioid analgesia should be used sparingly during postoperative ileus. Use of paracetamol, non-steroidal anti-inflammatories and tramadol may be effective	All
Provide PN if prolonged	+ OS	Commence parenteral nutrition if patient is unable to tolerate adequate oral intake for 7 days postoperatively. Can commence earlier if evidence of preoperative malnutrition	Selective use as required
Alvimopan	+/–	Alvimopan reduces the incidence of postoperative ileus after colorectal surgery. Not yet proven to reduce the duration of an established ileus	Await further studies
Hyperosmolar radiocontrast media (Gastrografin)	+ RCTs	Gastrografin given at the onset of prolonged postoperative ileus may improve time to tolerance of diet and passage of flatus/stool. Further studies are required	Await further studies

SR Systematic review, *RCT* Randomised Clinical Trial, *OS* Observational Studies, *NG* Nasogastric

References

1. van Bree SH, Bemelman WA, Hollmann MW, Zwinderman AH, Matteoli G, El Temna S, et al. Identification of clinical outcome measures for recovery of gastrointestinal motility in postoperative ileus. Ann Surg. 2014;259(4):708–14.
2. Vather R, Trivedi S, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. J Gastrointest Surg. 2013;17(5):962–72.
3. van den Heijkant TC, Costes LM, van der Lee DG, Aerts B, Osinga-de Jong M, Rutten HR, et al. Randomized clinical trial of the effect of gum chewing on postoperative ileus and inflammation in colorectal surgery. Br J Surg. 2015;102(3):202–11.
4. Peters EG, Smeets BJ, Dekkers M, Buise MD, de Jonge WJ, Slooter GD, et al. The effects of stimulation of the autonomic nervous system via perioperative nutrition on postoperative ileus and anastomotic leakage following colorectal surgery (SANICS II trial): a study protocol for a double-blind randomized controlled trial. Trials. 2015;16:20.
5. Vilz TO, Pantelis D, Lingohr P, Fimmers R, Esmann A, Randau T, et al. SmartPill(R) as an objective parameter for determination of severity and duration of postoperative ileus: study protocol of a prospective, two-arm, open-label trial (the PIDuSA study). BMJ Open. 2016;6(7):e011014.
6. Kronberg U, Kiran RP, Soliman MS, Hammel JP, Galway U, Coffey JC, et al. A characterization of factors determining postoperative ileus after laparoscopic colectomy enables the generation of a novel predictive score. Ann Surg. 2011;253(1):78–81.
7. Wolthuis AM, Bislenghi G, Fieuws S, de Buck van Overstraeten A, Boeckxstaens G, D'Hoore A. Incidence of prolonged postoperative ileus after colorectal surgery: a systematic review and meta-analysis. Color Dis. 2016;18(1):O1–9.
8. Yorkshire Surgical Research Collaborative. Multicentre observational study of gastrointestinal recovery after elective colorectal surgery. Color Dis. 2018;20(6):536–44.
9. Scarborough JE, Schumacher J, Kent KC, Heise CP, Greenberg CC. Associations of specific postoperative complications with outcomes after elective colon resection: a procedure-targeted approach toward surgical quality improvement. JAMA Surg. 2017;152(2):e164681.
10. Vather R, Josephson R, Jaung R, Kahokehr A, Sammour T, Bissett I. Gastrografin in prolonged postoperative ileus: a double-blinded randomized controlled trial. Ann Surg. 2015;262(1):23–30.
11. Goldstein JL, Matuszewski KA, Delaney C, Senagore A, Chiao E, Shah M, et al. Inpatient economic burden of postoperative ileus associated with abdominal surgery in the United States. P T. 2007;32(2):82–90.
12. Iyer S, Saunders WB, Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. J Manag Care Pharm. 2009;15(6):485–94.
13. Vather R, O'Grady G, Bissett IP, Dinning PG. Postoperative ileus: mechanisms and future directions for research. Clin Exp Pharmacol Physiol. 2014;41(5):358–70.
14. Artinyan A, Nunoo-Mensah JW, Balasubramaniam S, Gauderman J, Essani R, Gonzalez-Ruiz C, et al. Prolonged postoperative ileus-definition, risk factors, and predictors after surgery. World J Surg. 2008;32(7):1495–500.
15. Millan M, Biondo S, Fraccalvieri D, Frago R, Golda T, Kreisler E. Risk factors for prolonged postoperative ileus after colorectal cancer surgery. World J Surg. 2012;36(1):179–85.
16. Chapuis PH, Bokey L, Keshava A, Rickard MJ, Stewart P, Young CJ, et al. Risk factors for prolonged ileus after resection of colorectal cancer: an observational study of 2400 consecutive patients. Ann Surg. 2013;257(5):909–15.
17. Vather R, Josephson R, Jaung R, Robertson J, Bissett I. Development of a risk stratification system for the occurrence of prolonged postoperative ileus after colorectal surgery: a prospective risk factor analysis. Surgery. 2015;157(4):764–73.
18. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. Br J Anaesth. 2013;111(1):52–8.
19. Bragg D, El-Sharkawy AM, Psaltis E, Maxwell-Armstrong CA, Lobo DN. Postoperative ileus: recent developments in pathophysiology and management. Clin Nutr. 2015;34(3):367–76.
20. Delaney CP. Clinical perspective on postoperative ileus and the effect of opiates. Neurogastroenterol Motil. 2004;16(Suppl 2):61–6.
21. Ferguson JF, Patel PN, Shah RY, Mulvey CK, Gadi R, Nijjar PS, et al. Race and gender variation in response to evoked inflammation. J Transl Med. 2013;11:63.
22. Huskisson EC. Catecholamine excretion and pain. Br J Clin Pharmacol. 1974;1(1):80–2.
23. Kalff JC, Schraut WH, Simmons RL, Bauer AJ. Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. Ann Surg. 1998;228(5):652–63.
24. Vather R, Bissett IP. Risk factors for the development of prolonged post-operative ileus following elective colorectal surgery. Int J Color Dis. 2013;28(10):1385–91.
25. Chowdhury AH, Lobo DN. Fluids and gastrointestinal function. Curr Opin Clin Nutr Metab Care. 2011;14(5):469–76.
26. Venara A, Duchalais E, Dariel A, Aubert P, Durand T, Meurette G, et al. Anti-inflammatory effects of enhanced recovery programs on early-stage colorectal cancer surgery. World J Surg. 2018;42(4):953–64.
27. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr. 2010;29(4):434–40.
28. Bagnall NM, Malietzis G, Kennedy RH, Athanasiou T, Faiz O, Darzi A. A systematic review of enhanced recovery care after colorectal surgery in elderly patients. Color Dis. 2014;16(12):947–56.
29. VandeHei MS, Papageorge CM, Murphy MM, Kennedy GD. The effect of perioperative fluid management on postoperative ileus in rectal cancer patients. Surgery. 2017;161(6):1628–32.
30. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. Lancet. 2002;359(9320):1812–8.
31. Gomez-Izquierdo JC, Trainito A, Mirzakandov D, Stein BL, Liberman S, Charlebois P, et al. Goal-directed fluid therapy does not reduce primary postoperative ileus after elective laparoscopic colorectal surgery: a Randomized Controlled Trial. Anesthesiology. 2017;127(1):36–49.
32. Kalyan JP, Rosbergen M, Pal N, Sargen K, Fletcher SJ, Nunn DL, et al. Randomized clinical trial of fluid and salt restriction compared with a controlled liberal regimen in elective gastrointestinal surgery. Br J Surg. 2013;100(13):1739–46.
33. Myles PS, Bellomo R, Corcoran T, Forbes A, Peyton P, Story D, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med. 2018;378(24):2263–74.
34. Chapman SJ, Pericleous A, Downey C, Jayne DG. Postoperative ileus following major colorectal surgery. Br J Surg. 2018;105(7):797–810.
35. Short V, Herbert G, Perry R, Atkinson C, Ness AR, Penfold C, et al. Chewing gum for postoperative recovery of gastrointestinal function. Cochrane Database Syst Rev. 2015;2:CD006506.
36. Guay J, Nishimori M, Kopp S. Epidural local anaesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, vomiting and pain after abdominal surgery. Cochrane Database Syst Rev. 2016;7:CD001893.

37. Halabi WJ, Kang CY, Nguyen VQ, Carmichael JC, Mills S, Stamos MJ, et al. Epidural analgesia in laparoscopic colorectal surgery: a nationwide analysis of use and outcomes. JAMA Surg. 2014;149(2):130–6.
38. Gavriilidis P, Katsanos K. Laparoscopic versus open transverse colectomy: a systematic review and meta-analysis. World J Surg. 2018;42(9):3008–14.
39. Schwenk W, Bohm B, Haase O, Junghans T, Muller JM. Laparoscopic versus conventional colorectal resection: a prospective randomised study of postoperative ileus and early postoperative feeding. Langenbeck's Arch Surg. 1998;383(1):49–55.
40. Basse L, Madsen JL, Billesbolle P, Bardram L, Kehlet H. Gastrointestinal transit after laparoscopic versus open colonic resection. Surg Endosc. 2003;17(12):1919–22.
41. van Bree SH, Vlug MS, Bemelman WA, Hollmann MW, Ubbink DT, Zwinderman AH, et al. Faster recovery of gastrointestinal transit after laparoscopy and fast-track care in patients undergoing colonic surgery. Gastroenterology. 2011;141(3):872–80 e1–4.
42. Delaney CP, Weese JL, Hyman NH, Bauer J, Techner L, Gabriel K, et al. Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery. Dis Colon Rectum. 2005;48(6):1114–25; discussion 25–6; author reply 27–9
43. Ludwig K, Enker WE, Delaney CP, Wolff BG, Du W, Fort JG, et al. Gastrointestinal tract recovery in patients undergoing bowel resection: results of a randomized trial of alvimopan and placebo with a standardized accelerated postoperative care pathway. Arch Surg. 2008;143(11):1098–105.
44. Viscusi ER, Goldstein S, Witkowski T, Andonakakis A, Jan R, Gabriel K, et al. Alvimopan, a peripherally acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery: results of a randomized, double-blind, controlled study. Surg Endosc. 2006;20(1):64–70.
45. Wolff BG, Michelassi F, Gerkin TM, Techner L, Gabriel K, Du W, et al. Alvimopan, a novel, peripherally acting mu opioid antagonist: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. Ann Surg. 2004;240(4):728–34; discussion 34–5
46. Narita K, Tsunoda A, Takenaka K, Watanabe M, Nakao K, Kusano M. Effect of mosapride on recovery of intestinal motility after hand-assisted laparoscopic colectomy for carcinoma. Dis Colon Rectum. 2008;51(11):1692–5.
47. Brown TA, McDonald J, Williard W. A prospective, randomized, double-blinded, placebo-controlled trial of cisapride after colorectal surgery. Am J Surg. 1999;177(5):399–401.
48. Milne TGE, Jaung R, O'Grady G, Bissett IP. Nonsteroidal anti-inflammatory drugs reduce the time to recovery of gut function after elective colorectal surgery: a systematic review and meta-analysis. Color Dis. 2018;20(8):O190–O8.
49. Smith SA, Roberts DJ, Lipson ME, Buie WD, MacLean AR. Postoperative nonsteroidal anti-inflammatory drug use and intestinal anastomotic dehiscence: a systematic review and meta-analysis. Dis Colon Rectum. 2016;59(11):1087–97.
50. Dulskas A, Klimovskij M, Vitkauskiene M, Samalavicius NE. Effect of coffee on the length of postoperative ileus after elective laparoscopic left-sided colectomy: a randomized, prospective single-center study. Dis Colon Rectum. 2015;58(11):1064–9.
51. Vather R, Bissett I. Management of prolonged post-operative ileus: evidence-based recommendations. ANZ J Surg. 2013;83(5):319–24.
52. Milne TGE, Vather R, O'Grady G, Miquel J, Biondo S, Bissett I. Gastrografin may reduce time to oral diet in prolonged postoperative ileus: a pooled analysis of two randomized trials. ANZ J Surg. 2018;88:E578–82.
53. Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al. ESPEN guideline: clinical nutrition in surgery. Clin Nutr. 2017;36(3):623–50.
54. Sandstrom R, Drott C, Hyltander A, Arfvidsson B, Schersten T, Wickstrom I, et al. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. Ann Surg. 1993;217(2):185–95.

Acute Surgical Intestinal Failure. Sepsis and Enterocutaneous Fistula(s)

Akash Mehta, Carolynne Vaizey, Jeremy M.D. Nightingale, and Gordon Carlson

Key Points

1. Sepsis is the main cause of death in patients with acute intestinal failure so must be continually suspected, detected and treated.
2. Up to 50% of post-operative fistula(s) heal spontaneously.
3. Oral/enteral feeding can be used in preference to parenteral feeding if small bowel effluent is draining adequately rather than collecting and there is more than 100 cm functional small intestine available.
4. Definitive surgery for enterocutaneous fistula(s) should be delayed until the patient's condition has been fully optimised. In many cases, notably with fistulation in an open abdomen, this involves a delay of 6 months or more after fistulation occurred.

Introduction

Acute intestinal failure has been recognized as a specific clinical entity for many years [1], and occurs when there is a potentially reversible cause (Table 1). In surgical patients acute intestinal failure is usually associated with enterocutaneous fistulas, intestinal obstruction and ileus. In these circumstances, fluid and electrolyte absorption, as opposed to nutrient absorption, may be the principal clinical problem.

Most cases of acute intestinal failure are short lived, require artificial nutritional support for fewer than 14 days and are managed in non-specialized units. Although the incidence of acute intestinal failure in these circumstances is unknown, it is extremely common, and the vast majority of such cases present to and are managed in non-specialized units. When an epidemiological assessment is restricted to those cases in which referral to a specialist intestinal failure unit is made for the management of severe acute intestinal failure, the annual incidence of intestinal failure requiring specialist treatment is slightly in excess of 5.5 new patients per million population [2]. This figure may be an underestimate of the true incidence of acute intestinal failure associated with intestinal fistula, complex metabolic derangement or postoperative abdominal sepsis, as many of these cases are managed with difficulty in non-specialist centres.

Table 1 Causes of acute intestinal failure. Adapted from Pettigrew and Hill 1984 [16]

When the gastrointestinal tract is 'blocked'
Mechanical obstruction
Paralytic ileus
Intestinal pseudo-obstruction
When the intestinal tract is too short
Massive resection
Internal or external fistulas
When the intestinal tract is inflamed
Inflammatory bowel disease
Severe infective enteritis
Radiotherapy
Chemotherapy
When the gastrointestinal tract fails to function adequately for other reasons
Intra-abdominal sepsis
Multiple organ failure
Acute pancreatitis

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Table 2 Criteria for referring patients with acute intestinal failure to a specialist unit

Persistent intestinal failure beyond 6 weeks complicated by venous access problems
Multiple fistulas within a totally dehisced abdominal wound
Total or near total (<30 cm remaining) enterectomy
Recurrent venous access problems due to sepsis or thrombosis
Persistent severe abdominal sepsis
Persistent nutritional or metabolic problems associated with a high output stoma or fistula
Any patient with an intestinal fistula beyond the expertise of the referring hospital

In the UK, future estimates of the true incidence of severe acute intestinal failure are likely to become more accurate following the development of specialized integrated intestinal failure centres for the management of patients (Table 2).

Small Bowel Obstruction

Small bowel obstruction is usually short-lived and, in most patients, will only cause type 1 intestinal failure. It is one of the most common causes of emergency surgery presentations and admissions and is mostly managed in non-specialized units [3], with only a small proportion of patients transitioning into type 2 intestinal failure and requiring more specialist input.

Acute bowel obstruction occurs due to interruption to the antegrade flow of intestinal contents; the most common cause of small bowel obstruction in industrialised countries is postoperative adhesions (70%), followed by malignancy, inflammatory bowel disease, and hernias. Malignancy and volvulus are the commonest causes of large bowel obstruction [3].

The management of acute small bowel obstruction is well established and encompasses early contrast-enhanced cross-sectional imaging, with early consultant-led multidisciplinary decision-making regarding surgery (and a possible role for enteric water-soluble contrast agents).

Although intestinal failure caused by (adhesional) small bowel obstruction is usually type 1 and therefore short-lived, 2 recent reports on the assessment and management of (small) bowel obstruction in the United Kingdom and Ireland have highlighted the relatively low levels of early nutritional assessment and intervention in this patient category, with poor nutritional status at admission being an independent predictor of reduced survival after presentation with small bowel obstruction [3, 4]. In particular, patients not undergoing immediate surgery to address small bowel obstruction were less likely to receive parenteral nutritional support [4].

In a minority of patients, small bowel obstruction either recurs early after surgery, persists despite intervention, or cannot be operated on immediately and requires an elective operation. In these cases, ongoing intestinal decompression alongside active nutritional intervention is necessary; this may be achieved by insertion of a venting gastrostomy/jejunostomy or, rarely, a long-term nasogastric tube. Venting gastrostomy/jejunostomy placement is typically achieved either endoscopically (PEG or PEJ) or, for gastrostomies, by interventional radiology (RIG); however, specifically in patients with ongoing small bowel obstruction, percutaneous access to the stomach or small bowel may be hindered by the presence of dilated loops of small bowel interposed between the anterior abdominal wall and stomach or jejunum. In these instances, a long-term indwelling nasogastric tube may be the only means of achieving and maintaining adequate decompression, but this should obviously not be considered a permanent solution.

The above demonstrates that surgical intestinal failure, whether type 1 or type 2 (the focus of the remainder of this chapter), is a serious condition, associated with high rates of mortality, and early nutritional assessment and intervention is warranted in all such patients.

Aetiology and Pathogenesis

Acute intestinal failure occurs as a consequence of conditions which primarily or secondarily affect the gastrointestinal tract (Table 1). Within a specialized intestinal failure unit, the most common underlying condition responsible for intestinal failure is Crohn's disease (Fig. 1), and the principal

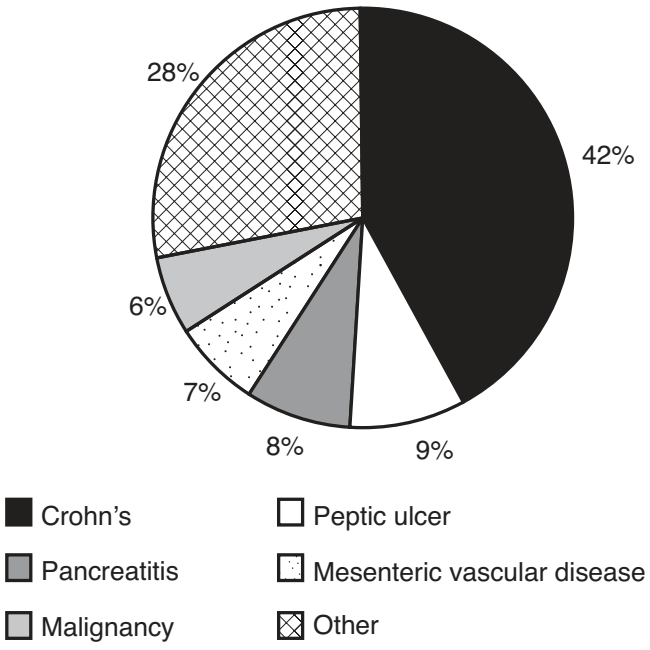


Fig. 1 Aetiology of acute intestinal failure in a specialized unit. (Adapted from Scott et al. [2])

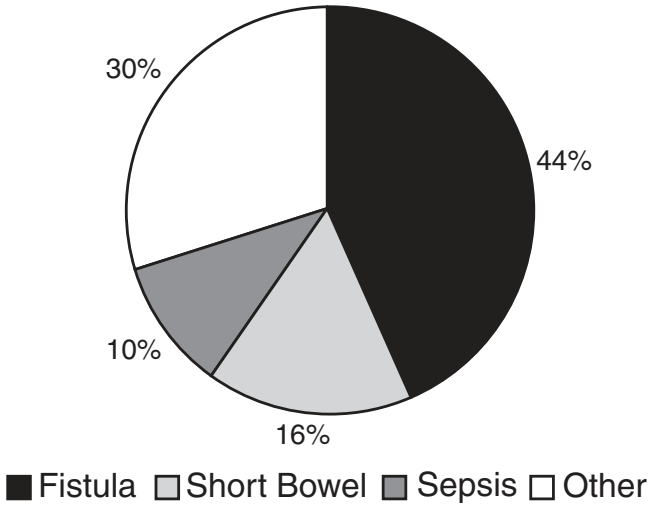


Fig. 2 Clinical problems leading to acute intestinal failure. (Adapted from Scott et al. [2])

reason for acute intestinal failure is the development of an intestinal fistula (Fig. 2). This population of patients is very different to that seen in most hospitals, because the majority of cases (62%) referred to specialized units will require surgical treatment [2].

Intestinal Fistulas

A fistula is defined as an abnormal communication between two epithelialized surfaces. A fistula communicating with a hollow viscus is called an internal fistula and one communicating with the skin an external fistula. In some cases, notably when a fistula has developed within an open abdomen, there is said to be an "enteroatmospheric fistula". A fistula can be single or complicated. An intestinal fistula is said to have a high output if more than 500 ml is produced in 24 h [5].

In non-Crohn's patients enterocutaneous fistulas most commonly develop as a postoperative complication from either partial breakdown of an intestinal anastomosis or inadvertent bowel injury (Table 3). Death from enterocutaneous fistulas is most commonly due to sepsis (>80% of deaths); other causes of death include electrolyte imbalance (e.g. due to high fistula outputs), undernutrition, massive bleeding or progression of the underlying disease. Spontaneous closure of a fistula may occur within 6 weeks of its first appearance in up to 50% of patients. This tends to occur only in postoperative fistulation. Table 4 lists some of the factors that make spontaneous closure unlikely. In the vast majority of such cases a fistula will fail to heal because there is mucocutaneous continuity, distal obstruction or disease at the fistula site. Although there is little published evidence, the chance of spontaneous closure of a fistula may also be reduced if a patient is undernourished, septic (as indicated by a low serum albumin or transferrin) or has another systemic problem (e.g. cardiac, respiratory, renal or hepatic failure).

Table 3 Aetiology & pathogenesis of enterocutaneous fistula

Surgery
Anastomotic leak
Abdominal closure
Serosal tear
Obstruction / Stricture (adhesions)
Peri-operative management
Abdominal sepsis
Smoking
Poor glucose control
Low albumin
Excessive fluid resuscitation
Disease
Crohn's
Malignancy
Diverticula(s)
Irradiation damage

Table 4 Factors indicating an enterocutaneous fistula is unlikely to close spontaneously

Distal bowel obstruction
Diseased bowel at the fistula site (e.g. Crohn's, irradiation or malignancy)
Discontinuity of the bowel ends
Active disease, foreign body or continuing sepsis/abscess at the site of the fistula
Mucocutaneous continuity (i.e. bowel mucosa is visible on the surface of the abdomen)
Short fistula track
Multiple (complicated) fistulas

The pathogenesis of acute intestinal failure is often multifactorial and complex. For example, many patients with an intestinal fistula also have an intra-abdominal abscess. In some cases, an intestinal fistula may have developed as a consequence of impaired anastomotic healing because the anastomosis was constructed within a pre-existing abscess cavity (typically in Crohn's disease) or in a patient with established sepsis.

Management

The initial priorities in the management of the patient with acute intestinal failure are the correction of electrolytes and hydration, the detection and management of sepsis, wound management and pain control (Table 5).

It is important to note that the management of sepsis is of overwhelming importance because inadequately treated sepsis is the most common cause of death in patients with complicated acute intestinal failure. In the management of intestinal fistulas, control of sepsis has been shown to be the major determinant of successful outcome [6].

Table 5 Principles of managing acute intestinal failure

Immediate (minutes-hours)	Early (1–2 days)	Late (2–12 weeks)
Resuscitation including water/electrolyte (Na^+, Mg^{2+}) balance	Nutrition	Anatomy—mapping – fistula—site/drainage – proximal + distal gut – length/quality – presence and nature of abdominal wall defect
Treat sepsis	Reduce stoma/fistula output	Procedure—this should preferably be carefully planned and may need to be deferred for at least 6 months
Wound management	Psychosocial	Treatment of underlying disease
Pain control	Mobility	

Diagnosis and Management of Acute Intestinal Failure

Acute intestinal failure is a complex condition requiring a truly multidisciplinary management strategy. Various useful algorithms have been suggested for the different components of such strategies, of which SNAP (Sepsis management, Nutritional optimisation, Anatomical mapping, Planning of surgery) is the most popular. It was devised to resemble the ABC of trauma resuscitation, listing the most serious issues in order of importance. Regardless of the mnemonic employed, the management strategy for patients with acute intestinal and concomitant abdominal wall failure should always address the management of sepsis, wound care, nutritional support and optimisation (including the management of high fistula/stoma outputs), intestinal mapping, prehabilitation and surgical planning.

Intravenous correction of electrolytes and hydration is an immediate and potentially life-saving priority for these patients. Ongoing control of hypotonic fluid intake is usually required for high output fistulas and stomas.

As stated above, the management of sepsis is of overwhelming importance because inadequately treated sepsis is the most common cause of death in patients with complicated acute intestinal failure (Table 6). In the management of intestinal fistulas, control of sepsis has been shown to be the major determinant of successful outcome [6].

Table 6 Principles causes of death in enterocutaneous fistula patients

Sepsis
Electrolyte imbalance
Bleeding
Undernutrition
Underlying disease

Diagnosis and Management of Abdominal Sepsis

There is evidence that intestinal function is impaired in sepsis, as a consequence of mucosal oedema [7], defective enterocyte maturation [8] and down-regulation of nutrient transporters [9]. When combined with the increased metabolic demand and impaired fuel utilization associated with sepsis [10], the presence of impaired intestinal function may lead rapidly to a state of cachexia not unlike that observed in advanced malignant disease [11]. In addition, nutritional support, however aggressive, is unlikely to be successful in the restoration of lean body mass in the presence of sepsis [12]. A major priority in managing the patient with acute intestinal failure is therefore to detect and eradicate sepsis. Other factors may also be of importance in the development or maintenance of acute intestinal failure, particularly in the setting of critical illness: changes in intestinal motility undoubtedly occur and although their aetiology is unclear, may cause difficulty with enteral feeding. In general, reduced intestinal motility is observed [13], possibly as a consequence of impaired absorption of fluid, altered nervous and regulatory peptide control of motility patterns [14], decreased intestinal blood flow [15], and bacterial colonization of the small intestine (which may itself develop as a consequence of impaired motility [16]). In addition, handling of the gut at surgical operation may result in ileus because of the development of an inflammatory response within the intestinal muscle [17]. Finally, other factors that may contribute to impaired motility are pulmonary and liver disease and centrally acting sedative and narcotic drugs [18]. The net effect of these changes, which may disturb gastric and colonic motility to a greater extent than small intestinal motility, is to cause abdominal distension, nausea and vomiting.

The diagnosis of sepsis should be entertained in any patient with a history of gastrointestinal surgery who is fail-

Table 7 Markers of hidden sepsis

1. Pyrexia (often absent in malnutrition)
2. Tachycardia
3. Raised inflammatory markers
• WBC, Platelets
• CRP
• Ferritin/B_{12}
4. Persistent hypoalbuminaemia
5. Abnormal liver function tests (jaundice)
6. Hyponatraemia
7. Low phosphate
8. Failure of muscle mass to increase with nutritional support

ing to make satisfactory progress (Table 7). Failure to respond to adequate nutritional support is a classical sign of sepsis. The classical picture of a high white cell count and high CRP may not be present but more subtle signs of raised platelets and low ferritin and B12 should be heeded. Although swinging pyrexia, leucocytosis and abdominal signs are classical features of sepsis, they are not invariably present, especially in malnourished patients. Hypoalbuminaemia, hyponatraemia, hypophosphataemia or unexplained jaundice may be more subtle signs of abdominal sepsis and should lead to a careful search for a septic focus. In some cases this may prove to be within the chest or urinary tract or may relate to central venous lines but the abdomen should be suspected whenever abdominal surgery has been performed.

Whilst ultrasound may be of value in the detection of subphrenic or pelvic collections this may be difficult to perform in the presence of large abdominal wounds, stomas and drains [19]. A plain chest radiography may show elevation of the diaphragm and basal collapse with a 'sympathetic' pleural effusion indicative of a subphrenic abscess.

Computed tomography (CT) is, in general, the most effective imaging modality (Fig. 3) and, if combined with oral contrast, will distinguish intra-abdominal or pelvic abscesses from immotile, fluid-filled loops of bowel [20, 21]. The diagnostic accuracy of CT scanning in abdominal sepsis is of the order of 97%.

Especially when intestinal failure first becomes apparent, patients may be profoundly septic. The compulsion to "jump in" in an attempt to surgically address the underlying issue (especially in case of iatrogenic intestinal failure) may lead to further enteric injury and loss of intestinal mass. Every attempt should be made to manage sepsis with a combination of antimicrobial treatment and targeted percutaneous (radiological) drainage procedures, with due consideration given to targeted and careful surgical drainage procedures for clinically significant collections not amenable to radiological drainage [5].

Once a focus of abdominal or pelvic sepsis has been diagnosed, prompt drainage is mandatory. Antibiotic therapy may be of value in the management of patients with sepsis

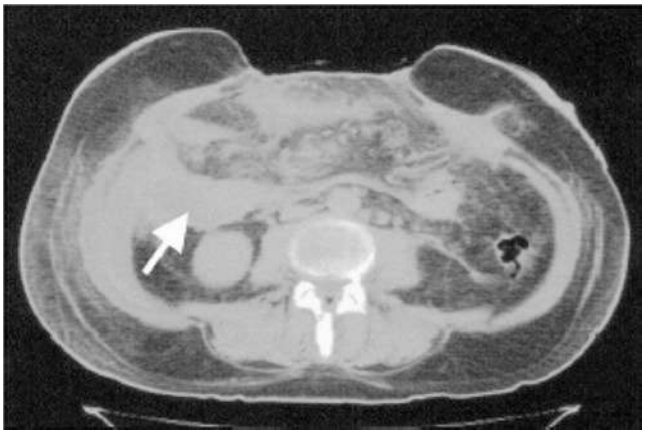


Fig. 3 CT scan showing intra-abdominal abscess (arrowed)

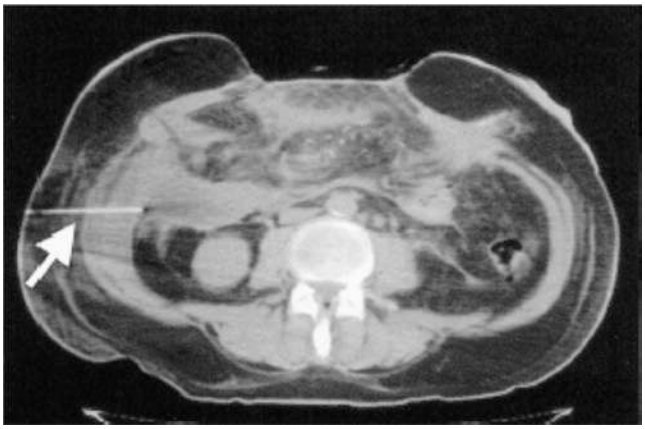


Fig. 4 CT scan showing percutaneous drainage (arrowed) of intra-abdominal abscess shown in Fig. 3

but it will not lead to the resolution of sepsis unless combined with treatment of the abscess cavity itself. Fortunately, it is increasingly possible to use percutaneous drainage of abscesses under radiological guidance because of improved imaging and drainage techniques. As abscess cavities enlarge, they tend to assume a globular shape and push neighbouring structures aside [21]. Large drains (8–10 F) can be inserted into abscess cavities under local anaesthetic (Fig. 4). Drains can also be upsized under local anaesthesia. If more than one drain is inserted simultaneously, the cavity can be irrigated regularly with saline to ensure adequate and prolonged drainage. Often, the drains are kept in place and a contrast study performed through one of them to ensure that the abscess cavity has collapsed prior to drain removal.

Increased size of percutaneous drains and the ability to insert multiple drains and irrigate means that the need for surgical exploration has markedly reduced.

However, in some cases, percutaneous drainage of abscesses is likely to be ineffective. This is particularly likely where there is discontinuity between the bowel ends, or a CT

scan has shown multiple interloop abscesses, and where the pus is of particularly thick consistency (for example in infected pancreatic necrosis). In such cases surgical exploration may be required, especially if sepsis persists or deteriorates. Intestinal manipulation should be kept to a minimum and the surgical exploration should be aimed at drainage and, in some cases, exteriorization of the proximal bowel.

Where intra-abdominal contamination is severe and sepsis continues, with further collections of infected fluid, or where the underlying focus of sepsis cannot be removed (for example in necrotizing pancreatitis), further attempts to deal with sepsis are necessary. A variety of approaches have been advocated, including radical peritoneal debridement [22], and continuous postoperative peritoneal lavage [23], neither of which has been shown to be effective. Other options include repeated laparotomies, either on demand or as planned procedures. Controlled trials of repeated planned laparotomy for severe abdominal sepsis have not shown that it improves survival and the therapeutic value of each successive operation diminishes with an associated risk of intestinal injury, leading to secondary intestinal fistula formation [24–26].

An alternative approach in such cases is to leave the abdomen open and fashion a laparostomy. As discussed in more detail in the "Abdominal Wall Repair in Intestinal Failure" chapter, although laparostomies have a role in damage control settings (primarily trauma and mesenteric ischemia), they are to be avoided in other settings [27–29]. Moreover, if the abdomen is left open at the index operation, there must be a definitive plan to achieve delayed primary fascial closure [29]. The open abdomen is fistulogenic; moreover, laparostomies create a significant problem for the future with the formation of a giant incisional hernia, which is difficult to repair with good outcomes and low morbidity.

Although there are many strategies to avoid having to leave the abdomen open and/or to achieve delayed fascial closure, the technique of choice is that of mesh mediated fascial traction (MMFT) combined with negative pressure wound therapy (NPWT) [27–29], as described in more detail in the "Abdominal Wall Repair in Intestinal Failure" chapter.

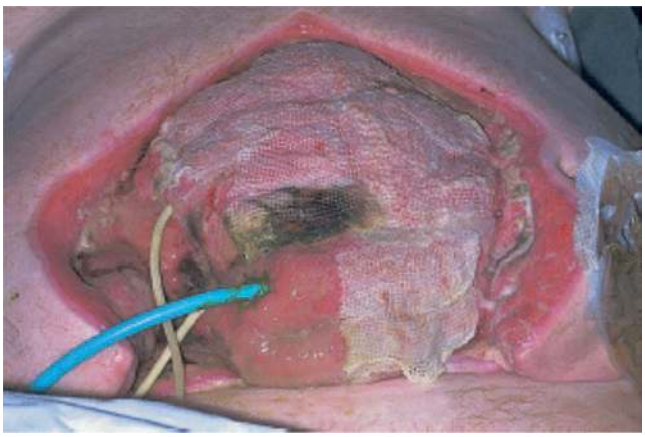


Fig. 5 Newly-created laparostomy wound

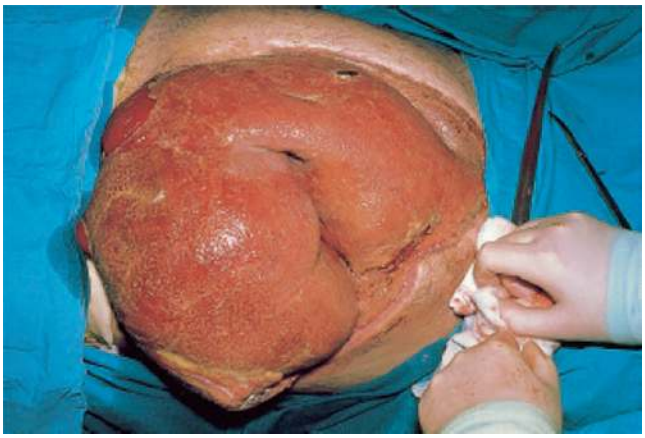


Fig. 6 Laparostomy wound after 6 weeks, showing viscera covered with dense granulation tissue

In the (hopefully rare) instances that an abdomen is left open, the laparostomy (Fig. 5) is allowed to heal by secondary intention and, initially, fistulating loops of bowel become fixed within a dense mass of granulation tissue (Fig. 6). Intestinal continuity can generally be safely established by a further laparotomy undertaken 6 months later when the peritoneal cavity has become re-established [30]; the best indication of this is prolapse of the fistulating bowel segments (Fig. 7) [5].

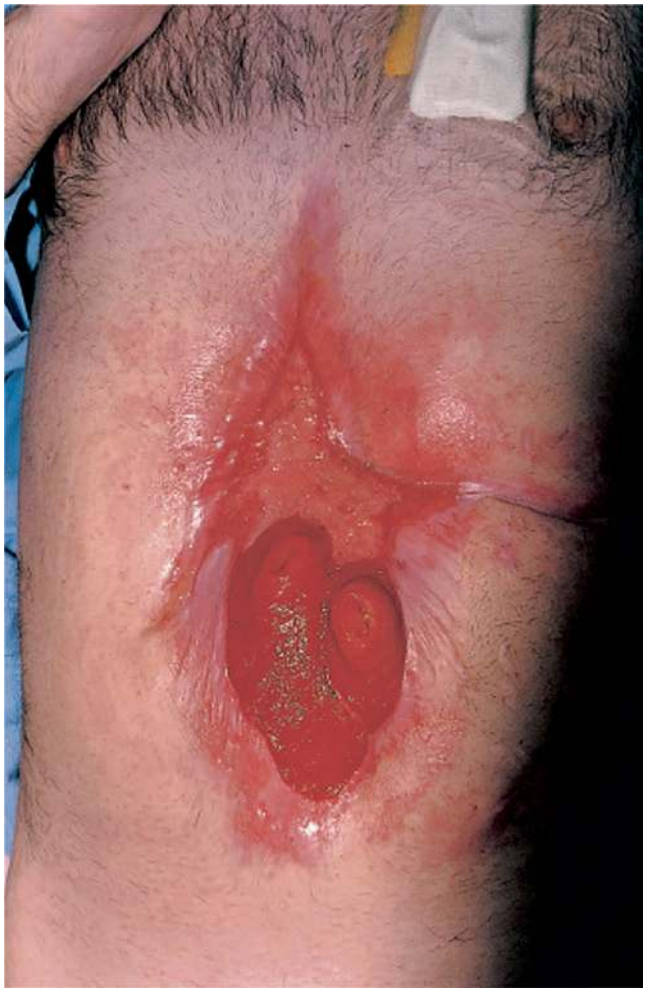


Fig. 7 Prolapse of a fistula within a completely healed laparostomy wound

Wound Care

In the presence of an intestinal fistula, maintenance of skin integrity is of major importance and should be considered at an early stage. The output of intestinal fistulas, particularly from the proximal gastrointestinal tract may be massive and if inadequately controlled, may cause widespread skin destruction. It is important therefore to involve a stoma nurse specialist in the care of such patients. Fortunately, a wide variety of stoma and fistula appliances are presently available (see Chapter "Care of intestinal stoma and enterocutaneous fistula(s)"). Large Eakin bags can be cut to suit the shape of the abdominal wall and, when combined with suction catheters and Stomahesive® paste, will control the vast majority of fistulas. In certain cases it may be almost impossible to adequately control the output of a fistula. This is, for example, likely to be the case where a high output fistula has developed in the base of a deep or an irregularly shaped wound or in a large area of granulation tissue. Improved stoma care products including fistula isolation may be employed to avoid repeated leakages. In some cases, it may be necessary to undertake a limited surgical exploration, simply to exteriorize a loop stoma proximal to the fistula. A period with a well-fashioned high output proximal loop stoma is usually preferable to an unmanageable fistula.

Intestinal failure is often accompanied by abdominal wall failure which, especially in the presence of enteric fistulas, poses significant challenges to patients, family and nursing staff. Mortality is especially high in patients who fistulate within an open abdomen (enteroatmospheric fistulas), particularly because of the difficulties in controlling abdominal sepsis. The development and application of a custom-made wound management system (traditionally by tissue viability and stoma care nurses) is an often laborious and time-intensive process, but crucial to avoid further wound breakdown and ongoing low-grade sepsis in the abdominal wall.

Nutritional Support and Optimisation

Early nutritional intervention in these often catabolic patients is essential in order to prevent and mitigate further deconditioning and encourage wound healing as well as increase the likelihood of spontaneous closure of enteric fistulae and increase the success rate of further major surgical procedures whilst limiting the associated morbidity. Although a substantial proportion of patients will require parenteral nutritional support, efforts should be made to explore the possibilities of enteral feeding, supplemented by enteroclysis/fistuloclysis ("distal limb feeding") [5, 31].

High stoma and fistula outputs should be assessed in the context of the patient's intestinal anatomy and any intra-abdominal sepsis. Once the latter has been sufficiently addressed, management of the high output state should focus on addressing not just the volumes, but also the nature of oral intake and include the use of antimotility and antisecretory medication (Table 8) (see Chapter "Management of a high output stoma, jejunotomy or uncomplicated enterocutaneous fistula").

In general, the aim of nutritional support in the patient with acute intestinal failure is to provide at least basal requirements of energy and nitrogen until normal diet can be tolerated. Nutritional intervention should be considered whenever [32]:

- Starvation for longer than 5 days is expected or has occurred, whether as a result of impaired intake or gastrointestinal disease.
- The underlying disease has led to an increase in nutritional requirements beyond that which can be provided by a 'normal diet'.
- Nutritional depletion already existed prior to the onset of acute gastrointestinal failure.

Table 8 Therapy to reduce a stoma/fistula output

Drink little hypotonic fluid (up to 1 L/24 h)		
Drink a glucose-saline solution (sodium 90–120 mmol/L, up to 1 L/24 h)		
Drug therapy	– antimotility	– loperamide up to 40 mg qds
		– codeine phosphate up to 60 mg qds
	– antisecretory	– omeprazole 40 mg bd (titrate so stomal pH >5)
		– occasionally octreotide 50 μgm bd
Magnesium correction		– oral magnesium aspartate or oxide, or topical magnesium chloride
		– hexahydrate spray
		– 1 alpha cholecalciferol
Nutrition		– low fibre/residue diet

The vast majority of patients with acute intestinal failure will require nutritional support. In many cases with a short-lived period of intestinal failure (e.g. ileus), this will only be necessary until intestinal function has returned to normal. However, in patients with severe acute intestinal failure associated, for example, with a proximal intestinal fistula, nutritional support is likely to be required until the fistula has closed spontaneously or until optimal conditions for surgery to close the fistula have been achieved. In the case of the patient with a combination of a fistula and an open abdomen, this may take more than 6 months and under these circumstances it may be appropriate, in an otherwise fit individual with satisfactory home circumstances, to discharge the patient with a suitable regimen of artificial feeding, pending definitive surgery. The decision regarding the optimal route of nutritional support (enteral versus parenteral) depends on the developmental "stage" of a given enterocutaneous fistula and the length of proximal small bowel (Fig. 8).

In general, the presence of a complex fistula with an associated cavity is usually a contraindication to enteral feeding, and successful enteral feeding requires an adequate length of healthy bowel above the fistula track without an associated abscess.

There is some anecdotal evidence to suggest that, in patients who are well nourished, the time to maturation of a fistula track is relatively short, whereas in patients who are already undernourished, the process of maturation can be much slower.

There is some evidence that administration of proximal enteral feedings even in the presence of a high output distal enterocutaneous fistula is of no harm and may help enhance fistula closure [33].

Especially in patients with a degree of intestinal obstruction/stricturing distal to the fistula, a low fibre enteral support option would be appropriate. In patients without distal obstruction, serious consideration should be given to the possibility of distal limb feeding by enteroclysis/fistuloclysis [5, 31].

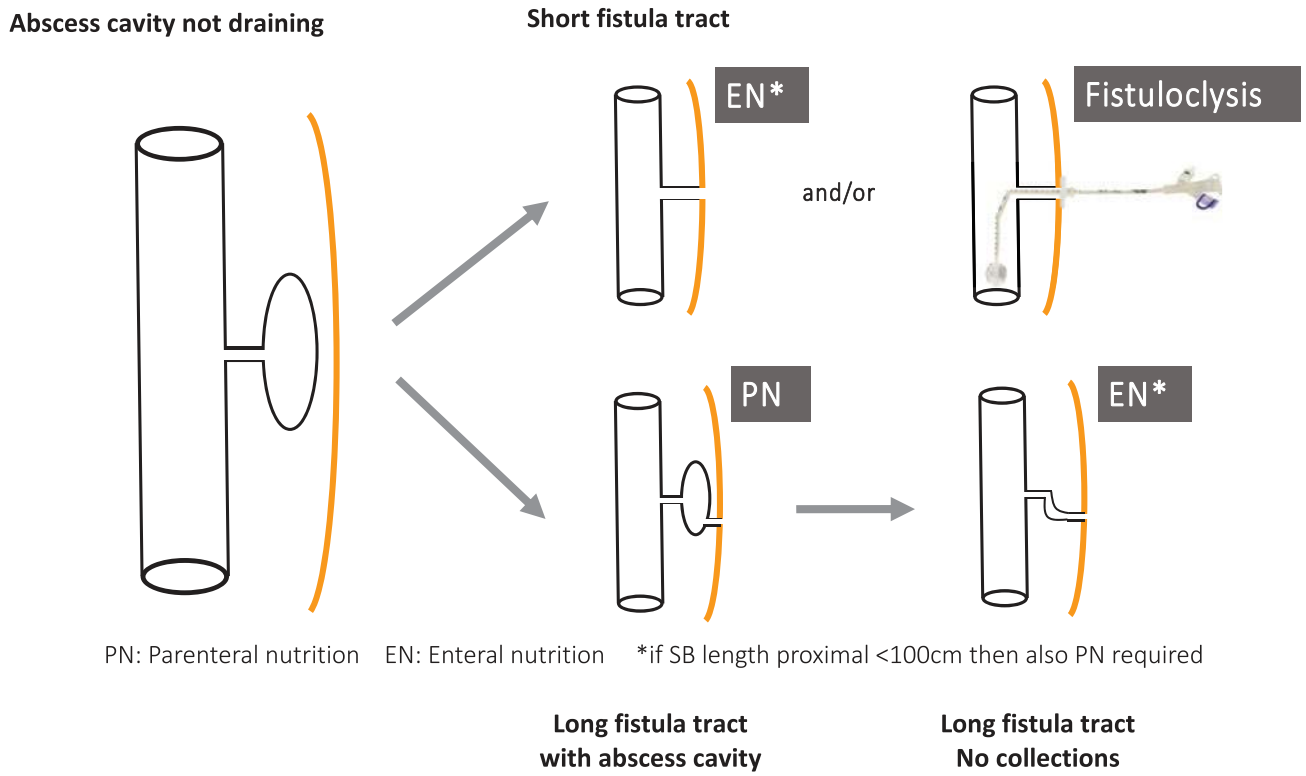
The decision regarding optimal route of nutritional support also depends on the length of small bowel still in circuit. Although this can be more accurately assessed on contrast-enhanced cross-sectional imaging, the aspect (colour and consistency) of fistula effluent often provides clues as to the length of upstream small bowel and the preferred route of nutrition.

In patients with an estimated small bowel length of <50 cm upstream of a fistula, parenteral nutrition will be necessary to ensure adequate nutritional support; in patients with >100 cm, enteral support may be sufficient, although this may need to be supplemented by intravenous fluid/electrolyte supplementation.

Therefore, the traditional treatment of enterocutaneous fistulas of almost exclusive TPN + NBM may no longer be appropriate in a substantial proportion of patients; in the early stages of fistulation, TPN may be appropriate but may be replaced by enteral nutrition once a fistula track has become firmly established.

Enteral Nutrition

As a general principle, the enteral route should be used for nutritional support whenever possible. Enteral feeding is safer, more physiological, may preserve intestinal mucosal integrity and is certainly far less expensive than parenteral nutrition. There is no evidence to suggest that enteral nutrition is inferior to parenteral nutrition in the maintenance of nutritional status or in allowing the spontaneous closure of enterocutaneous fistulas, provided enteral feed can be delivered to healthy intestine [33]. In acute intestinal failure, however, enteral feeding may be impractical or inappropriate. Although postoperative 'ileus' generally affects predominantly the stomach and colon, rather than the small intestine, the resulting abdominal distension may cause intolerance of enteral feeding, with nausea and vomiting. One study of aggressive early postoperative enteral feeding after upper gastrointestinal surgery has suggested that the resulting abdominal distension may lead to respiratory impairment [34]. Nevertheless, successful enteral feeding has been achieved early in the postoperative period [35]. A combination of nasoenteric tube, prokinetic drugs and thoracic epidural analgesia (allowing the avoidance of opiates) may make enteral nutrition easier to tolerate [36, 37], and studies have also indicated that enteral feeding may even be safe and effective in acute pancreatitis [38]. Enteral nutrition may prove satisfactory in patients with a low output distal ileal or colonic fistula but is inappropriate when there is obstruction



Note there is often a stricture of the bowel just distal to the fistula site. Image kindly provided by Dr Simon Gabe (St Mark's Hospital) redrawn from Dr Jeremy Nightingale lecture slide.

Fig. 8 Development of enterocutaneous fistulas and consequences for nutrition. (Note there is often a stricture of the bowel just distal to the fistula site. Image kindly provided by Dr. Simon Gabe (St Mark's Hospital) redrawn from Dr. Jeremy Nightingale lecture slide)

or a fistula of the upper gastrointestinal tract, unless access can be gained to the gut below the diseased segment.

As stated, consideration should be given to "using" the distal, out of circuit bowel for nutritional support as well as to prevent mucosal atrophy [5, 31]. Distal feeding, either with enteral feed alone or by chyme reinfusion, requires specialist nursing and dietetic input, as well as quite an effort on the part of the patient; however, preliminary data shows that the defunctioned gut, once distally fed, changes its metabolome and microbiome to that of healthy, in-circuit intestine. Limited data also suggests that, in selected patients with enough small bowel in situ distal to a proximal fistula, distal feeding might reduce the dependence on parenteral nutrition [39].

Parenteral Nutrition

For the majority of patients with acute intestinal failure, parenteral nutrition will be the preferred modality of nutritional support. This may either be because of the presence of disease of the intestine, which precludes satisfactory enteral nutrition, an inability to tolerate enteral nutrition or altered nutritional requirements such as those associated with severe sepsis or injury.

If the anticipated period of nutritional support is fewer than 14 days, parenteral nutrition can be provided safely via a peripheral vein. However, the ability to provide TPN for prolonged periods via the peripheral route is limited by the development, in many cases, of thrombophlebitis [40]. This can be minimized by the use of lipid-containing regimens (which have a lower osmolality than glucose-based regimens and are therefore less irritant to venous endothelium) [41], by adding heparin and hydrocortisone to the feed and by the application of nitrate patches to promote venodilatation at the feeding site [42]. While standard intravenous cannulae can be used, purpose-designed peripheral feeding lines, which are of extremely small calibre and made of inert polyurethane are available and have been used with success [41, 43]. Despite these manoeuvres it may not be possible to administer more than 3 L of TPN without phlebitis because of the flow rates required in small veins. Central venous TPN is therefore recommended in patients with large fluid requirements or acutely ill adult patients, who may have

energy requirements greater than 2000 kcal/day. Central venous TPN is also necessary where it is evident that a prolonged period of parenteral feeding is likely to be required. For expected relatively short periods of TPN (months rather than years), peripherally inserted central venous catheters (PICCs) may be used, whilst for patients requiring prolonged (years rather than months) TPN, true central vascular access (e.g. Hickmann or Broviac catheters) will be more appropriate [44].

The ability to manage complex cases of acute intestinal failure associated with abdominal sepsis or fistulas is, to a very considerable extent, dependent upon the ability to provide complication-free parenteral nutrition. Irrespective of the route chosen for venous access, a strict aseptic technique is essential. The lines used for nutritional support should be set aside for this purpose alone and maintained by dedicated nursing teams according to a strict aseptic protocol. It has clearly been established that under these conditions, catheter-related sepsis rates are negligible [2].

Intestinal Mapping

The anatomy of the digestive tract and abdominal wall is almost always significantly disrupted in patients with acute intestinal failure. These changes will often affect decisions regarding nutritional support, the likelihood of spontaneous fistula closure and, ultimately, the proposed strategy for definitive surgical procedures. Crucial information regarding the current anatomy of the digestive tract may often be gained by meticulous perusal of operative records; this will also often yield valuable information on what, if any, attempts were made at abdominal wall closure, whether prosthetic mesh was used, and, if so, in which plane and position. Further mapping of the intestinal anatomy is based on imaging; in most centres, the mainstay of this mapping is a CT of the abdomen and pelvis with intravenous and positive oral contrast (supplemented with arterial phase scans for patients with a history of mesenteric ischemia). In addition, contrast-enhanced studies of those sections of the digestive tract which are out of circuit and not amenable to oral contrast enhancement, are often warranted, especially to assess the patency and length of distal bowel when distal limb feeding is being considered and to rule out any distal obstruction which might need to be addressed prior to or during definitive surgical management; these modalities include loopograms, tubograms and fistulograms. In Crohn's disease, full restaging of the disease (both of the small bowel and the colorectum) should be considered. Intravenous urography, endoscopic retrograde cholangiopancreatography, CT-mesenteric angiography and other mapping modalities may also be required, depending upon the anatomy of the fistula.

Taken together, the information gathered from these various sources forms a comprehensive map of the patient's anatomy which can be used to guide further management and optimisation, as well as to enable adequate planning of the definitive surgical procedure(s). Most clinicians have found it helpful to amalgamate all the information from different sources and schematically represent these in one single anatomical diagram, which has been useful for other healthcare professionals involved in the care of the patient, in determining the challenges to enteral nutrition and to inform patients about their own anatomy and what further surgery would involve. It has also proved useful in planning surgical procedures. Figure 9 below provides an example of this schematic representation of the anatomy of a patient who, after undergoing an abdominoperineal excision of rectum, underwent a repeat laparotomy due to stoma necrosis and full thickness dehiscence; his abdominal wall defect was bridged with an absorbable mesh and unfortunately, he developed multiple enterocutaneous fistulae (ECFs). A CT of the abdomen and pelvis with intravenous and positive oral contrast was performed, followed by a series of fistulograms to assess the segments of small bowel between the various ECFs as well as the distal small bowel, and a water-soluble contrast enema study via his end colostomy to assess the colon.

A similar approach can be used to document postoperative anatomy, where surgery has deliberately led to temporary intestinal failure and temporary enteroclysis is being considered, as well as to guide further targeted imaging, etc. An example of this is provided in Fig. 10 below, showing the anatomy of a patient who had previously undergoing a partial jejunal resection en bloc with the splenic flexure, an ileocolic resection with a double barreled ileocolostomy and more recently underwent resection of a fistulating ileal Crohn's phlegmon; during this procedure he underwent restoration of continuity of his ileocolostomy as well as his left-sided colon, defunctioned by exteriorising his ileal resection limbs as a double barreled stoma.

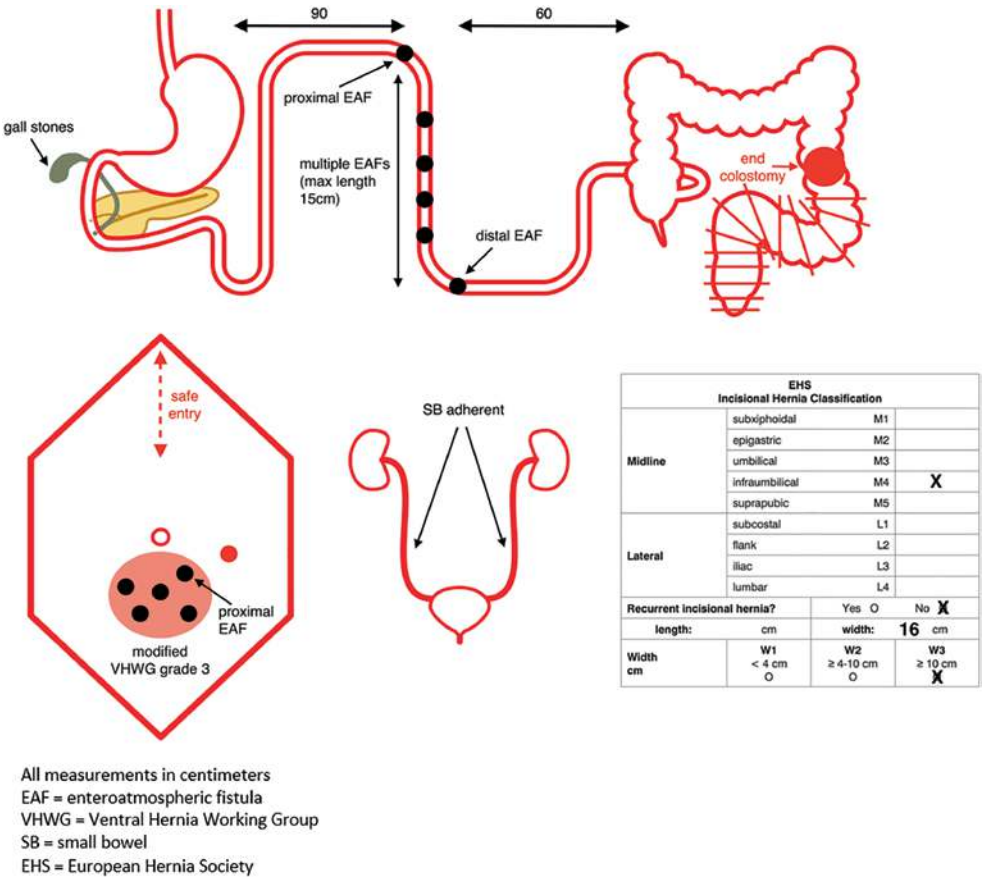


Fig. 9 Diagram to show mapping of a patient with multiple enterocutaneous fistulas

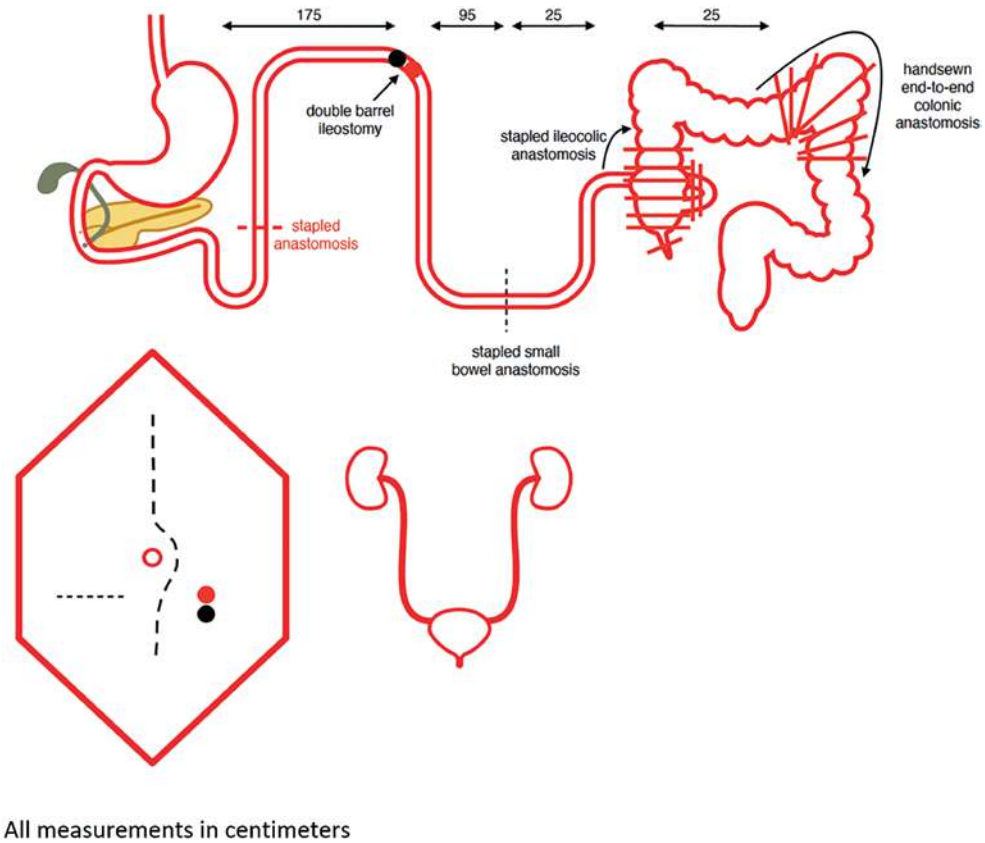


Fig. 10 Diagram to show mapping of a patient with double barrel (loop) ileostomy

Prehabilitation

Prehabilitation encompasses all of the aforementioned considerations regarding nutrition and wound care, but goes beyond these principles in formulating a pathway (quite often personalised) to enable the team and the patient to work towards their common goal of offering the patient a definitive procedure with the highest possible chance of success with the lowest possible risk of complications. Although individualised, basic components of such a prehabilitation "programme" should include the following:

- Exercise and cardiovascular fitness.
- Smoking cessation.
- Nutritional assessment and optimisation including micronutrient status and consideration of distal limb feeding (also as a trial of integrity of downstream bowel over and above radiology).
- Controlled weight loss (ideally to a BMI of less than 30).
- Acceptable diabetic control (measured by HbA1C levels with a cut-off point frequently agreed at 7.3% or 56.3 mmol/mol).
- Anaemia and iron status correction.
- Psychological well-being and preparation, expectation management, shared decision making on priorities and what the patient considers a good outcome.
- Assessment of superficial abdominal lipocutaneous tissues if significant weight loss from when catabolic and what to do with pannus.
- Analgesics and opiate weaning preop to provide headroom for perioperative analgesia.

Definitive Treatment

Once sepsis has been excluded or eradicated and nutritional and metabolic support initiated, the management of acute intestinal failure is directed at the underlying cause. Clearly, definitive treatment will depend upon the exact cause of intestinal failure. In many cases, the cause will be self-limiting (for example in paralytic ileus, severe infective diarrhoea or uncomplicated acute pancreatitis) and recovery can be expected.

Aggressive medical therapy may be required to deal with the underlying cause in some cases (e.g. high-dose steroid therapy for Crohn's disease, or anticoagulation for patients who have sustained a mesenteric vascular occlusion because of thrombophilia). Patients who have undergone resections due to mesenteric ischemia on a background of thrombo-occlusive vascular disease may need to be considered for arterial revascularization prior to restoration of intestinal continuity. Specialist (endo)vascular input into the MDT is essential for this relatively small but highly complex group of IF patients.

Attempts should be made to alleviate any obstructions/strictures distal to a fistula. For example, a patient with an enterocutaneous fistula proximal to a strictured ileostomy will benefit from either stoma dilatation or a stoma revision (via a local approach), even if just as a temporizing measure to mitigate fistula output.

Many fistulas (possibly up to 60%) will close spontaneously within 4–6 weeks of supportive treatment. One major intestinal failure unit has reported 46.4% spontaneous closure rate with conservative management alone after a median follow-up of nearly 2 years, with borderline significant difference in fistula closure rates between low versus high output fistulas (58.8% vs. 18.2%, respectively) [45]. In addition, epithelialization of the track negatively affects fistula healing; long fistula tracks epithelialize slowly and therefore have a greater chance of healing. The range for closure is estimated 3–90 days and, although closure can still occur beyond 90 days, the chances of this are quite small.

Medical Therapy for Enterocutaneous Fistula(s)

The role of medical agents in promoting fistula closure is controversial. Somatostatin was discovered in 1972 and is a naturally occurring peptide hormone. It has an inhibitory effect on gastrointestinal secretion. It is used in the management of upper gastrointestinal hemorrhage, secretory diarrhea, dumping syndrome, and peptide-secreting neuro endocrine tumors because of its antisecretory action. As the plasma half-life is 1 to 2 min, it must be administered by continuous intravenous infusion. Somatostatin reduces the secretion of a range of gastrointestinal hormones, including gastrin and cholecystokinin, which in turn reduce gastric and pancreatic secretions. In addition, somatostatin reduces splanchnic blood flow, reduces the rate of gastric emptying, and inhibits gallbladder contraction. As a result of the short half-life, a number of synthetic analogues have been developed, and of these, octreotide is used most commonly in the treatment of gastrointestinal fistula. Its significantly longer half-life allows it to be given by intermittent subcutaneous injection (usually 3 times daily). Despite the similarities, the receptor binding properties of somatostatin and octreotide are not identical and their actions may not be equivalent. Somatostatin receptors comprise a family of 5 heptahelical membrane proteins encoded by 5 related genes that map to separate chromosomes. The clinically used somatostatin analogues, octreotide and lanreotide, act mainly by binding to somatostatin receptors 2 and 5 and this may contribute to a comparatively less effective outcome (Fig. 11).

Fig. 11 Somatostatin receptors subtypes and affinity of somatostatin and octreotide for each

	Receptor subtype				
	SSTR 1	*SSTR 2*	*SSTR 3*	*SSTR 4*	*SSTR 5*
Somatostatin-14	++	++	++	++	++
Octreotide	–	++	+	–	++

+ +, high affinity; +, moderate affinity; –, does not bind

The evidence regarding the role of somatostatin and its analogues in non-pancreatic intestinal fistulas is conflicting and inconclusive at best. Although several small, uncontrolled trials suggest that octreotide (a somatostatin-analogue) may reduce fistula output and decrease the time to fistula closure, the expected effect on fistula closure rate with somatostatin and its analogues is small, and the effect on more distal fistula outputs is not well established [46, 47]. Although a meta-analysis did show favourable outcomes with use of somatostatin and analogues in the treatment of enterocutaneous fistulas, the studies included in the meta-analysis were small, with wide variability in study design and patient characteristics. On balance, it seems unlikely that octreotide will help fistula closure where local factors are in favour of continued fistula patency, however, and, in addition, the use of octreotide is not supported by the findings of more carefully designed randomized trials which have failed to show evidence of benefit [48–50]. The European Society of Coloproctology consensus statement on the surgical management of intestinal failure in adults does not support the routine use of somatostatin and its analogues in patients with enterocutaneous fistulas [5].

Other non-surgical strategies aimed at closure of enterocutaneous fistulas have been developed and reported, with varying degrees of success. Percutaneous catheter management of abscess-fistula complexes and fistula tracks has been reported to lead to fistula closure in 57–100% of patients, although it is unclear what the criteria for this treatment were and how many of these fistulas would have closed spontaneously without any intervention. Fistula track embolization has been reported utilizing a wide range of substances, including fibrin glue, synthetic glues, and biological plugs. None of these has been studied in a controlled fashion and many have been reported in the successful closure of low-output fistulas, where spontaneous closure may have been reasonably expected without any intervention.

Definitive surgical treatment for acute intestinal failure attributable to intestinal fistulas will be required if spontaneous fistula closure does not occur. Internal fistulas will not, in general, close spontaneously. External gastrointestinal fistulas are unlikely to close spontaneously if the factors outlined in Table 4 are present.

Table 9 The risk of mortality and ECF recurrence associated with reconstructive surgery relative to the last laparotomy

	Early	3–12 weeks	6–12 months	>12 months
Mortality	30–100%	7–20%	3–9%	0–3%
ECF recurrence	40–60%	17–31%	10–14%	3%

Patients who are referred to a specialized unit for management have usually selected themselves by virtue of the underlying pathology or failure of spontaneous fistula closure. The exact nature of surgery required will depend upon the anatomy and aetiology of the fistula but the general principles are as follows: attempts to deal definitively with the fistula should not be made until the patient is well, free from sepsis and adequately nourished. Surgical intervention should be planned and is usually delayed. In the case of IF associated with ECF, early operative intervention to close the fistula is contraindicated by the associated high mortality due to re-fistulisation, sepsis, malnutrition and difficulties with fluid balance [51].

Delaying surgery for 6–12 months after the last operation has been shown to reduce both the mortality and fistula recurrence rates at subsequent definitive surgery (Table 9) [45, 52–54].

It is desirable to leave at least 6 months between the previous laparotomy and definitive surgical treatment to allow for softening of adhesions within the abdomen. This may necessitate discharging the patient on home parenteral nutrition. Re-operative surgery of this nature is extremely technically demanding and adequate amounts of time should be set aside. Sharp, rather than blunt dissection is required to avoid tearing the bowel at the site of adhesions and segments of bowel with fistulas should be resected rather than bypassed. Intestinal anastomosis should only be attempted if the patient is free from sepsis, well-nourished and local conditions are entirely favourable. It is particularly important to avoid leaving an anastomosis within an old abscess cavity as this will inevitably lead to re-fistulation. In patients with a jejunostomy and an intact colon, consideration should be given to intestinal re-anastomosis, even if it will not prevent the need for long-term parenteral nutrition. Once intestinal continuity

is restored the additional absorptive area of the colon may reduce fluid and electrolyte requirements and thus the frequency and/or volume of TPN required. Diarrhoea is often surprisingly easy to control with loperamide, codeine phosphate and/or cholestyramine.

Outcome of Treatment for Acute Intestinal Failure

Acute intestinal failure varies widely in nature, from transient postoperative ileus after major abdominal surgery, to life-threatening abdominal sepsis with multiple intestinal fistulas. Generalized statements about outcome are therefore unlikely to be helpful. Prior to the antibiotic era and the use of nutritional support, the mortality associated with the development of an enterocutaneous fistula was in excess of 60%, with many patients succumbing to the combined effects of sepsis and undernutrition [55]. Prior to the advent of safe parenteral nutrition [56], it proved impossible to maintain nutritional status in patients who had undergone massive enterectomy, and death inevitably resulted from progressive inanition.

The prognosis for patients with even the most complex manifestations of acute intestinal failure has improved considerably over the last three decades, as a result of improvements in surgical technique, intensive care medicine, antimicrobial chemotherapy, stoma/skin care and nutritional support. The principle factors which now adversely affect outcome are sepsis (which if severe is still associated with a mortality in excess of 30%), co-morbidity and underlying disease. A large prospective study of 300 admissions with intestinal failure to a specialized unit over a 7-year period recorded a mortality rate of 13%. The major adverse prognostic factors on admission were increasing age and hypoalbuminaemia, the latter indicative of severe sepsis. The healthcare costs associated with the management of patients with complicated acute intestinal failure have not been published but may be considerably in excess of £60,000 per consultant episode in the UK and it is appropriate that expertise be concentrated in a small number of specialized units. The multifaceted nature of the problems faced by patients with acute intestinal failure makes a team approach to management mandatory and it is important to note that nurses, dieticians, pharmacists and physiotherapists are all essential, in addition to medical practitioners, for a successful outcome [5, 57].

References

1. Fleming CR, Remington M. Intestinal Failure. In: Hill GL, editor. Nutrition and the Surgical Patient. Edinburg: Churchill Livingstone; 1981. p. 219–35.
2. Scott NA, Leinhardt D, O'Hanrahan T, et al. Spectrum of intestinal failure in a specialised unit. Lancet. 1991;337:471–3.
3. The National Confidential Enquiry into Patient Outcome and Death. Delay in Transit. 2020. London.
4. Lee MJ, Sayers AE, Drake TM, et al. National prospective cohort study of the burden of acute small bowel obstruction. BJS Open. 2019;3:354–66.
5. Vaizey CJ, Maeda Y, Barbosa E, et al. European Society of Coloproctology consensus on the surgical management of intestinal failure in adults. Color Dis. 2016;18:535–48.
6. Soeters PB, Ebeid AM, Fischer JE. Review of 404 patients with gastrointestinal fistulas. Impact of parenteral nutrition. Ann Surg. 1979;190:189–202.
7. Hersch M, Gnidec AA, Bersten AD, et al. Histologic and ultrastructural changes in nonpulmonary organs during early hyperdynamic sepsis. Surgery. 1990;107:397–410.
8. Rafferty JF, Noguchi Y, Fischer JE, Hasselgren P-O. Sepsis in rats stimulates cellular proliferation in the mucosa of the small intestine. Gastroenterology. 1994;107:121–7.
9. Gardiner K, Barbul A. Review: Intestinal Amino Acid Absorption During Sepsis. J Parenter Enter Nutr. 1993;17:277–83.
10. Little RA, Carlson G. Insulin resistance and tissue fuels. In: Kinney JM, Tucker HN, editors. Organ metabolism and nutrition: ideas for future critical care. New York: Raven Press; 1994. p. 49–68.
11. Carlson G, Irving MH. Infection, recognition and management in critically ill surgical patients. In: Hanson G, editor. Critical care of the surgical patient. London: Chapman & Hall; 1997. p. 273–90.
12. Streat SJ, Beddoe AH, Hill GL. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. J Trauma. 1987;27:262–6.
13. Dive A, Moulart M, Jonard P, Jamart J, Mahieu P. Gastroduodenal motility in mechanically ventilated critically ill patients. Crit Care Med. 1994;22:441–7.
14. Thompson JS. The intestinal response to critical illness. Am J Gastroenterol. 1995;90:190–200.
15. Dahn MS, Lange P, Lobdell K, et al. Splanchnic and total body oxygen consumption differences in septic and injured patients. Surgery. 1987;101:69–80.
16. Marshall JC, Christou NV, Meakins JL. The gastrointestinal tract. The "undrained abscess" of multiple organ failure. Ann Surg. 1993;218:111–9.
17. Kalff JC, Schraut WH, Simmons RL, Bauer AJ. Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. Ann Surg. 1998;228:652–63.
18. Schiller L. Drug-induced changes in bowel function. Contemp Gastroenterol. 1989;2:29–35.
19. Knochel JQ, Koehler PR, Lee TG, Welch DM. Diagnosis of abdominal abscesses with computed tomography, ultrasound, and 111In leukocyte scans. Radiology. 1980;137:425–32.
20. Gerzof SG, Johnson WC. Radiologic Aspects of Diagnosis and Treatment of Abdominal Abscesses. Surg Clin N Am. 1984;64:53–65.
21. Gerzof SG, Oates ME. Imaging Techniques for Infections in the Surgical Patient. Surg Clin N Am. 1988;68:147–65.

22. Polk HC Jr, Fry DE. Radical peritoneal debridement for established peritonitis. The results of a prospective randomized clinical trial. Ann Surg. 1980;192:350–5.
23. Jennings WC, Wood DC, Guernsey JM. Continuous postoperative lavage in the treatment of peritoneal sepsis. Dis Colon Rectum. 1982;25:641–3.
24. Hau T. Planned Relaparotomy vs Relaparotomy on Demand in the Treatment of Intra-abdominal Infections. Arch Surg. 1995;130:1193.
25. Anderson ID, Fearon KCH, Grant IS. Laparotomy for abdominal sepsis in the critically ill. Br J Surg. 1996;83:535–9.
26. van Ruler O, Mahler CW, Boer KR, et al. Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis: a randomized trial. JAMA. 2007;298:865–72.
27. Atema JJ, Gans SL, Boermeester MA. Systematic review and meta-analysis of the open abdomen and temporary abdominal closure techniques in non-trauma patients. World J Surg. 2015;39:912–25.
28. Lopez-Cano M, Garcia-Alamino JM, Antoniou SA, et al. EHS clinical guidelines on the management of the abdominal wall in the context of the open or burst abdomen. Hernia. 2018;22:921–39.
29. Miller AS, Boyce K, Box B, et al. The Association of Coloproctology of Great Britain and Ireland consensus guidelines in emergency colorectal surgery. Color Dis. 2021;23:476–547.
30. Scripcariu V, Carlson G, Bancewicz J, Irving MH, Scott NA. Reconstructive abdominal operations after laparostomy and multiple repeat laparotomies for severe intra-abdominal infection. Br J Surg. 1994;81:1475–8.
31. Teubner A, Morrison K, Ravishankar HR, et al. Fistuloclysis can successfully replace parenteral feeding in the nutritional support of patients with enterocutaneous fistula. Br J Surg. 2004;91:625–31.
32. Chandran VP, Sim AJ. Nutritional support in acute intestinal failure. Baillieres Clin Gastroenterol. 1991;5:841–60.
33. Voitk AJ, Echave V, Brown RA, Gurd FN. Use of Elemental Diet During the Adaptive Stage of Short Gut Syndrome. Gastroenterology. 1973;65:419–26.
34. Watters JM, Kirkpatrick SM, Norris SB, Shamji FM, Wells GA. Immediate postoperative enteral feeding results in impaired respiratory mechanics and decreased mobility. Ann Surg. 1997;226:369–80.
35. Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. Gut. 1996;39:833–5.
36. Kehlet H. Balanced analgesia: a prerequisite for optimal recovery. Br J Surg. 1998;85:3–4.
37. Kehlet H, Rung GW, Callesen T. Postoperative opioid analgesia: Time for a reconsideration? J Clin Anesth. 1996;8:441–5.
38. Windsor AC, Kanwar S, Li AG, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. Gut. 1998;42:431–5.
39. Coetzee E, Rahim Z, Boutall A, Goldberg P. Refeeding enteroclysis as an alternative to parenteral nutrition for enteric fistula. Color Dis. 2014;16:823–30.
40. May J, Murchan P, MacFie J, et al. Prospective study of the aetiology of infusion phlebitis and line failure during peripheral parenteral nutrition. Br J Surg. 1996;83:1091–4.
41. Williams N, Wales S, Irving MH. Prolonged peripheral parenteral nutrition with an ultrafine cannula and low-osmolality feed. Br J Surg. 1996;83:114–6.
42. Tighe MJ, Wong C, Martin IG, McMahon MJ. Do Heparin, Hydrocortisone, and Glyceryl Trinitrate Influence Thrombophlebitis During Full Intravenous Nutrition via a Peripheral Vein? J Parenter Enter Nutr. 1995;19:507–9.
43. Plusa SM, Horsman R, Kendall-Smith S, Webster N, Primrose JN. Fine-bore cannulas for peripheral intravenous nutrition: polyurethane or silicone? Ann R Coll Surg Engl. 1998;80:154–6.
44. Alhimyary A, Fernandez C, Picard M, et al. Safety and efficacy of total parenteral nutrition delivered via a peripherally inserted central venous catheter. Nutr Clin Pract. 1996;11:199–203.
45. Rahbour G, Gabe SM, Ullah MR, et al. Seven year experience of enterocutaneous fistula with univariate and multivariate analysis of factors associated with healing:development of a validated scoring system. Color Dis. 2013;15(9):1162–70. https://doi.org/10.1111/codi.12363:n/a-n/a.
46. Paran H, Neufeld D, Kaplan O, Klausner J, Freund U. Octreotide for treatment of postoperative alimentary tract fistulas. World J Surg. 1995;19:430–3.
47. Tassiopoulos AK, Baum G, Halverson JD. Small bowel fistulas. Surg Clin N Am. 1996;76:1175–81.
48. Carlson GL, Scott NA, Irving MH, et al. Somatostatin in gastroenterology More studies needed. BMJ. 1994;309:604.
49. Sancho JJ, di Costanzo J, Nubiola P, et al. Randomized double-blind placebo-controlled trial of early octreotide in patients with postoperative enterocutaneous fistula. Br J Surg. 1995;82:638–41.
50. Scott NA, Finnegan S, Irving MH. Octreotide and gastrointestinal fistulae. Digestion. 1990;45:66–71.
51. Chapman R, Foran R, Dunphy JE. Management of intestinal fistulas. Am J Surg. 1964;108:157–64.
52. Conter RL, Roof L, Roslyn JJ. Delayed reconstructive surgery for complex enterocutaneous fistulae. Am Surg. 1988;54:589–93.
53. Lynch AC, Delaney CP, Senagore AJ, et al. Clinical outcome and factors predictive of recurrence after enterocutaneous fistula surgery. Ann Surg. 2004;240:825–31.
54. Datta V, Engledow A, Chan S, et al. The Management of Enterocutaneous Fistula in a Regional Unit in the United Kingdom: A Prospective Study. Dis Colon Rectum. 2010;53:192–9.
55. Edmunds LH Jr, Williams GM, Welch CE. External fistulas arising from the gastro-intestinal tract. Ann Surg. 1960;152:445–71.
56. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Can intravenous feeding as the sole means of nutrition support growth in the child and restore weight loss in an adult? An affirmative answer. Ann Surg. 1969;169:974–84.
57. Irving M, White R, Tresadern J. Three years' experience with an intestinal failure unit. Ann R Coll Surg Engl. 1985;67:2–5.

Mesenteric Ischemia

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Key Points

1. Mesenteric ischaemia can be acute or chronic, non-occlusive (low-flow states, vasospasm) or occlusive (venous or arterial thrombosis or embolism), segmental or extensive.
2. In those less than 60 years old the aetiology is likely to be a haematological abnormality and in those older than 60 atherosclerosis or a cardiovascular abnormality.
3. An acute mesenteric ischemia is suspected from the history of sudden unremitting abdominal pain. Normal plasma lactate levels are observed in the early stage of mesenteric ischemia and cannot rule out the diagnosis. Contrast-enhanced computed tomography (CT) is the most definitive way of making the diagnosis and differentiating an arterial from venous infarction.
4. If an early diagnosis is made an attempt should be made to revascularize the gut, even before a resection for a definite infarction. However if advanced ischaemia there may be a severe reperfusion injury. Surgeon should aim to restore blood flow before doing a resection, except in the case of instable patients in whom emergent resection is indicated first
5. After the resection, secondary elective reanastomosis of remaining small bowel to ileum/colon reduces the need for parenteral support, increases survival and quality of life.
6. A specialized intestinal stroke center may improve the acute management of these patients allowing revascularization, preventing irreversible necrosis, and when a laparotomy is necessary reducing the amount of bowel that is resected.

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Introduction

Acute mesenteric ischemia (or intestinal ischemia) represents the most severe and the most challenging of digestive vascular disease. The progression to mesenteric infarction (or intestinal necrosis) is an irreversible complication potentially leading to a resection of a large amount of small intestinal and resulting in short bowel syndrome or death [1]. Thus, any intestinal ischemia should be recognized and treated at a reversible, early or chronic stage [2]. In the absence of validated and available biomarkers, the diagnosis requires a high degree of clinical suspicion and an urgent specific therapy with two linked objectives: saving the gut, to save the life of the patient [3]. Developed on the model of "stroke units", a new intensive care unit dedicated to the acute care of AMI offering expert multimodal and multidisciplinary 24/7 management has been implemented in Paris, France. The first results of this intestinal stroke center have shown high rates of survival without intestinal resection in most patients. In this chapter, the latest scientific and clinical knowledge on AMI as well as a treatment strategy will be presented.

Definition of Mesenteric Ischemia and Anatomy

Mesenteric ischemia is defined by (1) an intestinal injury, secondary to (2) a vascular insufficiency in the territory of the splanchnic vessels, in (3) the absence of an alternative

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diagnosis. The perfusion disorder can be acute or chronic, non-occlusive (low-flow states, vasospasm) or occlusive (venous or arterial thrombosis or embolism), segmental or extensive [1, 4].

The digestive tract vascularization is ensured by the three main arteries originating from the anterior face of the abdominal aorta (Fig. 1 and Table 1):

- the celiac artery (CA) which supplies the stomach, the duodenum, the first centimeters of the jejunumn, the bile ducts, the pancreas and the spleen;
- the superior mesenteric artery (SMA) which supplies the small bowel, the ileocecal valve and the right colon;
- the inferior mesenteric artery (IMA) which supplies the colon from the right angle to the upper rectum. The middle and lower rectums are supplied by the middle and lower rectal arteries, branches of the internal iliac arteries.

The topography of digestive ischemic lesions generally depends on the territories of vessel involved. Consequently, the distal occlusion of a branch of the SMA (embolism or vasculitis of small vessels, for instance) may lead to a segmental and focal ischemia, while a proximal thrombus is more likely to be complicated by extensive intestinal and right-side colon necrosis. Conversely, non-occlusive ischemia is more likely to present as multifocal ischemia, involving watershed areas of the GI tract with large superficial mucosal injuries rather than wall deep.

The GI tract arteries are terminal (straight vessels), perforating the digestive wall on the mesenteric edge, dividing into intramural arterioles penetrating through each villus up to its summit and connecting on a wide submucosal capillary network without constituting an arterial-venous shunt. These capillaries form intramural venules which run parallel to the arterioles, at the base of the villus. This micro-vascular network facilitates the diffusion of oxygen at the base of the villus and makes of the top of the villus the most sensitive area to ischemia. The villous venules merge into straight veins and empty into the mesenteric veins and the portal system. The right and left parts of the colon are vascularized by the superior and inferior mesenteric arteries, respectively. Left-side colon ischemia, which represents the most common type of digestive vascular injury, is generally mild, self-limited and the consequence of a transient decrease in microvascular blood flow from a non-occlusive (vasospasm) and/or drug-induced origin [5]. Instead, ischemia affecting the right colon is associated with a vascular lesion of the

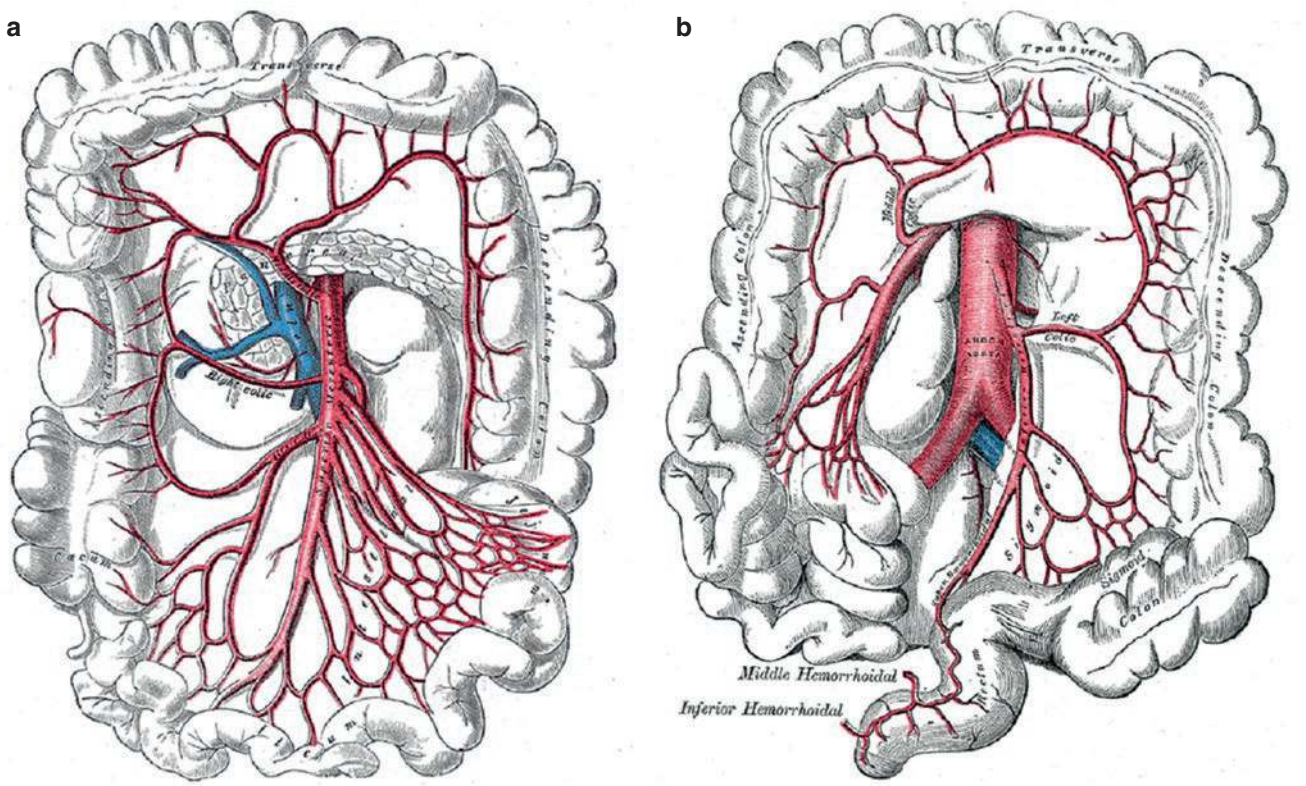

Fig. 1 Gastrointestinal tract arterial vascularization. (Source: Anatomy of the human body. 20th edition. Henry 1918). The superior mesenteric artery supplies the entire small bowel and the right side of the colon (**a**), whereas the left side of the colon is supplied by the inferior mesenteric artery (**b**)

Table 1 Intestinal injury location depending on the mechanism and the type of vascular insufficiency

Splanchnic vessel	Organ supplied	Intestinal injury location	
		Proximal occlusive ischemia *(ex: atherosclerotic thrombosis)*	Non-occlusive, or distal occlusive, ischemia *(ex: embolus, vasculitides)*
Celiac artery	Stomach, Duodenum, proximal jejunum, Gallbladder and bile ducts, Pancreas, Liver, Spleen	Gastric & duodenal or duodeno-jejunal ulcers, cholecystitis, pancreatitis, spleen infarcts	Gastro-intestinal segmental and multiterritory ischemia
Superior mesenteric artery and vein	Jejunum, ileum Right and traverse colon	Extensive small bowel and/or right-side colon ischemia	
Inferior mesenteric artery and vein	Left-side colon, upper rectum	Left-side colon ischemia with frequent rectum sparing	

SMA in 25% of patients and then should be considered as a segmental form of AMI [6].

Pathophysiology

Acute mesenteric ischemia (AMI) should be considered as one stage of a multistep process (Fig. 2) leading, from a digestive vascular insufficiency, to intestinal necrosis, organ failure and death. Ischemia begins early and superficially and then spreads in deep and surface of the intestinal wall. Vascular insufficiency is initially the trigger for an inadequacy between inputs and requirements for energy substrates by overcoming the adaptive processes of a digestive territory. This loss of homeostasis results from a sudden decrease or interruption of the splanchnic-mesenteric blood flow. The decrease in splanchnic blood flow in the proximal circulation induces a deep extension of the ischemia which then becomes transmural and gangrenous.

Conversely, when perfusion abnormalities relate to intraparietal arterioles, lesions of ischemia remain superficial. Intestinal vascular insufficiency leads to hypoxia, first with mucosal and submucosal consequences. The hypoperfusion of the intestinal mucosa is responsible for an early hypoxic cellular desquamation of the intestinal villi. Polymorphonuclear neutrophils are early major actors that adhere and migrate to the ischemic site to ensure the removal of tissue debris during necrosis. Mucosal and submucosal cells switch to anaerobic glycolysis with local production of lactate which initially is fully metabolized by the liver. The increase in intracellular acidosis blocks the anaerobic metabolism and the membrane pumps involved with ionic and acid-base regulation. This leads to a profound alteration of cellular homeostasis and, ultimately, to cell death by apoptosis [7–9].

Initially, there is a dissociation between high portomesenteric blood lactate levels and normal peripheral blood lactate levels due to the active liver metabolism [4]. Systemic lactic acidosis is, therefore, a late phenomenon, which often indicates intestinal necrosis and the onset of organ failures [10]. Associated endothelial lesions can lead to platelet, pro- and anti-thrombotic agents (protein C, S, and antithrombin) consumption that cause a hemorrhagic syndrome.

Furthermore, the intestinal neuro-hormonal regulation of vasomotricity is associated with the activation of the renin-angiotensin-aldosterone system, to try to maintain a mucosal oxygen extraction rate. This induces a reflex splanchnic arterial vasospasm, irrespective of the initial vascular mechanism, that may prolong and worsen ischemia despite the revascularization treatment. This vasoconstriction accompanies, for example, situations of hypovolemia, during which digestive ischemia develops before clinical hemodynamic instability [11, 12].

The disruption of the epithelial barrier resulting from mucosal alterations (Fig. 3) leads to interactions between microorganisms, bacterial antigens, endotoxins of the intestinal lumen and the mucosal and submucosal immune system. The stimulation of innate immunity will result in local then systemic inflammatory pathways activation such as TLR, NF-KB or TNF [13, 14]. Through the bloodstream, bacteria, endotoxins, cells degradation products and activated immune cells translocate and promote systemic inflammation response syndrome (SIRS). Cytokines, chemokines, cellular and bacterial debris can also reach the pulmonary circulation from the lymphatic circulation and thus cause acute respiratory distress syndromes [15, 16]. The translocation of bacteria and/or bacterial products into the mesenteric lymph nodes and/or bloodstream is reported in intestinal ischemia in up to 25–100% of experimental animal models. It further increases the SIRS making the ischemic small bowel an infection site [17]. The absence of a rapid recovery of a sufficient digestive perfusion leads to irreversible transmural necrosis with peritonitis. Without intestinal resection, the SIRS leads to multiple organ failure and death [16].

In the model of the "gut origin of sepsis", the gut was considered to be the 'motor' of multi-organ failure [11, 15, 16, 18]. Aside from its barrier function, the gut contains growth factors, adenosine, and hormones, which are potential mediators for the modulation of intestinal inflammation and repair, due to their roles in cellular proliferation, differentiation, migration, apoptosis, and autophagy [19–23]. Physiologically, the gut could initiate and propagate sepsis due to the ability of bacteria, endotoxins, and other antigens

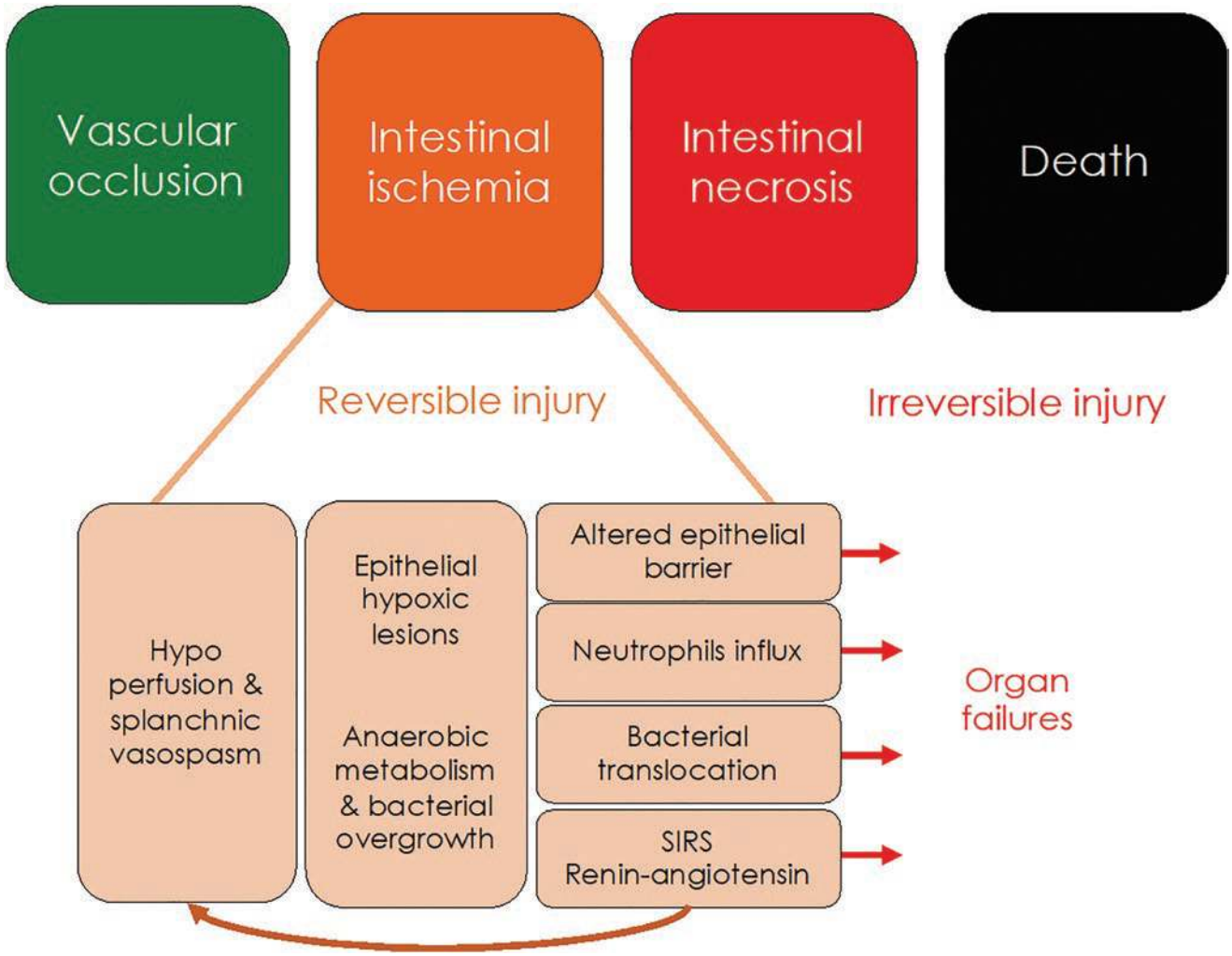

Fig. 2 Multistep pathophysiology of acute mesenteric ischemia. *Intestinal ischemia should be considered as the reversible stage of a pathophysiological multistep process leading to necrosis and death*

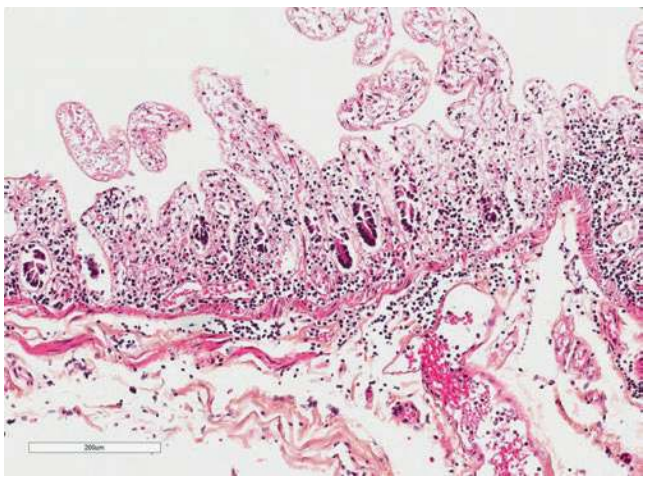

Fig. 3 Pathological analysis of acute ileal ischemia. *Acute ileal ischemia characterized grossly by congestive small bowel loops and superficial mucosal ischemia starting at the tip of the villi*

to translocate, along with the production of pro-inflammatory cytokines and toxins [11]. In The 'Three Hits Model' Deitch et al. added the phenomenon of reperfusion injury [24]. In the 'Gut-Lymph' theory, bacteria, cellular components, immune cells, cytokines and chemokines generated by the injured gut travel via the lymphatics to reach the pulmonary circulation, activating alveolar macrophages, and contributing to acute lung injury, acute respiratory distress syndrome and multi-organ failure related to AMI [15, 16, 25]. The systemic consequences of bowel ischemia and necrosis are lethal in most patients in the absence of curative treatment including revascularization [26, 27]. However, reoxygenation of the digestive mucosa can also paradoxically worsen epithelial and vascular lesions, due to an oxidative burst mechanism causing the influx and death of neutrophils with the formation of neutrophil extracellular traps and the secretion of their granular content [28].

Another mechanism of epithelial self-digestion would contribute to aggravate this alteration of the gut barrier function via proteolysis of tight enterocytic junctions by bilio-pancreatic secretory enzymes [22]. This quite recent concept describes the effect of pancreatic enzymes on the intestinal barrier altered by ischemia. Self-digestion contributes to the worsening of intestinal ischemic lesions and the development of the related systemic inflammatory response. Degradation products of pancreatic enzymes, residues of bacterial products pass through the lymphatic, hematogenous or peritoneal barrier and are likely to induce a loco-regional but also systemic reaction [20, 21]. In animal models, inhibition of these enzymes results in a decrease in intra-parietal micro-bleeding, in the systemic inflammatory response, and even in mortality in some studies [22]. The action of these enzymes would involve degradation of inter-enterocytic tight junction's proteins such as E-cadherin. Moreover, these enzymes would also induce a cleavage of the pro-metalloproteinases into active metalloproteinases [23].

Mesenteric vein thrombosis can be anterograde (primary occlusion of the straight veins, generally secondary to an enteritis or an intra-abdominal inflammatory process) or retrograde (primary occlusion of the portal vein, generally secondary to portal hypertension). In this context, the occurrence of intestinal ischemia may be more likely in case of the occlusion of second order radicles of the superior mesenteric vein and in the context of arterial insufficiency/associated arteriosclerosis [19]. Downstream the portal/mesenteric vein thrombosis, the hepatic consequences are weakly marked due to rapid compensatory mechanisms such as hepatic arterial vasodilation and the development of a cavernoma, visible as early as a few days after thrombosis.

Epidemiology

Incidence

Given that the clinical diagnosis of mesenteric ischemia is still a challenge, the incidence of digestive vascular diseases is still difficult to assess and then potentially largely underestimated. However, it is likely increasing due to an increase in the population at cardiovascular risk and improvements of its recognition by CT scanning [27].

Based on autopsy studies in Sweden, Acosta et al. estimated an incidence of 13/100,000 person-years between 1970 and 1982, when autopsy rate was 87% [29, 30]. In a US comprehensive database and population analysis in Maryland, Crawford et al. reported a statewide admission rate of 10/100,000 inhabitants per years during 2009–2013 [31]. These figures are consistent with epidemiological studies on chronic mesenteric ischemia with an estimated incidence of 9.2/100,000 inhabitants per years from a Dutch prospective database between 2014 and 2019 [32]. The incidence of arterial AMI increases exponentialy with age, with an incidence of 25/100,000 person-years after 70 years old, and a peak incidence of 217/100,000 person-years after 85 years-old [29, 30, 32].

Causes

Main causes of mesenteric ischemia can be classified according to the two main mechanisms of vascular insufficiency, often associated: (1) occlusive mesenteric ischemia (85%), due to atherosclerotic lesions, embolism or thrombosis, involving splanchnic artery (70%) and/or vein (15%), and (2) non-occlusive mesenteric ischemia (15%) caused by mesenteric vasospasm secondary to a systemic low flow or a vasoconstrictive drug. Each of these forms can occur on pathological vessels (atheroma, dissection, dysplasia, vasculitis) or on healthy vessels. In the latter case, the origin of the occlusion is often due to a systemic cause of thromboembolism (cardiogenic embolism, thrombophilia, myeloproliferative syndrome) and/or a regional risk factor (inflammatory or infectious intra-abdominal process or neoplasm, portal hypertension).

The main cause of arterial mesenteric ischemia is atherosclerosis. Although the prevalence of significant splanchnic arterial atheromatous stenosis in the general population is high (17 to 50%), most are asymptomatic [33]. In this setting, the incidence and predictive factors for the onset of mesenteric ischemia are unknown. Other causes of mesenteric arterial occlusion include embolism, vasculitides, infectious arteritis, fibromuscular dysplasia, median arcuate ligament syndrome, dissection and hypercoagulability [1, 4]. Their respective prevalence and incidence have not been precisely evaluated.

Causes of venous mesenteric ischemia include portal hypertension, intra-abdominal inflammatory processes (pancreatitis, inflammatory bowel disease, sepsis, trauma), malignancies, hematologic disorders, and thrombophilia.

Risk factors for non-occlusive mesenteric ischemia include vasoconstrictors (noradrenaline, cocaine (not uncommon in young adults)) and hypovolemia (sepsis, hypotension, dialytic depletion) [18, 34]. (Table 2) The knowledge on the risk factors of AMI might be incomplete given that half of patients, no prior cardiovascular or prothrombotic history is found [35]. As a result, AMI should be considered regardless of the patient's age and cardiovascular history.

Table 2 Main causes of mesenteric ischemia

Mesenteric ischemia		Causes et facteurs favorisants à rechercher
Occlusive	Vascular disease	– Atherosclerosis – thrombosis – Embolism (cardiogenic and arteriogenic) – Aneurysm, dissection – Fibromuscular dysplasia – Vasculitides, neuro-endocrin tumors, radiation enteritis – Vascular injury (endovascular or open vascular surgery, trauma, compression by a mesenteric malignancy)
	Hypercoagulability	– Intra-abdominal inflammatory process, cancer or surgery – Inherited thrombophilia (prothrombin gene mutation G20210A, favtor V Leiden, antithrombin, protein S and C deficiencies, increased factor VIII) – Hematological disorders (polycythhaemia, myelofibrosis, thrombocythemia, JAK2 V617F mutation, antiphospholipid antibodies, paroxysmal noctrunal haemoglobinuria) – Malignancies – Oral contraceptive, pregnancy, obesity – Portal hypertension, congestive heart failure – Other: CMV, nephrotic syndrome, SARS-COV-2 infection
Non-occlusive		– Low flow states (hypovolemia, shock, dialysis) – Extra-corporal life support, clamping in vascular surgery – Toxic/iatrogenic (cocaine, amphetamine, catecholamines) – Sickle cell disease, leukostasis – Heavy exercise (marathon runners) – Electrocution and burns

Prognosis

In a systematic review of 45 studies including 3692 patients, acute mesenteric ischemia (AMI) was consistently fatal without adequate treatment [26]. Despite treatment, mortality varied from 40% (venous ischemia) to more than 80% (arterial ischemia), the main prognostic factors being the precocity of the diagnosis and treatment, the occurrence of transmural necrosis, the mechanism of ischemia (venous vs arterial) and the age of the patient [36]. In the 2010s, our most recent results have shown that multimodal and multidisciplinary SURVI management made it possible to obtain a survival of 91%, without intestinal resection in 58% of cases, [4, 10] making AMI a potentially disease fully reversible at its early stage [2]. However, the late recognition of the diagnosis and intestinal necrosis, at the stages of peritonitis and multi-visceral failure, explain the mortality still reported today by other centers and the prevalence of short bowel syndrome in survivors [37].

Diagnosis of Mesenteric Ischemia

Clinical Suspicion

In the absence of a biomarker allowing a rapid non-invasive diagnosis, the clinician's only weapon remains his diagnostic suspicion and confirmation by the contrast-enhanced abdominal CT scan. At this stage, the time of onset of acute abdominal pain should be considered as the starting point for a countdown leading, without prompt and adequate treatment, to intestinal necrosis and death. Contrary to popular belief, most patients with AMI present to the emergency department at a potentially reversible, but still insufficiently recognized early stage. Indeed, 50% of patients present initially with no known cardiovascular history, without surgical abdomen, without organ failure and without elevation of plasma lactate [35, 38, 39].

The acute abdominal pain is constant, apart from the particular case of the intensive care patient receiving a sedation [1, 4]. Pain can be inaugural or succeed to symptoms of chronic mesenteric ischemia in 30% of patients, the diagnosis of which is most often overlooked [29, 35]. Pain is typically sudden ("vascular") or rapidly progressive, intense and requiring opioids, continuous and relentless, peri-umbilical or diffuse, and contrasts with an abdominal palpation initially falsely reassuring. It can be associated with vomiting (48%), diarrhea (31%), digestive hemorrhage (18%) and an inflammatory biological syndrome which, inconstant and/or too late have no diagnostic value [10, 39].

Biomarkers

While biologic abnormalities—such as leucocytosis or lactic acidosis – have been documented in patients with AMI, their performance to establish the early diagnosis is poor [40, 41]. Worse, in a cohort study, a delayed diagnosis was more likely when initial plasma lactate levels were <2 mmol/L suggesting that physicians might be misguided by unremarkable plasma lactate levels. The high complexity of the layered intestinal wall structure increases the diversity of the proteins and metabolites released in AMI. Their hepatic metabolism through the hepatic portal system results in substantial overlap with liver proteins and metabolites. These factors, along with the heterogeneity of the disease, explain why identifying clinically reliable biological early markers of

AMI has been unsuccessful so far [1, 4, 41]. Three blood biomarkers have gained attention over the past decades: citrulline, a marker of enterocyte function; I-FABP, a marker of enterocyte damage; and D-lactate, a marker of intestinal barrier dysfunction and microbial translocation [41–44]. As a result, these tests are increasingly used in basic and clinical research as indirect markers of an ischemic intestinal injury in a broad range of emergency clinical settings. However, their alleged diagnostic performances have only been assessed in small heterogeneous cohorts. Besides, conflicting results have been reported, and most of the studies consist of preoperative data in late-stage necrotic AMI patients [45]. Early diagnosis remains a critical clinical and research challenge as it would allow early management and consequently improve the dire prognosis of AMI. To meet this challenge, relevant new biomarkers may be identified using non-targeted multi-omics discovery approaches in large cohorts of early-stage AMI patients admitted in dedicated units.

Diagnostic Imaging

The cornerstone of the diagnosis is contrast-enhanced computed tomography (CT). Its excellent reported sensitivity and specificity [46] suggest that it may be used as the first-line imaging technique. However, lower sensitivities were reported when the CT scan was performed during both arterial and venous phases (83%) or venous phase only (72%) [35], or when in the real-life setting, the clinical suspicion was not always mentioned to the radiologist, [47] resulting in either an inappropriate IV contrast protocol and/or an analysis that did not focus on the mesenteric vessels [48]. Finally, the unenhanced CT scan should be avoided because it does not detect signs of AMI, causing a significant delay in diagnosis [35]. A recent study focused on the impact of contrast-enhanced multidetector CT on the survival in patients with acute superior mesenteric artery occlusion; in-hospitality mortality rate was 42% for patients who underwent contrast-enhanced multidetector CT, *versus* 71% for patients not examined with CT [48]. As a result, CT should be performed as quickly as possible after the onset of symptoms in all patients, and include contrast-enhanced images to visualize both mesenteric vessels and digestive structures, including in the presence of renal insufficiency, the risk of overlooking an AMI greatly exceeding that of the injection of the contrast agent [1, 4, 49, 50].

CT plays a double role in patients with AMI. First, diagnosis is reached based on the combination of two sets of features that parallel the pathophysiology of the disease: 1/ vascular insufficiency, and 2/ ischemic intestinal injury. Second, CT should help identify negative prognostic factors, suggestive of extensive necrosis, or complications which will guide the treatment of revascularization, [51] and the indication for digestive surgery [10].

Vascular Imaging Findings

Intra-luminal defects or occlusions of the mesenteric vessels are highly specific for the diagnosis (94–100%), but reported sensitivity is rather low (12–15%) [52]. Yet, in our experience, vascular anomalies are encountered in more than 75% of patients. In occlusive forms of AMI, CT allows visualization of the site of the vascular obstruction and helps distinguish emboli from thrombosis. It also depicts other vascular anomalies such as calcified or non-calcified plaques, or rare dissections. In non-occlusive mesenteric ischemia, CT may show narrowed veins, flattened inferior vena cava [53], diffuse irregularities or stenoses of the SMA and SMA branches, and poor visualization of intestinal arcades and intramural vessels [54], as described by Siegelman et al. with angiography [55].

Bowel Imaging Findings

Numerous findings associated with intestinal ischemic injury, including bowel wall thickening or thinning, spontaneous wall hyper-attenuation on unenhanced CT acquisition, decreased or absent bowel wall enhancement, bowel dilatation, pneumatosis intestinalis and portal venous gas, peritoneal fat stranding and ascites. These features are often associated, and bear different prognostic value [49] (Fig. 4).

Prognostic Value of CT

CT helps distinguish early from late forms of AMI by depicting imaging features of necrosis or complications. (Fig. 4) From this perspective, radiologists should not only recognize bowel ischemia on CT, but also differentiate it from bowel necrosis that requires surgical resection. Free intraperitoneal gas is the only pathognomonic finding of bowel perforation, and therefore of wall necrosis in patients with AMI [56]. Yet, it is a delayed feature, and patients need to be diagnosed and treated before this occurs. Another important finding is pneumatosis intestinalis. Importantly, pneumatosis intestinalis may occur in ischemic bowel segments that have not yet undergone transmural infarction. Duron et al. found that 47% of patients with AMI showing pneumatosis still had viable bowel, with only partial mural ischemia without transmural infarction on surgical or pathological analysis [57]. Patients with associated porto-mesenteric venous gas are more likely to have transmural infarction than those with pneumatosis intestinalis alone. In AMI of arterial origin, bowel dilatation and decreased wall enhancement have been shown to be more frequent in cases of bowel necrosis [10]. A recent prospective study from our group identified both features in univariate analysis, with necrosis in 68% of cases when bowel wall enhancement was decreased, and in 64%

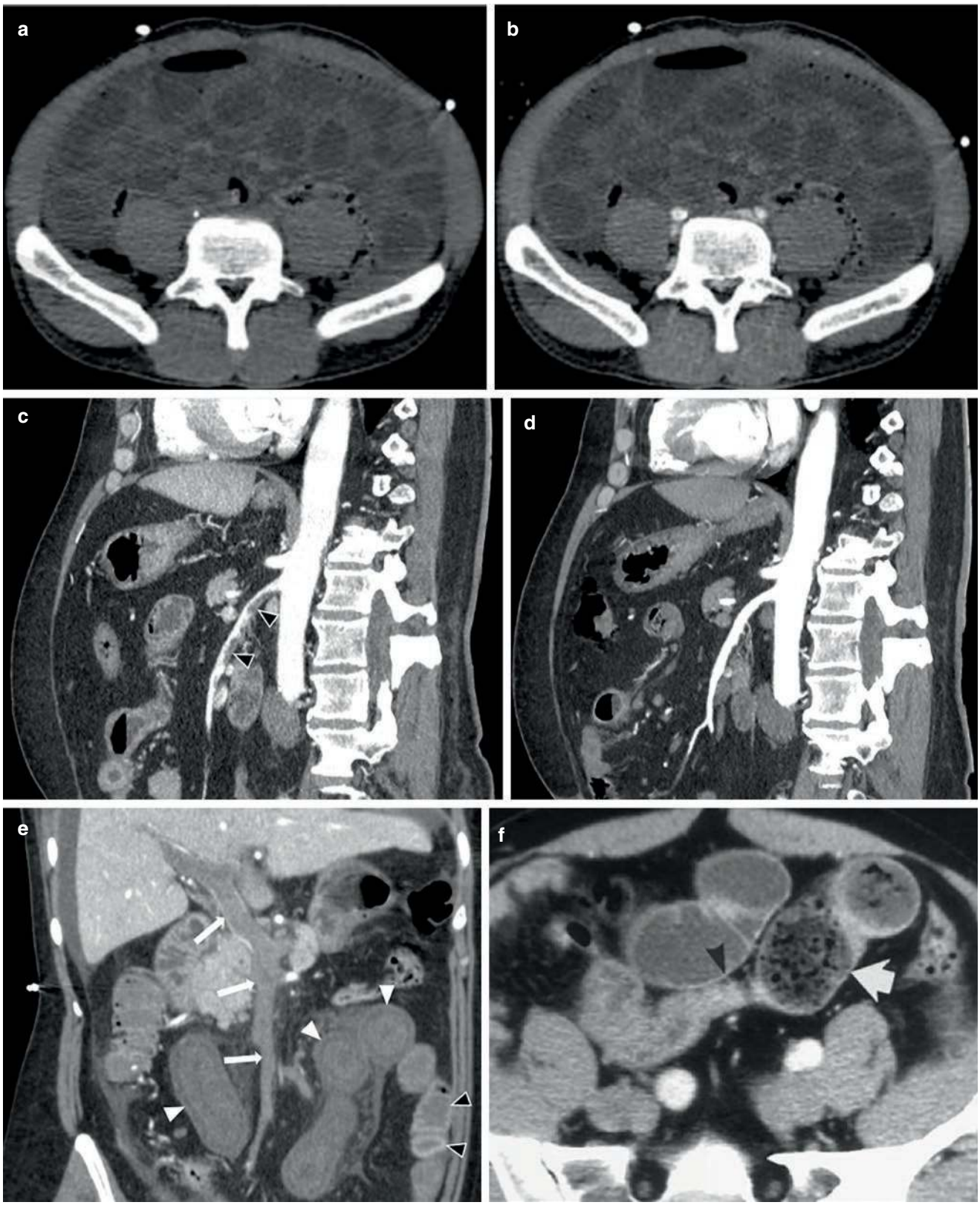

Fig. 4 The contrast-enhanced abdominal CT-scan: the cornerstone of the diagnosis. (**a** and **b**): Axial view, (**a**) showing a spontaneous hyperdensity of the intestinal wall at the non-contrast time, not to mistake with wall enhancement (**b**) unchanged after contrast injection. (**c** and **d**) Sagittal view, arterial phase, 90% stenosis by thrombi of the superior mesenteric artery (black arrows) before (**c**) and after intra-arterial thrombolysis (**d**). (**e** and **f**) CT-signs of transmural intestinal necrosis. (**e**) Axial view, venous phase, porto-mesenteric extensive thrombosis (arrows) with small bowel dilatation and decreased wall enhancement of the proximal jejunum (white arrowheads) when compared to normal ileum (black arrowheads). (**f**) Sagittal view, venous phase, small bowel dilatation and feces sign (arrows)

when bowel loops were dilated. Only bowel dilatation was significant in multivariate analysis [10].

Treatment of Acute Mesenteric Ischemia

Management in Dedicated Stroke Units

In the 2010s, our unit showed that a multimodal and multidisciplinary management of AMI, focused on preserving intestinal viability in a specialized intestinal stroke center, could decrease the rate of intestinal resection, as well as improve short- and long-term survival [58]. These results demonstrated that intestinal ischemic injury during AMI is potentially reversible, and that intestinal necrosis could be considered an unwanted outcome and a late complication [2, 10]. Following these results, in 2016, a 8-bed dedicated intestinal stroke unit was created at Beaujon Hospital, Paris University, France, that provides 24/7 standardized multimodal and multidisciplinary care to AMI patients referred from all hospitals in the Paris area.

Preventing the progression from reversible to irreversible intestinal ischemic injury should be a primary goal in the management of AMI. Indeed, in our experience mortality goes from 2% in early AMI to 35% when intestinal ischemia is treated at the stage of irreversible necrosis [59]. The treatment strategy developed in our intestinal stroke unit simultaneously follows three main objectives: (Fig. 5).

1. Prevent worsening, SIRS and organ failure by a specific medical protocol for intestinal ischemia (Table 3);
2. Preserve the non-necrotic intestine by systematic revascularization;
3. Resect intestinal necrosis according to a non-invasive risk score (Fig. 5), before its complications (perforation, peritonitis).

This multidisciplinary emergency strategy is coordinated by a gastroenterologist and requires a structure with available 24-h revascularization and intestinal resection, in an intensive care environment and in collaboration with an intestinal failure unit. A specific medical protocol targeting each step of the pathophysiological process of intestinal ischemia is administered upon diagnostic confirmation, regardless of the mechanism and form of the AMI. Systematic administration of oral antibiotics yielded a protective effect against transmural intestinal necrosis (HR = 0.16, 95% CI: 0.03–0.62, $p = 0.01$) [59]. Oral antibiotics may prevent intestinal necrosis by (1) decreasing the luminal bacterial load which interacts with the intestinal innate immune system through the disrupted epithelial barrier, (2) limiting local and systemic inflammation which results from bacterial interaction/translocation, and (3) improving their luminal bioavailability in the context of vascular occlusion or low flow. Given the life-threatening risk of translocation in AMI, most experts recommend early and widespread use of antibiotics consistent with our experience [1, 36, 60, 61].

The effectiveness of the treatment is judged on the disappearance of the pain. Any persistent digestive clinical symptom (pain, food intolerance, hemorrhage, persistence of a failure) should suspect for residual ischemia. Exclusive parenteral nutrition is offered until the ischemia is relieved, especially when there is pre-existing undernutrition or a short bowel syndrome. Although a Chinese study suggests that enteral nutrition should be systematically considered, many biases inherent in the retrospective and univariate nature of the analysis limit its interpretation [62]. In practice, oral and / or enteral feeding should be resumed gradually only after joint disappearance of pain and biological inflammatory syndrome.

In the particular case of non-occlusive ischemia, the therapeutic priority is to restore and maintain sufficient splanchnic hemodynamics by treating the cause of hypoperfusion (hypovolemia, sepsis, heart failure, hemorrhage), by preferring fluids to the use of catecholamines (Figs. 5 and 6). Despite the absence of vascular occlusion, the similar ischemic injury of the digestive mucosa justifies the maintenance of the common medical protocol. In the absence of rapid improvement, an arteriography with intra-arterial infusion of vasodilators (papaverine) is recommended. Surgical treatment is therefore offered as a last step in case of the patient worsening or immediately in the event of peritonitis / perforation.

Revascularization

As with any vascular emergency, early revascularization is the only therapy that can prevent/limit irreversible necrosis and its life-threatening complications [58]. Depending on the accessibility of vascular lesions and local expertise, arterial revascularization is ideally carried out percutaneously first and before any digestive surgery in order to preserve a maximum of viable small intestine [4, 51].

Endovascular Strategies

If a vascular impairment is reachable, percutaneous revascularization (intra-arterial thrombolysis, angioplasty-stenting, thrombectomy) should be considered. Recent literature reports a success rate of endovascular revascularization of 87% [63]. The choice of techniques depends on the etiology, and the localization of the vascular occlusion.

To date, no randomized controlled studies have compared an up-front endovascular approach with open surgery for the treatment of AMI. Because AMI is a relatively rare and urgent condition, such trials are unlikely to be performed.

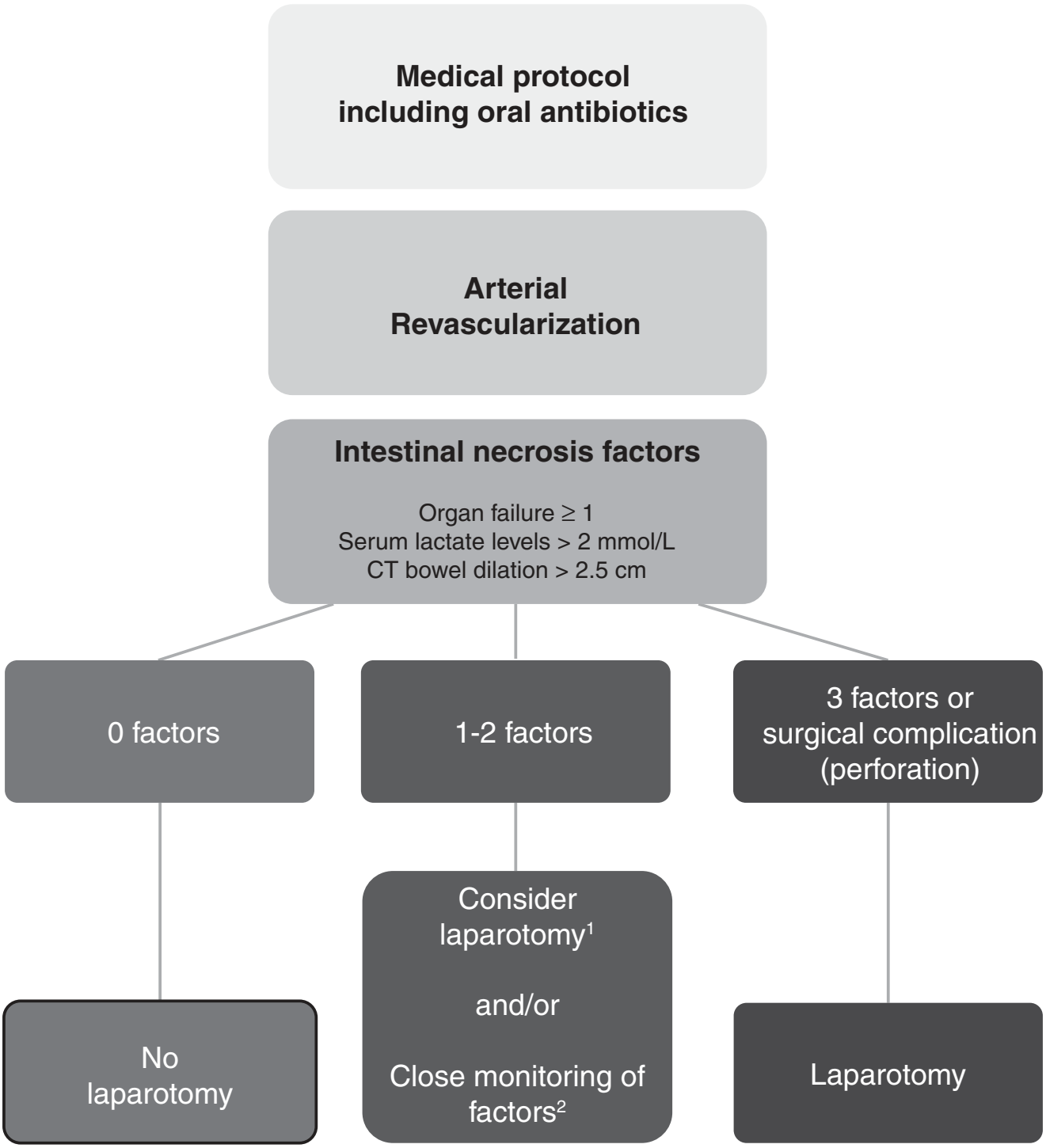

Fig. 5 Treatment algorithm used in the intestinal stroke unit. (1) Consider laparotomy, especially when the factors value is high and when a revascularization is not feasible. (2) Consider close monitoring, especially when the factor value is close to the upper normal cut-off and when an improvement is expected with successful revascularization

Most published studies are therefore retrospective monocentric series, with all methodological biases associated with such study design. A group from the University Hospital of Kuopio, Finland, recently reported a consecutive series of patients with AMI treated over a five-year period. Endovascular treatment was applied as first-line in 88% of the patients [64]. Mortality was acceptable (32%) yet the endovascular strategy failed in 50% of the patients, and a surgical bypass was finally achieved. The 30-day mortality rate was lower than that reported by Endean et al. after surgi-

Table 3 Systematic medical protocol provided in the intestinal stroke unit [58.

Common medical protocol	Blood volume resuscitation (Mean arterial pressure >65 mm Hg, Urine output >0.5 mL kg−1 h−1)
	Curative unfractionated heparin therapy (Anti-Xa target: 0.4–0.8)
	Oral digestive decontamination
	PO gentamicin 80 mg/d
	PO metronidazole 1.5 g/day
	IV proton pump inhibitors
	IV pantoprazole, 80 mg/day
	Oxygen therapy
	Food resting
	PN if prolonged >5 day
Conditional medical protocol	IV aspirin 100 mg/day if arterial thrombosis or revascularization
	IV piperacillin-tazobactam 12 g/day if SIRS or organ failure
	Upper gastrointestinal aspiration if ileus
	Blood transfusion if hemoglobin level

IV intravenous, *PO* orally, *SIRS* systemic inflammatory response syndrome

cal strategy alone (62%) [65]. Recently, a review conducted by Zhao et al. reported that radiological revascularization should be considered as a first-line therapy in patients with a low suspicion of intestinal necrosis [66].

The analysis of population registers makes it possible to obtain data of greater value. Swedvasc, the Swedish vascular register, founded in 1987 comprises more than 90% of all vascular surgical procedures in a country of 9.5 million inhabitants. Two publications from Swedvasc reported the results of revascularization of the superior mesenteric artery for AMI for the periods 1987–1998 and 1999–2006 [67, 68]. Overall, total surgical activity quadrupled from 1999 to 2006, while the number of endovascular revascularizations increased sixfold. If overall mortality decreased, this decline was observed only in patients treated with endovascular strategy. Long-term survival was also better after endovascular strategy. The difference between the two periods could be explained by a difference in patient severity, but the length of the resected intestine was similar in both groups and the endovascular strategy was identified as an independent factor of survival in multivariate analysis (odds ratio 3.7). However, as in the Kuopio Hospital experience, one of the main reasons for successful endovascular strategy was the possibility of surgical revascularization if the former fails.

Similar observations emerge from the analysis of the National Inpatient Sample (NIS) based in the United States [69]. The NIS is a database of 20% of the hospitalization episodes of nearly 1000 hospitals. Of the 679 patients with AMI treated between 2005 and 2009, 514 (76%) were treated by surgical revascularization and 165 (24%) by endovascular procedure. The proportion of patients who had endovascular repair increased from 12% in 2005 to 30% in 2009. Mortality was 39% after surgery and 25% after endovascular procedure. Among survivors, the proportion of patients requiring total parenteral nutrition was also significantly higher after surgery than after endovascular strategy (24% versus 14%) [69]. Thus, although Level I evidence is lacking, this data seems convincing.

This approach of surgery *versus* endovascular revascularization, seems to us to be limited and erroneous. If endovascular interventions are sometimes performed alone, optimal patient management must combine the two approaches in a complementary perspective, the benefits of each being able to support those of the other. Indeed, the majority of patients treated with the endovascular route have laparotomy and intestinal resection in a second phase. However, the mean length of the resected small intestine is significantly shorter than with surgery alone [51].

Open Vascular Surgery

Vascular surgery is often required to restore the mesenteric revascularization in order to improve the prognostic of the AMI (increase survival and prevent intestinal failure). The most common situations when revascularization is done surgically are:

- surgical abdominal exploration is needed and urgent
- surgical exploration has already been done by the visceral surgeon
- endovascular procedures failed to restore the mesenteric revascularization
- vascular surgeon and/or radiologist consider that the case not appropriate for endovascular revascularization
- contraindication to endovascular technique (local thrombolysis for example)
- visceral surgeon is not familiar with endovascular procedures but is able to perform basic vascular surgery (embolectomy for example)

In our experience, the three most common surgical vascular procedures to restore the blood flow in the superior mesenteric artery (SMA) are: (1) the SMA embolectomy, (2) the retrograde SMA bypass, (3) the retrograde open SMA stenting. The vascular surgeon may need to harvest a segment of saphenous or femoral vein. Hence, we recommend having one of the thighs prepared in the surgical field in anticipation of possible access. A radiologic system to perform arteriography during the procedure is mandatory (C-arm fluoroscopy or hybrid operating room). All the vascular surgical procedures need systemic heparinization.

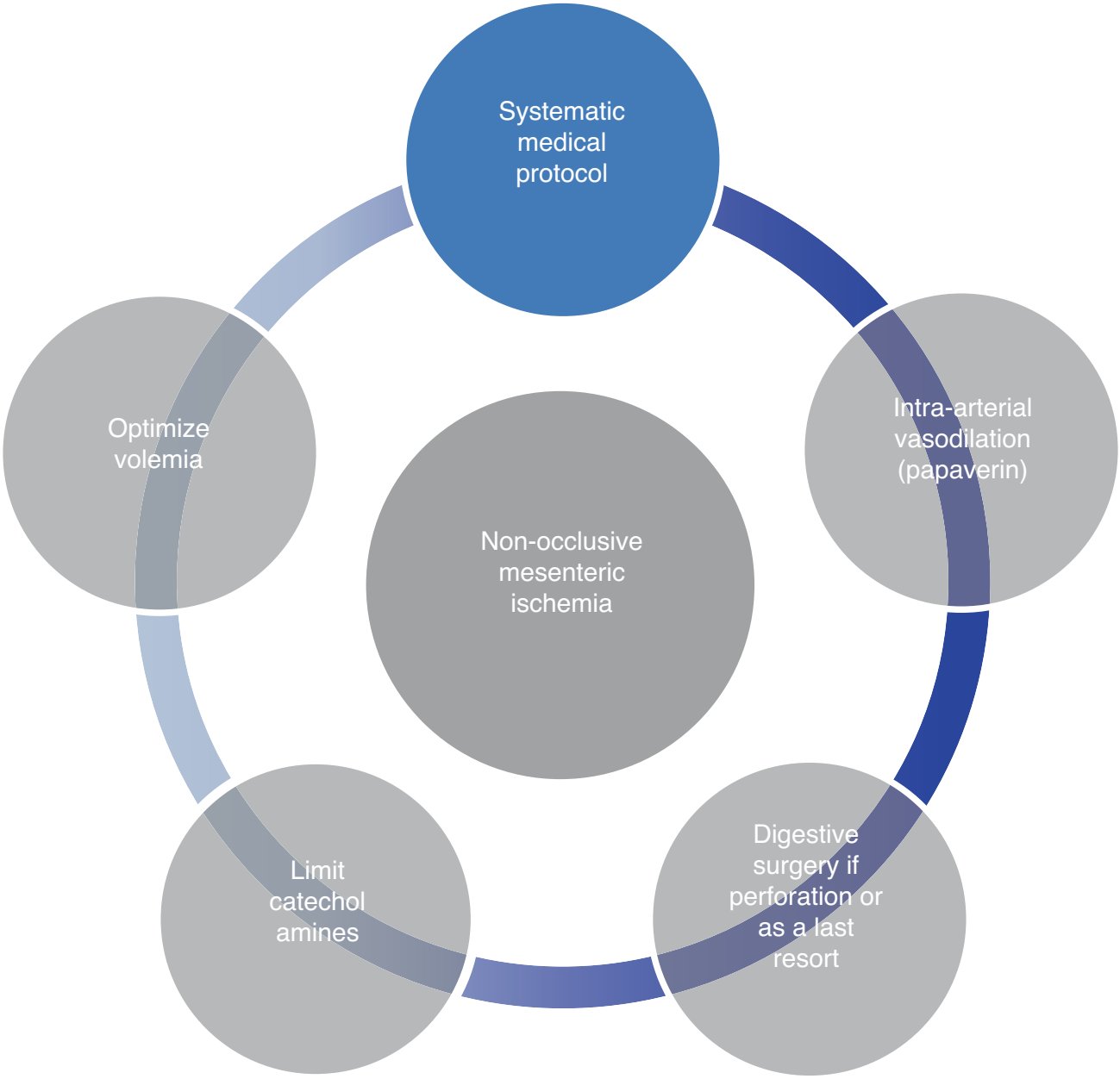

Fig. 6 Treatment principles of non-occlusive mesenteric ischemia

SMA Embolectomy

Anterior exposure to the SMA for straightforward embolectomy is achieved by elevating the omentum and transverse colon, the small intestine is wrapped and retracted to the right. A segment of the proximal SMA between the middle and the right colic branches is isolated. Circumferantial dissection is required to isolate and to control any of the jejunal branches in this segment. The artery is open transversely if the SMA has a sufficient diameter and is not too atheromatous. For diminutive or diseased vessels, we firmly recommend performing a longitudinal arteriotomy using a patch closure (prosthetic or a saphenous patch). Great care must be taken to avoid damage or rupture to fragile collaterals of the SMA. When necessary, small Fogarty embolectomy catheters are used. After all macroscopic clot is cleared, we can consider administration of a single dose of thrombolytic agent into the distal mesenteric vessels. An arteriogram can be performed at the end of the procedure to assess the quality of the revascularization.

Retrograde SMA Bypass

Antegrade bypass using the distal thoracic aorta or suprarenal aorta as the inflow source is not recommended in case of AMI. A retrograde bypass based on the infrarenal aorta,

a previous aortic graft, or the iliac artery is strongly preferred with the advantage of avoiding cross-clamping the aorta. Most retrograde reconstruction deals with only the SMA, but reconstruction of the common hepatic artery can also be achieved by tunneling the graft retroperitoneally or via the transverse mesocolon. As the graft assumes a C-shaped configuration, it is important to avoid graft elongation, angulation or kinking. Synthetic bypass grafts (Dacron or externally supported polytetrafluoroethylene) are preferred because of the better size match, ease of handling, availability and kink resistance. The choice of conduit is heavily influenced by the degree of abdominal contamination and the perceived risk of subsequent infection. Therefore, if good-quality vein is available (saphenous vein or femoral thigh vein), it is preferred in the presence of significant peritoneal soilage. In the presence of a diseased SMA, an endarterectomy may be necessary before doing the distal anastomosis. Reports suggest that retrograde grafts perform as well as antegrade grafts [70].

Retrograde Open SMA Stenting (ROMS)

The ROMS technique uses a hybrid approach via midline laparotomy to expose de SMA combined with endovascular retrograde stenting. Because several of these patients already have an indication for laparotomy to address advanced bowel gangrene or ischemia, direct surgical exposure of the SMA allows expeditious access for direct puncture. The proximity of the sheath to the lesion affords excellent support to cross a difficult occlusion with less risk of distal embolization by occlusion of side branches. Furthermore, primary stenting is an excellent method of revascularization that avoids the need to reconstruct the vessel by surgical bypass, minimizing surgical dissection and potentially eliminating the need to harvest a vein or to use a prosthetic graft for conduit.

We recommend the use of covered balloon expandable stent, 7 mm diameter stent are most often used [71, 72]. In our experience, a majority of the SMA needs an endarterectomy and we recommend to perform a longitudinal arteriotomy using a patch closure (prosthetic or a saphenous patch). ROMS during emergent laparotomy for AMI is a very promising technique and an attractive alternative to emergent surgical bypass.

Intestinal Resection

Non-invasive Predictors of Transmural Necrosis

The cornerstone of acute mesenteric ischemia surgical management in the acute phase is the diagnosis of intestinal necrosis, that will not be reversible despite revascularizations procedures [3, 51, 73]. However, the identification of patients with intestinal necrosis has been shown as difficult. Indeed, no clinical sign or laboratory study is specifically associated to intestinal necrosis, [60, 61] as even serum lactate might be normal in necrotic patients or elevated in patients with reversible ischemia, due to dehydration and decreased oral intake [60]. In this setting, we performed a prospective cohort study of 67 patients with acute mesenteric ischemia, of which 34% presented with intestinal necrosis [10]. From this group organ failure, elevated serum lactate≥ 2, and bowel loop dilation (defined as a diameter > 2.5 cm) on CT scan were independent factors predictive of intestinal necrosis. On the basis of these findings, the incidence of intestinal necrosis rose from 3% in patients with no predictive factor to 38%, 89%, and 100% in patients with 1, 2, and 3 factors, respectively. Therefore, in routine clinical practice, we consider that all patients presenting with 2 or more factors should undergo immediate explorative surgery to assess for intestinal viability [10] (Fig. 5).

If a surgical exploration is decided upon, this procedure should be, whenever possible, carefully planned according to the feasibility of a revascularization procedure. In highly unstable patients and/or in patients with overt peritonitis, we advocate a primary blood flow restoration procedure prior to a surgical resection, as this might reduce the extent of intestinal resection and reduce the risk of secondary necrosis of the remnant bowel [51]. In all other patients, we routinely perform a radiological or surgical revascularization procedure prior to the explorative laparotomy, for the same reasons.

Surgical Approach

Very few studies reported the use of laparoscopic approach for the management of acute mesenteric ischemia [74–78]. Despite this small series, the European Society for Trauma and Emergency Surgery guidelines does not recommend the use of minimally invasive approach for acute mesenteric ischemia, due to the paucity of reported evidence [60]. In our experience, laparoscopic approach is not the gold standard approach for the management of acute mesenteric ischemia as: (1) the complete visualization and viability assessment of the small bowel and colon might be difficult, (2) patients' tolerance of the pneumoperitoneum might be compromised, especially in unstable patients, (3) surgical revascularization procedures require an open approach. We usually perform an open approach in our patients, reserving a laparoscopic approach in cases of difficult diagnosis and especially in non-occlusive patients [76].

Bowel Viability Assessment

Most of the time, necrotic bowel will be clearly identifiable during the laparotomy, and will be based on the bowel color, motility and bleeding of cut ends [60, 79, 80]. (Fig. 7) As described before, this viability should be assessed after revascularization procedure, whenever possible. However, viability assessment might sometimes be difficult, especially

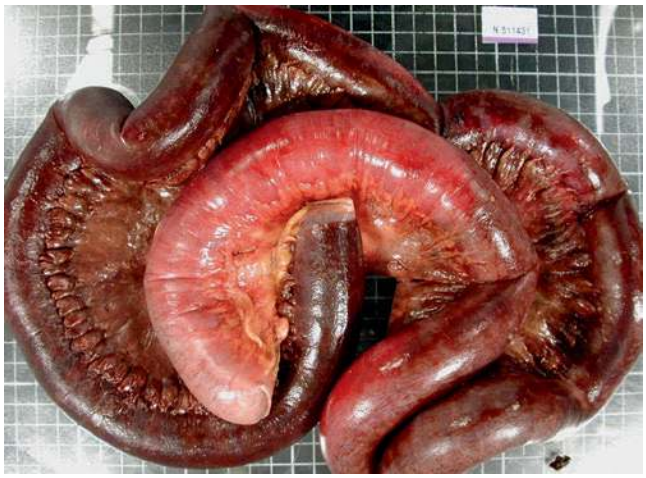

Fig. 7 Acute arterial mesenteric infarction. Resection specimen showing transmural intestinal necrosis from arterial intestinal ischemia

in cases of hypotension, vascular impairment, and the concurrent use of vasopressors. In such patients, the use of doppler ultrasound of the vascular arcade, [81] fluorescein angiography, [82] and indocyanine green angiography [83] have been reported but have failed to gain widespread use. In our practice, we usually perform a frozen section examination in order to avoid unnecessary extensive resection.

Vacsular surgeons from our center use to feel for the arterial SMA pulse, but it is not indicative of the quality of the reperfusion and the quality of revascularization of the collaterals of the SMA and distal arteries. CT angiography is preferred for this purpose. Differentiating arterial from venous infarction is also done using the the CT-scan images. At surgery venous AMI usually leads to more congestive "blue" colored bowel, a more proximal injury (jejunum), but lower/slower progression to infarction than arterial AMI.

Damage Control Surgery

The strategy of Damage Control Surgery includes an abbreviated laparotomy with resection of necrotic bowel and the absence of anastomosis or stoma [79, 84, 85], in an attempt to reduce the operative time and to prioritize the resuscitation in intensive care unit. For many surgeons, it has become the standard of care for acute mesenteric ischemia management. However, this strategy imposes the realization of a second-look surgery, which is usually performed 48 h after the primary procedure.

In our routine practice, we do not advocate such strategy for all patients. As stated in the European Society for Trauma and Emergency Surgery guidelines published in 2016, Damage Control Surgery might only be performed in patients with severe septic shock, [60] which in fact represent a minority of patients. We favor a strategy that includes the establishment of stomas of all resected bowel segments, as this may have several advantages: (1) To avoid unnecessary second look laparotomy – indeed, Park *et al.* reported the outcomes of patients operated on for acute mesenteric ischemia and reported that an additional bowel resection was performed during the second look in the minority of patients (11/23), thus exposing the majority of patients to the risk of an unnecessary laparotomy; [86] (2) The presence of a stoma allows the direct evaluation of the remnant bowel viability, as the mucosa can be easily evaluated and, if necessary, biopsied; and (3) this strategy does not expose the patient of the complications of intestinal anastomosis, as anastomotic leakage is frequent is those patients that will receive intensive resuscitation and vasopressor injections [60]. We never perform any anastomosis in the acute phase of acute mesenteric ischemia management. In this setting, during bowel resection, care should be taken to facilitate the intestinal continuity restoration. Double end stomas should be preferred over single stomas in separate incisions, as this will allow to perform intestinal continuity restoration through an elective approach, rather than a midline laparotomy.

Extensive Bowel Resection

In severe patients, with extensive intestinal necrosis requiring large bowel resection, the surgeon might face a philosophical decision whether to expose the patient to a short bowel syndrome, requiring total parenteral nutrition, or not to do anything. This decision may be based on the associated comorbidities, and the long-term probability of patient discharge from medical assistance. In the past the difficult decision to close the abdomen and not resect was often made after intra-operative discussions with the intensivists, the gastroenterologist, and the nutritionist in charge of the patient. However with the success of long-term parenteral support and the fact that many patients, even if the remaining small bowel length is very short (less than 50 cm), will stop the parenteral support when the colon is in continuity [38, 87] and/or if a growth factor (e.g. teduglutide [88]) is given, this decision is now rarely made and we propose an aggressive strategy regarding small resection.

Follow-Up and Rehabilitation

Post-ischemic Stenoses and Disorders

When it does not progress to transmural necrosis, any mesenteric ischemia can cause functional intestinal "sequelae", especially dysmotility disorders. In most cases, these lesions may appear when the intestinal injury has exceeded the healing capacity mechanisms and has progressed to stenosing parietal fibrosis and/or chronic mucosal ulcers. Occurring within a variable delay after refeeding, post-ischemic disorders present as pseudo-occlusive syndrome, chronic diarrhea and/or septic episodes of digestive origin (microbial translo-

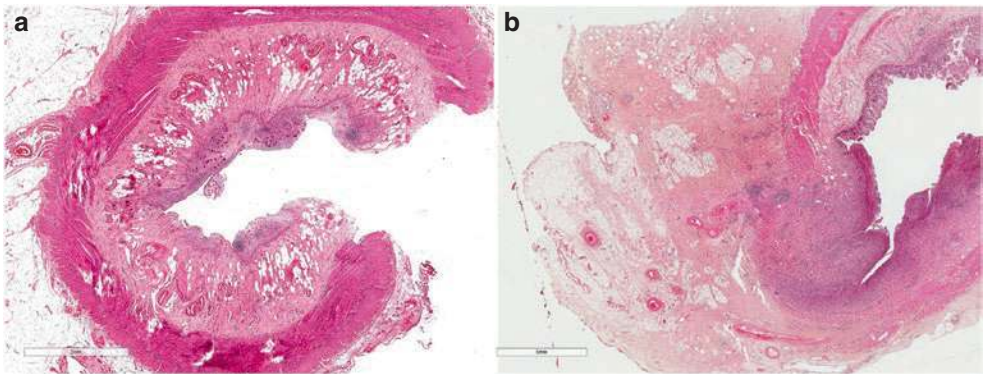

Fig. 8 Histopathological picture of post-ischemic enteritis. (**a**) Resection specimen showing a non-penetrating chronic post-ischemic enteritis: the mucosa is destroyed, ulcerated with submucosal fibrosis, increased angiogenesis, and normal underlying muscularis propria. (**b**) Resection specimen showing a chronic post-ischemic enteritis with fistula: the mucosa is ulcerated with a deep fistula infiltrating a fibrosed muscularis propria

cations). The treatment is generally surgical. In some cases, the motility disorder is transient and could be linked to the intestinal smooth muscle response to ischemia-reperfusion. Indeed, recent physio-morphological studies of gastrointestinal peristalsis by magnetic enteromyography, have shown that peristalsis was early and significantly decreased in the case of chronic mesenteric ischemia and normalized after revascularization [89]. This could explain some functional GI disorders, such as gastroparesis, which refeeding after revascularization could unveil [90].(Fig. 8).

Nutritional, Vascular and Intestinal Rehabilitation

In the event of multiple vascular involvement, primary revascularization of the superior mesenteric artery should always be offered. If this is impossible, and due to the collateral network between the digestive arteries, revascularization of the celiac trunk and / or the inferior mesenteric artery can lead to resolution of the IIC [91]. In the extreme, in the patient not eligible for revascularization, clinical improvement occurred in 4 of 6 patients after infusion of iloprost (ilomedine®), a prostacyclin analog having a peripheral vasodilator, antiaggregating and immunomodulatory effect and used in the Raynaud syndrome, critical ischemia of the lower limbs and high blood pressure [92].

Proximal and/or extensive resection of intestinal necrosis can be complicated by a transient or definite short bowel syndrome. The care of these patients must be provided in collaboration with an expert intestinal failure unit [38, 93]. Rehabilitation after mesenteric infarction is threefold:

– Nutritional: screening and correction of hydro-electrolytic, caloric and / or vitamin / trace element deficits, and parenteral support;
– Vascular: detection of persistent ischemia related to a residual vascular stenosis, and secondary cardiovascular prevention with long-term anti-thrombotic treatment; [94]
– Digestive with the restoration of continuity with possible interposition of a reverse loop [95].

Reanastomosis of Defunctioned Bowel

Patients, who are maintained with parenteral support, and have had an extensive bowel resection with defunctioned ileum and/or colon remaining in situ should, if possible, have bowel continuity restored. Preference is for doing this after the acute AMI stage (the acute ischemia/reperfusion injury may compromise anastomosis healing and lead to septic complications and further infarction and resction). This restoration of continuity is usually done at least six weeks after the initial surgery, when the patient is healthy with a normal BMI, and when the aetiology of the infarction has been identified (thrombophilia screen, echocardiogram, 24 h tape and CT angiography) and treated (e.g. under 60 years old and a haematological/clotting abnormality given anticoagulation). Before surgery the defunctioned bowel is outlined radiologically to check mainly that there is no obstruction, and endoscopically to check that there is no sign of chronic mesenteric ischemia. For the latter point, CT angiography may be repeated to check that the remnant gut blood supply is sufficient. Trophic distal feeding may be given into the defunctioned ileum/colon after careful assessment of its viability and vascular patency (see Chapter “Distal feeding and hydration”). Following the re-anastomosis/stoma closure there will be a reduction in parenteral requirements (volume, energy and more nights off PS), stool frequency will decrease (althought the stool is likely to be malodourous), there is less chance of cholestasis and survival is increased. In one series

32% of patients (n = 28) with a residual small bowel length of less than 51 cm had stopped parenteral nutrition completely by 5 years from the time when continuity was re-established [38]. There is no need for a routine defunctioning colostomy (to reduce stool frequency) even when the residual small bowel length is very short (e.g. less than 20 cm).

Conclusion

Acute mesenteric ischemia is today potentially reversible when diagnosed and treated early and appropriately. The development of specialized intestinal stroke units coordinated by gastroenterologists and offering 24/24 revascularization, intestinal resection, in an intensive care environment, and in close collaboration with an intestinal failure unit, constitute both therapeutic and diagnostic hope. Moreover, the recruitment into dedicated medical and research teams is an essential prerequisite for clinical and research progress, and nurtures the hope for the future of obtaining a biomarker for early diagnosis, the clinical application of which could be generalized in the assessment and management of any abdominal pain and whose place could be major in the gastroenterology and emergency medicine of tomorrow.

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References

1. Clair DG, Beach JM. Mesenteric Ischemia. N Engl J Med. 2016;374(10):959–68.
2. Nuzzo A, Corcos O. Reversible Acute Mesenteric Ischemia. N Engl J Med. 2016;375(15):e31.
3. Nuzzo A, Corcos O. Management of mesenteric ischemia in the era of intestinal stroke centers: The gut and lifesaving strategy. Rev Med Interne. 2017;38(9):592–602.
4. Corcos O, Nuzzo A. Gastro-intestinal vascular emergencies. Best Pract Res Clin Gastroenterol. 2013;27(5):709–25.
5. Brandt LJ, Feuerstadt P, Longstreth GF, Boley SJ. American College of G. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). Am J Gastroenterol. 2015;110(1):18–44; quiz 5
6. Ten Heggeler LB, van Dam LJ, Bijlsma A, Visschedijk MC, Geelkerken RH, Meijssen MA, et al. Colon ischemia: Right-sided colon involvement has a different presentation, etiology and worse outcome. A large retrospective cohort study in histology proven patients. Best Pract Res Clin Gastroenterol. 2017;31(1):111–7.
7. Chiu CJ, McArdle AH, Brown R, Scott HJ, Gurd FN. Intestinal mucosal lesion in low-flow states. I. A morphological, hemodynamic, and metabolic reappraisal. Arch Surg. 1970;101(4):478–83.
8. Deitch EA. Multiple organ failure. Pathophysiology and potential future therapy. Ann Surg. 1992;216(2):117–34.
9. Zimmerman BJ, Granger DN. Mechanisms of reperfusion injury. Am J Med Sci. 1994;307(4):284–92.
10. Nuzzo A, Maggiori L, Ronot M, Becq A, Plessier A, Gault N, et al. Predictive factors of intestinal necrosis in acute mesenteric ischemia: prospective study from an intestinal stroke center. Am J Gastroenterol. 2017;112:597–605.
11. Boley SJ, Brandt LJ, Sammartano RJ. History of mesenteric ischemia. The evolution of a diagnosis and management. Surg Clin North Am. 1997;77(2):275–88.
12. Boley SJ, Sprayregan S, Siegelman SS, Veith FJ. Initial results from an agressive roentgenological and surgical approach to acute mesenteric ischemia. Surgery. 1977;82(6):848–55.
13. Martin C, Boisson C, Haccoun M, Thomachot L, Mege JL. Patterns of cytokine evolution (tumor necrosis factor-alpha and interleukin-6) after septic shock, hemorrhagic shock, and severe trauma. Crit Care Med. 1997;25(11):1813–9.
14. Hietbrink F, Besselink MG, Renooij W, de Smet MB, Draisma A, van der Hoeven H, et al. Systemic inflammation increases intestinal permeability during experimental human endotoxemia. Shock. 2009;32(4):374–8.
15. Deitch EA, Xu D, Kaise VL. Role of the gut in the development of injury- and shock induced SIRS and MODS: the gut-lymph hypothesis, a review. Front Biosci. 2006;11:520–8.
16. Senthil M, Brown M, Xu DZ, Lu Q, Feketeova E, Deitch EA. Gut-lymph hypothesis of systemic inflammatory response syndrome/multiple-organ dysfunction syndrome: validating studies in a porcine model. J Trauma. 2006;60(5):958–65; discussion 65-7
17. Alverdy JC, Chang EB. The re-emerging role of the intestinal microflora in critical illness and inflammation: why the gut hypothesis of sepsis syndrome will not go away. J Leukoc Biol. 2008;83(3):461–6.
18. Kumar S, Sarr MG, Kamath PS. Mesenteric venous thrombosis. N Engl J Med. 2001;345(23):1683–8.
19. Elkrief L, Corcos O, Bruno O, Larroque B, Rautou PE, Zekrini K, et al. Type 2 diabetes mellitus as a risk factor for intestinal resection in patients with superior mesenteric vein thrombosis. Liver Int. 2014;34(9):1314–21.
20. Fishman JE, Sheth SU, Levy G, Alli V, Lu Q, Xu D, et al. Intraluminal nonbacterial intestinal components control gut and lung injury after trauma hemorrhagic shock. Ann Surg. 2014;260(6):1112–20.
21. Pontell L, Sharma P, Rivera LR, Thacker M, Tan YH, Brock JA, et al. Damaging effects of ischemia/reperfusion on intestinal muscle. Cell Tissue Res. 2011;343(2):411–9.
22. Chang M, Kistler EB, Schmid-Schonbein GW. Disruption of the mucosal barrier during gut ischemia allows entry of digestive enzymes into the intestinal wall. Shock. 2012;37(3):297–305.
23. Altshuler AE, Richter MD, Modestino AE, Penn AH, Heller MJ, Schmid-Schonbein GW. Removal of luminal content protects the small intestine during hemorrhagic shock but is not sufficient to prevent lung injury. Physiol Rep. 2013;1(5):e00109.
24. Deitch EA. Gut-origin sepsis: evolution of a concept. Surgeon. 2012;10(6):350–6.
25. Badami CD, Senthil M, Caputo FJ, Rupani BJ, Doucet D, Pisarenko V, et al. Mesenteric lymph duct ligation improves survival in a lethal shock model. Shock. 2008;30(6):680–5.
26. Schoots IG, Koffeman GI, Legemate DA, Levi M, van Gulik TM. Systematic review of survival after acute mesenteric ischaemia according to disease aetiology. Br J Surg. 2004;91(1):17–27.
27. Kassahun WT, Schulz T, Richter O, Hauss J. Unchanged high mortality rates from acute occlusive intestinal ischemia: six year review. Langenbeck's Arch Surg. 2008;393(2):163–71.
28. Parks DA, Jacobson ED. Physiology of the splanchnic circulation. Arch Intern Med. 1985;145(7):1278–81.

29. Acosta S. Epidemiology of mesenteric vascular disease: clinical implications. Semin Vasc Surg. 2010;23(1):4–8.
30. Acosta S, Ogren M, Sternby NH, Bergqvist D, Bjorck M. Incidence of acute thrombo-embolic occlusion of the superior mesenteric artery--a population-based study. Eur J Vasc Endovasc Surg. 2004;27(2):145–50.
31. Crawford RS, Harris DG, Klyushnenkova EN, Tesoriero RB, Rabin J, Chen H, et al. A Statewide Analysis of the Incidence and Outcomes of Acute Mesenteric Ischemia in Maryland from 2009 to 2013. Front Surg. 2016;3:22.
32. Terlouw LG, Verbeten M, van Noord D, Brusse-Keizer M, Beumer RR, Geelkerken RH, et al. The incidence of chronic mesenteric ischemia in the well-defined region of a dutch mesenteric ischemia expert center. Clin Transl Gastroenterol. 2020;11(8):e00200.
33. Kolkman JJ, Bargeman M, Huisman AB, Geelkerken RH. Diagnosis and management of splanchnic ischemia. World J Gastroenterol. 2008;14(48):7309–20.
34. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113(11):e463–654.
35. Nuzzo A, Joly F, Ronot M, Castier Y, Huguet A, Paugam-Burtz C, et al. Normal Lactate and Unenhanced CT-Scan Result in Delayed Diagnosis of Acute Mesenteric Ischemia. Am J Gastroenterol. 2020;115(11):1902–5.
36. Kozuch PL, Brandt LJ. Review article: diagnosis and management of mesenteric ischaemia with an emphasis on pharmacotherapy. Aliment Pharmacol Ther. 2005;21(3):201–15.
37. Leone M, Bechis C, Baumstarck K, Ouattara A, Collange O, Augustin P, et al. Outcome of acute mesenteric ischemia in the intensive care unit: a retrospective, multicenter study of 780 cases. Intensive Care Med. 2015;41(4):667–76.
38. Adaba F, Rajendran A, Patel A, Cheung YK, Grant K, Vaizey CJ, et al. Mesenteric Infarction: Clinical Outcomes After Restoration of Bowel Continuity. Ann Surg. 2015;262(6):1059–64.
39. Kougias P, Lau D, El Sayed HF, Zhou W, Huynh TT, Lin PH. Determinants of mortality and treatment outcome following surgical interventions for acute mesenteric ischemia. J Vasc Surg. 2007;46(3):467–74.
40. Derikx JP, Schellekens DH, Acosta S. Serological markers for human intestinal ischemia: A systematic review. Best Pract Res Clin Gastroenterol. 2017;31(1):69–74.
41. Peoc'h K, Nuzzo A, Guedj K, Paugam C, Corcos O. Diagnosis biomarkers in acute intestinal ischemic injury: so close, yet so far. Clin Chem Lab Med. 2018;56(3):373–85.
42. Evennett NJ, Petrov MS, Mittal A, Windsor JA. Systematic review and pooled estimates for the diagnostic accuracy of serological markers for intestinal ischemia. World J Surg. 2009;33(7):1374–83.
43. Sun DL, Cen YY, Li SM, Li WM, Lu QP, Xu PY. Accuracy of the serum intestinal fatty-acid-binding protein for diagnosis of acute intestinal ischemia: a meta-analysis. Sci Rep. 2016;6:34371.
44. Treskes N, Persoon AM, van Zanten ARH. Diagnostic accuracy of novel serological biomarkers to detect acute mesenteric ischemia: a systematic review and meta-analysis. Intern Emerg Med. 2017;12(6):821–36.
45. Nuzzo A, Ronot M, Maggiori L, Corcos O. Early Acute Mesenteric Ischemia: Many Rivers to Cross. Ann Surg. 2018;268(6):e41.
46. Menke J. Diagnostic accuracy of multidetector CT in acute mesenteric ischemia: systematic review and meta-analysis. Radiology. 2010;256(1):93–101.
47. Lehtimaki TT, Karkkainen JM, Saari P, Manninen H, Paajanen H, Vanninen R. Detecting acute mesenteric ischemia in CT of the acute abdomen is dependent on clinical suspicion: Review of 95 consecutive patients. Eur J Radiol. 2015;84(12):2444–53.
48. Wadman M, Block T, Ekberg O, Syk I, Elmstahl S, Acosta S. Impact of MDCT with intravenous contrast on the survival in patients with acute superior mesenteric artery occlusion. Emerg Radiol. 2010;17(3):171–8.
49. Copin P, Ronot M, Nuzzo A, Maggiori L, Bouhnik Y, Corcos O, et al. Inter-reader agreement of CT features of acute mesenteric ischemia. Eur J Radiol. 2018;105:87–95.
50. Oliva IB, Davarpanah AH, Rybicki FJ, Desjardins B, Flamm SD, Francois CJ, et al. ACR Appropriateness Criteria (R) imaging of mesenteric ischemia. Abdom Imaging. 2013;38(4):714–9.
51. Roussel A, Castier Y, Nuzzo A, Pellenc Q, Sibert A, Panis Y, et al. Revascularization of acute mesenteric ischemia after creation of a dedicated multidisciplinary center. J Vasc Surg. 2015;62(5):1251–6.
52. McCarthy E, Little M, Briggs J, Sutcliffe J, Tapping CR, Patel R, et al. Radiology and mesenteric ischaemia. Clin Radiol. 2015;70(7):698–705.
53. Wasnik A, Kaza RK, Al-Hawary MM, Liu PS, Platt JF. Multidetector CT imaging in mesenteric ischemia--pearls and pitfalls. Emerg Radiol. 2011;18(2):145–56.
54. Woodhams R, Nishimaki H, Fujii K, Kakita S, Hayakawa K. Usefulness of multidetector-row CT (MDCT) for the diagnosis of non-occlusive mesenteric ischemia (NOMI): assessment of morphology and diameter of the superior mesenteric artery (SMA) on multi-planar reconstructed (MPR) images. Eur J Radiol. 2010;76(1):96–102.
55. Siegelman SS, Sprayregen S, Boley SJ. Angiographic diagnosis of mesenteric arterial vasoconstriction. Radiology. 1974;112(3):533–42.
56. Yikilmaz A, Karahan OI, Senol S, Tuna IS, Akyildiz HY. Value of multislice computed tomography in the diagnosis of acute mesenteric ischemia. Eur J Radiol. 2011;80(2):297–302.
57. Duron VP, Rutigliano S, Machan JT, Dupuy DE, Mazzaglia PJ. Computed tomographic diagnosis of pneumatosis intestinalis: clinical measures predictive of the need for surgical intervention. Arch Surg. 2011;146(5):506–10.
58. Corcos O, Castier Y, Sibert A, Gaujoux S, Ronot M, Joly F, et al. Effects of a multimodal management strategy for acute mesenteric ischemia on survival and intestinal failure. Clin Gastroenterol Hepatol. 2013;11(2):158–65. e2
59. Nuzzo A, Maggiori L, Paugam-Burtz C, Cazals-Hatem D, Ronot M, Huguet A, et al. Oral antibiotics reduce intestinal necrosis in acute mesenteric ischemia: a prospective cohort study. Am J Gastroenterol. 2019;114(2):348–51.
60. Tilsed JV, Casamassima A, Kurihara H, Mariani D, Martinez I, Pereira J, et al. ESTES guidelines: acute mesenteric ischaemia. Eur J Trauma Emerg Surg. 2016;42(2):253–70.
61. Bala M, Kashuk J, Moore EE, Kluger Y, Biffl W, Gomes CA, et al. Acute mesenteric ischemia: guidelines of the World Society of Emergency Surgery. World J Emerg Surg. 2017;12:38.
62. Yang S, Guo J, Ni Q, Chen J, Guo X, Xue G, et al. Enteral nutrition improves clinical outcome and reduces costs of acute mesenteric ischaemia after recanalisation in the intensive care unit. Clin Nutr. 2019;38(1):398–406.
63. Arthurs ZM, Titus J, Bannazadeh M, Eagleton MJ, Srivastava S, Sarac TP, et al. A comparison of endovascular revascularization with traditional therapy for the treatment of acute mesenteric ischemia. J Vasc Surg. 2011;53(3):698–705.

64. Karkkainen JM, Lehtimaki TT, Saari P, Hartikainen J, Rantanen T, Paajanen H, et al. Endovascular therapy as a primary revascularization modality in acute mesenteric ischemia. Cardiovasc Intervent Radiol. 2015;38(5):1119–29.
65. Endean ED, Barnes SL, Kwolek CJ, Minion DJ, Schwarcz TH, Mentzer RM Jr. Surgical management of thrombotic acute intestinal ischemia. Ann Surg. 2001;233(6):801–8.
66. Zhao Y, Yin H, Yao C, Deng J, Wang M, Li Z, et al. Management of acute mesenteric ischemia: a critical review and treatment algorithm. Vasc Endovasc Surg. 2016;50(3):183–92.
67. Bjorck M, Acosta S, Lindberg F, Troeng T, Bergqvist D. Revascularization of the superior mesenteric artery after acute thromboembolic occlusion. Br J Surg. 2002;89(7):923–7.
68. Block TA, Acosta S, Bjorck M. Endovascular and open surgery for acute occlusion of the superior mesenteric artery. J Vasc Surg. 2010;52(4):959–66.
69. Beaulieu RJ, Arnaoutakis KD, Abularrage CJ, Efron DT, Schneider E, Black JH 3rd. Comparison of open and endovascular treatment of acute mesenteric ischemia. J Vasc Surg. 2014;59(1):159–64.
70. Bjorck M, Koelemay M, Acosta S, Bastos Goncalves F, Kolbel T, Kolkman JJ, et al. Editor's choice—management of the diseases of mesenteric arteries and veins: clinical practice guidelines of the european society of vascular surgery (ESVS). Eur J Vasc Endovasc Surg. 2017;53(4):460–510.
71. Oderich GS, Macedo R, Stone DH, Woo EY, Panneton JM, Resch T, et al. Multicenter study of retrograde open mesenteric artery stenting through laparotomy for treatment of acute and chronic mesenteric ischemia. J Vasc Surg. 2018;68(2):470–80. e1
72. Roussel A, Della Schiava N, Coscas R, Pellenc Q, Boudjelit T, Goeau-Brissonniere O, et al. Results of retrograde open mesenteric stenting for acute thrombotic mesenteric ischemia. J Vasc Surg. 2019;69(4):1137–42.
73. Nuzzo A, Ronot M, Maggiori L, Corcos O. Rather than surgical technique, dedicated stroke centers improve bowel and life outcomes in acute mesenteric ischemia. J Clin Gastroenterol. 2017;53:1539–2031.
74. Baeshko AA, Bondarchuk AG, Podymako NS, Sologub IM, Krukovich EA. Laparoscopy in diagnosis of intestinal mesentery acute circulatory disturbance. Khirurgiia (Mosk). 2000;5:18–20.
75. Yanar H, Taviloglu K, Ertekin C, Ozcinar B, Yanar F, Guloglu R, et al. Planned second-look laparoscopy in the management of acute mesenteric ischemia. World J Gastroenterol. 2007;13(24):3350–3.
76. Cocorullo G, Mirabella A, Falco N, Fontana T, Tutino R, Licari L, et al. An investigation of bedside laparoscopy in the ICU for cases of non-occlusive mesenteric ischemia. World J Emerg Surg. 2017;12:4.
77. Tshomba Y, Coppi G, Marone EM, Bertoglio L, Kahlberg A, Carlucci M, et al. Diagnostic laparoscopy for early detection of acute mesenteric ischaemia in patients with aortic dissection. Eur J Vasc Endovasc Surg. 2012;43(6):690–7.
78. Stefanidis D, Richardson WS, Chang L, Earle DB, Fanelli RD. The role of diagnostic laparoscopy for acute abdominal conditions: an evidence-based review. Surg Endosc. 2009;23(1):16–23.
79. Acosta S. Surgical management of peritonitis secondary to acute superior mesenteric artery occlusion. World J Gastroenterol. 2014;20(29):9936–41.
80. Wyers MC. Acute mesenteric ischemia: diagnostic approach and surgical treatment. Semin Vasc Surg. 2010;23(1):9–20.
81. Kaser SA, Glauser PM, Maurer CA. Venous small bowel infarction: intraoperative laser Doppler flowmetry discriminates critical blood supply and spares bowel length. Case Rep Med. 2012;2012:195926.
82. Herbert GS, Steele SR. Acute and chronic mesenteric ischemia. Surg Clin North Am. 2007;87(5):1115–34, ix
83. Yamamoto M, Orihashi K, Nishimori H, Wariishi S, Fukutomi T, Kondo N, et al. Indocyanine green angiography for intra-operative assessment in vascular surgery. Eur J Vasc Endovasc Surg. 2012;43(4):426–32.
84. Freeman AJ, Graham JC. Damage control surgery and angiography in cases of acute mesenteric ischaemia. ANZ J Surg. 2005;75(5):308–14.
85. Weber DG, Bendinelli C, Balogh ZJ. Damage control surgery for abdominal emergencies. Br J Surg. 2014;101(1):e109–18.
86. Park WM, Gloviczki P, Cherry KJ Jr, Hallett JW Jr, Bower TC, Panneton JM, et al. Contemporary management of acute mesenteric ischemia: Factors associated with survival. J Vasc Surg. 2002;35(3):445–52.
87. Beyer-Berjot L, Joly F, Maggiori L, Corcos O, Bouhnik Y, Bretagnol F, et al. Segmental reversal of the small bowel can end permanent parenteral nutrition dependency: an experience of 38 adults with short bowel syndrome. Ann Surg. 2012;256(5):739–44; discussion 44-5
88. Billiauws L, Bataille J, Boehm V, Corcos O, Joly F. Teduglutide for treatment of adult patients with short bowel syndrome. Expert Opin Biol Ther. 2017;17(5):623–32.
89. Somarajan S, Muszynski ND, Cheng LK, Bradshaw LA, Naslund TC, Richards WO. Noninvasive biomagnetic detection of intestinal slow wave dysrhythmias in chronic mesenteric ischemia. Am J Physiol Gastrointest Liver Physiol. 2015;309(1):G52–8.
90. Gauci JL, Stoven S, Szarka L, Papadakis KA. Prolonged idiopathic gastric dilatation following revascularization for chronic mesenteric ischemia. Ann Gastroenterol. 2014;27(3):273–5.
91. Wohlauer M, Kobeiter H, Desgranges P, Becquemin JP, Cochennec F. Inferior Mesenteric Artery Stenting as a Novel Treatment for Chronic Mesenteric Ischemia in Patients with an Occluded Superior Mesenteric Artery and Celiac Trunk. Eur J Vasc Endovasc Surg. 2014;27(3):e21–e3.
92. Nuzzo A, Soudan D, Billiauws L, Bataille J, Maggiori L, Ronot M, et al. Iloprost Use in Patients with Persistent Intestinal Ischemia Unsuitable for Revascularization. Ann Vasc Surg. 2017;42:128–35.
93. Joly F, Baxter J, Staun M, Kelly DG, Hwa YL, Corcos O, et al. Five-year survival and causes of death in patients on home parenteral nutrition for severe chronic and benign intestinal failure. Clin Nutr. 2018;37(4):1415–22.
94. Roussel A, Nuzzo A, Pellenc Q, Castier Y, De Blic R, Cerceau P, et al. Surgical revascularization of the celiac artery for persistent intestinal ischemia in short bowel syndrome. Int J Surg. 2018;49:39–44.
95. Layec S, Beyer L, Corcos O, Alves A, Dray X, Amiot A, et al. Increased intestinal absorption by segmental reversal of the small bowel in adult patients with short-bowel syndrome: a case-control study. Am J Clin Nutr. 2013;97(1):100–8.

Crohn's Disease

Mattias Soop and Simon Lal

Key Points

1. The limited data on the risk of a patient with Crohn's disease developing intestinal failure (IF) indicate a risk of at least 8.5% in 20 years following index abdominal surgery.
2. Crohn's disease remains one of the most prevalent underlying diagnoses among patients referred to an IF unit.
3. Half of the patients with Crohn's disease who develop IF do so due to abdominal septic complications following surgery.
4. The incidence of abdominal surgery in Crohn's disease is decreasing in population-based studies.
5. Recognition of the risk factors in abdominal surgery for Crohn's disease and judicious usage of double-barrelled stomas are vital in reducing abdominal septic complications.
6. Preoperative optimisation includes: delaying surgery until certain medications are reduced or weaned, malnutrition and anaemia are corrected by enteral or parenteral nutrition (may be exclusive), smoking cessation and eradication of phlegmons and abscesses may allow safer primary anastomosis and improve outcomes.
7. The 'Sepsis-Nutrition-Anatomy-Plan (SNAP)' algorithmic approach fosters a cohesive and systematic approach for the multi-disciplinary team required to care for patients with type II intestinal failure. This includes detailed anatomical evaluation to define fistula(s), stricturing and areas of disease activity.
8. Characterisation of the patient's pre-operative Crohn's disease phenotype and response to previous medications will facilitate a tailored approach to post-operative therapy. A pro-active approach to post-operative therapy is required, where appropriate, with early radiological and endoscopic surveillance and adjustment of medical therapy for recrudescent disease.
9. Following surgery, attention must be given to subsequent Crohn's disease management that aimed at preventing recurrent disease.

Introduction

Intestinal surgery for Crohn's disease may be for obstruction, bleeding, perforation, abscess/fistula or rarely carcinoma. Intestinal failure (IF) is a feared complication of Crohn's disease. It is traditionally assumed that the main mechanism is repeated surgical resections leading a short bowel [1]. This assumption has led to a focus on bowel-sparing strategies such as resection limited to macroscopic disease [2] and strictureplasty [3]. While such strategies appear sensible, data on the epidemiology and mechanisms of IF in Crohn's disease are limited. By reviewing these data, we will identify practices that have the greatest potential to minimise the risk of IF in Crohn's, and review special considerations in the management of IF in the context of Crohn's disease.

Epidemiology of Intestinal Failure in Crohn's Disease

In reports from intestinal failure units, Crohn's disease is frequently the most prevalent underlying diagnosis. Between 1987 and 2011, 545 patients received home parenteral nutrition (HPN) at the National Intestinal Failure Unit in Salford. Of those, 168 or 31% had Crohn's disease [4]. The corresponding proportion from the Lennard-Jones Intestinal Failure Unit at St Mark's Hospital in Harrow is 32% [5]. Notably, the proportion of patients with IF who have Crohn's disease has reduced in the last few years in Salford; while Crohn's was the

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leading cause of IF in the 1980s, in recent years, the principal cause of IF in patients referred to the unit has been surgical complications in non-Crohn's conditions [4]. The same trend has also been seen in a large cohort of managed at the Rigshospitalet in Copenhagen over the last four decades [6].

For people with Crohn's disease and clinicians managing this condition, the converse statistic, the risk of developing IF in Crohn's disease, is more important. Unfortunately, the prevalence and incidence of IF in Crohn's disease are largely unknown quantities. The only published large study addressing this question is a Japanese multi-centre study of the incidence of chronic, or type III, IF after index surgery for Crohn's [7]. In this unique study, some 1700 patients were prospectively followed over an extended time period following index abdominal surgery. The cumulative incidence of type III IF (defined here as home parenteral nutrition for a period of more than 12 months) was 0.8%, 3.6% and 8.5% over 5, 10 and 20 years, respectively [7]. As some patients with Crohn's disease will develop IF as a result of extensive mucosal disease, without prior surgery, the overall risk of IF in Crohn's remains unclear. Nonetheless, the study by Watanabe et al. indicates the potential magnitude of the risk, at least following surgery [7].

Mechanisms of Intestinal Failure in Crohn's Disease

It is widely thought and taught that successive bowel resections resulting in a short bowel is the main mechanism of IF in Crohn's disease. This has led to development of bowel-sparing techniques such as resection limited to macroscopic disease [2], strictureplasty [3] and endoscopic balloon dilatation, in efforts to minimise loss of small bowel.

Few data exist on this issue. A recent study of the cause of IF in 121 consecutive patients with Crohn's disease referred to a national unit in England found that successive bowel resections were the cause only in 31% of patients referred [8]. This study found that 51% of referred patients with Crohn's disease had developed IF as a direct consequence of abdominal septic complications to intestinal surgery. Patients in this group all had re-laparotomies to address septic complications, resulting in enterocutaneous fistulation, loss of small bowel, or both. In many cases, the index operation was an elective ileocaecal resection complicated by anastomotic dehiscence or overlooked enterotomy. In this study, a further 12% of referred patients developed IF directly due to extensive mucosal disease without surgery, and the remaining 6% had a proximal small bowel stoma [8]. This large study confirms findings in an earlier study from the same centre [9].

Therefore, existing data, although scant, suggest that most patients with Crohn's disease who develop IF do so following abdominal surgery complicated by abdominal sepsis requiring re-laparotomy and that, cumulative loss of small bowel is the mechanism in a smaller proportion of patients. Minimising the risk for abdominal septic complications is therefore the most important priority in reducing the risk for IF in people with Crohn's disease.

Several studies report attempts to single out demographic characteristics and phenotype at presentation of patients with Crohn's disease who develop IF. Given that complications of abdominal surgery are the main mechanism, it is not surprising that associations between such characteristics and IF have been found to be weak; [10] not least because septic complications following any operation are likely to be more strongly associated with surgical factors, perioperative physiology and medications, rather than patient demographics and phenotype. Nevertheless, such studies have reported associations between IF and an early diagnosis of Crohn's disease, family history of inflammatory bowel disease, and penetrating disease at diagnosis [10, 11]. It must be remembered that the small number of cases in such studies limit the validity of multivariable regression performed.

Alternatives to Surgery in Crohn's Disease

Given that surgery, and specifically complications of surgery, cause most cases of IF in Crohn's disease, evidence-based and multi-disciplinary efforts to reduce both the number of operations required, and the associated risk of septic complications, will be the most effective strategies to reduce IF in this population.

The overall incidence of abdominal surgery in Crohn's disease is currently falling. Recent population-based studies have shown that the rate of abdominal surgery in people with Crohn's disease has decreased steadily during the past decades in Canada, the Netherlands, Sweden and other regions [12–14]. This observation, as well as the relative reduction in Crohn's disease as a principal cause of IF in the UK and Denmark as outlined earlier, [4, 6] may be attributed to shifts in medical management of the disease, improved training and specialisation of inflammatory bowel disease (IBD) clinicians, centralisation of IBD care, increasing multidisciplinary management and, perhaps, increased patient empowerment in the management of the disease through advocacy through patient organisations leading to increased awareness of therapeutic options available. Indeed, cohesive working between the patient, physicians, dietitians, IBD nurses, pharmacists, psychologists and surgeons is now recognized as the cornerstone to ensuring optimal care is tailored to the individual [15].

Many interventions have been shown to directly reduce the rates of surgery or the risk of postoperative recrudescent Crohn's disease. Smoking is the strongest modifiable risk factor for recrudescent disease following surgery for Crohn's disease, increasing this risk by 150% [16]. Smoking cessa-

tion should therefore be a central component in the management of Crohn's disease. This intervention needs to be intensive and prolonged, necessitating investment of adequate resource, in order to be successful [17].

Biologic monoclonal antibody therapy has become the backbone of medical therapy for Crohn's disease, and population-based data suggest that the emergence of this class of medication has been associated with a reduced rate of abdominal surgery, [18]. One in five patients with luminal Crohn's disease present with a so-called Crohn's mass, due to an abscess or a phlegmon [19]. Traditionally, the finding of a Crohn's mass has been considered an indication for laparotomy and bowel resection, as medical therapy alone has been thought insufficient to heal penetrating disease. Data from the current biologic era suggests this may no longer be an absolute rule. In a small case series of 13 patients who presented with a phlegmon or an abscess at Beth Israel Hospital in Boston, 11 avoided surgery using a combination of antibiotics, percutaneous drainage and infliximab, while two required delayed surgery [20]. In a larger study, 55 of 95 patients who presented with an intra-abdominal abscess at Mayo Clinic in Rochester were managed non-operatively with a combination of percutaneous drainage, antibiotics and immunomodulator and/or anti-TNF therapy. While all patients in this group responded to non-operarative treatment, 12 of the 55 patients required abdominal surgery during the subsequent 45 months [21]. A meta-analysis of the role of percutaneous drainage in intra-abdominal abscesses in Crohn's disease suggests that this approach may help avoid laparotomy in up to 30% of patients [22].

As the above studies indicate, case selection is important and many patients with intra-abdominal collections will still require surgical resection. Also in this group, a staged approach with initial percutaneous drainage is likely to reduce morbidity and stoma rates and may make laparoscopic resection more realistic. Percutaneous drainage, rather than surgery, is therefore the initial approach recommended by the European Crohn's and Colitis Organisation (ECCO) [23]. Furthermore, when septic complications following surgery do occur, percutaneous drainage has an additional important role in treating peri-anastomotic abscesses, thereby avoiding immediate relaparotomy in selected cases [24].

In recent years, endoscopic balloon dilatation has also taken a key place in the management of short strictures, in particular anastomotic strictures. In the largest case series to date, 776 dilatations were performed in 178 patients with strictures <5 cm in length. The technical success rate was 89% and the perforation rate 1.4%. After 5 years, 64% of patients had avoided surgery [25]. The ECCO guidelines place endoscopic balloon dilatation as the preferred technique to manage symptomatic short anastomotic strictures, but such procedures should only be performed by an experienced practitioner and in an institution with 24-h surgical service due to the risk of early or delayed perforation [23].

Reducing Postoperative Morbidity in Abdominal Surgery for Crohn's Disease

Despite strategies aimed at reducing the need for surgery discussed above, bowel resection will remain a pillar of management in Crohn's disease. Indeed, a recent multi-centre randomised trial demonstrated that laparoscopic ileocaecal resection of primary unifocal disease may result in better outcomes than initial medical therapy, suggesting that surgery should be part of 'top-down' management [26, 27].

A key strategy to prevent IF in Crohn's disease is to reduce the risk of abdominal septic complications when surgery is required. Specifically, this entails reducing the risk of sepsis from anastomotic dehiscence and overlooked enterotomies.

The data on risk factors for anastomotic complications in Crohn's disease are abundant and relatively consistent [28–30]. The low number of events (dehiscence) is a caveat for multivariable regressions often presented in such studies. Nevertheless, risk factors that are frequently identified include: intra-abdominal abscess at the time of surgery, steroid usage (≥10 mg prednisolone daily or equivalent) within 2 weeks of surgery and preoperative weight loss (>10%). Recrudescent disease, hypoalbuminaemia and smoking are other risk factors identified in some studies [17, 28].

A contested issue in inflammatory bowel disease surgery is whether concurrent biologic therapy increases perioperative morbidity, and anastomotic complications in particular. The largest prospective published study on this issue in Crohn's disease is a French multi-centre study in 592 patients. Following adjustments for differences in disease severity, an increase of overall morbidity and intraabdominal septic complications in patients treated by preoperative anti-TNF therapy was demonstrated [31]. It is important to note that data associating systemic steroid therapy and postoperative morbidity are stronger and more consistent than the data on biologic agents, hence most clinicians regard steroid therapy as the more hazardous of the two classes [32–34].

Recognition of risk factors present enables a more informed decision-making at surgery, in particular regarding whether to form a primary anastomosis at resection. For patients with significant risk factors, a double-barrelled (split) stoma should instead be formed, which can then subsequently be reversed via a peristomal incision when risk factors have been fully addressed [34].

Importantly, nearly all of the risk factors discussed above are modifiable. Preoperative optimisation pathways for surgery for Crohn's disease have recently been proposed, combining interventions that correct or minimise the impact of

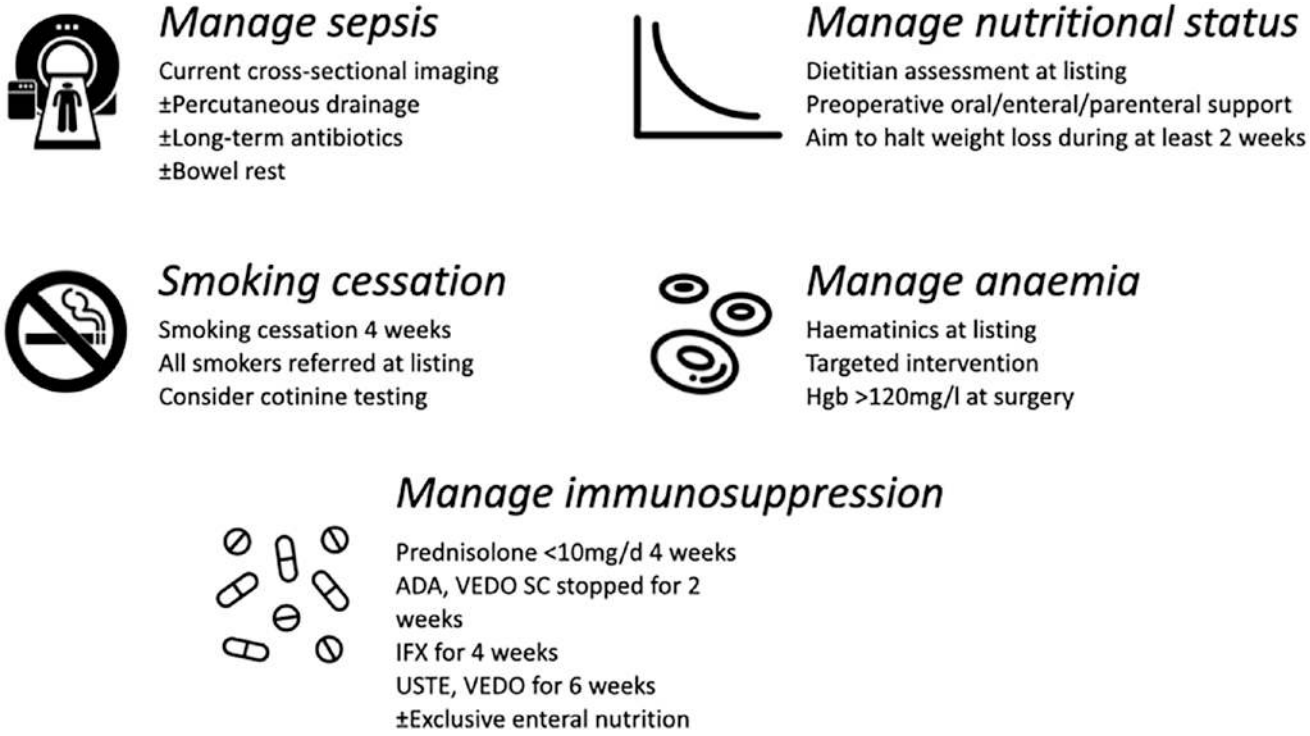

Fig. 1 Example of a preoperative optimisation pathway that can be used in surgery for Crohn's disease. As data are still emerging on several components, chosen targets are pragmatic. ADA, adalimumab. IFX, infliximab. VEDO, vedolizumab. USTE, ustekinumab

identified risk factors [35–37]. Such pathways complement enhanced-recovery pathways for patients undergoing surgery for Crohn's disease [38]. They aim to reduced overall risk, reduce the risk of anastomotic complication and minimise stoma rates.

Furthermore, by down-staging Crohn's disease and eradicating Crohn's masses, a laparoscopic approach may be possible in more cases. Laparoscopy has specific benefits in Crohn's disease. In addition to the well-described short-term benefits on postoperative recovery, [39] laparoscopy results in less wound morbidity and reoperation rates than laparotomy [40]. Cumulatively, this advantage becomes increasingly important in the patient with Crohn's disease who may require several abdominal operations during their life. Laparoscopy is therefore the recommended modality for surgery for Crohn's disease in the ECCO guidelines, [23] and is possible also in penetrating disease treated prior to surgery [41].

The duration of preoperative optimisation pathways described varies from 4–8 weeks, during which malnutrition, smoking, sepsis and steroid and/or biologic therapy are addressed. For steroid therapy, one proposed target is to reduce the dose to <10 mg prednisolone daily (or equivalent) for a period of 4 weeks [29]. For biologic agents, safety data are still emerging. In practice, an estimate of safe wash-out periods for each drug has to be made. During this period, exclusive enteral diet is increasingly used to minimise the risk of disease flare-up and to correct malnutrition, [42, 43] and often parenteral nutrition is indicated. An example of a preoperative optimisation pathway for IBD surgery is summarised in Fig. 1.

It is important to monitor patients during such preoperative optimisation, and to recognise that some patients are too unwell to allow full optimisation. In those cases, early surgery is safer, with exteriorisation of the bowel as stomas, and laparotomy rather than laparoscopy is often required.

Reducing the Risk of Recrudescent Disease After Surgery for Crohn's Disease

A well functioning IBD unit with clear communication between surgical and medical teams is required to time initiation of medications aimed at reducing the risk of recrudescent disease and resume monitoring of disease activity.

The literature on post-resectional medical therapy is too large to summarise here. A large network meta-analysis has comprehensively reviewed this literature in 2015 [44]. This landmark status update demonstrated that anti-TNF monotherapy is by far the most efficient therapy (relative risk of clinical recrudescence 0.04 compared to placebo) followed by antibiotics (RR 0.26), immunomodulator therapy (RR

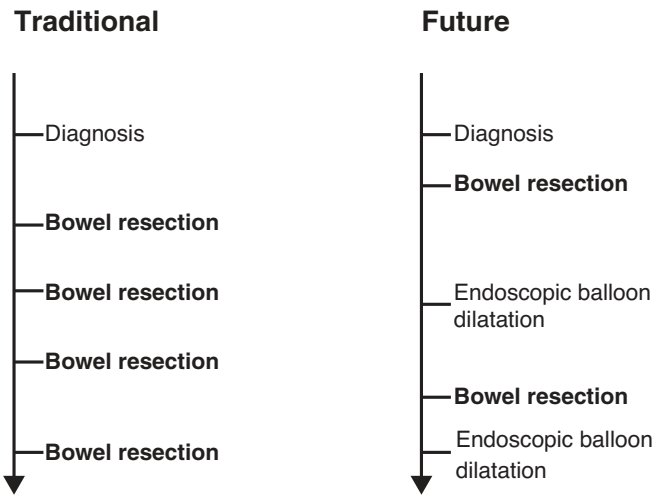

Fig. 2 A challenge in contemporary management of Crohn's disease: To reduce the lifetime incidence of abdominal surgery, and to make each operation safer, as compared to traditional surgery. Current data from several regions of the world suggest that these changes are already occurring

0.36) and mesalasine (RR 0.60). Therapy should be tailored to the individual patient, taking into account factors such as disease phenotype and previous surgeries. Regardless of post-resectional medical therapy, early surveillance with ileocolonoscopy after 6 months after ileocaecal resection, with step-up of medical therapy when recrudescent mucosal disease is found, has been shown to reduce the risk of endoscopic recrudescence on colonoscopy performed at 18 months [45].

With optimal disease surveillance, medical therapy, judicious surgery with preoperative optimisation and usage of endoscopic balloon dilatation when possible, a picture emerges with safer operations being performed more widely spaced out during the lifetime of people with Crohn's disease, (Fig. 2) as indeed demonstrated by recent population-based studies. Future data will show whether this will result in a reduced incidence of intestinal failure in Crohn's.

Management of Type II Intestinal Failure in Crohn's Disease

The management of IF in Crohn's disease is no different than the general management of IF and, indeed, much of the SNAP (Sepsis, Nutrition, Anatomy, Procedure) protocol (see Chapter "Acute surgical intestinal failure. Sepsis and enterocutaneous fistula(s)") was developed specifically for Crohn's disease [46].

Briefly, sepsis control is the first priority, because sepsis is the cause of death in the majority of the 10% of patients with type II IF who do not survive [47–49]. In addition, sepsis prevents anabolism and recovery despite aggressive parenteral nutrition if it is allowed to prevail [50]. Early interventional radiology is a key resource in management of type II IF, as it achieves source control in most cases [51]. Occasionally, early relapatotomy is required for source control [52].

Clinicians who do not regularly manage type II IF may be tempted to embark on definitive surgery early after presentation, in an attempt to restore gastrointestinal continuity and discharge the patient in nutritional autonomy. However, early reconstructive surgery is detrimental for two important reasons. Firstly, a majority of postoperative enterocutaneous fistulas heal spontaneously within the first 8 weeks. Bowel rest and parenteral nutrition may be helpful and are reasonable interventions during this period [48]. Secondly and more importantly, results of definitive surgery for persistent fistulas are directly related to the interval allowed for local, physiological and psychological recovery to occur. Fistula recurrence rates are as high as 25% when definitive surgery is performed within the first couple of months, [53] but below 5% after 12–18 months. During this interval, most patients are at home with parenteral nutrition while they recover nutritionally, and also psychologically, from previous surgery and complications.

In Crohn's disease, surveillance of disease remains important during this phase. Disease recrudescence is rarely seen in practice during this phase, perhaps because the gastrointestinal tract is rarely in continuity and the amount of small bowel may be reduced. Rarely, aggressive medical therapy is indicated once, of course, any sepsis has been eradicated.

Management of Type III Intestinal Failure in Crohn's Disease

Safe HPN allows long-term survival in type III IF. In the longest and largest series published, data collected over 30 years suggest that long-term survival depends primarily on underlying diagnosis [4]. Overall 10-year survival was 59% in this series for all disease types, with patients with Crohn's disease having the best survival of the diagnostic groups [4].

As in type II IF, it is an empirical observation that flare-ups of Crohn's disease activity are rare. This may be due to reduction of the intestinal length, lack of gastrointestinal continuity, particularly lack of colonic continuity reducing any risk of anastomotic recurrence. When it does occur, it can present insidiously as increasing fistula or stoma output, failure to thrive, weight loss, jaundice or unexplained systemic inflammation.

When flares do occur, standard medical management principles apply, modified by often impaired absorption of orally administered medications. It is important to consider the individual's previous phenotype in this setting and, in those with a previous aggressive small bowel phenotype

should be considered for prophylactic Crohn's disease therapy, with on-going monitoring for recurrence. While concern may exist for catheter-related infections in patients receiving immunosuppressive medications, recent data from the authors' unit demonstrate that the risk of such infections is not increased in patients with Crohn's disease receiving therapy and that a meticulous approach to catheter care and training is the cornerstone to preventing catheter infections, enabling very low infection rates to be achieved over many decades in experienced units that foster a multidisciplinary approach to care [4, 54].

Mortality directly related to HPN accounts for some 15% of deaths, and is caused specifically by catheter related bloodstream infections, and more rarely, IF-associated liver disease [4]. Furthermore, there is no doubt that HPN can negatively impact on an individual's quality of life [55]. For the large proportion of patients where standard gastrointestinal reconstructive surgery is not possible, such as in true short bowel syndrome, life-long HPN has been the only option until recently.

Over the past decade, three novel therapies have emerged that allow selected patients with type III IF to become less dependent on HPN, and in some cases to entirely wean off HPN. Patients who develop either IF-associated liver disease requiring intestine and liver transplantation or those with loss of reliable venous access are candidates for intestinal transplantation. In the UK, Crohn's disease is the most common underlying condition [56].

A less invasive surgical approach, possible in some patients, is intestinal lengthening and tapering, procedures initially developed in children to treat bacterial overgrowth associated with a short bowel (see Chapter "Surgery for Patients with a Short Bowel and Tissue Engineering"). The first procedure, longitudinal intestinal lengthening and tailoring (LILT), was developed in the 1970s by Bianchi in Manchester, UK, [57] and was complemented some 30 years later by the serial transverse enteroplasty procedure (STEP) developed by Kim in Boston, MA [58]. In adults, these are rare procedures and case series totalling 30 cases have recently been published with favourable results [59, 60]. Patients with Crohn's disease who have a low risk for recrudescent disease have undergone intestinal lengthening in the United States with good outcomes, although data are limited [1, 60].

Finally, growth factor therapy has recently emerged as an alternative for selected patients with short bowel syndrome (see Chapter "Pro-adaptive Hormones in the Rehabilitation of Adult Patients with a Short Bowel"). So far, a glucagon-like peptide 2 (GLP-2) analogue has been the most successful agent in reducing dependency on HPN [61]. The published experience in type III IF associated with Crohn's disease is favourable [62].

Case selection is key for favourable outcomes and safety for these three novel therapies. In England, proposed surgical candidates are discussed at the bimonthly National Adult Small Intestinal Transplantation forum, which advises on whether to proceed.

References

1. Nyabanga C, Kochhar G, Costa G, Soliman B, Shen B, Abu-Elmagd K. Management of Crohn's disease in the new era of gut rehabilitation and intestinal transplantation. Inflamm Bowel Dis. 2016;22(7):1763–76.
2. Fazio VW, Marchetti F, Church M, Goldblum JR, Lavery C, Hull TL, et al. Effect of resection margins on the recurrence of Crohn's disease in the small bowel. A randomized controlled trial. Ann Surg. 1996;224(4):563–71; discussion571–3
3. Roy P, Kumar D. Strictureplasty. Br J Surg. 2004;91(11):1428–37.
4. Dibb M, Soop M, Teubner A, Shaffer J, Abraham A, Carlson G, et al. Survival and nutritional dependence on home parenteral nutrition: Three decades of experience from a single referral centre. Clin Nutr. 2017;36(2):570–6.
5. Lloyd DAJ, Vega R, Bassett P, Forbes A, Gabe SM. Survival and dependence on home parenteral nutrition: experience over a 25-year period in a UK referral centre. Aliment Pharmacol Ther. 2006;24(8):1231–40.
6. Brandt CF, Hvistendahl M, Naimi RM, Tribler S, Staun M, Brøbech P, et al. Home parenteral nutrition in adult patients with chronic intestinal failure: the evolution over 4 decades in a tertiary referral center. JPEN J Parenter Enteral Nutr. 2017;41(7):1178–87.
7. Watanabe K, Sasaki I, Fukushima K, Futami K, Ikeuchi H, Sugita A, et al. Long-term incidence and characteristics of intestinal failure in Crohn's disease: a multicenter study. J Gastroenterol. 2014;49(2):231–8.
8. Soop M, Khan H, Nixon E, Teubner A, Abraham A, Carlson G, Lal S. Causes and Prognosis of Intestinal Failure in Crohn's Disease: An 18-year Experience From a National Centre. J Crohns Colitis. 2020;14(11):1558–64.
9. Agwunobi AO, Carlson GL, Anderson ID, Irving MH, Scott NA. Mechanisms of intestinal failure in Crohn's disease. Dis Colon Rectum. 2001;44(12):1834–7.
10. Gearry RB, Kamm MA, Hart AL, Bassett P, Gabe SM, Nightingale JM. Predictors for developing intestinal failure in patients with Crohn's disease. J Gastroenterol Hepatol. 2013;28(5):801–7.
11. Uchino M, Ikeuchi H, Bando T, Matsuoka H, Takahashi Y, Takesue Y, et al. Risk factors for short bowel syndrome in patients with Crohn's disease. Surg Today; 2012;42(5):447–452.
12. Frolkis AD, Dykeman J, Negrón ME, deBruyn J, Jette N, Fiest KM, et al. Risk of Surgery for Inflammatory Bowel Diseases Has Decreased Over Time: A Systematic Review and Meta-analysis of Population-Based Studies. Gastroenterology. 2013;145(5):996–1006.
13. Jeuring SFG, van den Heuvel TRA, Liu LYL, Zeegers MP, Hameeteman WH, Romberg-Camps MJL, et al. Improvements in the Long-Term Outcome of Crohn's Disease Over the Past Two Decades and the Relation to Changes in Medical Management: Results from the Population-Based IBDSL Cohort. Am J Gastroenterol. 2017;112(2):325–36.
14. Kalman TD, Everhov ÅH, Nordenvall C, Sachs MC, Halfvarson J, Ekbom A, Ludvigsson JF, Myrelid P, Olén O. Decrease in primary but not in secondary abdominal surgery for Crohn's disease: nationwide cohort study, 1990–2014. Br J Surg. 2020;107(11):1529–38.

15. Morar PS, Sevdalis N, Warusavitarne J, Hart A, Green J, Edwards C, et al. Establishing the aims, format and function for multidisciplinary team-driven care within an inflammatory bowel disease service: a multicentre qualitative specialist-based consensus study. Front Gastroenterol. 2017;9(1):29–36.
16. Reese GE, Nanidis T, Borysiewicz C, Yamamoto T, Orchard T, Tekkis PP. The effect of smoking after surgery for Crohn's disease: a meta-analysis of observational studies. Int J Colorectal Dis. 2008;23(12):1213–21.
17. Thomsen T, Villebro N, Møller AM. Interventions for preoperative smoking cessation. Cochrane Database Syst Rev. 2014;3:CD002294.
18. Costa J, Magro F, Caldeira D, Alarcão J, Sousa R, Vaz-Carneiro A. Infliximab reduces hospitalizations and surgery interventions in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19(10):2098–110.
19. Bruining DH, Siddiki HA, Fletcher JG, Tremaine WJ, Sandborn WJ, Loftus EV. Prevalence of penetrating disease and extraintestinal manifestations of Crohn's disease detected with CT enterography. Inflamm Bowel Dis. 2008;14(12):1701–6.
20. Cullen G, Vaughn B, Ahmed A, Peppercorn MA, Smith MP, Moss AC, Cheifetz AS. Abdominal phlegmons in Crohn's disease: outcomes following antitumor necrosis factor therapy. Inflamm Bowel Dis. 2012;18(4):691–6.
21. Nguyen DL, Sandborn WJ, Loftus EV, Larson DW, Fletcher JG, Becker B, et al. Similar outcomes of surgical and medical treatment of intra-abdominal abscesses in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2012;10(4):400–4.
22. Clancy C, Boland T, Deasy J, McNamara D, Burke JP. A Meta-analysis of Percutaneous Drainage Versus Surgery as the Initial Treatment of Crohn's Disease-related Intra-abdominal Abscess. J Crohns Colitis. 2016;10(2):202–8.
23. Adamina M, Bonovas S, Raine T, Spinelli A, Warusavitarne J, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, Doherty G, El-Hussuna A, Ellul P, Fiorino G, Frei-Lanter C, Furfaro F, Gingert C, Gionchetti P, Gisbert JP, Gomollon F, González Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Kucharzik T, Lytras T, Maaser C, Magro F, Marshall JK, Myrelid P, Pellino G, Rosa I, Sabino J, Savarino E, Stassen L, Torres J, Uzzan M, Vavricka S, Verstockt B, Zmora O. ECCO Guidelines on therapeutics in crohn's disease: surgical treatment. J Crohns Colitis. 2020;14(2):155–68.
24. Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease. Curr Manag. 2010;35:28–62.
25. Gustavsson A, Magnuson A, Blomberg B, Andersson M, Halfvarson J, Tysk C. Endoscopic dilation is an efficacious and safe treatment of intestinal strictures in Crohn's disease. Aliment Pharmacol Ther. 2012;36(2):151–8.
26. Ponsioen CY, de Groof EJ, Eshuis EJ, Gardenbroek TJ, Bossuyt PMM, Hart A, Warusavitarne J, Buskens CJ, van Bodegraven AA, Brink MA, Consten ECJ, van Wagensveld BA, Rijk MCM, Crolla RMPH, Noomen CG, Houdijk APJ, Mallant RC, Boom M, Marsman WA, Stockmann HB, Mol B, de Groof AJ, Stokkers PC, D'Haens GR, Bemelman WA, LIR!C study group. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. Lancet Gastroenterol Hepatol. 2017;2(11):785–92. Erratum Nov;2(11):e7
27. Stevens TW, Haasnoot ML, D'Haens GR, Buskens CJ, de Groof EJ, Eshuis EJ, Gardenbroek TJ, Mol B, Stokkers PCF, Bemelman WA, Ponsioen CY, LIR!C study group. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: retrospective long-term follow-up of the LIR!C trial. Lancet. Gastroenterol Hepatol. 2020;5(10):900–7.
28. Alves A, Panis Y, Bouhnik Y, Pocard M, Vicaut E, Valleur P. Risk factors for intra-abdominal septic complications after a first ileocecal resection for Crohn's disease: a multivariate analysis in 161 consecutive patients. Dis Colon Rectum. 2007;50(3):331–6.
29. Tzivanakis A, Singh JC, Guy RJ, Travis SPL, Mortensen NJ, George BD. Influence of risk factors on the safety of ileocolic anastomosis in Crohn's disease surgery. Dis Colon Rectum. 2012;55(5):558–62.
30. Morar PS, Hodgkinson JD, Thalayasingam S, Koysombat K, Purcell M, Hart AL, et al. Determining Predictors for Intra-abdominal Septic Complications Following Ileocolonic Resection for Crohn's Disease--Considerations in Pre-operative and Peri-operative Optimisation Techniques to Improve Outcome. J Crohn's Colitis. 2015;9(6):483–91.
31. Brouquet A, Maggiori L, Zerbib P, Lefevre JH, Denost Q, Germain A, Cotte E, Beyer-Berjot L, Munoz-Bongrand N, Desfourneaux V, Rahili A, Duffas JP, Pautrat K, Denet C, Bridoux V, Meurette G, Faucheron JL, Loriau J, Guillon F, Vicaut E, Benoist S, Panis Y, GETAID Chirurgie Group. Anti-TNF Therapy Is Associated With an Increased Risk of Postoperative Morbidity After Surgery for Ileocolonic Crohn Disease: Results of a Prospective Nationwide Cohort. Ann Surg. 2018;267(2):221–8.
32. El-Hussuna A, Krag A, Olaison G, Bendtsen F, Gluud LL. The effect of anti-tumor necrosis factor alpha agents on postoperative anastomotic complications in Crohn's disease. Dis Colon Rectum. 2013;56(12):1423–33.
33. Lau C, Dubinsky M, Melmed G, Vasiliauskas E, Berel D, McGovern D, et al. The Impact of preoperative serum anti-TNFα therapy levels on early postoperative outcomes in inflammatory bowel disease surgery. Ann Surg. 2015;261(3):487–96.
34. Myrelid P, Söderholm JD, olaison G, Sjodahl R, Andersson P. Split stoma in resectional surgery of high-risk patients with ileocolonic Crohn's disease. Colorect Dis. 2012;14(2):188–93.
35. Zerbib P, Koriche D, Truant S, Bouras AF, Vernier-Massouille G, Seguy D, et al. Pre-operative management is associated with low rate of post-operative morbidity in penetrating Crohn's disease. Aliment Pharmacol Ther. 2010;32(3):459–65.
36. Spinelli A, Allocca M, Jovani M, Danese S. Review article: optimal preparation for surgery in Crohn's disease. Aliment Pharmacol Ther. 2014;40(9):1009–22.
37. Patel KV, Darakhshan AA, Griffin N, Williams AB, Sanderson JD, Irving PM. Patient optimization for surgery relating to Crohn's disease. Nat Rev Gastroenterol Hepatol. 2016;13(12):707–19.
38. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Clin Nutr. 2012;31:783–800.
39. Maartense S, Dunker M, Slors J, Cuesta M, Pierik E, Gouma D, et al. Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. Ann Surg. 2006;243(2):143–9; discussion150–3
40. Eshuis EJ, Slors JFM, Stokkers PCF, MAG S, Ubbink DT, Cuesta MA, et al. Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease. Br J Surg. 2010;97(4):563–8.
41. Soop M, Larson DW, Malireddy K, Cima RR, Young-Fadok TM, Dozois EJ. Safety, feasibility, and short-term outcomes of laparoscopically assisted primary ileocolic resection for Crohn's disease. Surg Endosc. 2009;23(8):1876–81.
42. Heerasing N, Thompson B, Hendy P, Heap GA, Walker G, Bethune R, et al. Exclusive enteral nutrition provides an effective bridge to safer interval elective surgery for adults with Crohn's disease. Aliment Pharmacol Ther. 2017;45(5):660–9.
43. Li Y, Zuo L, Zhu W, Gong J, Zhang W, Gu L, et al. Role of exclusive enteral nutrition in the preoperative optimization of patients with Crohn's disease following immunosuppressive therapy. Medicine. 2015;94(5):e478.

44. Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV Jr. Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: a systematic review and network meta-analysis. Gastroenterology. 2015;148(1):64–76.e2; quiz e14
45. De Cruz P, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet. 2015;385(9976):1406–17.
46. Slade DA, Carlson GL. Takedown of enterocutaneous fistula and complex abdominal wall reconstruction. Surgical Clinics of NA2013;93(5):1163–1183.
47. Hollington P, Mawdsley J, Lim W, Gabe S, Forbes A, Windsor A. An 11-year experience of enterocutaneous fistula. Br J Surg. 2004;91(12):1646–51.
48. Visschers R, Olde Damink S, Winkens B, Soeters P, van Gemert W. Treatment strategies in 135 consecutive patients with enterocutaneous fistulas. World J Surg. 2008;32(3):445–53.
49. Martinez J, Luque-de-Leon E, Mier J, Blanco-Benavides R, Robledo F. Systematic management of postoperative enterocutaneous fistulas: factors related to outcomes. World J Surg. 2008;32(3):436–43; discussion 444
50. Streat S, Beddoe A, Hill G. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. J Trauma. 1987;27(3):262–6.
51. Felder SI, Barmparas G, Murrell Z, Fleshner P. Risk factors for failure of percutaneous drainage and need for reoperation following symptomatic gastrointestinal anastomotic leak. Am J Surg. 2014;208(1):58–64.
52. Soop M, Soop M, Carlson GL, Carlson GL. Recent developments in the surgical management of complex intra-abdominal infection. Br J Surg. 2017;104(2):e65–74.
53. Lynch A, Delaney C, Senagore A, Connor J, Remzi F, Fazio V. Clinical outcome and factors predictive of recurrence after enterocutaneous fistula surgery. Ann Surg. 2004;240(5):825.
54. Bond A, Teubner A, Taylor M, Cawley C, Varden J, Abraham A, et al. Catheter-related infections in patients with acute type II intestinal failure admitted to a national centre: Incidence and outcomes. Clin Nutr. 2019;38(4):1828–32.
55. Wilburn J, McKenna SP, Heaney A, Rouse M, Taylor M, Culkin A, et al. Development and validation of the Parenteral Nutrition Impact Questionnaire (PNIQ), a patient-centric outcome measure for Home Parenteral Nutrition. Clin Nutr. 2018;37(3):978–83.
56. Rutter CS, Amin I, Russell NK, Sharkey LM, Butler AJ, Middleton SJ. Adult Intestinal and multivisceral transplantation: experience from a single center in the United Kingdom. Transplant Proc. 2016;48(2):468–72.
57. Bianchi A. Intestinal loop lengthening--a technique for increasing small intestinal length. J Pediatr Surg. 1980;15(2):145–51.
58. Kim HB, Fauza D, Garza J, Oh J-T, Nurko S, Jaksic T. Serial transverse enteroplasty (STEP): A novel bowel lengthening procedure. J Pediatr Surg. 2003;38(3):425–9.
59. Abu-Elmagd KM, Costa G, McMichael D, Khanna A, Cruz RJ, Parekh N, et al. Autologous reconstruction and visceral transplantation for management of patients with gut failure after bariatric surgery: 20 years of experience. Ann Surg. 2015;262(4):586–601.
60. Sudan D, Thompson J, Botha J, Grant W, Antonson D, Raynor S, et al. Comparison of intestinal lengthening procedures for patients with short bowel syndrome. Ann Surg. 2007;246(4):593–604.
61. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011;60(7):902–14.
62. Kochar B, Long MD, Shelton E, Young L, Farraye FA, Yajnik V, et al. Safety and Efficacy of Teduglutide (Gattex) in Patients With Crohn's Disease and Need for Parenteral Support Due to Short Bowel Syndrome-associated Intestinal Failure. J Clin Gastroenterol. 2016;51(6):1–511.

Peritoneal Adhesions and Encapsulating Peritoneal Sclerosis

Titus Augustine, Alison Culkin, and Mattias Soop

Key Points

1. Adhesions are common after abdominal surgery and up to 5% will need a repeat admission for them. The chance of developing them increases with the number of abdominal operations.
2. Adhesions/intraperitoneal fibrosis may be caused by ischaemia, infection, abrasions, spillage of gastrointestinal contents, desiccation, excessive heat/light/electrocautery/sutures, fibres/glove powder and some medications. Reducing these factors reduces the chance of developing adhesions.
3. Adhesions may cause recurrent episodes (partial or complete) of bowel obstruction. These episodes may be reduced by a low fibre diet. They may also be associated with infertility.
4. Adhesions and adhesion-related readmission to hospital are more common after open than laparoscopic surgery
5. Topical agents reduce the formation of adhesions but have not been shown to reduce readmissions or reoperations for adhesions.
6. Encapsulating peritoneal sclerosis (EPS) is the most severe form of adhesions and may cause a frozen abdomen on which surgery is very difficult.
7. Patients with adhesions/EPS are encouraged to chew their food well before swallowing. A low insoluble fibre/low residue diet can reduce the chance of obstructive symptoms occurring.

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Adhesions

What Are They?

Adhesions in the peritoneal cavity are non-anatomical attachments between visceral and/or parietal peritoneal surfaces. They can be congenital or acquired. Congenital adhesions can range from complete peritoneal encapsulation, a rare cause of bowel obstruction in children and adults, to congenital bands that can cause internal herniation and volvulus. Studies reveal that 5–27% of those who have never had abdominal surgery have abdominal adhesions [1, 2]. This prevalence increases with age, suggesting that adhesions often form secondary to abdominopelvic events such as diverticulitis [2].

Adhesions are most prevalent in people who have had previous surgery. Prospective data from the pre-laparoscopic era demonstrated that the prevalence of adhesions in people undergoing laparotomy increased from 11.5% in people who had not undergone previous surgery to 93% in those who had [2]. Most of the adhesions noted had formed between the greater omentum and the abdominal wall scar.

Histological studies of postoperative adhesions reveal that they are typically collagenous bands initiated either by peritoneal injury or bleeding or a combination [1]. In the past, foreign bodies were the dominant cause of postoperative adhesions, but this has likely diminished as talcum powder, starch and textile materials have become replaced by safer materials [1].

Additional causes of acquired adhesions between surfaces in the peritoneal cavity include neoplasia, endometriosis, radiotherapy and a range of infections such as chlamydia and tuberculosis.

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Adhesions in the Context of General Surgery

Peritoneal adhesions play a role in the pathogenesis of an array of symptoms and conditions of affected organ systems. Gastrointestinal and gynaecological complaints are the most common. Here, we will focus on complaints seen in general surgery that may or may not be associated with adhesions.

Abdominal Pain

Chronic or recurring abdominopelvic pain is common after abdominal surgery and adhesions are often thought of as an important cause of such symptoms. However, the evidence linking adhesions themselves and pain is poor. There is supportive experimental evidence, such as the findings of sensory nerve fibers in adhesions [3, 4].

It is not straightforward to scientifically study the role of adhesions as a cause of symptoms, as intraperitoneal adhesions are so prevalent in the population [2]. We instead have to rely on studies of adhesiolysis to examine this role. In a landmark study from the Netherlands, 100 patients with long-term abdominal pain after laparotomy underwent diagnostic laparoscopy and, if adhesions were found, randomised to laparoscopic adhesiolysis or no further dissection [5]. Three to 12 months after laparoscopy, pain scores decreased in both study groups, with no differences between groups. This suggests a placebo effect, and no additional effect of adhesiolysis on pain.

Seventy-three patients were then followed up at 12 years [6], and at this timepoint significantly worse outcomes were found in the group that had undergone adhesiolysis, including more frequent pain and use of analgesics and, perhaps most significantly, an increased number of reoperations to address adhesions.

Thus, while it remains possible that adhesions cause abdominal pain, adhesiolysis has no benefit in the short term, and an adverse impact in the long term, on this symptom. It should be avoided as a therapy for pain alone.

Intestinal Obstruction

It is clear that peritoneal adhesions, whether congenital, postoperative or otherwise acquired, are a dominant cause of small bowel obstruction: meta-analysis suggests that 56% of cases are caused by adhesions [7].

The magnitude of the problem of postoperative adhesions has been extensively studied in the so-called SCAR studies, registry studies that followed large cohorts who had abdominal surgery in Scotland. In the SCAR-1 study, 29,790 patients who underwent laparotomy in 1986 were retrospectively studied for 10 years [8]. One in three patients were readmitted to hospital during this time period. Most were readmitted more than once, resulting in a total number of readmissions of 21,347. Of those readmissions, 5.7% were documented as being caused by adhesions, in most cases by findings at surgery. In a much larger number of readmissions, 38% of the 21,347, adhesions were judged to be "possibly" causative based on a set of criteria. The SCAR-1 study established that readmission to hospital after open abdominal surgery is common and frequently directly or possibly caused by adhesions. The subsequent SCAR-2 study assessed changes during the time period 1996–1999, observing no change in the risk of readmission after open abdominal surgery [9].

The SCAR-3 study further analysed a cohort operated in the financial year 1996 with regard to types of index surgery [10]. The risk of readmission for documented adhesions during the subsequent 5 years was 3.8% for the whole cohort, and 5.2% excluding appendectomy. The risk was particularly increased following panproctocolectomy (15.4%), total colectomy (8.8%) and ileostomy procedures (10.6%) and decreased following small bowel surgery (1.8%) and appendicectomy (0.9%) [10]. The risk in patients who previously had had open abdominal surgery was twice that of those who had not. Although multivariable analyses were not performed, univariable analyses suggested that increasing age appeared to protect against readmission for adhesions, and Crohn's disease did not change the risk [10].

The concept that some patients form adhesions more readily than others is supported by long-term follow-up in the LAPAD study from the Netherlands [11]. In this study of 604 patients who had elective abdominal surgery in a single centre from 2008 to 2010, 32% were found to have severe adhesions, mostly from previous laparotomies, while 68% had mild or no adhesions. During a relatively short median follow-up of 46 months, 38 of the 604 (6.3%) re-presented with adhesive bowel obstruction. On multivariable regression, the finding of severe adhesions at index surgery was a strong predictor of subsequent adhesive small bowel obstruction [11].

In summary, some 60% of cases of small bowel obstruction are caused by adhesions, and in the long term of 4–10 years, at least 5% of patients undergoing abdominal surgery will be readmitted with proven adhesive bowel obstruction. Of note, these data are from cohorts of patients who nearly all underwent open surgery. The impact of minimally invasive surgery on adhesion-related morbidity is examined below.

Morbidity During Future Operations

Another consequence of adhesions is lengthy adhesiolysis during future intraperitoneal operations. This is not only time-consuming, but is associated with increased morbidity. The initial LAPAD study focused on adhesiolysis as a risk factor for adverse outcomes [12]. In this prospective study, 755 elective open or laparoscopic abdominal operations were observed. Adhesiolysis was required in 475 operations, and in 50 of those (10.5%) an accidental enterotomy was made. Adhesiolysis added a median of 20 (range 1–177)

minutes to the operation. The risk was of enterotomy was particularly increased in operations requiring more than an hour of adhesiolysis. In the 280 operations during which adhesiolysis was not required, no enterotomies were made. The difference in enterotomy risk helps explain several associations between adhesiolysis and adverse outcomes seen in this study, such as postoperative sepsis, increased length of hospital stay and increased costs [12].

Cost to Healthcare Services

Calculating the economic costs of adhesions is complicated as it encompasses the costs of clinic and emergency visits, diagnostic tests, hospital admissions, surgery performed to treat adhesions, adhesiolysis during other peritoneal surgery, loss of income from admissions, and other costs.

The LAPAD study estimated that the mean hospital cost for each patient undergoing elective surgery increased from USD 14,063 in those without adhesions to USD 18,579 in those with adhesions in the Netherlands in 2010 [12].

A Finnish population-based study estimated that, at 1999 currency levels, annual direct hospital for small bowel adhesion in the country was GBP 2,077,796, similar to the costs of treating rectal cancer throughout the country [13].

Adhesions in the Context of Intestinal Failure

Although extensive peritoneal adhesions have long been recognised as a cause of intestinal failure [14], data on this association are scarce. In the largest published series of long-term (3 months or longer) parenteral nutrition, mechanical obstruction was the mechanism of intestinal failure in 20/545 (3.7%) of patients treated at the Irving National Intestinal Failure Unit in Manchester, UK during the period 1978–2011 [15]. In a snapshot study from the same unit in 2017, the proportion was 15/273 (5.5%) cases [16]. However, these studies included patients with cancer as the underlying diagnosis, and the number of patients with benign adhesions is likely to be less.

Given the prevalence of peritoneal adhesions in the population, the risk of developing intestinal failure through this mechanism can reasonably be assumed to be small. Empirically, cases where benign adhesions are the dominant cause of intestinal failure are unusual. Where this occurs, adhesions are often the result of multiple operations, previous peritonitis and/or implanted mesh.

A much more common clinical challenge is the patient with small bowel dysmotility who has previously undergone surgery, often subtotal colectomy for suspected slow-transit constipation. Such patients frequently have radiological findings consistent with both intestinal dysmotility and adhesive obstruction. Assessing the contribution of adhesions in such cases is crucial in order to predict the likelihood that surgical adhesiolysis will improve intestinal function. Helpful tools in this assessment include longitudinal imaging to identify any fixed transition points, histopathology with specific immunohistochemistry on full-thickness small bowel samples to identify known dysmotility disorders such as visceral myopathy [17], and in selected cases a trial of a loop enterostomy proximal to a suspected obstructive site to assess whether function in the proximal small bowel normalises.

Diagnosis

Diagnosing Adhesions

In the absence of concurrent small bowel obstruction, adhesions in the peritoneal cavity are not visualised by static radiological imaging such as computed tomography or magnetic resonance imaging. However, dynamic ultrasonography is emerging as a promising diagnostic modality, in particular in the obstetric field. In the so-called visceral slide test, the viscera are visualised by ultrasound in different regions of the abdomen, and the extent of movement in response to normal or forced respiration is assessed. Restricted or absent movement, or slide, is thought to reflect peritoneal adhesions. A recent meta-analysis of 25 observational studies focused on the periumbilical area, commonly used for laparoscopic access to the peritoneal cavity [18]. A positive predictive value of 60.4% and, more importantly, a negative predictive value of 99.2% was demonstrated [18]. The gold standard used in these studies was the findings on laparotomy or laparoscopy. While this finding has implications for minimally invasive surgical techniques, better data are needed on visceral slide sonography in the rest of the abdomen.

Abdominal dynamic magnetic resonance imaging, or cine-MRI, is a similar technique that has been evaluated with promising results [19]. In a head-to-head comparison, dynamic ultrasound and MRI both performed well, and cine-MRI was superior in detecting adhesions between viscera such as small bowel [20].

Dynamic imaging is yet to enter routine clinical practice, but the techniques are available and could prove valuable in investigating unclear symptoms or preparing for complex abdominal re-operative surgery. The gold standard in diagnosing adhesions remains direct visualisation at surgery. During surgery it is also possible to systemically assess and grade adhesions (Fig. 1). Several scores have been proposed. The Zühlke score described in 1990 is based on the histopathology of adhesions, grading them from weak to thick [22]. The increasingly used peritoneal adhesion index (PAI) instead describes the severity of adhesions in the regions of the abdomen, and provides a summative score (Fig. 2) [23]. In brief, adhesions observed at surgery are scored 0 (no adhesions)–3 (very strong vascularised adhesions). The

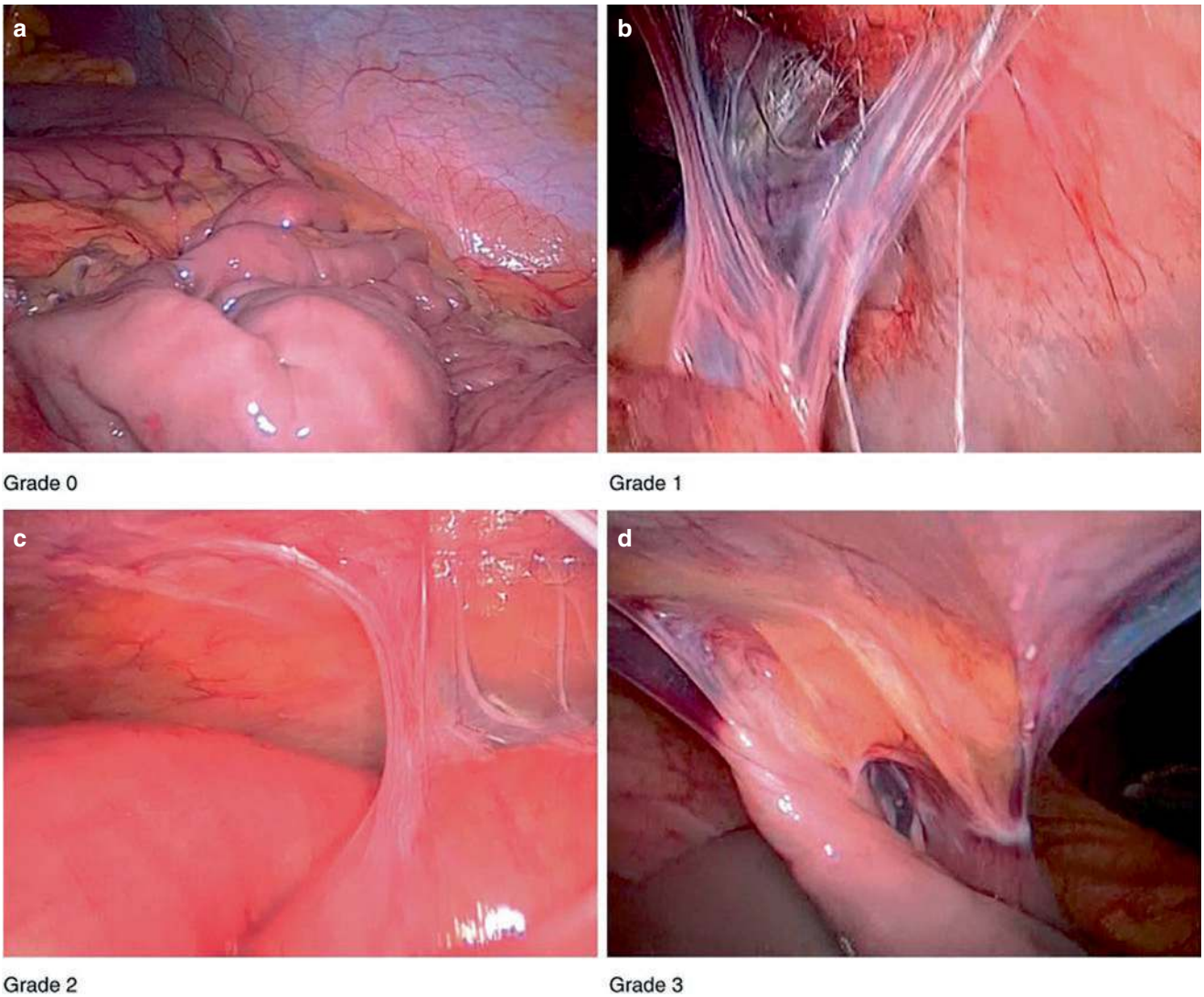


Fig. 1 Severity of adhesions. (**a**) no adhesions (grade 0); (**b**) flimsy thickness, avascular (grade 1); (**c**) moderate thickness, limited vascularity (grade 2); and (**d**) dense thickness, vascularized (grade 3). (Hull et al., Adhesions after laparoscopic and open ileal pouch–anal anastomosis surgery for ulcerative colitis, Br J Surg, 2012, 99(2);270–5, by permission of Oxford University Press [21])

abdomen is divided in nine even regions, and adhesions in each region are scored on this scale. A tenth score is determined for inter-loop adhesions. The ten scores are added up and the sum is the total PAI score.

Diagnosing Adhesive Intestinal Obstruction

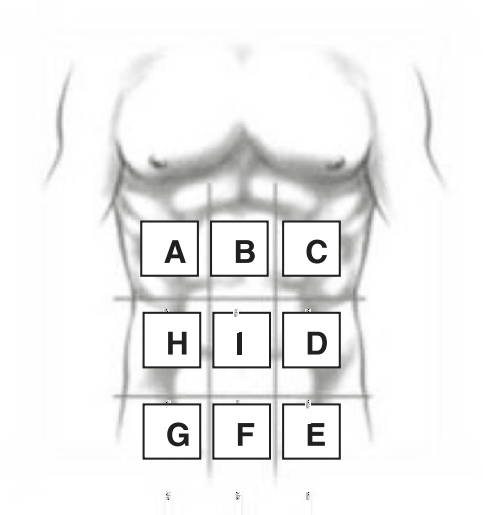
When adhesions are complicated by concurrent intestinal obstruction, the clinical presentation and radiological findings are more sensitive and specific. The patient often presents with a sudden onset of colicky central abdominal pain which is worse in the ileum than jejunum and may follow eating a fibrous/grisly bit of food (often not well chewed). This may be followed by vomiting, a yellow/green vomit suggest proximal small bowel obstruction and a dark brown fluid a more distal one. The bowel/stoma may stop working. The abdomen may be distended with loud bowel sounds. If an obstruction resolves it is followed for 1–3 days by diarrhoea or if a stoma a high output.

Useful radiology includes plain abdominal X-ray and cross-sectional imaging, and findings include dilated small bowel up to the point of obstruction (diameter above 3 cm), air–fluid levels and an absence of gas in the colon. Cross-sectional imaging often confers additional information, such as the cause of obstruction and can show signs of ischaemia.

A difficulty arises when a patient presents with intermittent symptoms suggesting small bowel obstruction. Ensuring that urgent diagnostic imaging is obtained before symptoms resolve is the only way to diagnose obstruction in such cases.

A similar problem is posed when diagnosing low-grade small bowel obstruction. Such relative obstruction may not

PERITONEAL ADHESION INDEX:



Regions:	Adhesion grade:
A Right upper	____
B Epigastrium	____
C Left upper	____
D Left flank	____
E Left lower	____
F Pelvis	____
G Right lower	____
H Right flank	____
I Central	____
L Bowel to bowel	____

Adhesion grade score:

0 No adhesions

1 Filmy adhesions, blunt dissection

2 Strong adhesions, sharp dissection

3 Very strong vascularized adhesions, sharp dissection, damage hardly preventable

PAI ☐

Fig. 2 Peritoneal Adhesion Index (adapted from Coccolini et al. [23]). Each area of the abdomen is ascribed an adhesion related score. The sum of the scores will result in the PAI

result in pre-stenotic dilatation, resulting in a sensitivity of CT in this condition of only 50% [24]. Enteroclysis, in which contrast is delivered directly into the small bowel at a high rate through a nasojejunal tube, is more sensitive to detect low-grade obstruction; indeed, some studies suggest the technique is near 100% sensitive [25].

Prevention

The literature reviewed above shows that surgical adhesiolysis is followed by formation of new adhesions. There is currently no other treatment of adhesions. Therefore, prevention in routine surgical practice is a crucial priority to reduce the considerable morbidity and costs associated with adhesions.

Surgical Technique

Several surgical techniques have been proposed to decrease adhesion formation following intraperitoneal surgery (Table 1). They include minimally invasive approaches; closure of the parietal peritoneum; avoidance of foreign bodies such as glove powder, sutures and meshes; prevention of infection; and peritoneal lavage. A 2012 meta-analysis found no effects of such techniques on rates of subsequent clinically significant adhesions or adhesions on subsequent surgery [26].

In regards to minimally invasive surgery, however, the amount of high-quality data has matured further since this meta-analysis. There is now high-grade evidence that supports the hypothesis that laparoscopic surgery significantly decreases subsequent adhesion-related morbidity. The SCAR study group retrospectively studied 72,270 patients who underwent laparoscopic or open abdominal or pelvic surgery in the period 2009–2011 [26]. After 5 years, 1.7% in the laparoscopic cohort vs. 4.3% in the open surgery cohort had been readmitted to hospital with proven adhesion-related morbidity, mainly adhesive small bowel obstruction. Adjusting for confounders, the authors found that laparoscopy reduced the risk of adhesion-related readmission within 5 years of surgery by 32% [27].

Data from the series of large randomised trials that first evaluated safety and efficacy of laparoscopic colon and rectal cancer resection have mostly been unable to demonstrate effects on long-term adhesion-related morbidity [28–30]. One recent randomised trial did demonstrate reduces rates of adhesions in the minimally invasive surgery group [31]. A recent meta-analysis of randomised trials pooled 4656 patients and did not find an association between laparoscopy and rates of adhesion-related morbidity [32]. The lack of effect in randomised trials is not surprising given the low event rate. Very large study groups would be required to definitively demonstrate an effect of laparoscopy on adhesions in a randomised design.

In summary, available randomised trials are small in relation to the event rate of measurable outcomes, and arguably the best evidence available is large clinical registry data. The recent, large SCAR study update provides strong support for the reasonable notion that less tissue damage results in less formation of adhesions.

It is also reasonable to suggest that, regardless of surgical approach, atraumatic surgical technique and meticulous attention to detail is important in preventing adhesion formation, although this factor is difficult to quantify and study. Both tissue injury and bleeding play a role in initiating adhesion formation, and are best minimised. Tissue injury is minimised by focused sharp dissection, avoiding blunt dissection, optimum settings in energy devices, careful retraction of tissues and using inert irrigation fluid at body temperature.

Table 1 Adhesion prevention strategies

Awareness of risk factors
Increasing age
Number of previous laparotomies
Complexity of the procedure
Location of the procedure (increased in pelvic procedures)
Crohn's disease
Resections for colonic cancer
Proctocolectomy, total colectomy, ileostomy
Conservatively treated localised peritonitis (appendicitis, diverticulitis)
Surgical technique
Careful tissue handling
Sharp dissection using sharp instruments
Avoid crushing tissue
Avoid unnecessary dissection
Attention to detail with ligatures
Optimum tissue beyond ligature to reduce ischemic tissue
Avoid excessive redundant ends of non-absorbable tissue
Avoid bowel exposure and desiccation
Avoid drying of tissue, in exposed area with adherence of clot
Use laparoscopic technique if possible
Robotic techniques
Avoid peritoneal suturing during wound closure
Use of physical antiadhesion barriers
Seprafilm® Adhesion Barrier (Cambridge, MA; Genzyme Corporation)
Gore Preclude Surgical Membrane Adhesion Barrier Flagstaff, AZ; Gore and Associates Inc.
Gynecare Interceed Absorbable Adhesion Barrier (Somerville, NJ; Johnson and Johnson)
Adept Solution: Adhesion Reduction Solution (Deerfield, IL; Baxter Healthcare Corporation)
Intercoat (AC AG Group, Kaltenkirchen, Germany)
Fibrin Sheet (TachoComb, Tokyo, Japan)
Antibiosis techniques to reduce bacterial translocation
Mechanical bowel preparation
Antibiotics
Pharmacologic agents (anecdotal and experimental)
Antiinflammatory agents (Steroids, NSAIDS)
Tamoxifen (Synthetic nonsteroidal antiestrogen agent, with antifibrotic properties)
Anticoagulants including heparin, ancrod.
Calcium channel blockers
Vitamin E
Halofuginone

Topical Biochemical Agents

Given the significant prevalence of adhesions following intraperitoneal surgery and their associated morbidity

and costs, their prevention by chemical and pharmacological agents has been a large and active research field. Strategies evaluated include systemic agents such as anti-inflammatory drugs and anticoagulants, and chemicals applied topically in the surgical wound. To summarise this field, to date none has been widely applied in clinical practice.

A Cochrane meta-analysis of randomised and pseudo-randomised trials of topical agents, most recently updated in 2009, concluded that a hyaluronic acid/carboxymethyl membrane reduced the incidence and severity of adhesions as assessed at a second, planned operation months later (Odds ratio 0.15), but did not affect the need for unplanned reoperation for adhesive small bowel obstruction (Odds ratio 0.84) [33]. It cautioned that some data suggested an increased risk of anastomotic dehiscence when the agent was applied near an anastomosis. The hyaluronic acid/carboxymethyl membrane was the only agent for which sufficiently high-quality data were available for meta-analysis [33].

A 2014 meta-analysis included non-randomised studies in addition to randomised trials, and made similar conclusions regarding effects of topical agents on adhesion formation, reoperative rates, and importantly on anastomotic complications [34]. Furthermore, other adverse effects were also evaluated, and found to be no different between treatment and control groups. These included wound healing complications and abscess formation. The latter conclusion has been challenged, however, as a preliminary report of a large observational study was not included [35]. This study of 1885 patients who underwent proctectomy and ileal pouch-anal anastomosis reported an increased incidence of pelvic sepsis in patients treated with hyaluronic acid/carboxymethyl membrane (10.2%) when compared to those who were not treated (6.8%, P 0.016) [36].

In the absence of clinical efficacy, it is difficult to support routine usage of hyaluronic acid/carboxymethyl membranes or any other agents to prevent adhesions. Some centres routinely use the membranes around the two limbs of a temporary diverting loop ileostomy as it traverses the abdominal wall, in order to reduce adhesions when it is taken down some 6–12 weeks later. Such usage appears safe and advantageous. It is also reasonable to consider the agent when reoperating patients with a known capacity to form troublesome adhesions.

Systemic Agents

Non-steroidal anti-inflammatory drugs are the most widely studied but their clinical efficacy is questionable. Corticosteroids have poor efficacy and are associated with immunosuppression and delayed wound healing. Fibrinolytics have a risk of impaired wound healing and/or bleeding.

Management in the Context of Intestinal Failure

While type 3 intestinal failure is rarely attributed solely to intraperitoneal adhesions, they are an important factor in the management of type 2 intestinal failure, specifically in determining the timing of reconstructive surgery. For many reasons discussed extensively in chapter "Acute Surgical Intestinal Failure. Sepsis and Enterocutaneous Fistula(s)", reconstructive surgery for IF is typically delayed until 6–12 months after the most recent surgery. One of the key considerations is the maturation and, ideally, resolution of adhesions. There is no longitudinal data on these processes, but it is a common clinical observation that reoperative surgery within the first 2–3 months is very technically challenging with dense and often still inflamed adhesions; that reoperative surgery after a period of years is much more frequently straightforward and the adhesions encountered soft and filmy. The difficulty is determining the ideal time point between these extremes when relaparotomy is reasonably safe.

Useful clinical tests are simple inspection and palpation of the abdomen. A soft, flexible abdominal wall is promising. If there is a stoma or an enterocutaneous fistula, it is highly useful to observe its movement when the patient coughs or strains; free movement and a slight prolapse of the bowel is a good sign that the abdominal viscera are not rigidly held in a frozen abdomen. If clinical examination suggests that the abdomen is dense and inflammation not yet resolved, it is best to delay reconstructive surgery and re-evaluate after 6 months.

In type 3 IF, adhesions are often present and the challenge is to assess their relevance. As mentioned above, this is particularly the case in conditions associated with impaired small bowel motility, such as dysmotility syndromes.

Encapsulating Peritoneal Sclerosis

Encapsulating peritoneal sclerosis (EPS) is the most severe form of adhesions/intraperitoneal fibrosis and is a descriptive abdominal manifestation of a spectrum of aetiologic conditions [37]. A diagnosis of EPS in the current era is considered synonymous with the clinic-pathologic syndrome which is an important morbidity of long-term peritoneal dialysis. All forms of peritoneal sclerosis with or without encapsulation can lead to intestinal dysfunction and eventual intestinal failure. The pathophysiologic mechanism in the different diseases varies depending on the specific aetiology. Clinical manifestations occur when there is the formation of a membrane or peritoneal sclerosis which causes adhesions, between bowel loops, and also between the bowel and the parietal peritoneum, causing restriction of gut

motility. With progression of disease, the gut can become cocooned and completely encased, causing progressive intestinal failure. The biologic processes underlying the individual aetiology, disease progression and presentation are varied and multifactorial and clinical presentations can be subtle and mimic other pathology, leading to delayed diagnosis or late presentations. The overarching clinical picture however is one of GI dysfunction associated with intraperitoneal inflammation associated with progressive nutritional deficiency, eventually leading, if untreated to an acute presentation requiring surgical intervention. On a background of significant associated comorbidity, there may be a high risk of mortality or intestinal failure.

The diagnosis of EPS is often made late and in a large number of cases only at surgery. Early diagnosis requires a knowledge and suspicion of the condition in the clinical context, and is confirmed by combining the clinical history, presentation and imaging, surgical findings and histology. EPS is not a histological diagnosis. Surgery remains the mainstay of treatment, and best results are obtained in centres which have experience with managing this relatively rare condition. However, the overall management is complex, requiring a number of disciplines, with nutritional support and surgery playing a key role in management.

The Peritoneum Structure, Physiology and Function

The peritoneal cavity is a potential space, separating the parietal peritoneum, covering the inner walls of the abdomen and the pelvis and the visceral peritoneum covering the abdominal viscera and the bowel. The surface area of the peritoneum is over 1.8 m^2 in area, with an interface of peritoneal fluid, of approximately 100 mL, which allows lubrication and free movement of the bowel. The fluid is an ultrafiltrate of plasma, providing a frictionless environment for the abdominal organs.

The peritoneal surface is formed of a single layer of cells lining the peritoneal cavity, first described by James Douglas in 1730, and then later called the mesothelium by Binot in 1980. These mesothelial cells are 25 μm in diameter, are derived from the mesoderm and possess both mesenchymal and epithelial characteristics (Figs. 3 and 4).

Physiologically, the peritoneum plays an important role in maintaining the intra-abdominal homeostatic equilibrium. The functions of the peritoneal membrane include, transport of fluid and particulate matter, regulation of leucocyte migration, control of coagulation and fibrinolysis, antigen presentation, synthesis of inflammatory cytokines, growth factors and extracellular matrix for repair. These multiple functions enable the several important clinical therapeutic interventions via the peritoneal cavity, including peritoneal dialysis, chemotherapy and immunotherapy [39]. Kastelein et al. have provided an excellent up to date review of the embryology, anatomy, physiology, pathophysiology and pathophysiology of the peritoneum and peritoneal vasculature [40]. More recently studies suggest that exosomes contribute to peritoneal function, by the intracellular transfer of DNA, mRNA, proteins, and lipids. They are thought to play a part in regulating peritoneal membrane function [41].

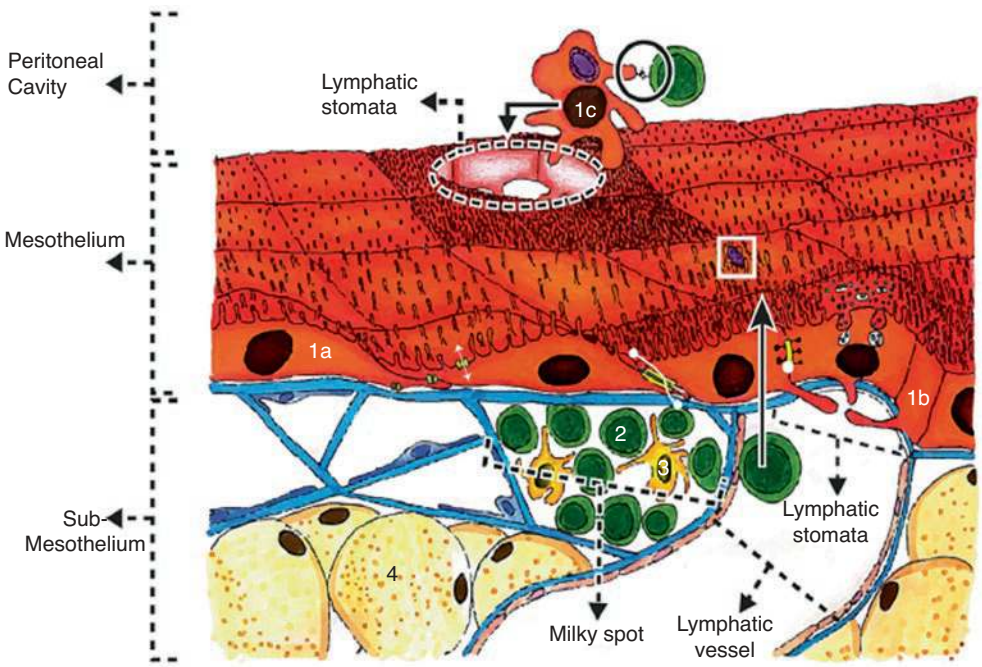


Fig. 3 A schematic representation of the peritoneum with mesothelial organization and functions. The mesothelium is composed of flat mesothelial cells (1a), and cuboidal mesothelial cells (1b). Water transport (two headed white arrow) occurs through aquaporins, while zonula adherens (two headed dot arrow) and tight junctions (white dot) give support and selective barrier properties. Mesothelial cell can also trap pathogens (white square), detach (1c), phagocyte pathogens and present antigen (black circle) for immune induction. The sub-mesothelium contains the basal membrane, the connective tissue, adipocytes (4) and the milky spots were mainly lymphocytes (2) and macrophages are found (3). Reproduced from [38]

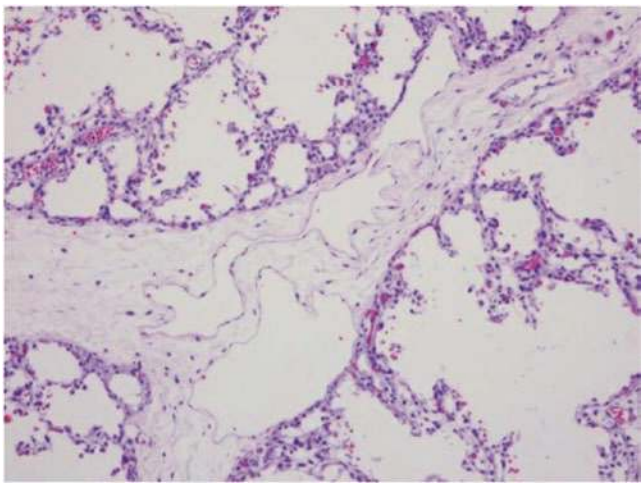


Fig. 4 Photomicrograph of normal visceral peritoneum

Classification and Aetiology of EPS

Encapsulating Peritoneal Sclerosis is currently considered synonymous with the condition which is seen as a long term morbidity of peritoneal dialysis first described by Gandhi in 1980 [42]. However there are a variety of peritoneal sclerosing conditions described unrelated to peritoneal dialysis but associated with specific other pathology. Owtschinnikow described a case of *peritonitis chronica fibrosa incapsulata* as early as 1907 [43]. The abdominal cocoon has been described as a specific entity, unrelated to renal failure or other causes. This presentation has mainly been described in China, India and the African continent with sporadic cases in the temperate regions. Various infective conditions including abdominal tuberculosis has also been described presenting with cocooning of the bowel as a clinical manifestation.

Various descriptive terms have been used to describe the abdominal presentation of these different entities, including sclerosing peritonitis [44], sclerosing obstructive peritonitis [45], sclerosing encapsulating peritonitis [46, 47] and progressive calcifying peritonitis [48]. While the combination of terms are varied, they all fundamentally describe a pathologic process, which is, a sclerosing and fibrosing inflammatory condition, which encapsulates and restricts the gut, leading to bowel obstruction.

Taking into account the incidence, clinical presentations, associations with different aetiology and the clinical and pathologic mechanisms, of the different types of peritoneal sclerotic and encapsulating conditions, it can be broadly classified into three main groups. (a) EPS secondary to peritoneal dialysis, (b) EPS as a consequence of other pathology, unrelated to peritoneal dialysis, and the specific entity (c) Primary encapsulating peritoneal sclerosis. While it can be classified clearly on the basis of etiopathology, it may be difficult to accurately classify it prior to diagnosis [49].

After its initial description in association with peritoneal dialysis by Gandhi [42], the condition has in the last four decades, become recognised as a definite entity which is an uncommon but potentially fatal complication of peritoneal dialysis. EPS associated with long term PD is potentially the most significant of these encapsulating conditions as it can be associated with significant morbidity and mortality. It is a relatively uncommon complication of PD which varies between centres, countries and over time periods. The prevalence of EPS varies from 0.4% to 8.9%, its incidence rate between 0.7 and 13.6 per 1000 patient-years. This observed variability may be multifactorial, including genetic predisposition, significant variation in practice, diagnosis, treatment and follow up of patients [50].

The Pathophysiology of Development of EPS

Due to the large number of patients on peritoneal dialysis globally and the relatively increased numbers of PD related EPS compared to the other secondary and primary EPS, the pathophysiology of this condition has been most studied.

It is now well understood that in the vast majority of cases, development of EPS requires a predisposing factor and also inciting factors. There is not much literature on genetic predisposition; however extrapolating from other genetic fibrosing conditions, there is a strong likelihood there will be a genetic predisposition in association, with long term PD. While peritoneal dialysis is considered more physiological than haemodialysis, the peritoneal dialysis solutions are hyperosmolar are have relative degrees of bioincompatibility, which causes changes to the peritoneal membrane it is in contact with. Factors which cause the bioincompatibility and peritoneal inflammatory reactions are the glucose degradation products (GDPs) after heat sterilisation, the lactate content and the low pH. The pathophysiologic process caused by these factors is similar to a sterile chronic inflammatory process or a chemical burn. It causes denudation of the peritoneal mesothelial cells, epithelial to mesenchymal transdifferentiation, and cytokine release of proinflammatory, proangiogenic cytokines, namely TGFbeta 1, IL-6, CCN2 and VEGEF (Figs. 5 and 6).

Although several precipitating factors have been described for the development of EPS, the main factor appears to be the length of peritoneal dialysis [53] and the recurrent episodes of infective peritonitis. These processes lead to the continued peritoneal inflammatory changes and a cytokine cascade and in genetically susceptible individuals, progression to clinical manifestation as EPS.

The organisms grown in infected peritoneal fluid in patients who go on to develop EPS are mainly Staphylococcus aureus, Propionibacterium acnes [54], Pseudomonas species or Fungal Peritonitis.

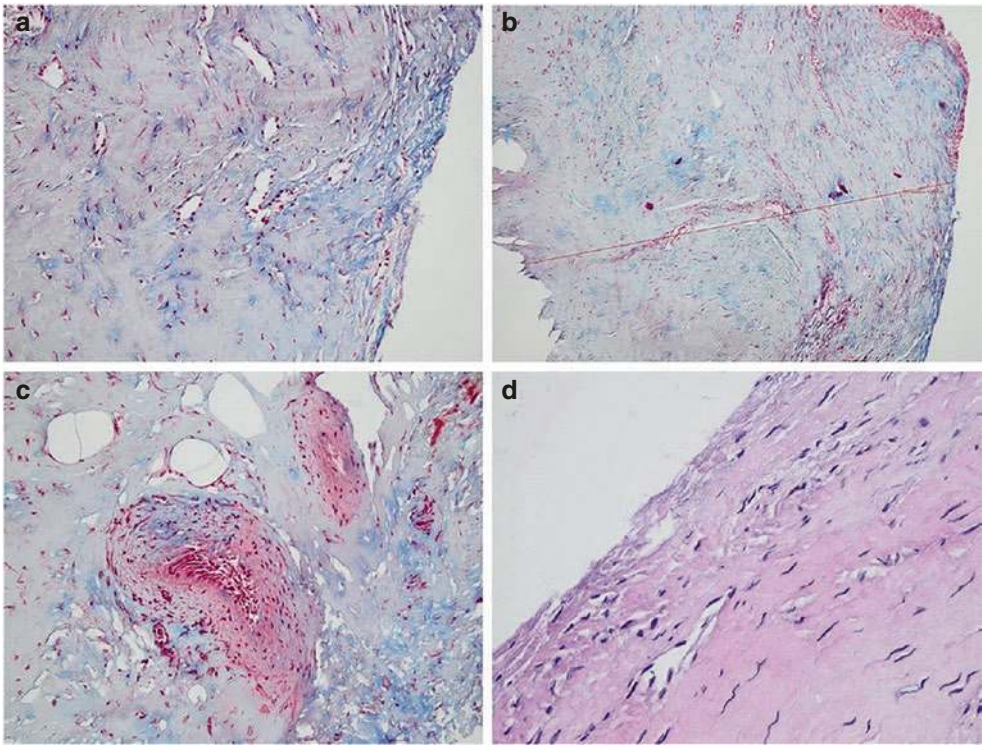


Fig. 5 Peritoneal histological examination: (**a**, **b**) the fibrous components of recent deposition, still rich in mucopolysaccharides, is in a pale color, while the more ancient fibrotic component, consisting almost exclusively of collagen, is highlighted in deeper blue. This staining highlights a recent beginning of the fibrotic process: blue is still poorly represented compared to the pale colour. The thickness of the peritoneal membrane is increased (638 μm). (**c**) Also in perivascular areas, the fibrosis spreads from the submesothelial layer towards the inside. (**d**) Marked thinning of the mesothelial layer. (Adapted from [51])

EPS has been described sporadically after organ transplantation. Lee et al. have described two cases after liver transplantation treated with a combination of surgery, steroids tamoxifen and mTOR inhibitor [55].

It has also been described as a rare complication of intestinal transplantation. In the case described, after confirmatory surgery, the patient was commenced on Sirolimus, and increased steroids and tacrolimus. There was complete resolution of the obstructive symptoms with recovery of intestinal transit [56]. EPS presenting after kidney transplantation is quite well described.

While elements of the predisposing and inciting factors play a part in the other secondary and potentially primary peritonitis, there are other interlinked disease specific factors in addition which will be briefly touched upon.

Secondary Peritoneal Sclerosing Conditions Not Related to Peritoneal Dialysis

Secondary Peritoneal Sclerotic conditions unrelated to peritoneal dialysis encompasses a very large and disparate group of conditions (Table 2). They span a spectrum of aetiopathology with, the clinical manifestations caused by, both the primary disease and the superimposed effects of peritoneal sclerosis with or without membrane formation and/or encapsulation.

The earliest cases of encapsulation were related to foreign material introduced during surgical procedures. The use of Talc, has been known to cause fibrosis [57] Talc powder was used as a lubricant for surgical gloves in the past, before its detrimental effects were identified. Silica is a component of talc, and causes fibrosis, with a characteristic and diagnostic histologic feature, the Maltese cross. EPS has been reported in a drug abuser where it is postulated that silica got into the abdomen through abdominal injections [58]. Povidone iodine used for peritoneal lavage after surgical procedures has also been reported to cause EPS [59]. Dacron fibres as a cause in an individual has been reported, however this patient was on peritoneal dialysis, and the EPS was precipitated after change of the dialysis catheter [60].

Other than externally introduced material, body fluids could precipitate EPS. Encapsulation after abdominal trauma has been described [61]. It is hypothesized that subclinical peritonitis may be the underlying cause in this case. Similarly EPS secondary to rupture of a Dermoid cyst has been reported where the authors postulate the mechanism to be a chemical peritonitis from the cyst contents [62].

Sigaroudinia et al. describe EPS as a complication of long term ventriculo-peritoneal shunts two children who required surgical enterolysis. Both of them presented with acute intestinal obstruction. The CSF was sterile in both these patients. No specific mechanism is postulated other than chronic irritation [63].

EPS has also been described as part of manifestation of systemic inflammatory diseases. It is described along with recurrent ascites in SLE. The mechanism may be related to the inflammation of serosal membranes, including perito-

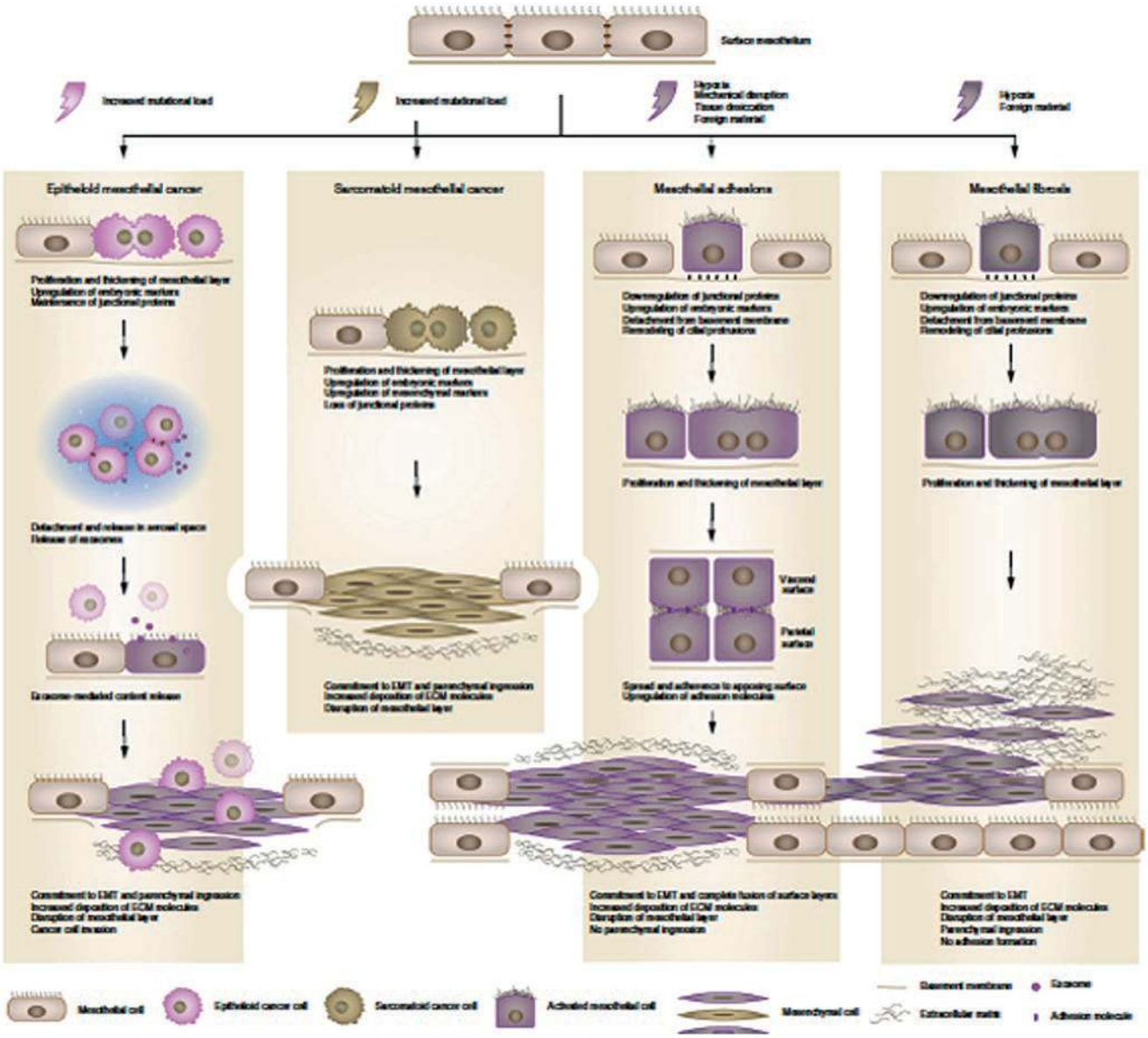


Fig. 6 Schematic representation of a cross section of the peritoneum showing mesothelial-to-mesenchymal transition (MMT) as a consequence of cancer or, for example long-term peritoneal dialysis. Reproduced from Tim Koopmans, Yuval Rinkevich: Mesothelial to mesenchyme transition as a major developmental and pathological player in trunk organs and their cavities [52]

neum, pericardium and pleura associated with SLE. On the background of a genetic predisposition, encapsulation and ascites develops [64, 65]. A similar mechanism may occur in Familial Mediterranean Fever which is associated with polyserositis [66].

Another group of diseases which are associated with EPS are the ovarian tumours. Leutenising thecomas are most closely associated with the condition. The link was first described by Clement in 1994, in six patients, where leutenizing thecomas were associated with peritoneal sclerosis [67]. The thickened peritoneum was made up of a proliferation of fibroblasts and myofibroblasts separated by collagen, fibrin and chronic inflammatory cells. The causative relation was thought to be enigmatic. Altman et al. have reviewed the linkage and identified 43 cases, and on immunohistochemistry, vimentin+/keratin+/CD34+ was found [68].

One of the first drug related causes was reported in 1975 in association with practolol for angina [69]. The patient required surgery for obstruction, where there was fibrinous adhesions and cocooning of gut which required excision and enterolysis. Subsequently other drugs in the beta blocker class have also been found to cause EPS including Timolol. Antiepileptic drugs like phenytoin have also been implicated with the authors postulating that like gingival hyperplasia, the mechanism might be increased collagen and glycosaminoglycans and peritoneal inflammations with

Table 2 Classification of encapsulating peritoneal sclerosis

A: EPS secondary to peritoneal dialysis
B: EPS secondary to other well-defined pathology
Drug related
Practolol
Methotrexate
Antiepileptic drugs
Intraperitoneal chemotherapy
Infections
Tuberculosis
Non-tuberculous mycobacteria
Bacterial peritonitis
Cytomegalovirus infections
Fungal infections
Parasitic infections
Neoplasms
Leutenising thecomas
Leutinising granulosa cell tumours
Abdominal trauma
Foreign bodies
Talcum powder
Asbestos
Silica
Endometriosis
Dermoid cyst rupture
Systemic inflammatory conditions
Sarcoidosis
Systemic lupus erythematosus
Familial Mediterranean fever
C: Primary EPS (the abdominal cocoon)

adhesions and cocooning [70]. Methotrexate has also been reported as an aetiological factor [71–73]. EPS associated with direct intraperitoneal chemotherapy has been reported [74, 75].

Intraabdominal tuberculosis can also present with the granulomatous tissue encasing the bowel and presenting as an abdominal cocoon. It is important that a preoperative diagnosis is made as anti-tuberculous treatment may resolve the problem. However if it presents as bowel obstruction not responding to treatment or an acute surgical emergency, surgery has to be carried out and histological confirmation obtained [76–78].

Mycobacterium fortuitum, an atypical mycobacterium has been reported, however in association with peritoneal dialysis [79]. There are several case reports of EPS associated with fungal infections,

Primary EPS

Foo et al. in 1978 published on series of cases in young girls from Singapore where the gut was encased in a membrane causing obstruction [80]. The condition was termed the abdominal cocoon. Histologically the membrane was made of thickened collagenized fibrous tissue with mild vascularization. Subsequently there have been several reports of this condition mainly from the tropics and subtropical regions. The largest number of publications on this condition comes from China, India, Turkey and Nigeria. However there have been cases also described in temperate zones [81, 82].

No underlying cause can be ascertained in primary encapsulating peritoneal sclerosis and hence the name and the differentiation from the secondary group of EPS. There have been several hypotheses, on the aetio-pathologic processes of development of this condition, including retrograde menstruation, superadded viral infection, retrograde peritonitis via the fallopian tubes and immunological reasons [83]. The condition is however also seen in men, premenopausal women and children. It is difficult to diagnose clinically preoperatively, but a CT scan can make the diagnosis. Careful dissection and excision of the thick sac with release of the small intestine leads to complete recovery in the vast majority of cases [84].

Diagnosis of EPS

The diagnosis of EPS requires knowledge of the condition and index of suspicion in patients presenting under the different contexts referred in the classification above. It should be considered in the differential diagnosis of an individual on long term peritoneal dialysis who presents with abdominal symptoms with progressive decline in nutritional status and raised inflammatory markers. The majority of patients on long term peritoneal dialysis do not develop EPS. However EPS should be considered and ruled out in any patient who has had peritoneal dialysis for a number of years (over 5), and especially so in someone with a history of multiple episodes of peritonitis.

In susceptible patients it may present soon after a transferring from peritoneal dialysis to haemodialysis, or after transplantation in someone who has been on long term peritoneal dialysis. The exact mechanism of how EPS is precipitated after this modality change is unknown.

It should also be considered in patients who have had previously had peritoneal dialysis who present with recurrent episodes of unexplained ascites, especially after transplantation or after conversion to HD.

In a significant number of patients, the diagnosis is made late after investigations for other pathology have drawn a blank. If the condition is not considered early, patients often decompensate nutritionally while being investigated for other potential pathology and in that period continue to decompensate nutritionally. In parallel with these changes, if the individual is still on peritoneal dialysis reduction in ultrafiltration will be noted along with a high transporter status. The deterioration is hastened by the underlying inflamma-

tory process in the peritoneal cavity driven mainly by the thickened and inflamed membrane.

In the early stages patients may present with vague abdominal symptoms, and then develop refractory anaemia which does not respond to iron supplementation or erythropoietin. This is also related to the chronic inflammatory process, from the thickened membrane and also pockets of loculated peritoneal collections. These collections usually contain debris, clots and fibrinous material and organisms. The CRP will be raised right from the outset and along with disease progression and there will be a downward trend in albumin levels (Table 3).

In the non PD group of EPS, the diagnosis may be even more difficult, and diagnosis depends on knowledge of association of EPS with that condition, an index of suspicion and imaging.

A significant number are unfortunately diagnosed at surgical exploration. There can be rare and unexpected presentations [85, 86]. There are also instances, where EPS can present without any pre-existing symptoms [87].

Table 3 Symptoms and clinical features of EPS

History
Peritoneal dialysis, with episodes of peritonitis
Increased risk if peritoneal dialysis over 5 years
Change of modality of dialysis within last 6 months or transplantation
Symptoms of fullness, discomfort
Abdominal distension or bloating
Fullness, early satiety, vomiting
Significant loss of weight
In late cases gross distension, obstruction
May also present acutely with obstruction, peritonitis or hemoperitoneum
Clinical features
Anaemia
Weight loss and cachexia in advanced cases
Abdominal distension
Fluid collection as ascites or loculated abdominal fluid
Palpable abdominal mass from the cocoon
Investigations
Anaemia
Raised CRP
Leucocytosis
Hypoalbuminemia
Imaging (X ray/US Scan/CT/MRI)
Thickened peritoneum
Ascites
Mesenteric retraction
Obstructive features with thickened bowel
Calcification

The above features are primarily consistent with EPS associated with peritoneal dialysis. In primary EPS and other forms of secondary EPS, the diagnosis, is one of exclusion mainly of other causes, and considering individual clinical presentations

Diagnostic Tests and Pathway for Suspected EPS

There are no specific single blood tests that point to EPS, however the combination of refractory anaemia, often a leucocytosis, hypoalbuminemia and a persistently raised CRP in the context of a patient receiving of having received PD is suggestive.

In individuals who develop post-transplant EPS, there may be derangement of transplant kidney function from a combination of inflammation, infection and dehydration from intraperitoneal fluid collections.

In the other secondary causes of EPS, the relevant disease specific investigation screens along with abdominal imaging may help make the diagnosis.

Imaging in EPS

A plain X-ray may show areas of peritoneal calcification, especially in long standing cases. Characteristic calcification on the bowel surface and the peritoneum is an important diagnostic feature which could alert the clinician to the diagnosis. An erect abdominal film may show some evidence of early obstructive features, such as air fluid levels or evidence of frank obstruction in an acute presentation. Other than these features which may enhance diagnostic suspicion of EPS, in the modern era, the role of the plain abdominal X-ray in these conditions may be redundant.

Abdominal Ultrasound is helpful in that it may show ascites and peritoneal fluid collections and in classic cases, can demonstrate the thickened membrane cocooning the gut, and dilated loops of obstructed gut (Fig. 7). For these findings to be diagnostic, they should be considered along with the clinical context. Abdominal ultrasonography is important in guiding paracentesis in some patients who present with recurrent accumulation of ascites. It is also important in the diagnosis of postoperative intraabdominal collections after enterolysis and peritonectomy.

The CT scan is the modality of choice in the diagnosis of EPS. Diagnostic features of a CT scan are peritoneal thickening, abdominal tethering, dilated gut, fluid accumulation as loculations of fluid or frank ascites, and areas of localised or generalised calcification of the peritoneum (Fig. 8). The CT findings depend on the stage and severity of the disease. In the early stage, the thickening of the peritoneum may be subtle, however, there may be suggestive features of gut tethering with some localised dilatation of loops of bowel [88, 89].

MRI Scans are also as valuable or sometimes provide more definitive detail of the pathology [90]. However either the CT scan or the MRI scan will provide diagnostic radiologic features that could lead to a confirmatory diagnosis of

EPS (Fig. 9). Cine MRI has been used as an experimental modality [91], where pathologic features of the encapsulation along with the restrictive effects of the cocoon can be demonstrated.

Vadi SK et al. have reported the use of ^{18}F-FDG PET-CT as a modality in the diagnosis of the abdominal cocoon associated with tuberculosis (Fig. 10) [92].

Laparoscopy

Once a diagnosis of EPS is considered, it can be arrived at by correlating the clinical history, clinical examination, blood tests and the radiologic imaging. However, there are situations when symptoms will still remain unexplained and obscure but point to an intraabdominal source. In these situations, laparoscopy may be useful for visualising the peritoneal cavity for definitive diagnosis, ruling out pathology and also for obtaining diagnostic samples.

The critical points in laparoscopy are to ensure that there is no perforation due to the cocooning (Fig. 11). An important decision when carrying out laparoscopy for diagnosing EPS, is planning intervention. If EPS is definitely found on laparoscopy, it may be best for surgical intervention to be planned at a later date.

Histologic Features of EPS

The diagnosis of EPS is a clinical diagnosis and not histological. Histology of the peritoneal membrane in a patient with EPS may show characteristic features that confirm the clinical diagnosis. It is also important in ruling out, secondary causes of peritoneal sclerosis or pathology including tuberculosis or malignancies. Histologic changes reflect the effect on the peritoneum caused by the hyperosmolar dialysis fluid and is seen in both the parietal and visceral peritoneum. The peritoneal membrane thickens and scleroses in long standing peritoneal dialysis, along with mesothelial

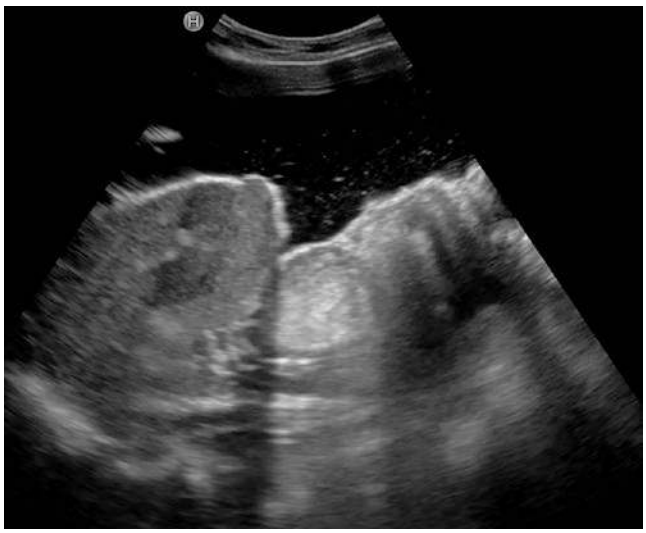


Fig. 7 A single static ultrasound image showing the liver with calcification on the surface, ascites and cocooned gut with calcification on the surface

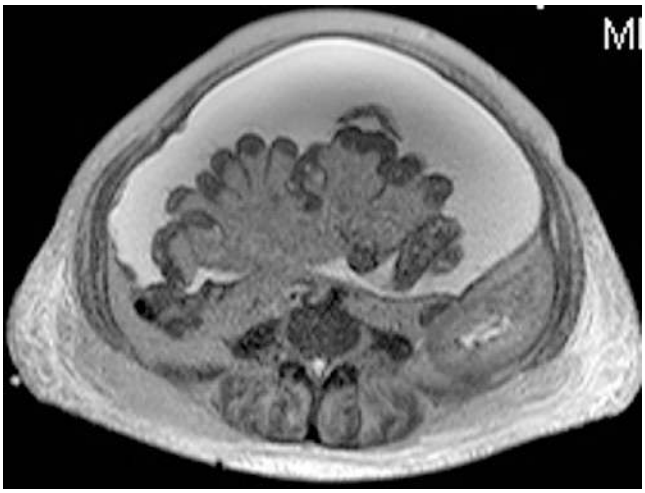


Fig. 9 An MRI scan showing the same features in the same patient, with subtle differences. The calcification is not as prominent, and the thickening of the peritoneum is not as evident in MRI scan compared to the CT scan

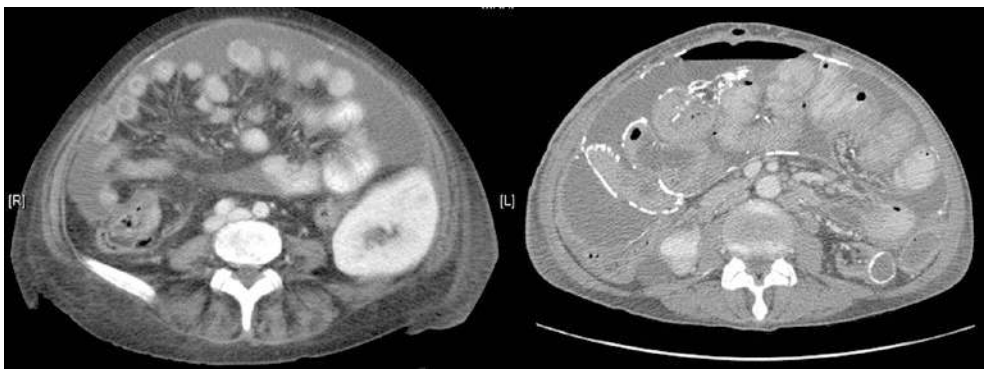


Fig. 8 CT scans demonstrating free fluid, thickening of both parietal and visceral peritoneum with certain areas of calcification, mesenteric retraction and some gut dilatation. The first image is of a patient with post-transplant EPS and there is a good functioning kidney in the left flank

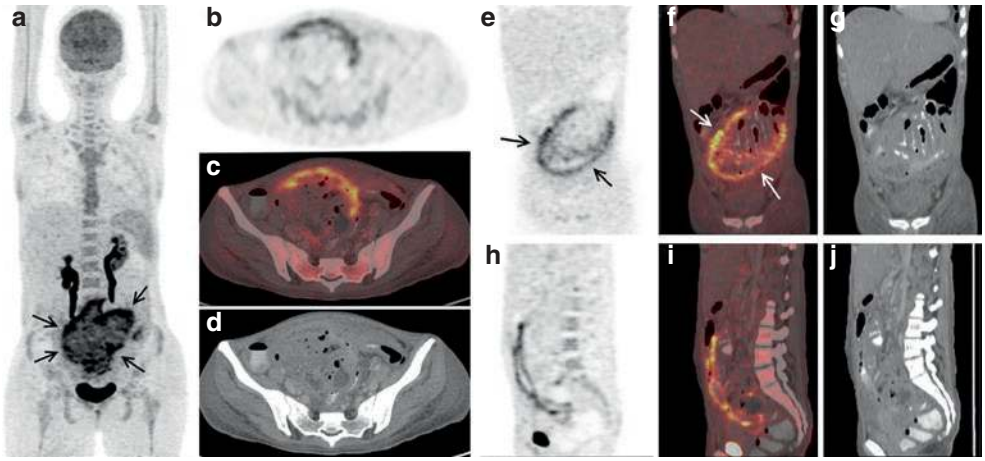


Fig. 10 FDG-avid peritoneal thickening encapsulating around the clumped jejunal and ileal loops forming a tracer-avid "cocoon" in the abdomen as shown in the MIP (**a**; arrows), axial PET (**b**), fused PET/CT (**c**), axial CT (**d**), and corresponding coronal (**e**, **f**; arrows and **g**) and sagittal (**h**, **i**, and **j**) images, suggesting sclerosing encapsulating peritonitis (SEP)

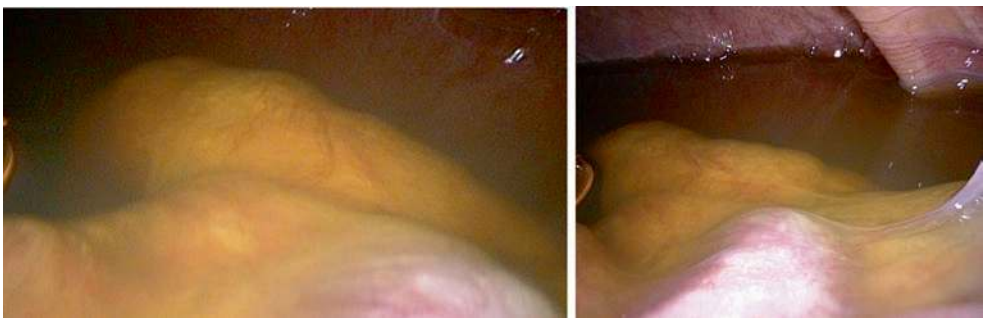


Fig. 11 A laparoscopic image showing early EPS in evolution. The ascitic fluid is turbid and there is encapsulation of the gut with neovascularization of the surface. The membrane can been seen and is thin and flimsy as it is early in its formation. If left undiagnosed or untreated, it will develop into the thick constricting collagenous membrane seen in advanced disease and will eventually calcify

denudation. Below the mesothelial layer, the compact zone thickens and is formed of myofibroblasts and fibrous collagen [93]. The vasculature in this layer undergoes changes, with medial sclerosis and hyalinization, along with neoangiogenesis [94]. Honda et al. have also described fibrin deposition, increase in the size of the fibroblasts, capillary angiogenesis and mononuclear cell infiltration were more common features of EPS rather than simple sclerosis [95]. Advanced glycosylation end-products are found in the mesothelial and sub-mesothelial layer of PD patients [96, 97].

Additional histological findings identified by different investigators include, positive immuno-histochemical staining for podoplanin [98] and upregulation of vascular endothelial growth factor (VGEF) and downregulation of mast cells [99, 100]. All these findings however are not specifically related to EPS, and could be seen in the different peritoneal fibrosing conditions.

Histology of Non-renal EPS

Histologic features of secondary encapsulating peritoneal sclerosis or peritoneal fibrosing conditions are more specific and often diagnostic when compared to EPS associated with peritoneal dialysis. Examples are peritoneal tuberculosis where typical granulomatous inflammation is seen with or without necrosis and acid fast bacilli.

In malignant encapsulation, the histologic features will depend on the specific malignancy which is causing the pathologic manifestation.

In the primary or idiopathic cases of EPS, histologically, the peritoneum will show a proliferation of fibro-connective tissue, inflammatory infiltrates, and dilated lymphatics. There will be no evidence of granulomas, giant cells or birefringent material.

Treatment of EPS

As soon as a diagnosis of EPS is made in PD related cases, it is imperative that the patient discontinues peritoneal dialysis and is established on haemodialysis. A strategy that has been tried in preventing the development of EPS is regular peritoneal lavages after discontinuation of PD. Regular lavage has been shown to help mesothelial cell repair [101].

While this is a strategy that can be attempted in the very early stages without mechanical obstruction, nutritional deficiency or significantly raised inflammatory markers, it

should perhaps be carried out in conjunction with additional medical therapy. There is no robust scientific basis.

In the group of patients presenting mainly with significant and recurrent ascites, paracentesis will be required for relief of discomfort. More than one attempt at paracentesis will be required as the peritoneal fluid may continue to reaccumulate. Depending on the individual clinical context, concomitant medical therapy may be required. In these clinical situations where there is no overt mechanical obstruction, a decision on surgical intervention, may be difficult to justify. However if there is recurrent, re-accumulation of fluid, there may be justification in surgery with a view to a peritonectomy of the thickened membrane. The membrane in these situations is often a strong impermeable fibrocollagenous membrane overboth the parietal and visceral peritoneum which prevents the reabsorption of peritoneal fluid. Once stripped off, and peritoneum excised, there is the establishment of fresh peritoneum which aids in absorption.

Medical Therapy for EPS

Various medical forms of therapy have been described for EPS, however most medical interventions are anecdotal without any specific clinical trials to determine the effectiveness of therapy and outcomes. It will also be very difficult to evaluate the impact of the medical therapy on the natural progression of EPS.

Steroids

Corticosteroids have been used as medical therapy by different teams at different points in the disease process. The rationale for steroid use is that it inhibits collagen synthesis and maturation by suppressing the inflammatory process. The beneficial effects of estradiol propionate was experimentally demonstrated in nonuremic Wistar Albino rats [102]. Kuriyama has reported good outcomes in all patients treated with steroids compared to poor outcomes in those not on steroids [103]. Several other groups have also reported on the beneficial effects of steroids in EPS [104, 105].

Tamoxifen

With a solitary case report in 1999, Tamoxifen began to be used as medical therapy largely because there was no well-defined consensus strategy for therapy of EPS once diagnose. The rationale of the authors was that Tamoxifen, a selective estrogen receptor modulator interferes with TGF beta 1, a probiotic cytokine [106]. Transforming growth factor beta 1 (TGF B1) has a stimulatory effect on matrix metalloproteins (MMP 2 and 9). MMP9 degrades Type IV and denatured collagens, TGF beta 1 production, which is stimulated by tamoxifen, might favour mesothelial healing by facilitating the removal of denatured collagen. It has been successfully used in the treatment of retroperitoneal fibrosis [107, 108] and long term therapy for idiopathic RPF has been found to be effective and safe [109].

Immunosuppression

Immunosuppressive agents other than steroids have been used to good effect by different teams. Azathioprine in combination with steroids has been shown to be effective [110]. mTOR (Mammalian target of Rapamycin) inhibitors, including Sirolimus, have been used by several groups especially in patients after transplantation, including liver transplantation with response [111, 112].

Novel Agents

Danford et al. hypothesise that while mechanical obstruction is the main underlying factor, dysmotility may play a role through the disruption of the myenteric plexus by fibrosis and increased endogenous opioids from activated lymphocytes inhibiting both propulsive motor and secretory activity in the gut [113]. Methylnaltrexone to combat inflammation associated dysmotility has been described in anti-Hu associated intestinal pseudo-obstruction [114]. Altman et al. have suggested targeting vimentin+/keratin+/CD34+ tissue in patients with leutenizing thecomas and sclerosing peritonitis [68]. ACE inhibitors may make peritoneal fibrosis progress more slowly [115]. Animal studies have found hepatocyte growth factor [116], TNP-470 [117] and antisense oligonucleotides to reduce peritoneal fibrosis [118].

Caveats in Medically Treating EPS

While medical therapy may be attractive for both the patient and the treating clinician from the point of view of avoiding a major surgical procedure with associated morbidity and mortality, it is based on anecdotal reports and small case series. There is always the potential risk that the diagnosis may be incorrect. Steroids may mask inflammation and cause continued progression of disease. Defining length of medical therapy may be difficult and disease progression during medical therapy may cause acute obstructive, infective, and haemorrhagic complications including perforations. This may require emergency surgical intervention. Surgical intervention in acute situations in patients on steroids and mTor agents can cause significant unwanted morbidity. This is due to the friability of tissue and difficult healing, increasing the overall chances of morbidity and mortality.

Surgery for EPS

There is universal consensus that in patients with encapsulating sclerosis presenting with intestinal obstruction, surgery is the most effective treatment. The underlying problem in these patients, is mechanical bowel obstruction caused by a combination of the thickened inflamed peritoneum, the fibrocollagenous membrane and adhesions. Bowel is in most instances encased in this pathologic tissue.

The principles of surgery are the very careful release of the obstructing, sclerotic and encapsulating membrane and releasing, gut so that it remains free in the peritoneal cavity, with the reestablishment of peristalsis. Surgery requires meticulous attention to detail and technique and dissection, and ensuring that in the process of releasing obstructed gut, a perforation is not made or there is bleeding from vascular tissues or vascular structures. One of the main reasons for reported poor outcomes in EPS in international literature and the high mortality is the fact that if surgical teams do not have experience with this entity, decision making and judgement during acute presentations proves extremely difficult. With acute presentations in patients especially in renal failure and on dialysis, who have decompensated nutritionally over long periods of time, managing a hostile encapsulated abdomen can prove extremely challenging. Hence best outcomes are achieved by teams who have experience in the management of the condition.

There are only a handful of centres in the world which have significant experience in the surgical management of the condition. Clinical outcomes from these centres have improved. Various different terms are used for surgery, including peritonectomy and enterolysis (PEEL) procedure [119]. Another limited procedure which has been described is Capsulotomy [120].

Preoperative Preparation and Planning

Once a definitive diagnosis of EPS has been made, therapy has to be tailored to the individual patient. A risk benefit balance decision has to be critically made after, a thorough evaluation of the patient, investigations and imaging. If the CT scans show cocooning of the gut, surgery is indicated as it is highly unlikely that any medical therapy will reverse the gut problems. Surgery is the gold standard treatment for the condition except for the most early of cases. There are numerous individual case reports and small series reports on surgery and outcomes. A small number of international centres have consolidated experience in surgical management [119, 121]. Surgical intervention is planned depending on the overall clinical state.

All patients should have a full cardiovascular assessment for anaesthesia, including an echocardiogram and if possible a cardiopulmonary exercise test. Respiratory physiotherapy prior to surgery will improve operative outcomes. Patients should be managed by experienced anaesthetists, skilled in the anaesthesia for patients with chronic renal failure with significant morbidity.

If patients present as an emergency with evidence of peritonism, where surgery is indicated immediately, it has to be carried out, although the mortality and morbidity associated with emergency surgery in EPS is over 50%. In an elective or semi elective situation, all patients should have a thorough nutritional assessment as a significant percentage of these patients will have evidence of poor nutrition [122]. Anthropometrics, will identify depleted fat and lean body mass which can increase surgical morbidity and mortality [123]. All patients undergoing surgery should have augmented and intensive preoperative nutrition including parenteral nutrition. Parenteral nutrition will in all likelihood need to be continued well into the postoperative phase, as return of gut motility with the ability for oral intake may be prolonged. It is of critical importance that parenteral nutrition be given through a dedicated access line, with all the precautions and care taken to ensure asepsis and sterility. An infected access line could cause significant morbidity and mortality. In a significant majority of these patients, there will need to be alternate access for haemodialysis.

As perioperative fluid management is critical, and inadequate dialysis can lead to fluid retention and increase perioperative morbidity, it is imperative that all patients have optimum haemodialysis prior to surgery, and ideally daily dialysis.

The aims of surgery in EPS are fundamentally to relieve the mechanical gut obstruction which is contributing to the symptoms and malnutrition and also clear as much as possible of the thickened and inflamed membrane which is contributing to the chronic inflammatory process and the anaemia. Both the parietal and visceral peritoneum will be thickened and where there is obstruction, the gut proximal to the obstruction will be thickened (Fig. 12). The surface of the bowel below the membrane will be tanned and of the thickened and encapsulating membrane however has to be balanced on the requirement to relieve intestinal obstruction and the need to avoid iatrogenic gut perforations which can precipitate enteric fistulas and exponentially increase postoperative mortality.

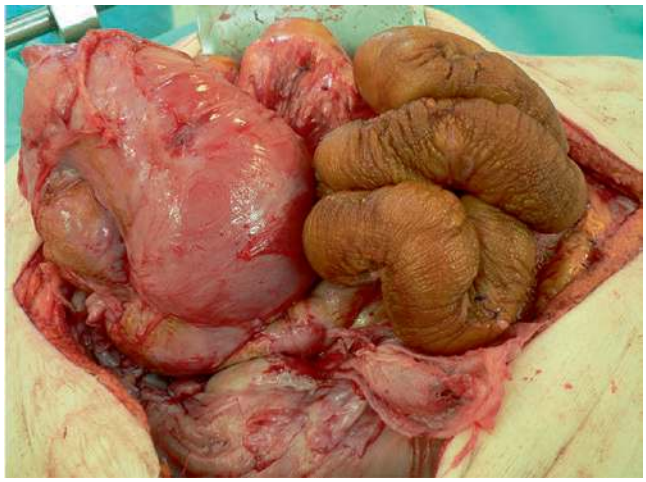


Fig. 12 Dilated proximal gut with released tanned, distal encapsulated segment, during enterolysis

Surgical Technique

Abdominal entry is through a long midline incision, after recent cross sectional CT images have been reviewed. It is important to first enter an area of the peritoneal cavity where gut is not adherent to the anterior abdominal wall, to avoid a perforation. If a perforation occurs during surgery, primary closure almost invariably fails due to the thickened and diseased tissue, leading to an enteric fistula and significantly increased mortality. The technique used in the author's centre is to develop a plane outside the abdominal cocoon, bilaterally. Once that plane has been developed, the cocoon is entered in an area where there is fluid (Fig. 13). Progress of surgery is dictated by findings on abdominal entry. Once the peritoneal cavity is entered in a suitable area, all fluid and debris is aspirated, after samples are taken for culture and sensitivity, biochemistry and for acid fast bacilli.

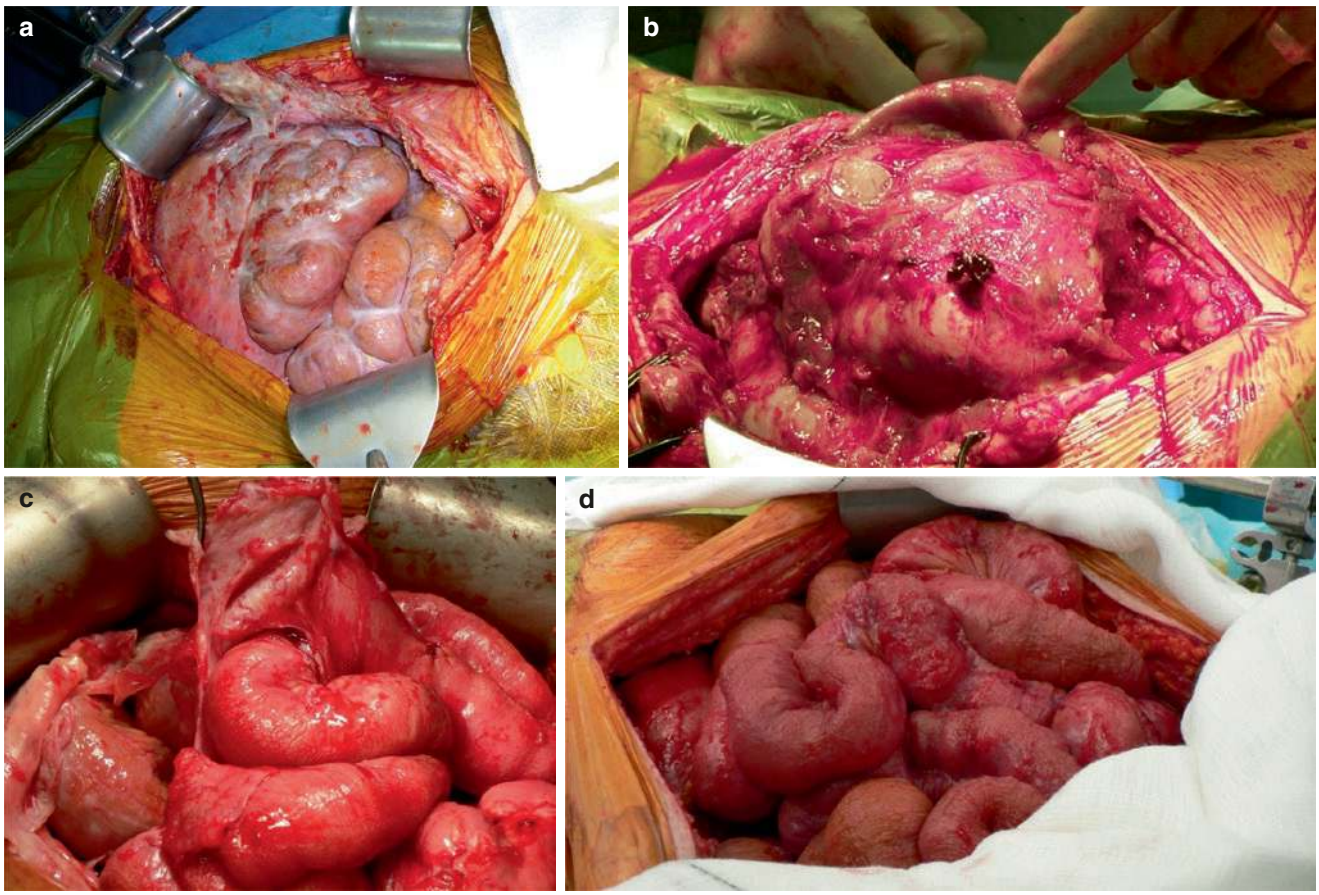


Fig. 13 The encapsulated gut with dense sclerotic adhesions between loops of bowel and also the encapsulated gut and the liver (**a** on entry outside the cocooned bowel, **b** after some dissection, **c** releasing fibrotic membrane from gut and **d** after completed enterolysis). The extremely thickened and almost calcific parietal peritoneum can also be seen and adhesions also between the sclerotic mass and the abdominal wall

The peritoneal cavity is then inspected and the exact degree of the encapsulation understood. Dissection is then commenced in an area and then meticulously extended, releasing loops of bowel, which are clumped together by the membrane. The membrane is adherent to the gut surface, by a firm interface. With careful blunt and sharp dissection the membrane can be dissected off, however it is critical that there are no perforations made. If perforations are made, the propensity for post-operative leaks and fistulation, increases significantly. A decision is made about simple closure or a stoma formation. Dissection is then carried out, releasing the entire gut, right from the DJ flexure till the ileo-caecal junction. The terminal ileum is one of the most important areas as it is the most common area affected by the sclerotic membrane.

Localised EPS

While EPS is in most situations generalised, there are situations where cocooning can be entirely localises to a segment of gut, especially the terminal ileal region [124].

The Management of Advanced Cases Where Enterolysis and Peritonectomy Is Not Possible

Cases may present acutely from time to time where at surgery the abdomen is too rigidly encased in sclerotic tissue, or badly calcified, where enterolysis and peritonectomy is technically impossible. Attempting lysis in these situations may cause perforations, bowel fistulae and mortality. In these situations, the most appropriate course of action would be to close the abdomen and considering long term parenteral nutrition. However, there are several case reports in literature where individual cases have been managed with different techniques including a loop jejunostomy in a case of recurrent EPS where the original presentation was a uretero-ileal fistula [125]. The same group has also described placement of a percutaneous gastrostomy tube with jejunal extension, to drain gastric and proximal gut secretions while providing total parenteral nutrition [126]. Combined bowel and kidney transplantation has also been reported [127]. It demonstrates the feasibility of the technique, and where renal failure too is addressed by the transplanted kidney.

Recurrent EPS

In spite of the best surgical treatment, there may be a significant risk of recurrence of up to 25% [128]. The Japanese group which has one of the largest international experiences with the condition, have utilised different techniques, including fixing the bowel with a long intestinal tube, to maintain patency, and the use of the Noble Plication technique [129].

The management of recurrent disease is exactly the same with repeat surgery and further enterolysis and peritonectomy.

Encapsulating Peritoneal Sclerosis in Children

EPS has been described in children who have had long term PD. The prevalence of EPS in European children on PD is comparable with that of the adult patients. A high index of suspicion is required for diagnosis in children with longer dialysis duration, peritonitis rate and UF failure [130, 131].

Dietary Therapy (to Avoid Obstructive Symptoms with Adhesions and EPS)

Occasionally a completely liquid diet is required to avoid obstructive type pains in patients with adhesions or EPS. Review by an experienced dietitian should be provided for all patients with chronic symptoms.

Definitions

Dietary fibre has been defined as carbohydrate polymers with ten or more monomeric units, which are not hydrolysed by the endogenous enzymes in the small intestine of humans and belong to the following categories [132]:

- Edible carbohydrate polymers naturally occurring in the food as consumed
- Carbohydrate polymers, which have been obtained from food raw material by physical, enzymatic or chemical means and which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities
- Synthetic carbohydrate polymers which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities

Plants often contain a mixture of soluble and insoluble fibre. Soluble fibre increases the viscosity of bowel contents, slowing down digestion and the absorption of nutrients. Insoluble fibre has a high water binding capacity which results in softer and bulkier bowel contents to aid the acceptable functioning of the gut. Cereal fibre is reported to have the greatest bulking effect [133]. It is these effects which has led to the use of low fibre diets in the treatment of adhesions and obstruction.

In 2014 the British Dietetic Association published a systematic review on the management of Crohn's disease. This review was unable to identify any trials to recommend the use of low fibre diets in structuring disease to minimise the risk of bowel obstruction or reduce symptoms [134]. The opinion of the group, which consisted of expert Dietitians, was that fibre should be avoided in stricturing Crohn's disease to reduce the possibility of a mechanical obstruction. In addition, a low fibre diet may be helpful in reducing peristomal pain from excess gas production. The lack of scientific evidence to support the use of a low fibre diet does not negate their use in clinical practice as it is difficult, from an ethical perspective, to conduct clinical trials where dietary fibre could result in a mechanical obstruction. The BOUNCED feasibility study at the Royal Surrey County Hospital NHS Foundation Trust is aiming to investigate the use of dietary manipulation in bowel obstruction (see below). It is envisaged the results will be influential in establishing a consensus and provide the standard for dietary guidelines for bowel obstruction.

Low Fibre

There are no clear definitions in the literature on what constitutes a low fibre diet. One study investigating the effect of a low fibre diet in patients with IBS aimed for 10 g of fibre per day [135]. Another study used <10 g of fibre as bowel preparation 1 week pre surgery [136] and therefore not applicable in the long term setting of bowel obstruction.

Low Residue

To date there are no agreed definitions of what constitutes residue and in 2012 the American Academy of Nutrition and Dietetics removed the term "low residue diet" from the Nutrition Care Manual [137]. This is because the amount of residue produced during the passage of food through the gut cannot be quantified as includes undigested food, microorganisms, gastrointestinal secretions and cells from the intestine. Therefore, for the purposes of this chapter the term low fibre will be used.

Causes of Bowel Obstruction

There is limited literature describing the dietary intake of patients with bowel obstruction but patients with recurrent bowel obstruction are known to have a reduced quality of life and their condition has an impact on their dietary intake. In a study of 48 patients with recurrent bowel obstruction ranging from two episodes during their life to monthly episodes, 90% of patients reported an impact on their diet [138]. There are many case reports in the literature regarding different types of food causing bowel obstruction in both patients who have had previous abdominal surgery and those with a virgin abdomen (Table 4).

Due to the intermittent nature of bowel obstruction, different levels of restriction may be required depending on symptoms and the degree of obstruction. Radiological images may help ascertain the degree of obstruction and inform the dietary restrictions required. Patients with severe adhesions or strictures may require a liquid diet whereas patients with partial obstruction may be able to manage some fibre containing foods. The BOUNCED study from the Royal Surrey County Hospital NHS Foundation Trust is investigating the use of a 4-step bowel obstruction diet in patients with cancer (step 1 clear fluids, step 2 all thin liquids, step 3 smooth or pureed foods only low fibre, step 4 soft sloppy foods low fibre) [139].

Each patient will have different tolerance levels which may change over time Therefore, it is important that restrictions are reviewed regularly and if possible lifted to allow

Table 4 Foods reported to have caused bowel obstruction

Foods
Fruit
• Cherry tomato
• Dried apricot
• Dried fruit
• Persimmon
• Dates
• Grapes
• Orange pith
• Peach stone
• Plum stone
• Apricot stone
Vegetables
• Artichoke
• Mushrooms
• Shitake mushrooms
• Olives
Nuts
• Brazil
• Chestnut
Seeds
• Prickly pear
• Granadilla
• Medlar
• Sunflower
Other
• Bran
• Oat bran
• Ginger
• Egg yolk
• Rice cakes

Table 5 Principles of a low fibre diet

• Wholemeal bread to white bread
• Brown rice to white rice
• High fibre breakfast cereals to low fibre versions
• Wholewheat pasta to white pasta
• No skins on potatoes
• One portion of fruit a day
• One portion of vegetables a day
• Meat, fish, cheese, eggs, tofu to be recommended to meet protein requirements

as normal a diet as tolerated to minimise symptoms. The principles of a low fibre diet (Table 5) include reducing fibre containing carbohydrates to lower fibre or fibre free alternatives. Fruit and vegetables will need to be peeled, no skins, no pips, no seeds, no pith, no stalks. It is often recommended that only one portion of fruit and one portion of vegetables are taken daily. Beans are high in fibre and therefore should be limited unless vegetarian or vegan when other low fibre protein substitutes should be encouraged (e.g. tofu).

Fluid and Electrolytes

Patients with bowel obstruction are at risk of dehydration and electrolyte abnormalities due to a reduced oral intake and vomiting [140]. Therefore, careful attention should be paid to ensuring patients are meeting fluid and electrolyte requirements as the risk of acute kidney injury (AKI) is high. The National audit of small bowel obstruction in UK found 22% of the patients were admitted with an acute kidney injury [141]. Patients should be educated about the most appropriate fluids (+/− electrolytes) to drink (if not vomiting) to maintain hydration and electrolyte status especially during an acute episode.

Micronutrients

There is no data available on the micronutrient status of patients with bowel obstruction. The low fibre diet which is inherently low in fruits and vegetables, a significant source of micronutrients, means that deficiencies may develop if the obstruction is prolonged and appropriate supplementation will be required. A clinical examination to identify deficiencies should be completed if this is suspected and a complete supplement such as Forceval® or Centrium® recommended. A Registered Dietitian can provide advice on maintaining the nutritional adequacy of a low fibre diet which is why it is important that these patients are referred for advice.

General Advice: Chew and Teeth

Many case studies have also identified the issues of poor dentition and mastication as a contributing cause of bowel obstruction [142–144]. Patients should have any dental issues identified and referral to a dentist if poor dentition is an issue.

Medications

Many medications can cause a reduction in saliva production and therefore a review of medications can be helpful to ensure only essential medication are prescribed. It is known that pharmacobezoars can form from the ingestion of drugs such as cholestyramine and antacids and so their continued use should be evaluated [145]. Furthermore, reports of obstruction resulting from the use of guar gum-containing diet pills have been reported [146] which is why a detail drug history is essential.

Fibre Containing Enteral Nutrition

Whilst there is no evidence to support the view that enteral feeds containing fibre are contraindicated, some authors support this view due to the potential risk of obstruction in those with structuring Crohn's disease [147]. A review of enteral nutrition bezoar formation [148] found 14 cases of obstruction of which at least eight occurred during feeding with a fibre containing enteral formula. Other compounding factors included anatomical changes post operatively, reduced pH, dysmotility, dehydration and medication and therefore the enteral feed may not be the sole causative agent. However, it seems prudent to avoid fibre containing enteral nutrition in cases of severe strictures and adhesions until further research is published.

In conclusion the recommendation to follow a low fibre diet will be determined by the level of the bowel obstruction and likely resolution. Patients will require a Registered Dietitian to provide education and ensure that the diet is nutritionally complete and that reintroduction of fibre containing foods can occur when it is safe to do so.

References

1. Weibel M-A, Majno G. Peritoneal adhesions and their relation to abdominal surgery. Am J Surg. 1973;126:345–53.
2. Menzies D, Ellis H. Intestinal obstruction from adhesions--how big is the problem? Ann R Coll Surg. 1990;72:60–3.

3. Sulaiman H, Gabella G, Davis C, Mutsaers SE, Boulos P, Laurent GJ, et al. Presence and distribution of sensory nerve fibers in human peritoneal adhesions. Ann Surg. 2001;234:256–61.
4. Kligman I, Drachenberg C, Papadimitriou J, Katz E. Immunohistochemical demonstration of nerve fibers in pelvic adhesions. Obstet Gynecol. 1993;82:566–8.
5. Swank D, Swank-Bordewijk S, Hop W, van Erp W, Janssen I, Bonjer H, et al. Laparoscopic adhesiolysis in patients with chronic abdominal pain: a blinded randomised controlled multi-centre trial. Lancet. 2003;361:1247–51.
6. Molegraaf MJ, Torensma B, Lange CP, Lange JF, Jeekel J, Swank DJ. Twelve-year outcomes of laparoscopic adhesiolysis in patients with chronic abdominal pain: a randomized clinical trial. Surgery. 2017;161:415–21.
7. ten Broek RPG, Issa Y, van Santbrink EJP, Bouvy ND, Kruitwagen RFPM, Jeekel J, et al. Burden of adhesions in abdominal and pelvic surgery: systematic review and met-analysis. BMJ Clin Res Ed. 2013;347:f5588.
8. Ellis H, Moran BJ, Thompson JN, Parker MC, Wilson MS, Menzies D, et al. Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study. Lancet. 1999;353:1476–80.
9. Parker MC, Wilson MS, Menzies D, Sunderland G, Thompson JN, Clark DN, et al. Colorectal surgery: the risk and burden of adhesion-related complications. Color Dis. 2004;6:506–11.
10. Parker MC, Wilson MS, Menzies D, Sunderland G, Clark DN, Knight AD, et al. The SCAR-3 study: 5-year adhesion-related readmission risk following lower abdominal surgical procedures. Color Dis. 2005;7:551–8.
11. Strik C, Stommel MWJ, Schipper LJ, van Goor H, ten Broek RPG. Long-term impact of adhesions on bowel obstruction. Surgery. 2016;159:1351–9.
12. ten Broek RPG, Strik C, Issa Y, Bleichrodt RP, van Goor H. Adhesiolysis-related morbidity in abdominal surgery. Ann Surg. 2013;258:98–106.
13. Kössi J, Salminen P, Rantala A, Laato M. Population-based study of the surgical workload and economic impact of bowel obstruction caused by postoperative adhesions. Br J Surg. 2003;90:1441–4.
14. Nightingale J, Woodward JM. Guidelines for management of patients with a short bowel. Gut. 2006;55:iv1.
15. Dibb M, Soop M, Teubner A, Shaffer J, Abraham A, Carlson G, et al. Survival and nutritional dependence on home parenteral nutrition: three decades of experience from a single referral centre. Clin Nutr. 2017;36:570–6.
16. Bond A, Taylor M, Abraham A, Teubner A, Soop M, Carlson G, et al. Examining the pathophysiology of short bowel syndrome and glucagon-like peptide 2 analogue suitability in chronic intestinal failure: experience from a national intestinal failure unit. Eur J Clin Nutr. 2018;73:751–6.
17. Paine P, McLaughlin J, Lal S. Review article: the assessment and management of chronic severe gastrointestinal dysmotility in adults. Alim Pharm Thera. 2013;38:1209–29.
18. Limperg T, Chaves K, Jesse N, Zhao Z, Yunker A. Ultrasound visceral slide assessment to evaluate for intra-abdominal adhesions in patients undergoing abdominal surgery - a systematic review and meta-analysis. J Minim Invas Gynecol. 2021;28:1993–2003.e10.
19. Lang RA, Buhmann S, Hopman A, Steitz H-O, Lienemann A, Reiser MF, et al. Cine-MRI detection of intraabdominal adhesions: correlation with intraoperative findings in 89 consecutive cases. Surg Endosc. 2008;22:2455–61.
20. Yasemin A, Mehmet B, Omer A. Assessment of the diagnostic efficacy of abdominal ultrasonography and cine magnetic resonance imaging in detecting abdominal adhesions: a double-blind research study. Eur J Radiol. 2020;126:108922.
21. Hull TL, Joyce MR, Geisler DP, Coffey JC. Adhesions after laparoscopic and open ileal pouch-anal anastomosis surgery for ulcerative colitis. Br J Surg. 2012;99(2):270–5.
22. Zühlke HV, Lorenz EM, Straub EM, Savvas V. [Pathophysiology and classification of adhesions]. Langenbecks Archiv Für Chir Suppl Ii Verhandlungen Der Deutschen Gesellschaft Für Chir Deutsche Gesellschaft Für Chir Kongress. 1990;1009–1016.
23. Coccolini F, Ansaloni L, Manfredi R, Campanati L, Poiasina E, Bertoli P, et al. Peritoneal adhesion index (PAI): proposal of a score for the "ignored iceberg" of medicine and surgery. World J Emerg Surg. 2013;8:6.
24. Maglinte DD, Reyes BL, Harmon BH, Kelvin FM, Turner WW, Hage JE, et al. Reliability and role of plain film radiography and CT in the diagnosis of small-bowel obstruction. Am J Roentgenol. 1996;167:1451–5.
25. Maglinte DD, Balthazar EJ, Kelvin FM, Megibow AJ. The role of radiology in the diagnosis of small-bowel obstruction. Am J Roentgenol. 1997;168:1171–80.
26. ten Broek RPG, Krant NK, Bakkum EA, Bleichrodt RP, van Goor H. Different surgical techniques to reduce post-operative adhesion formation: a systematic review and meta-analysis. Hum Reprod Update. 2012;19:12–25.
27. Krielen P, Stommel MWJ, Pargmae P, Bouvy ND, Bakkum EA, Ellis H, et al. Adhesion-related readmissions after open and laparoscopic surgery: a retrospective cohort study (SCAR update). Lancet. 2020;395:33–41.
28. Schölin J, Buunen M, Hop W, Bonjer J, Anderberg B, Cuesta M, et al. Bowel obstruction after laparoscopic and open colon resection for cancer: results of 5 years of follow-up in a randomized trial. Surg Endosc. 2011;25:3755–60.
29. Petersson J, Koedam TW, Bonjer HJ, Andersson J, Angenete E, Bock D, et al. Bowel obstruction and ventral hernia after laparoscopic versus open surgery for rectal cancer in a randomized trial (COLOR II). Ann Surg. 2019;269:53–7.
30. Taylor GW, Jayne DG, Brown SR, Thorpe H, Brown JM, Dewberry SC, et al. Adhesions and incisional hernias following laparoscopic versus open surgery for colorectal cancer in the CLASICC trial. Br J Surg. 2010;97:70–8.
31. Bartels SAL, Vlug MS, Hollmann MW, Dijkgraaf MGW, Ubbink DT, Cense HA, et al. Small bowel obstruction, incisional hernia and survival after laparoscopic and open colonic resection (LAFA study). Br J Surg. 2014;101:1153–9.
32. Udayasiri DK, Skandarajah A, Hayes IP. Laparoscopic compared with open resection for colorectal cancer and long-term incidence of adhesional intestinal obstruction and incisional hernia: a systematic review and meta-analysis. Dis Colon Rectum. 2020;63:101–12.
33. Kumar S, Wong PF, Leaper DJ. Intra-peritoneal prophylactic agents for preventing adhesions and adhesive intestinal obstruction after non-gynaecological abdominal surgery. Cochrane Database Syst Rev. 2009;(1):CD005080.
34. Robb WB, Mariette C. Strategies in the prevention of the formation of postoperative adhesions in digestive surgery: a systematic review of the literature. Dis Colon Rectum. 2014;57:1228–40.
35. Waldron M. Errors, omissions, and publication bias. Dis Colon Rectum. 2015;58:e53.
36. Cornish J, Tekkis P, Kiran R, Kirat H, Tan E, Remzi F, et al. The effect of seprafilm on septic complications and bowel obstruction following primary restorative proctocolectomy. The American Society of Colon and Rectal Surgeons Annual Meeting Abstracts; 2008, p. 647.
37. Habib SM, Betjes MG, Fieren MW, Boeschoten EW, Abrahams AC, Boer WH, Struijk DG, Ruger W, Krikke C, Westerhuis R, de Sévaux RG, van der Sande FM, Gaasbeek A, Korte MR. Eps Registry. Management of encapsulating peritoneal sclerosis:

a guideline on optimal and uniform treatment. Neth J Med. 2011;69(11):500–7.
38. Isaza-Restrepo A, Martin-Saavedra JS, Velez-Leal JL, Vargas-Barato F, Riveros-Dueñas R. The peritoneum: beyond the tissue—a review. Front Physiol. 2018;9:738. https://doi.org/10.3389/fphys.2018.00738.
39. Beyene RT, Kavalukas SL, Barbul A. Intra-abdominal adhesions: anatomy, physiology, pathophysiology, and treatment. Curr Probl Surg. 2015;52(7):271–319.
40. Kastelein AW, Vos LMC, de Jong KH, van Baal JOAM, Nieuwland R, van Noorden CJF, Roovers JWR, Lok CAR. Embryology, anatomy, physiology and pathophysiology of the peritoneum and the peritoneal vasculature. Semin Cell Dev Biol. 2019;92:27–36.
41. Yu M, Shi J, Sheng M. Exosomes: the new mediator of peritoneal membrane function. Kidney Blood Press Res. 2018;43(3):1010–22.
42. Gandhi VC, Humayun HM, Ing TS, Daugirdas JT, Jablokow VR, Iwatsuki S, Geis WP, Hano JE. Sclerotic thickening of the peritoneal membrane in maintenance peritoneal dialysis patients. Arch Intern Med. 1980;140(9):1201–3.
43. Owtschinnikow PJ. Peritonitis chronica fibrosa incapsulata. Arch für Klin Chir. 1907;83:623–34.
44. Rigby RJ, Hawley CM. Sclerosing peritonitis: the experience in Australia. Nephrol Dial Transplant. 1998;13(1):154–9.
45. Oreopoulos DG, Khanna R, Wu G. Sclerosing obstructive peritonitis after CAPD. Lancet. 1983;2(8346):409.
46. Klimopoulos S, Katsoulis IE, Margellos V, Nikolopoulou N. Sclerosing encapsulating peritonitis secondary to CAPD: the effect of fibrotic debridement on further dialysis. J R Coll Surg Edinb. 2002;47(2):485–90.
47. Tan FL, Loh D, Prabhakaran K. Sclerosing encapsulating peritonitis in a child secondary to peritoneal dialysis. J Pediatr Surg. 2005;40(5):e21–3.
48. Marichal JF, Faller B, Brignon P, Wagner D, Straub P. Progressive calcifying peritonitis: a new complication of CAPD? Report of two cases. Nephron. 1987;45(3):229–32.
49. Allam H, Al Yahri O, Mathew S, Darweesh A, Suliman AN, Abdelaziem S, Khairat M, Toro A, Di Carlo I. The enigma of primary and secondary encapsulating peritoneal sclerosis. BMC Surg. 2016;16(1):81.
50. Nitsch D, Davenport A. Designing epidemiology studies to determine the incidence and prevalence of encapsulating peritoneal sclerosis (EPS). Perit Dial Int. 2015;35(7):678–82.
51. Li Cavoli G, Amato A, Mongiovì R, Schillaci O, Giammarresi C, Bono L, Turdo R, Carollo C, Zagarrigo C, Servillo F, Oliva B, Tralongo A, Caputo F. Early histological changes in post-transplant encapsulating peritoneal sclerosis. Blood Purif. 2018;46(4):323–5.
52. Koopmans T, Rinkevich Y. Mesothelial to mesenchyme transition as a major developmental and pathological player in trunk organs and their cavities. Commun Biol. 2018;1:170. https://doi.org/10.1038/s42003-018-0180-x.
53. Korte MR, Sampimon DE, Lingsma HF, Fieren MW, Looman CW, Zietse R, Weimar W, Betjes MG. Dutch Multicenter EPS Study. Risk factors associated with encapsulating peritoneal sclerosis in Dutch EPS study. Perit Dial Int. 2011;31(3):269–78.
54. Bayston R, Ashraf W, Barker-Davies R, Tucker E, Clement R, Clayton J, Freeman BJ, Nuradeen B. Biofilm formation by Propionibacterium acnes on biomaterials in vitro and in vivo: impact on diagnosis and treatment. J Biomed Mater Res A. 2007;81(3):705–9.
55. Lee KW, Cho CW, Lee N, Lee S, Kim JM, Choi GS, Kwon CH, Joh JW, Lee SK. Encapsulating peritoneal sclerosis in liver transplant recipients: a report of 2 cases. Ann Surg Treat Res. 2017;92(3):164–7.
56. Rumbo C, Zambernardi A, Cabanne A, Rumbo M, Gondolesi G. Sclerosing peritonitis, a rare complication after intestinal transplant. Report of one case successfully treated with adjustment of immunosuppression. Pediatr Transplant. 2013;17(5):E125–9.
57. Klink B, Boynton CJ. Starch peritonitis. A case report and clinicopathologic review. Am Surg. 1990;56(11):672–4.
58. Castelli MJ, Armin AR, Husain A, Orfei E. Fibrosing peritonitis in a drug abuser. Arch Pathol Lab Med. 1985;109(8):767–9.
59. Keating JP, Neill M, Hill GL. Sclerosing encapsulating peritonitis after intraperitoneal use of povidone iodine. Aust N Z J Surg. 1997;67(10):742–4.
60. Árnadóttir M, Jónasson JG, Indridason ÓS. Encapsulating peritoneal sclerosis following a peritoneal foreign body reaction to Dacron fibres-a case report. NDT Plus. 2011;4(2):107–9.
61. Kaur S, Doley RP, Chabbhra M, Kapoor R, Wig J. Post trauma abdominal cocoon. Int J Surg Case Rep. 2015;7C:64–5.
62. Fossey SJ, Simson JN. Sclerosing encapsulating peritonitis secondary to dermoid cyst rupture: a case report. Ann R Coll Surg Engl. 2011;93(5):e39–40.
63. Sigaroudinia MO, Baillie C, Ahmed S, Mallucci C. Sclerosing encapsulating peritonitis--a rare complication of ventriculoperitoneal shunts. J Pediatr Surg. 2008;43(5):E31–3.
64. Odama UO, Shih DJ, Korbet SM. Sclerosing peritonitis and systemic lupus erythematosus: a report of two cases. Perit Dial Int. 1999;19(2):160–4.
65. Pepels MJ, Peters FP, Mebis JJ, Ceelen TL, Hoofwijk AG, Erdkamp FL. Sclerosing peritonitis: an unusual cause of ascites in a patient with systemic lupus erythematosus. Neth J Med. 2006;64(9):346–9.
66. Dabak R, Uygur-Bayramiçli O, Aydin DK, Dolapçioglu C, Gemici C, Erginel T, Turan C, Karadayi N. Encapsulating peritonitis and familial Mediterranean fever. World J Gastroenterol. 2005;11(18):2844–6.
67. Clement PB, Young RH, Hanna W, Scully RE. Sclerosing peritonitis associated with luteinized thecomas of the ovary. A clinicopathological analysis of six cases. Am J Surg Pathol. 1994;18(1):1–13.
68. Altman AD, Bentley JR, Rittenberg PV, Murray SK. Luteinized thecomas ("Thecomatosis") with sclerosing peritonitis (LTSP): report of 2 cases and review of an enigmatic syndrome associated with a peritoneal proliferation of specialized (vimentin+/keratin+/CD34+) submesothelial fibroblasts. J Obstet Gynaecol Can. 2016;38(1):41–50.
69. Windsor WO, Durrein F, Dyer NH. Fibrinous peritonitis: a complication of practolol therapy. Br Med J. 1975;2(5962):68.
70. Nauen DW, Martin A, Katz A, Cohen D, Ranganathan S. A case of luteinizing thecoma with sclerosing peritonitis: revisiting a link with anti-epileptic drugs. Pediatr Blood Cancer. 2010;54(3):470–2.
71. Sachdev A, Usatoff V, Thaow C. Sclerosing encapsulating peritonitis and methotrexate. Aust N Z J Obstet Gynaecol. 2006;46(1):58–9.
72. Zimmermann S, Zaman K, Wolfer A, Jacot W. Severe peritonitis induced by methotrexate during treatment of persistent gestational trophoblastic disease. Oncologist. 2012;17(8):e18–20.
73. Sarker S, Kodali S, Weber F. A new meaning to butterflies in the stomach. Gastroenterology. 2015;148(1):e12–3.
74. Takebayashi K, Sonoda H, Shimizu T, Ohta H, Ishida M, Mekata E, Endo Y, Tani T, Tani M. Successful surgical approach for a patient with encapsulating peritoneal sclerosis after hyperthermic intraperitoneal chemotherapy: a case report and literature review. BMC Surg. 2014;14:57.
75. Mangan C, Moinuddin Z, Summers A, de Reuver P, van Dellen D, Augustine T. Encapsulating peritoneal sclerosis following hyperthermic intraperitoneal chemotherapy. ANZ J Surg. 2019;89(10):E468–9.

76. Lalloo S, Krishna D, Maharajh J. Case report: abdominal cocoon associated with tuberculous pelvic inflammatory disease. Br J Radiol. 2002;75(890):174–6.
77. Sharma V, Mandavdhare HS, Rana SS, Singh H, Kumar A, Gupta R. Role of conservative management in tubercular abdominal cocoon: a case series. Infection. 2017;45(5):601–6.
78. Sharma V, Singh H, Mandavdhare HS. Tubercular abdominal cocoon: systematic review of an uncommon form of tuberculosis. Surg Infect. 2017;18(6):736–41.
79. Simbli MA, Niaz FA, Al-Wakeel JS. Encapsulating peritoneal sclerosis in a peritoneal dialysis patient presenting with complicated Mycobacterium fortuitum peritonitis. Saudi J Kidney Dis Transpl. 2012;23(3):635–41.
80. Foo KT, Ng KC, Rauff A, Foong WC, Sinniah R. Unusual small intestinal obstruction in adolescent girls: the abdominal cocoon. Br J Surg. 1978;65(6):427–30.
81. Serafimidis C, Katsarolis I, Vernadakis S, Rallis G, Giannopoulos G, Legakis N, Peros G. Idiopathic sclerosing encapsulating peritonitis (or abdominal cocoon). BMC Surg. 2006;6:3. https://doi.org/10.1186/1471-2482-6-3.
82. Cleffken B, Sie G, Riedl R, Heineman E. Idiopathic sclerosing encapsulating peritonitis in a young female-diagnosis of abdominal cocoon. J Pediatr Surg. 2008;43(2):e27–30.
83. Akbulut S. Accurate definition and management of idiopathic sclerosing encapsulating peritonitis. World J Gastroenterol. 2015;21(2):675–87.
84. Tannoury JN, Abboud BN. Idiopathic sclerosing encapsulating peritonitis: abdominal cocoon. World J Gastroenterol. 2012;18(17):1999–2004.
85. Kirkman MA, Heap S, Forgacs B, Williams R, Tavakoli A, Pararajasingam R, Shrestha B, Wilkie ME, Augustine T. Encapsulating peritoneal sclerosis presenting as acute limb ischemia. Perit Dial Int. 2010;30(5):578–80.
86. Forgacs B, Shiell K, Farquharson F, Tavakoli A, Makanjuola D, Augustine T, Pararajasingam R. Pseudoachalasia of the esophagus caused by encapsulating peritoneal sclerosis. Perit Dial Int. 2010;30(2):246–9.
87. Yiannoullou P, Kanesalingam K, van Dellen D, Augustine T. Encapsulating peritoneal sclerosis: presentation without preceding symptoms. Saudi J Kidney Dis Transpl. 2015;26(2):329–34.
88. Tarzi RM, Lim A, Moser S, Ahmad S, George A, Balasubramaniam G, Clutterbuck EJ, Gedroyc W, Brown EA. Assessing the validity of an abdominal CT scoring system in the diagnosis of encapsulating peritoneal sclerosis. Clin J Am Soc Nephrol. 2008;3(6):1702–10.
89. Upponi S, Butler AJ, Watson CJ, Shaw AS. Encapsulating peritoneal sclerosis--correlation of radiological findings at CT with underlying pathogenesis. Clin Radiol. 2014;69(1):103–9.
90. Jovani M, Baticci F, Bonifacio C, Omodei PD, Malesci A. Abdominal cocoon or idiopathic encapsulating peritoneal sclerosis: magnetic resonance imaging. Dig Liver Dis. 2014;46(2):192–3.
91. Wright B, Summers A, Fenner J, Gillott R, Hutchinson CE, Spencer PA, Wilkie M, Hurst H, Herrick S, Brenchley P, Augustine T, Bardhan KD. Initial observations using a novel "cine" magnetic resonance imaging technique to detect changes in abdominal motion caused by encapsulating peritoneal sclerosis. Perit Dial Int. 2011;31(3):287–90.
92. Vadi SK, Mittal BR, Parihar AS, Kumar R, Sharma V, Mandavdhare HS. Demonstration of tubercular "abdominal cocoon" (sclerosing encapsulating peritonitis) in 18F-FDG PET/CT. Clin Nucl Med. 2018;43(10):771–2.
93. Mateijsen MA, van der Wal AC, Hendriks PM, Zweers MM, Mulder J, Struijk DG, Krediet RT. Vascular and interstitial changes in the peritoneum of CAPD patients with peritoneal sclerosis. Perit Dial Int. 1999;19(6):517–25.
94. Honda K, Nitta K, Horita S, Yumura W, Nihei H. Morphological changes in the peritoneal vasculature of patients on CAPD with ultrafiltration failure. Nephron. 1996;72(2):171–6.
95. Honda K, Nitta K, Horita S, Tsukada M, Itabashi M, Nihei H, Akiba T, Oda H. Histologic criteria for diagnosing encapsulating peritoneal sclerosis in continuous ambulatory peritoneal dialysis patients. Adv Perit Dial. 2003;19:169–75.
96. Yamada K, Miyahara Y, Hamaguchi K, Nakayama M, Nakano H, Nozaki O, Miura Y, Suzuki S, Tuchida H, Mimura N, et al. Immunohistochemical study of human advanced glycosylation end-products (AGE) in chronic renal failure. Clin Nephrol. 1994;42(6):354–61.
97. Nakayama M, Kawaguchi Y, Yamada K, Hasegawa T, Takazoe K, Katoh N, Hayakawa H, Osaka N, Yamamoto H, Ogawa A, Kubo H, Shigematsu T, Sakai O, Horiuchi S. Immunohistochemical detection of advanced glycosylation end-products in the peritoneum and its possible pathophysiological role in CAPD. Kidney Int. 1997;51(1):182–6.
98. Braun N, Alscher MD, Fritz P, Latus J, Edenhofer I, Reimold F, Alper SL, Kimmel M, Biegger D, Lindenmeyer M, Cohen CD, Wüthrich RP, Segerer S. The spectrum of podoplanin expression in encapsulating peritoneal sclerosis. PLoS One. 2012;7(12):e53382.
99. Alscher DM, Braun N, Biegger D, Fritz P. Peritoneal mast cells in peritoneal dialysis patients, particularly in encapsulating peritoneal sclerosis patients. Am J Kidney Dis. 2007;49(3):452–61.
100. Braun N, Reimold F, Biegger D, Fritz P, Kimmel M, Ulmer C, Alscher MD. Fibrogenic growth factors in encapsulating peritoneal sclerosis. Nephron Clin Pract. 2009;113(2):c88–95.
101. Yamamoto T, Nagasue K, Okuno S, Yamakawa T. The role of peritoneal lavage and the prognostic significance of mesothelial cell area in preventing encapsulating peritoneal sclerosis. Perit Dial Int. 2010;30(3):343–52.
102. Bozkurt S, Yuzbasioglu MF, Bulbuloglu E, Gul M, Kale IT. Prevention of postoperative peritoneal adhesions by administration of estrogen. J Investig Surg. 2009;22(4):263–7.
103. Kuriyama S, Tomonari H. Corticosteroid therapy in encapsulating peritoneal sclerosis. Nephrol Dial Transplant. 2001;16(6):1304–5.
104. Nakayama M, Yamamoto H, Ikeda M, Hasegawa T, Kato N, Takahashi H, Otsuka Y, Yokoyama K, Yamamoto R, Kawaguchi Y, Hosoya T. Risk factors and preventive measures for encapsulating peritoneal sclerosis--Jikei experience 2002. Adv Perit Dial. 2002;18:144–8.
105. Lafrance JP, Létourneau I, Ouimet D, Bonnardeaux A, Leblanc M, Mathieu N, Pichette V. Successful treatment of encapsulating peritoneal sclerosis with immunosuppressive therapy. Am J Kidney Dis. 2008;51(2):e7–10.
106. Allaria PM, Giangrande A, Gandini E, Pisoni IB. Continuous ambulatory peritoneal dialysis and sclerosing encapsulating peritonitis: tamoxifen as a new therapeutic agent? J Nephrol. 1999;12(6):395–7.
107. Clark CP, Vanderpool D, Preskitt JT. The response of retroperitoneal fibrosis to tamoxifen. Surgery. 1991;109(4):502–6.
108. Bourouma R, Chevet D, Michel F, Cercueil JP, Arnould L, Rifle G. Treatment of idiopathic retroperitoneal fibrosis with tamoxifen. Nephrol Dial Transplant. 1997;12(11):2407–10.
109. van Bommel EF, Pelkmans LG, van Damme H, Hendriksz TR. Long-term safety and efficacy of a tamoxifen-based treatment strategy for idiopathic retroperitoneal fibrosis. Eur J Intern Med. 2013;24(5):444–50.
110. Wong CF, Beshir S, Khalil A, Pai P, Ahmad R. Successful treatment of encapsulating peritoneal sclerosis with azathioprine and prednisolone. Perit Dial Int. 2005;25(3):285–7.
111. Ghadimi M, Dashti-Khavidaki S, Khalili H. mTOR inhibitors for management of encapsulating peritoneal sclerosis: a review of literatures. Ren Fail. 2016;38(10):1574–80.

112. Messina M, Ariaudo C, Mella A, Cantaluppi V, Segoloni GP, Biancone L. mTOR inhibitors for medical treatment of post-transplantation encapsulating peritoneal sclerosis: a favourable single center experience. J Nephrol. 2015;28(2):245–9.
113. Danford CJ, Lin SC, Smith MP, Wolf JL. Encapsulating peritoneal sclerosis. World J Gastroenterol. 2018;24(28):3101–11.
114. Zhang C, Patel NJ, Jacobs WC, Ullman S, Berzin TM, Chuttani R, Lembo AJ, Wolf JL. Successful treatment with methylnaltrexone and IVIG for paraneoplastic syndrome-associated intestinal pseudo-obstruction. Gastroenterol Hepatol (N Y). 2013;9(1):48–51.
115. Jing S, Kezhou Y, Hong Z, Qun W, Rong W. Effect of renin-angiotensin system inhibitors on prevention of peritoneal fibrosis in peritoneal dialysis patients. Nephrology (Carlton). 2010;15(1):27–32.
116. Nishimura K, Ogawa K, Kawaguchi M, Fumoto S, Mukai H, Kawakami S. Suppression of peritoneal fibrosis by sonoporation of hepatocyte growth factor gene-encoding plasmid DNA in mice. Pharmaceutics. 2021;13(1):115.
117. Yoshio Y, Miyazaki M, Abe K, Nishino T, Furusu A, Mizuta Y, Harada T, Ozono Y, Koji T, Kohno S. TNP-470, an angiogenesis inhibitor, suppresses the progression of peritoneal fibrosis in mouse experimental model. Kidney Int. 2004;66(4):1677–85.
118. Nishino T, Miyazaki M, Abe K, Furusu A, Mishima Y, Harada T, Ozono Y, Koji T, Kohno S. Antisense oligonucleotides against collagen-binding stress protein HSP47 suppress peritoneal fibrosis in rats. Kidney Int. 2003;64(3):887–96.
119. Ulmer C, Braun N, Rieber F, Latus J, Hirschburger S, Emmel J, Alscher MD, Steurer W, Thon KP. Efficacy and morbidity of surgical therapy in late-stage encapsulating peritoneal sclerosis. Surgery. 2013;153(2):219–24.
120. Gingell-Littlejohn M, Hanif F, Junor B, Clancy M, Murio E. Peritoneal cocoon capsulotomy--an alternative surgical approach in treating encapsulating peritoneal sclerosis. Perit Dial Int. 2013;33(3):325–7.
121. Kawanishi H, Banshodani M, Yamashita M, Shintaku S, Dohi K. Surgical treatment for encapsulating peritoneal sclerosis: 24 years' experience. Perit Dial Int. 2019;39(2):169–74.
122. El-Sherbini N, Duncan N, Hickson M, Johansson L, Brown EA. Nutrition changes in conservatively treated patients with encapsulating peritoneal sclerosis. Perit Dial Int. 2013;33(5):538–43.
123. Campbell R, Augustine T, Hurst H, Pararajasingam R, van Dellen D, Armstrong S, Bartley C, Birtles L, Summers A. Anthropometrics identify wasting in patients undergoing surgery for encapsulating peritoneal sclerosis. Perit Dial Int. 2015;35(4):471–80.
124. Habib SM, Hagen SM, Korte MR, Zietse R, Dor FJ, Betjes MG. Localized encapsulating peritoneal sclerosis constricting the terminal ileum--an unusual appearance requiring surgical intervention. Perit Dial Int. 2013;33(5):503–6.
125. Banshodani M, Kawanishi H, Shintaku S, Yamashita M, Moriishi M, Tsuchiya S. Effective remedy for encapsulating peritoneal sclerosis with ureteroileal fistula. Perit Dial Int. 2017;37(6):648–9.
126. Banshodani M, Kawanishi H, Moriishi M, Shintaku S, Hashimoto S, Tsuchiya S. Percutaneous endoscopic gastrostomy with jejunal extension for an encapsulating peritoneal sclerosis refractory to surgical enterolysis. Perit Dial Int. 2016;36(5):562–3.
127. Waghray A, Nassar A, Hashimoto K, Eghtesad B, Aucejo F, Krishnamurthi V, Uso TD, Srinivas T, Steiger E, Abu-Elmagd K, Quintini C. Combined intestine and kidney transplantation in a patient with encapsulating peritoneal sclerosis: case report. Am J Transplant. 2013;13(12):3274–7.
128. Kawanishi H, Moriishi M, Tsuchiya S. Experience of 100 surgical cases of encapsulating peritoneal sclerosis: investigation of recurrent cases after surgery. Adv Perit Dial. 2006;22:60–4.
129. Kawanishi H, Ide K, Yamashita M, Shimomura M, Moriishi M, Tsuchiya S, Dohi K. Surgical techniques for prevention of recurrence after total enterolysis in encapsulating peritoneal sclerosis. Adv Perit Dial. 2008;24:51–5.
130. Shroff R, Stefanidis CJ, Askiti V, Edefonti A, Testa S, Ekim M, Kavaz A, Ariceta G, Bakkaloglu S, Fischbach M, Klaus G, Zurowska A, Holtta T, Jankauskiene A, Vondrak K, Vande Walle J, Schmitt CP, Watson AR, European Paediatric Dialysis Working Group. Encapsulating peritoneal sclerosis in children on chronic PD: a survey from the European Paediatric Dialysis Working Group. Nephrol Dial Transplant. 2013;28(7):1908–14.
131. Sharma V, Moinuddin Z, Summers A, Shenoy M, Plant N, Vranic S, Prytula A, Zvizdic Z, Karava V, Printza N, Vlot J, van Dellen D, Augustine T. Surgical management of Encapsulating Peritoneal Sclerosis (EPS) in children: international case series and literature review. Pediatr Nephrol. 2021;37:643. https://doi.org/10.1007/s00467-021-05243-0.
132. McCleary BV, Cox J. Evolution of a definition for dietary fiber and methodology to service this definition. Luminac Res. 2017;21(2):9–20.
133. Kumar V, Sinha AK, Wang H, De Boeck G. Fibre in gastrointestinal health. In: Lomer M, editor. Advanced nutrition and dietetics in gastroenterology. New York, NY: Wiley; 2014. p. 57–71.
134. Lee J, Allen R, Ashley S, Becker S, Cummins P, Gbadamosi A, Gooding O, Huston J, Le Couteur J, O'Sullivan D, Wilson S, Lomer MC. Gastroenterology Specialist Group of the British Dietetic Association. British Dietetic Association evidence-based guidelines for the dietary management of Crohn's disease in adults. J Hum Nutr Diet. 2014;27(3):207–18.
135. Woolner JT, Kirby G. Clinical effects of a low fibre diet on irritable bowel syndrome. J Hum Nutr Diet. 2000;13:249–53.
136. Lijoi D, Ferrero S, Mistrangelo E, et al. Bowel preparation before laparoscopic gynaecological surgery in benign conditions using a 1-week low fibre diet: a surgeon blind, randomized and controlled trial. Arch Gynecol Obstet. 2009;280(5):713–8.
137. Vanhauwaert E, Matthys C, Verdonck L, De Preter V. Low-residue and low-fiber diets in gastrointestinal disease management. Adv Nutr. 2015;6:820–7.
138. Rice AD, Wakefield LB, Patterson K, D'Avy Reed E, Wurn BF, Klingenberg B, King CR, Wurn LJ. Development and validation of a questionnaire to measure serious and common quality of life issues for patients experiencing small bowel obstructions. Healthcare. 2014;2:139–49.
139. Royal Surrey County Hospital NHS Foundation Trust. n.d.. https://www.royalsurrey.nhs.uk/download.cfm?doc=docm93jijm4n1328.pdf&ver=4344.
140. The National Confidential Enquiry into Patient Outcome and Death. Acute bowel obstruction. Delay in Transit. A review of the quality of care provided to patients aged over 16 years with a diagnosis of acute bowel obstruction. A report. London: National Confidential Enquiry into Patient Outcome and Death; 2020.
141. Lee MJ, Sayers AE, Drake TM, Hollyman M, Bradburn M, Hind D, Wilson TR, Fearnhead NS, NASBO Steering Group. UK-based, multisite, prospective cohort study of small bowel obstruction in acute surgical services: National Audit of Small Bowel Obstruction (NASBO) protocol. BMJ Open. 2017;7(10):e016796. https://doi.org/10.1136/bmjopen-2017-016796.
142. Ortiz-Hidalgo C, Cuesta-Mejías T, Cervantes-Castro J. Dry fruit bezoar causing acute small intestinal obstruction. Int J Surg Pathol. 2007;15(1):66–7.
143. Cox J, Grigg M. Small bowel obstruction by an intact grape. JAGS. 1986;34:550–2.
144. Yakan A, Şirinocak A, Telciler K, Tekeli M, Denecli A. A rare cause of acute abdomen: small bowel obstruction due to phytobezoar. Turk J Trauma Emerg Surg. 2010;16(5):459–63.

145. Occhionorelli S, et al. A rare case of a double phytobezoar causing gastric and jejunum obstruction in an adult man: a case report. J Med Case Rep. 2016;10:350.
146. Lewis J. Esophageal and small bowel obstruction from guar gum-containing "diet pills": analysis of 26 cases reported to the Food and Drug Administration. Am J Gastroenterol. 1992;87(10):1424–8.
147. Meier R, Gassull M. Consensus recommendations on the effects and benefits of fibre in clinical practice. Clin Nutr. 2004;1(Suppl 1):73–80.
148. Siddens ED, Al-Habbal Y, Bhandari M. Gastrointestinal obstruction secondary to enteral nutrition bezoar: a case report. World J Gastrointest Surg. 2020;12(8):369–76.

Bone Marrow and Haemopoietic Stem Cell Transplantation

Jennifer Clay, Maria Gilleece, and Clare Donnellan

Key Points

1. Haematopoietic stem cell transplantation (HSCT) may be autologous (using the patient's own cells) or allogeneic (using HLA-matched donor cells).
2. Autologous HSCT almost always uses peripheral blood stem cells and does not result in Graft versus Host disease.
3. Allogenic HSCT may use peripheral blood, aspirate from the bone marrow or, more rarely, umbilical cord blood
4. The most common indications for HSCT remain haematological malignancies; however it can be performed in patients with autoimmune conditions (multiple sclerosis, scleroderma) and has limited use in some solid malignancies (e.g. germ cell tumours)
5. The most common side-effects affect the GI tract and therefore nutritional status may be compromised.
6. The two situations in which nutritional support is commonly needed are patients with severe mucositis or those with GVHD affecting the gastrointestinal tract.
7. Regular dietetic assessment is vital—oral and enteral support should be preferred over parenteral, if this is possible

Introduction

The utility of chemotherapy alone to provide long term remission in some forms of haematological malignancy is limited, with higher doses of chemotherapy or radiotherapy being restricted by organ related toxicity, in particular the bone marrow. Stem cell transplant is utilised both to facilitate the use of higher dose cytotoxic therapy with stem cell rescue, whilst in the case of allogeneic transplant also providing a 'graft vs. tumour' effect and therefore the potential of long term remission or cure.

Both of these mechanisms have the potential to cause significant gastrointestinal toxicity, with the gastroenterology and nutrition team frequently involved with the management of such complications. The aim of this section is to provide an understanding of the process of stem cell transplant, its primary gastrointestinal complications and their management. Further details regarding stem cell transplant are available in specialised texts and reviews [1, 2].

Terminology

Bone marrow and haematopoietic Stem Cell Transplants (HSCTs) can be broadly categorised into two main classes, autologous and allogeneic.

Autologous

In autologous stem cell transplant the recipient's own stem cells are used to facilitate haematopoietic recovery following high dose chemotherapy/radiotherapy (referred to as conditioning). This is undertaken following several cycles of standard chemotherapy to debulk and control disease in the case of haematological malignancies. There is increasing use of autologous transplant for non-malignant conditions (e.g. multiple sclerosis), and in this setting no preceding chemo-

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therapy is necessary, however conditioning remains essential. Stem cells are harvested from the peripheral blood following mobilisation using haematopoietic growth factors (granulocyte colony-stimulating factor (GSCF)), with or without additional chemotherapy, allowing collection from the peripheral blood by apheresis. The cells are cryopreserved, and then thawed and infused following the conditioning regimen (Fig. 1). As the patient's own cells are used there is no immunological mismatch, therefore the procedure is not associated with graft versus host disease (GvHD) or immune mediated graft rejection, there is no requirement for post-transplant immunosuppression and immune reconstitution is relatively rapid. Transplant related mortality is 3–5%. The stages of autologous stem cell transplant are summarised below [3].

Allogeneic

In allogeneic transplant stem cells are sourced from an HLA matched donor and infused into the recipient following conditioning with chemotherapy/radiotherapy. The source of the stem cells may be a relative (full matched or half matched (haplo-identical)), an unrelated living donor or cryopreserved cord blood unit identified from international registries. The mechanisms of action of allogeneic transplant also includes high dose chemotherapy/radiotherapy (conditioning), but in addition whilst certain matching criteria need to be met there is always a degree of immunological mismatch between donor and recipient (except in the case of a syngeneic twin used as a donor), which results in a 'graft vs. leukaemia' effect thought to be essential for long term disease remission. The other side to this effect is 'graft vs. host disease (GvHD)', where the donor's immunological cells recognise recipient tissues as immunologically different and cause an inflammatory reaction. GvHD can be classified as acute (aGvHD) or chronic (cGvHD). The reverse of this is graft rejection which occurs in approximately 5% of transplants. Due to these potential immunological interactions patients require immunosuppression for 3–12 months following transplant, and potentially longer if GvHD develops. Due to the combination of

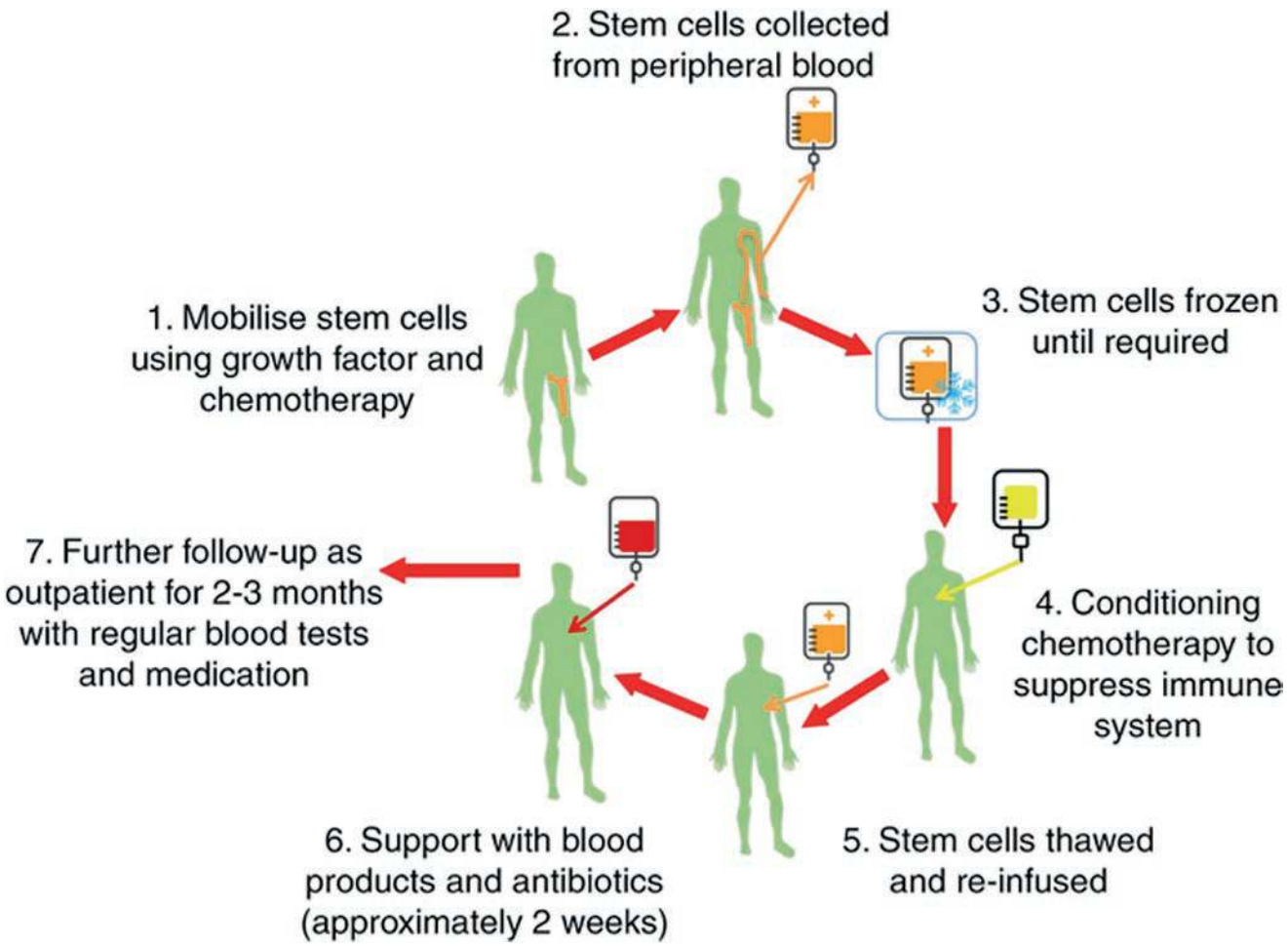

Fig. 1 The process of haematopoietic stem cell transplants (HSCT)

complications including slow immunological reconstitution, prolonged immunosuppression and GvHD the transplant related mortality (TRM) associated with allogeneic transplant is typically 10–50%.

Sources of Haemopoietic Stem Cells

Peripheral Blood Stem Cells

Peripheral blood stem cells (PBSC) are the most commonly used source of stem cells. The cells are obtained via peripheral blood apheresis following mobilisation using recombinant haematopoietic growth factors (granulocyte-colony stimulating factor (GCSF)). The circulating stem cells are then collected from the peripheral blood through a process called apheresis with blood filtered through a cell separator. PBSC have advantages over bone marrow harvested stem cells including typically a larger cell dose and faster neutrophil and platelet engraftment.

Bone Marrow

Bone marrow is collected by aspiration from the iliac crest. This procedure requires to the donor to have general anaesthetic but does not involve exposure to haemopoietic growth factors. Advantages to bone marrow stem cell source include lower rates of GvHD, and for this reason it is now most frequently used in the setting on of transplant for non-malignant conditions such as aplastic anaemia.

Umbilical Cord Blood

Cryopreserved umbilical cord blood units can be used as a stem cell source when other donor options are not available. In the paediatric setting single cord units can be used, however in the adult setting 2 units are generally required to provide adequate cell dose. Whilst a lesser degree of HLA matching is required for transplant of cord blood units compared to that required for other cell sources, the drawbacks of this cell source include slower neutrophil and platelet engraftment and delayed immune reconstitution.

Indications

Haematologic malignancy is the most common indication for HSCT. Factors considered when deciding between allogeneic and autologous stem cell transplants include the underlying disease, response to previous treatments, fitness of the patient, and donor availability. Allogeneic HSCT is performed for a number of non-malignant conditions including aplastic anaemia, thalassaemia and severe combined immunodeficiency. There is increasing interest in the utility of autologous transplant in patients with autoimmune conditions including multiple sclerosis, scleroderma and inflammatory bowel disease, along with limited use in some solid malignancies (e.g. germ cell tumours) (Fig. 2).

The British Society of Marrow and Stem Cell Transplant produce a comprehensive table of approved indications for transplant in the UK [5]. Table 1 summarises the principles of the HSCT procedure.

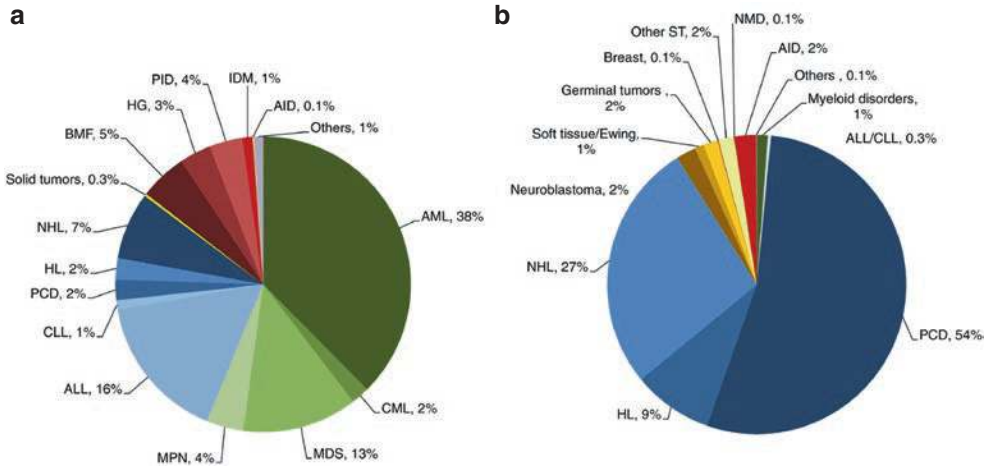

Fig. 2 Relative proportion of disease indications for HCT in Europe 2018. (**a**) Allogeneic HCT. (**b**) Autologous HCT [4]. *PID* primary immunodeficiency, *IDM* inherited disorders of metabolism, *AID* autoimmune disease, *AML* acute myeloid leukaemia, *CML* chronic myeloid leukaemia, *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasms, *ALL* acute lymphocytic leukaemia, *CLL* chronic lymphocytic leukaemia, *PCD* plasma cell disorder, *HL* Hodgkin's lymphoma, *NHL* Non Hodgkin's lymphoma, *BMF* bone marrow failure, *HG* haemoglobinopathies, *PCD* plasma cell disorders, *ST* solid tumours, *NMD* non malignant disorders

Table 1 Principles of HSCT procedure

1. Consideration of the patient for HSCT including MDT review.
2. Patient assessment
(a) Disease status: In general transplant outcomes are better for patient in a complete or partial response. Outcomes for those with refractory or progressive disease are universally poor.
(b) Assessment of fitness including assessment of cardiorespiratory function
3. Donor availability (allogeneic transplant only)
(a) HLA-tying (commonly called tissue typing) of patient and any potential related donors.
(b) Searching of international donor registries where a suitable related donor is not available
(c) All donors undergo medical assessment by an independent clinician to assess fitness to donate.
4. Transplant conditioning therapy
(a) Combination of chemotherapy/radiotherapy determined depending on disease and patient factors.
(b) The role of conditioning includes:
• Reduction or eradication of any residual disease present at the time of transplant
• To 'make space' to allow engraftment of infused stem cells
• Immunosuppression to prevent graft rejection and reduce the rate of GvHD
5. Transplant protocol
(a) A personalised schedule detailing conditioning, date of stem cell infusion and relevant prophylactic medications along with key donor/recipient details (e.g. HLA match, blood type, CMV status)
6. Patient undergoes transplant procedure as an inpatient or outpatient depending on local protocol.
7. Posttransplant care—initial intensive monitoring, ongoing care dependent on individual complications and disease monitoring requirements. All transplant patients will undergo long term late effects follow up.

Gastrointestinal Complications

The gastrointestinal complications of transplant can be broadly separated in to pre-engraftment (during conditioning and until 2–3 weeks post cell infusion), early (up to day 100) and late (day 100 onwards) post engraftment (Fig. 3). Pre-engraftment complications are predominantly related to the toxic effects of the conditioning protocol and medications used to manage early complications (e.g. antibiotics, anti-emetics). Post-engraftment complications are most commonly associated with GvHD and delayed immune reconstitution and therefore more frequently encountered following allogeneic transplantation than autologous.

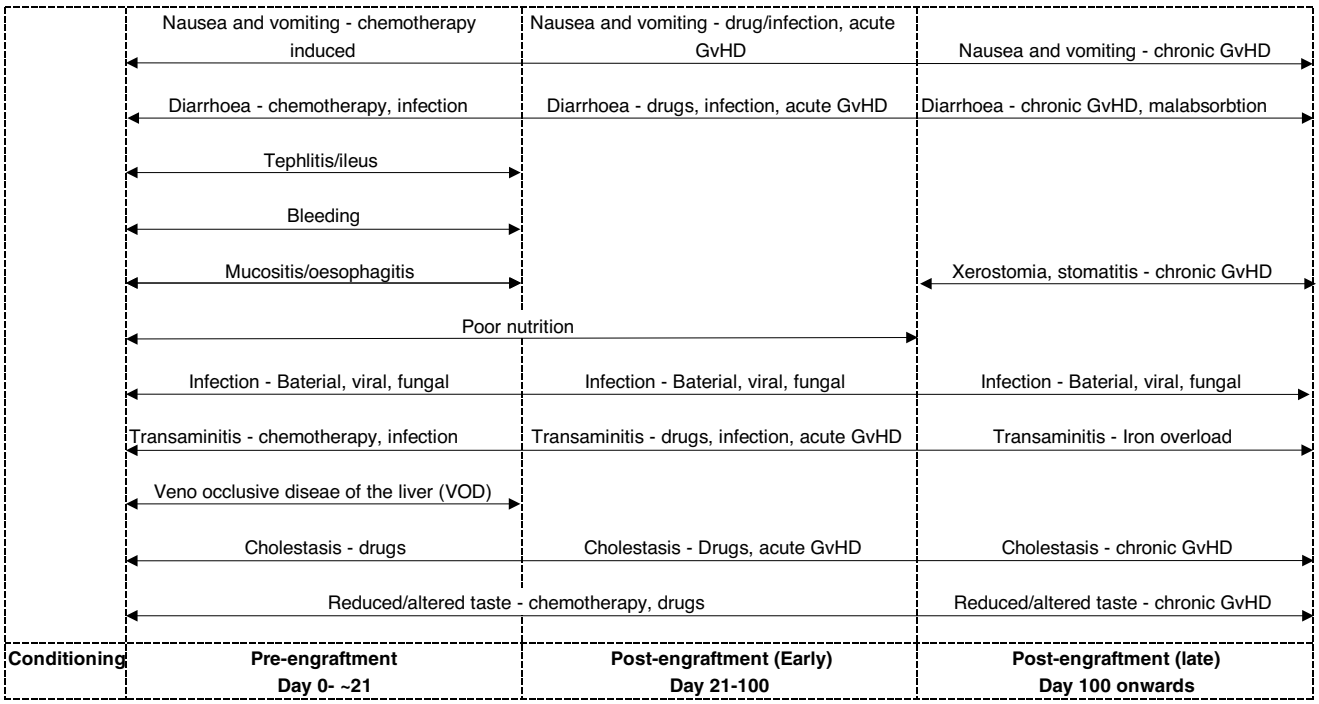

Fig. 3 The pre, early and late gastrointestinal complications of HSCT

Pre-engraftment Complications

Nausea and Vomiting

Nausea and vomiting are almost universal in the early stages following stem cell transplant due to the use of chemotherapy/radiotherapy in the conditioning regimen, the severity varies depending on the combination of chemotherapy, radiotherapy and the intensity of doses used. Preventative antiemetics should be used in all cases. Standard combinations generally include a 5-HT3 antagonist (e.g. Ondansetron) along with metoclopramide, typically given orally, intravenously or subcutaneously, depending on the patients' needs. Dexamethasone may be added to control delayed emesis associated with drugs such as cyclophosphamide and may be continued for several days [6].

In addition to the impact of chemotherapy/radiotherapy other pharmaceutical agents commonly used such as antimicrobials including co-trimoxazole and -azole antifungals along with agents used for GvHD prophylaxis such as cyclosporine and mycophenolate mofotil (MMF) may contribute to nausea.

Infection, most commonly oesophageal candidiasis, can cause nausea and vomiting and should be considered and investigated with upper GI endoscopy in cases of intractable nausea and vomiting. Due to the risk of viral reactivation staining for CMV of biopsies should be requested in all cases alongside the standard testing, this complication can occur in the absence of detectable CMV viraemia in the peripheral blood.

Mucositis

The degree of mucositis experienced by patients varies dramatically depending on the intensity of conditioning used, and in particular the use of high dose total body irradiation (TBI), with these patients almost universally experiencing severe mucositis. This complication should be considered as 'mucosal barrier injury' [7] with potentially the entire gastrointestinal tract being involved. Pain is predominantly related to oral/pharyngeal and oesophageal involvement, while diarrhoea, bloating abdominal pain and less commonly ileus are caused by lower GI involvement. Mucositis as a cause of diarrhoea is a diagnosis of exclusion, and faecal culture to exclude an infective cause should be undertaken in all cases.

Oral mucositis progresses in four phases: Phase 1—vascular/initial inflammatory, Phase 2—Epithelial, Phase 3—Ulcerative, Phase 4—Healing. Multiple scoring systems exist to enable consistent documentation of the severity of mucositis [8]. One example is the '*National Cancer Institute common toxicity criteria for grading of stomatitis*', which grades mucositis as follow:

- Grade 1—Painless ulcers, erythema or mild soreness
- Grade 2—Painful erythema, oedema, and ulceration but is able to eat
- Grade 3—Unable to eat
- Grade 4—requiring enteral or parenteral support

Where ulcers are present these should be swabbed to exclude infection, particularly of viral origin. Bleeding may occur locally in the mouth or throughout the GI tract; therefore platelet support is a key aspect of supportive care. Tranexamic acid can also be beneficial either systemically or dissolved and used as a mouthwash for oral bleeding.

Management of mucositis is predominantly aimed at symptomatic control, prevention of infection and provision of nutrition when patients are unable to eat. Prevention in the form of good oral hygiene and mouth washes such as saline and chlorhexidine are used before mucositis occurs. When patients become symptomatic analgesic mouth washes along with topical measures such as lignocaine lozenges can be helpful, however patients frequently require opioid analgesia, initially orally while able to swallow but ultimately often subcutaneously or intravenously. Subcutaneous administration through a syringe driver with a combination of opiates and antiemetics is commonly used. Diarrhoea can be managed with anti-diarrhoeal agents such as loperamide when infection has been excluded. There is a significant risk of infection with the breakdown of mucosal barriers, and most units use prophylactic anti-biotics when patients become neutropenic along with antiviral and antifungal prophylaxis. Whilst a number of agents have been used to modify locally the effect of cytotoxic therapy such as ice, prostaglandins and interleukin II benefit has not been proven.

The time to recovery from mucositis depends on the presence of infection, nutritional status and most importantly haematopoietic recovery. Whilst most patients experience a rapid improvement with neutrophil engraftment allowing them to start to eat and drink again many will experience persisting mucosal sensitivity, for example to spicy foods and loss of taste for weeks to months. In those who have been treated with TBI reduced salivary secretion may persist long term.

Infective and Neutropenic Colitis

Diarrhoea in the early post-transplant period is frequently multifactorial. Infection should always be considered and investigated. Due to the implementation of infection control measures, isolation and neutropenic diet in these patients the

rates of organisms traditionally associated with 'food poisoning' is low. The evidence surrounding 'neutropenic diets' is limited, however most units will implement restrictions such as those recommended by the British Dietetic Association [9]. Due to the use of broad spectrum antibiotics both as prophylaxis and treatment Clostridium difficile is common, with symptoms including profuse watery diarrhoea, abdominal pain and frequently fever. Treatment should be instigated depending on severity score, metronidazole, vancomycin and fidaxomicin are all included in NICE recommendations. Whilst viral reactivation is rare in the early stages post-transplant this should be considered, cases of CMV negative peripheral blood PCR but biopsy proven CMV colitis have been reported, therefore specific testing of biopsy samples for CMV should be undertaken.

Neutropenic colitis, also known as typhlitis is a rare complication thought to be caused by direct invasion of the colonic or caecal mucosa resulting in toxic mucosal necrosis. The diagnosis is predominantly radiological (colonoscopy should be avoided due to a heightened risk of perforation). Patients may complain of right iliac fossa pain. Treatment is predominantly with broad spectrum antibiotics and supportive measures including bowel rest and analgesia. Severe cases can result in megacolon or perforation, in this circumstance surgical intervention with subtotal colectomy and defunctioning colostomy may be considered, however due to the high risks associated with surgical intervention in early post-transplant patients due to pancytopenia and immunosuppression surgical intervention is deferred whenever possible [10].

Hepatic Complications

Veno-occlusive disease of the liver (VOD) is a potentially life-threatening complication following allogeneic stem cell transplant, with rates estimated to be around 8–14%. Whilst it can be seen following autologous transplant it is much less common, estimated around 3% [11]. The diagnosis is based on a clinical triad of jaundice, weight gain and tender hepatomegaly, with the potential to progress to multiorgan failure if left untreated. The pathogenesis of this condition relates to endothelial damage in hepatic venules resulting in disruption of fenestrae, inflammation and thrombus formation [12]. Historically several different scoring systems have been used (for example Seattle and Baltimore criteria), more recently the European Bone Marrow Transplant Society have developed a severity scoring system which incorporates diagnosis of late cases (after 21 days post-transplant) which are increasingly recognised to make up a significant minority of cases [13]. Investigations predominantly focus on exclusion of other causes. Liver ultrasound scan including Doppler is recommended in all suspected cases, with findings including hepatomegaly and reversal of hepatic flow considered consistent with the condition. Liver biopsy is the gold standard for diagnosis, however due to the risks associated with the procedure is very rarely undertaken. Whilst additional diagnostic investigations including biomarkers are under development, they are currently only available in clinical trials. The diagnosis of VOD remains a clinical one, and treatment should not be delayed whilst awaiting investigations.

Treatment comprises a combination of supportive care and defibrotide, an anti-thrombotic agent for treatment of VOD [14]. The mortality rate from untreated severe VOD with multiorgan failure is around 90%, therefore recognition and prompt treatment in the early stages of the condition is essential. Whilst other strategies including heparin anticoagulants and steroids have been used historically the evidence to support their use is not robust. Supportive care includes diuresis, salt restriction and in severe cases organ support.

Infection

Reactivation of both fungal and viral infections can occur in the early post-transplant stage. The widespread use of prophylactic -azole antifungals has resulted in a marked fall in systemic candida infections, with aspergillus species being the most common cause of fungal infections [15]. Presentation with liver dysfunction, hepatic tenderness and fever refractory to standard antibiotics should prompt consideration of fungal infection. Combined modality investigation with imaging, fungal biomarkers (Aspergillus antigen, Beta-D-glucan), peripheral blood cultures and where possible direct sampling of any discrete lesions should be undertaken.

Whilst CMV reactivation and other viral infections typically occur later post-transplant they should also be considered in the early phase.

Drugs and Therapeutics

There is an extensive list of medications, both prophylactic and those used to treat symptomatic and infective complications. Many of these have the potential to cause hepatic abnormalities and comprehensive review of medications and potential interactions should be undertaken in all cases of post-transplant hepatic dysfunction, with modification of agents or doses where possible.

Complications Beyond 2–3 Weeks

The majority of post engraftment gastrointestinal complications occur in the allogeneic population due to protracted and complex immune reconstitution which is variable depending

on donor-recipient factors along with stem cell source (i.e. cord vs. related donor). Following autologous transplantation there is generally rapid resolution of pre-engraftment complications, and whilst full immune reconstitution can take up to 12–18 month this rarely results in gastrointestinal manifestations.

Infection

Following allogeneic transplant both humoral and cellular mechanisms of immunity are impaired, with the process of immune reconstitution being complex and prolonged. A number of variables can impact this reconstitution, including donor-recipient compatibility, the age of the patient, presence and severity of GvHD. In addition, the use of T-cell depletion in conditioning and the need for prolonged immunosuppression for treatment of GvHD impact immune reconstitution. As such patients can be at risk of both standard and opportunistic infections for prolonged periods of time.

CMV reactivation can occur in the initial months post-transplant, with the risk dependent on the serostatus of the recipient and donor, recipient positive but donor negative representing the highest risk combination. Most centres will employ a pre-emptive strategy with regular PCR monitoring and treatment at a pre-defined level. A novel agent, Letermovir, is now available for use in CMV positive recipients to prevent reactivation [16]. CMV disease can present with a broad spectrum of organ involvement but can affect any part of the GI tract causing pain, protein losing enteropathy, ulceration, bleeding and occasionally perforation along with fever and rarely hepatitis.

Other organisms to consider include herpes simplex, adenovirus, enterovirus, cryptosporidium and candida. The differentiation of these organisms and GvHD requires endoscopic biopsy, and differentiation of infection from GvHD is essential due to treatment implications. Treatment of viral or bacterial infections with appropriate antimicrobial agents should occur, as per local guidelines.

Graft vs. Host Disease

Graft vs. host disease (GvHD) is classically separated into acute occurring within the first 100 days post-transplant, and chronic occurring after that time (Table 2). With changes to transplant protocols this boundary has become blurred with recognition of situations where acute GvHD can occur later than 100 days (for example following donor lymphocyte infusion). Table 2 outlines the current criteria used [1].

Table 2 Classification and features of Graft vs. host disease (GvHD)

Classification	Days after SCT	Features of acute GvHD	Features of chronic GvHD
Acute GvHD			
Classic acute	<100 days	Yes	No
Persistent, recurrent or late onset	>100 days	Yes	No
Chronic GvHD			
Classic chronic	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

Acute Graft Versus Host Disease (aGvHD)

Acute graft versus host disease principally affects the skin, gastrointestinal tract and liver, with the majority of cases occurring within the first 100 days post-transplant. Histologic appearances within the GI tract include lymphocytic crypt infiltration, with epithelial cell necrosis. Severity ranges from individual cell necrosis to crypt loss, ulceration and epithelial denudation. The most common pattern seen in hepatic involvement is small bile duct damage [17].

Whilst aGvHD can affect any part of the GI tract it rarely involves the mouth and oesophagus. Stomach and duodenal involvement cause nausea, vomiting, anorexia and dyspepsia. Bowel involvement causes diarrhoea which is characteristically green and watery. The severity is graded predominantly based on diarrhoea volume (Table 3). Whilst the diagnosis of gastrointestinal aGvHD is sometimes made based on clinical characteristics along with proven GvHD at other sites, endoscopic biopsy should be undertaken where possible to allow exclusion of infective causes. Hepatic aGvHD has a predominantly cholestatic picture due to small bile duct destruction, and whilst other liver functions tests are commonly deranged staging is based solely on bilirubin [18].

Treatment of acute GvHD requires a combination of supportive care and immunosuppression as first line, with the degree of treatment dependent on severity and range of organ involvement. First line treatment is with corticosteroids equivalent to 1 mg/kg methylprednisolone, escalated to 2 mg/kg in refractory cases. Budesonide can be used effectively as a steroid sparing agent. In addition, optimisation of calcineurin inhibitors, and sometimes addition of other agents, for example MMF in those with liver GvHD can be considered. Evidence for second line treatments is sparse, whilst numerous agents have been investigated evidence of response is lacking in most cases. The exception is extra extracorporeal photopheresis which does have evidence of effectiveness in steroid refractory aGvHD [19]. Supportive care is essential, gastrointestinal GvHD often requires gut rest with parenteral nutrition to support nutritional require-

Table 3 Glucksberg criteria

	Stage skin based on maculopapular rash	Liver based on bilirubin	Gastrointestinal based on quantity of diarrhoea
+	25% of surface	<34–50 μmol/L	500–1000 mL
++	25–50% of surface	51–102 μmol/L	1001–1500 mL
+++	Generalized erythroderma	103–255 μmol/L	>1500 mL
++++	Generalized erythroderma with bullae and desquamation	>255 μmol/L	Severe abdominal pain with and without ileus

ments. In cases of severe gastrointestinal GvHD electrolyte imbalance can be severe and challenging to manage. Due to unpredictable absorption drugs often need to be given intravenously.

Chronic Graft Versus Host Disease

Chronic graft versus host disease (cGvHD) can evolve from aGvHD (cross over) or occur de novo after 100 days. It frequently manifests as a multisystem disorder, along with the gastrointestinal tract other organ systems commonly involved include the skin (with sclerodermatous changes), eyes, lung and endocrine system. Treatment depends on both severity and organ involvement, with targeted local therapy along with systemic immunosuppression when indicated.

Gastrointestinal tract involvement commonly presents with upper tract features such lichenoid changes, erythema along with ulceration and mucoceles. Involvement of the salivary glands can also result in sicca symptoms. These manifestations can cause significant pain and dysphagia leading to weight loss. Oesophageal involvement results in dysmotility, dysphagia and reflux. Chronic GvHD of the gut is less common, but can cause mucosal atrophy, malabsorption and fibrosis which can progress to strictures. Hepatic cGvHD ranges from mild abnormalities of liver function tests to fulminant hepatic failure. Investigation aims to exclude infective and other cases (such as iatrogenic hepatic iron loading) to ensure appropriate treatment is instigated.

The treatment of cGvHD must be tailored to manifestations in individual cases, where possible targeted topical treatment should be utilised, with systemic immunosuppression used in refractory or multiorgan involvement due to the risks associated with long term immunosuppression. Topical therapies include steroid mouth wash, tacrolimus mouth wash and artificial saliva. Regular dental assessment is important to maintain dental health, along with surveillance for oral malignancies which this patient population are at increased risk of. Assessment for malabsorption and treatment of any underlying cause such as pancreatic insufficiency should be considered in those with intestinal cGvHD. Due to the complex and often multisystem nature of cGvHD a multidisciplinary approach is essential.

Other Late Effects

Iatrogenic iron overload is common and can be associated with transaminitis. It is managed with venesection on recovery of erythropoiesis [20]. In cases with chronic anaemia post-transplant synthetic erythropoietin can be used to stimulate erythropoiesis to facilitate venesection. If this is not successful, or in those requiring on going transfusion iron chelation should be instigated.

Post-transplant lymphoproliferative disorder, driven by Epstein-Barr virus, is a rare but serious post-transplant complication. Whilst the majority of cases manifest with rapidly progressive lymphadenopathy some may present with gastrointestinal or hepatic involvement. Diagnosis is histologic. Treatment involves B-cell directed monoclonal antibodies (alemtuzumab) with or without systemic chemotherapy.

Nutritional Support

There are two situations where nutritional support may be needed—patients with severe mucositis or those with GVHD affecting the gastrointestinal tract. All patients should be assessed by appropriately trained dietitians, ideally working as part of a nutrition support team. This allows early detection of patients struggling with nutrition as being underweight (Body Mass Index <18.5) is associated with poorer outcomes from HSCT [21, 22].

As with other clinical indications for nutrition support, management should consist of optimisation of oral diet first (typically trying soft, moist foods if mucositis is present). There appears to be no role for a 'neutropaenic' or 'low bacterial' diet [22]. Enteral nutrition (EN) support can be offered if oral intake is inadequate. Unfortunately some patients find any nasoenteral tubes too uncomfortable, due to severity of the inflammation.

Parenteral nutrition (PN) should only be used when the first two approaches have been unsuccessful and should be stopped as soon as nutrition has stabilised [22]. PN does not appear to provide additional benefits to EN and brings with it additional infective and metabolic complications [21, 22].

References

1. Carreras E, Dufour C, Mohty M, Kröger N. The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies. Cham: Springer; 2019.
2. Abutalib SA, Hari P. Clinical manual of blood and bone marrow transplantation. London: Wiley Blackwell; 2017.
3. Jessop H, Farge D, Sccardi R, et al. General information for patients and carers considering haematopoietic stem cell transplantation (HSCT) for severe autoimmune diseases (ADs): a position statement from the EBMT Autoimmune Diseases Working Party (ADWP), the EBMT Nurses Group, the EBMT Patient, Family and Donor Committee and the Joint Accreditation Committee of ISCT and EBMT (JACIE). Bone Marrow Transplant. 2019;54:933–42.
4. Passweg JR, Baldomero H, Chabannon C, et al. The EBMT activity survey on hematopoietic-cell transplantation and cellular therapy 2018: CAR-T's come into focus. Bone Marrow Transplant. 2020;55:1604. https://doi.org/10.1038/s41409-020-0826-4.
5. BSBMT. Indications table. n.d.. http://bsbmtct.org/indications-table/.
6. Berger MJ, Ettinger DS, Aston J, et al. NCCN guidelines insights: antiemesis, version 2.2017. J Natl Compr Cancer Netw. 2017;15(7):883–93.
7. Blijlevens NM, Donnelly JP, De Pauw BE. Mucosal barrier injury: biology, pathology, clinical counterparts and consequences of intensive treatment for haematological malignancy: an overview. Bone Marrow Transplant. 2000;25:1269–78.
8. Wilkes JD. Prevention and treatment of oral mucositis following cancer therapy. Semin Oncol. 1998;25:538–51.
9. BDA. Policy statement: neutropenic dietary advice for haematology patients. Birmingham: BDA: The Association of UK Dieticians; 2013.
10. Rodrigues FG, Dasilva G, Wexner SD. Neutropenic enterocolitis. World J Gastroenterol. 2017;23(1):42–7.
11. Carreras E, Bertz H, Arcese W. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. Blood. 1998;92(10):3599–604.
12. Fan CQ, Crawford JM. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). J Clin Exp Hepatol. 2014;4(4):332–46.
13. Mohty M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European society for blood and marrow transplantation. Bone Marrow Transplant. 2016;51(7):906–12.
14. Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood. 2016;127(13):1656–65.
15. Lortholary O, Gangneux JP, Sitbon K, et al. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005–2007). Clin Microbiol Infect. 2011;17:1882–9.
16. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med. 2017;377(25):2433–44.
17. Snover DC, Weisdorf SA, Vercellotti GM, et al. A histopathologic study of gastric and small intestinal graft-versus-host disease following allogeneic bone marrow transplantation. Hum Pathol. 1985;16:387–92.
18. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation. 1974;18:295–304.
19. Jagasia M, Greinix H, Robin M, et al. Extracorporeal photopheresis versus anticytokine therapy as a second line treatment for steroid-refractory acute GVHD: a multicenter comparative analysis. Biol Blood Marrow Transpl. 2013;19:1129–33.
20. Philippe Armand P, Kim HT, Virtanen JM, et al. Iron overload in allogeneic hematopoietic cell transplantation outcome: a meta-analysis. Biol Blood Marrow Transpl. 2014;20(8):1248–51.
21. Baumgartner A, Bargetzi A, Zueger N, et al. Revisiting nutritional support for allogeneic hematologic stem cell transplantation-a systematic review. Bone Marrow Transplant. 2017;52:506–13.
22. August DA, Huhmann MB, American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. Clinical Guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. J Parent Ent Nutr. 2009;33(5):472.

Non-surgical Cancer Treatments

Mary Booth, Fiona James, Andrew Viggars, Clare Shaw, and Mark Teo

Key Points

1. Cancer treatment may be curative, adjuvant (reduce chance of metastases), neoadjuvant (reduce size of tumour) or palliative.
2. Chemotherapy is usually given as combination therapy.
3. After bone marrow toxicity chemotherapy primarily affects the gut mucosa.
4. Nausea and vomiting after chemotherapy usually only last up to 48 h.
5. Mucositis occurs with antimetabolites and anthracycline antibiotics and commonly occurs between 5 and 14 days after treatment. This may cause acute intestinal failure needing parenteral nutrition.
6. Some chemotherapeutic drugs (e.g. vincristine, adriamycin) may cause an irreversible enteric neuropathy.
7. Newer targeted molecular treatments (e.g. immunotherapy, tyrosine kinase inhibitors) have direct and indirect side-effects on gut mucosa and nutrition requiring specialist input.
8. The toxicity from acute irradiation typically starts 1–2 weeks following the start of radiotherapy treatment and depending on dose, can last for a few short weeks following completion and can result in the breakdown of epithelial surfaces.

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Introduction

Malignant cells exhibit several hallmarks that distinguish them from normal cells [1].

These hallmarks are:

1. genomic instability,
2. sustained proliferative signalling,
3. an ability to evade growth suppressors,
4. resistance of cell death,
5. replicative immortality,
6. induction of angiogenesis,
7. cancer-related inflammation,
8. activation of invasion and metastatic spread,
9. the ability to re-programme energy metabolism, and
10. an ability to evade immune destruction.

Cancer treatments aim to target these hallmarks and preferentially eliminate cancer cells over normal cells. The availability of newer more potent cancer treatments, intensified combination multimodality regimens and earlier cancer detection has improved survival rates such that 69.3% of all cancer patients will be alive 5 years after diagnosis [2]. However, despite rapid developments in improved targeted cancer treatments, all treatments produce side effects varying in severity and according to the predominant types of target normal cells. Toxicity limits both the dose and the frequency of administration and may reduce the potential to cure some patients.

Each different cancer treatment modality can be delivered with different treatment intent (Table 1), which alters the strategy of managing treatment toxicities of complications. For example, for treatment with curative intent the focus is to maintain treatment intensity and dose by tackling toxicity aggressively with supportive measures including enteral or parenteral nutritional support, versus treatment with palliative intent where there is a lower threshold to lower dose or halt treatment.

J. M.D. Nightingale (ed.), *Intestinal Failure*, https://doi.org/10.1007/978-3-031-22265-8_10

Table 1 Cancer treatment intent and cancer site examples

Treatment intent	Aim	Cancer site examples
Curative	Cure cancer	*Chemotherapy:* Haematological and germ cell tumours
		Radiotherapy (often with concurrent chemotherapy as a radiosensitiser): Lung cancer, head and neck cancers
Adjuvant	Reduce chance of local and/or distant recurrence	*Chemotherapy:* Breast and colon cancer
		Endocrine: Breast and prostate cancer
		Monoclonal antibodies: Breast cancer
		Immunotherapy: Lung cancer
Neoadjuvant	Prior to curative treatment, to reduce size of cancer and/or to improve chance of cure	*Chemotherapy:* Breast and oesophageal cancers
		Radiotherapy: Rectal cancer
Palliative	To improve quality and/or quantity of life by reducing the disease burden, improve symptoms and extend life in palliative setting	*Chemotherapy:* Most tumour types
		Radiotherapy: Most tumour types
		Immunotherapy: Lung, kidney and melanoma cancers
		Small molecule inhibitors: Lung, kidney and melanoma cancers

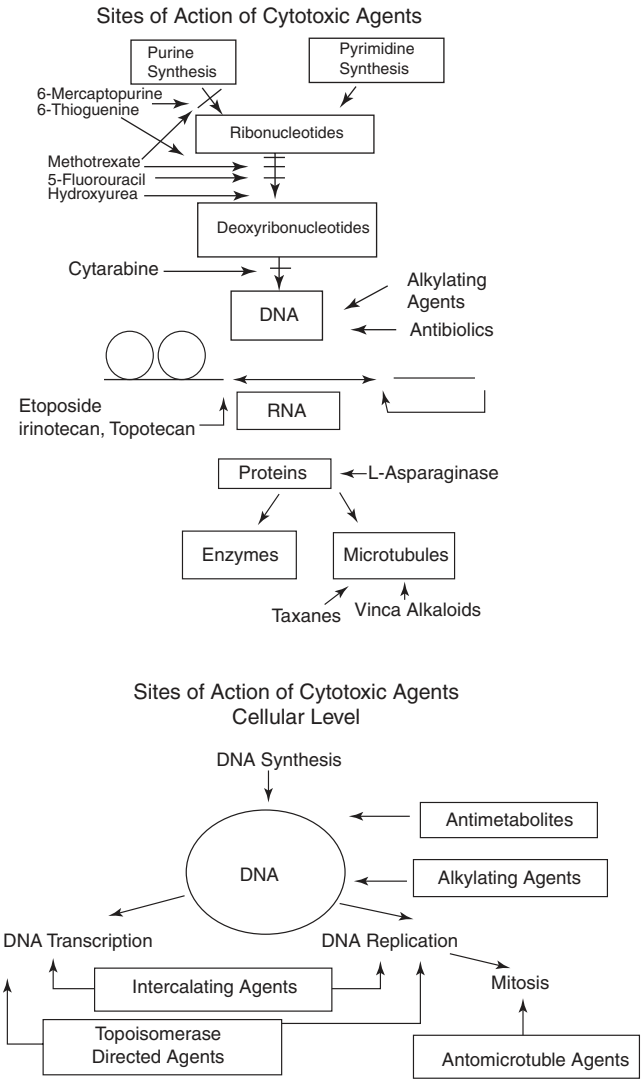

Fig. 1 Sites of action of cytotoxic chemotherapy agents

Although bone marrow suppression is a key toxicity following chemotherapy, the advent of haemopoietic growth factors, stem cell support and improved anti-microbial management protocols have reduced concerns about myelosuppression. By contrast, gastrointestinal toxicity remains a significant clinical problem frequently limiting the amount of systemic therapy that can be given, and is a common side-effect in most of the newer targeted therapies.

This chapter describes the general issues associated with non-surgical cancer treatments specifically cytotoxic chemotherapy, hormone (endocrine) treatments, monoclonal antibodies and small molecule inhibitors, immunotherapy and radiotherapy; and the role of the gastroenterologist and nutrition team in supporting patients on these treatments.

Cytotoxic Chemotherapy

Cytotoxic chemotherapy exerts its effects in a limited number of ways, leading to damage to cellular DNA. Due to the rapid proliferation and genetic instability of cancer cells, cancer cells are unable to repair chemotherapy-induced DNA damage as robustly and quickly as normal cells. Intermittent chemotherapy administration will thus lead to a steady reduction in the malignant population while, it is hoped, leaving the population of normal cells relatively unchanged [3].

Most cytotoxic drugs interfere with DNA or protein synthesis, but other mechanisms of action are increasingly utilised as rational drug development attempts to target specific differences in malignant cells but leave normal cells relatively spared (Fig. 1).

A review of all the individual cytotoxic drugs and their effects on the gut is beyond the scope of this book. Cytotoxic chemotherapy drugs are often classified into several groups according to their mechanisms of action (Table 2). Chemotherapy is rarely prescribed as a single agent, but usually takes the form of combination regimens. When combinations are used, individual agents are chosen on the basis of having different mechanisms of action and, preferably, different patterns of toxicity [4].

Table 2 Cytotoxic chemotherapy drug classes and mechanism of action

Class	Mechanism of action	Example agents
Alkylating and Platinum agents	Bind covalently with DNA, causing cross-linking of DNA strands, and DNA strand breaks, interfering with cell replication.	*Mustard gas derivatives:* Cyclophosphamide.
		Hydrazines and Triazines: Procarbazine, Temozolomide.
		Nitrosoureas: Carmustine, Lomustine.
		Platinums: Carboplatin, Cisplatin, Oxaliplatin.
Antimetabolites	Block metabolic pathways involved with DNA synthesis.	*Folic acid antagonist:* Methotrexate.
		Pyrimidine antagonist: 5-Fluorouracil, Capecitabine, Gemcitabine.
		Purine antagonist: 6-Mercaptopurine.
		Adenosine deaminase inhibitor: Fludarabine.
Cytotoxic antibiotics	Have pleiotropic effects, including alkylating activity and inhibition of topoisomerases.	*Anthracyclines:* Doxorubicin, Epirubicin.
		Other: Mitomycin C, Bleomycin.
Agents that target the mitotic spindle	Exert their action through alteration of microtubule function and thereby interfere with mitosis	*Vinca alkaloids:* Vincristine, Vinorelbine.
		Taxanes: Paclitaxel, Docetaxel.
Topoisomerase inhibitors	These agents inhibit either topoisomerase 1 or 2 and thereby prevent DNA replication	*Podophyllotoxins:* Etoposide.
		Camptothecan analogues: Irinotecan, Topotecan.
Miscellaneous	Ribonucleotide reductase inhibitor	Hydroxyurea
Miscellaneous	Retinoids	Isotretinoin, Tretinoin (ATRA)

Effect of Cytotoxic Chemotherapy on Normal Tissues

Cytotoxic agents generally have greater toxicity for cells that have higher rates of proliferation. Cell turnover varies between normal tissue types and is particularly high in the haemopoietic system, hair follicles and gastrointestinal tract. The effect of most cytotoxic drugs is not limited to malignant cells but is also seen in those normal cells that are undergoing division. It is the toxicity profile of individual drugs that is dose-limiting and governs how the agent is used.

The kinetics of chemotherapeutic agents frequently follow a dose-response curve similar to that seen with many drugs (Fig. 2a). The effects on normal tissues may be represented in similar graphs (Fig. 2b). The respective position of organs changes for different drugs. For tumour cell types in which cell death can be significantly increased with doses not limited by gut or other organ toxicity, the use of haemopoietic sparing techniques may offer significant improvement in survival rates (Fig. 2c). In cancers where tumour sensitivity is less than gut sensitivity to cytotoxic drugs, little benefit will be seen (Fig. 2d). The haemopoietic sparing techniques currently in use include treatment with haemopoietic growth factors, such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), and haemopoietic stem cell transplantation, which is discussed in the next chapter.

Effect of Cytotoxic Chemotherapy on the Gastrointestinal Tract

Anorexia, cachexia and malnutrition may be prominent presenting features of malignancy, causing morbidity and mortality in patients who have advanced disease [5]. Treatment of the malignancy with chemotherapy can worsen the cachexia and malnutrition, further compromising the health of the patient [6].

The gastrointestinal tract is widely recognised as an essential organ and is involved in vital life functions such as nutrition, waste excretion and protection from external microbes and toxins. It is a complex organ, involving mouth, oesophagus, stomach, small intestine, large intestine, anus and the enteric nervous and lymphoid system. All of these crucial components are vulnerable to the effects of chemotherapy.

The effects of chemotherapy on the gastrointestinal system are wide-ranging, frequent and can be long-lasting, even beyond the cessation of chemotherapy.

Chemotherapy related GI side-effects can affect 50–80% of patients with standard chemotherapy regimens with up to 30% developing severe side-effects [7].

The main symptoms experienced by patients include:

1. Nausea and vomiting
2. Mucositis
3. Diarrhoea
4. Constipation

Nausea and Vomiting

The nausea and vomiting induced by chemotherapy occurs when the vomiting centre in the medullary reticular formation is stimulated by the chemoreceptor trigger zone (CTZ) in the area postrema of the fourth ventricle or tractus solitarius [8, 9]. Stimuli to the vomiting centre may also arise

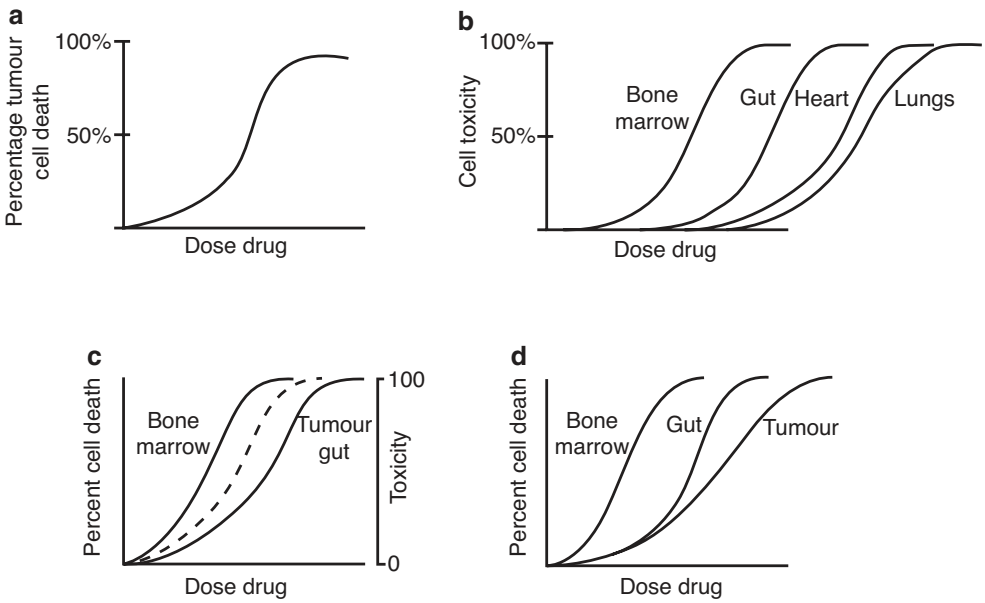

Fig. 2 (**a**–**d**) Schematic representation of the effects of cytotoxic chemotherapy on normal and malignant tissue

from afferent fibres located in the cerebral cortex, gastrointestinal tract (particularly the duodenum), heart, and vestibular apparatus. The CTZ is the predominant site of action initiating emesis caused by cytotoxic agents. The major neurotransmitters known to be involved in the emetic process are dopamine, serotonin, and tachykinins such as substance P.

Nausea and vomiting are the most common early manifestations of the toxicity caused by chemotherapy, and repeated studies have shown them to be the most distressing side effects—more so than alopecia, for example [10]. If the patient is fit, there may be no serious consequences, but in those who are already debilitated or malnourished following surgery and/or radiotherapy the addition of drug-related emesis may cause further marked deterioration in the clinical condition unless intensive nutrition support is provided.

Different chemotherapy drugs vary markedly in their emetogenic potential [11]. Nitrogen mustard, cisplatin, dacarbazine and streptozotocin induce vomiting in nearly all patients, whereas oral chlorambucil, melphalan and busulfan usually produce little nausea and vomiting. Nausea and vomiting induced by antimetabolite drugs often depends on dose and schedule. Methotrexate given in conventional doses rarely produces vomiting whereas high-dose infusions given to patients with osteosarcoma or to prevent CNS disease in lymphoma and leukaemia cause vomiting in the majority of patients.

In most patients, emesis commences within 1–6 h of administration and subsides after 24–36 h. Occasionally, delayed emesis may occur 24 or more hours after administration and may persist for up to a week (for example with cisplatin chemotherapy). Less frequently, chronic nausea and vomiting may follow chemotherapy and can be particularly difficult to treat. Once patients have experienced nausea and vomiting they may develop similar anticipatory symptoms before subsequent courses of treatment.

The management of emesis caused by chemotherapy has improved dramatically in the last 10 years. The availability of selective 5-HT_3 receptor antagonists, such as ondansetron and NK1 receptor antagonists, such as aprepitant, alongside more traditional anti-emetic drugs, such as; metoclopramide, cyclizine and corticosteroids has resulted in excellent control in the majority of patients, even with the most emetogenic regimens [11]. The aim of therapy should be to prevent emesis from the first course in order to avoid subsequent anticipatory symptoms.

Mucositis

Most GI mucositis and ulceration is caused by a direct toxic effect of chemotherapy on mucosal cells. A direct effect on mucosal cells can affect any part of the bowel and may severely compromise dietary intake. The antimetabolites and anthracycline antibiotics are the agents that most commonly damage the gastrointestinal mucosa. Symptoms usually occur 5–7 days after exposure and may last for 1–2 weeks.

The degree of damage varies according to the dose and schedule of administration of many of these drugs. The toxicity of methotrexate to the gastrointestinal epithelium, for example, depends on the duration of exposure rather than on peak concentrations [12]. Toxicity can be reduced if folinic acid rescue is given within 42 h of administration [13]. With 5-fluorouracil, toxicity is dependent on peak concentration with higher toxicity rates seen in bolus regimens compared to continuous infusions [14]. Even when mucosal damage is relatively mild, serious morbidity may ensue. Local infection with organisms such as *Candida* and herpes virus, particularly in the mouth, may cause pain and reduce subsequent

oral intake, further compromising the patient's nutritional status [15]. It is essential that the clinician is aware of this and that advice is given about topical mouth care with the provision, where appropriate, of antifungal, antibacterial and antiviral prophylactic therapy. For some patients, intravenous nutrition support or early NG/NJ feeding may be indicated if pain prevents swallowing.

Chemotherapy Induced Diarrhoea

Diarrhoea is one of the most common side effects of chemotherapy which can range from mild (with an increase in stool frequency up to 4–6 per day more than baseline) to severe with life-threatening complications. Although the underlying pathophysiology remains unclear, it is heavily associated with the development of mucositis due to direct cell toxicity and malabsorption. Studies in animal models have shown increased apoptosis in crypts within the jejunum and colon, and excessive secretions leading to diarrhoea [16].

Different chemotherapeutic regimes produce differing severities of diarrhoea, in particular those containing 5-FU and irinotecan are correlated with incidence of diarrhoea as high as 80% [7]. Management of chemotherapy induced diarrhoea involves identifying any infective causes, and contributing factors such as medications alongside supportive management and pharmacological treatment [17]. Loperamide, an oral opioid with no significant absorption from the gastrointestinal tract, is the anti-diarrhoeal agent of choice. Dosing requires an initial dose of 4 mg, followed by an additional 2 mg after each loose stool, up to a maximum of 16 mg/day. In severe or persistent diarrhoea, octreotide, a somatostatin analogue may be used.

Chemotherapy Induced Constipation

Chemotherapy induced constipation is a common issue which can also be exacerbated by antiemetic (e.g. 5-HT3 receptor antagonists) and other medications traditionally used alongside chemotherapy regimens. The vinca alkaloids (particularly vincristine), thalidomide and cisplatin cause autonomic nerve dysfunction leading to constipation in up to 90% of patients and can even cause an ileus [18–20]. The onset of symptoms usually occurs soon after drug administration, frequently within 3 days, and may be associated with peripheral neuropathy. It is important to provide prophylactic laxatives. Patients who develop an ileus should be managed conservatively with careful monitoring of fluid balance.

Hormone (Endocrine) Therapy

Hormones are substances that work as chemical messengers in the body. They affect cells throughout the body, often travelling through the bloodstream. The growth and proliferation of some cancers, such as breast and prostate cancers, are stimulated by hormones, and hence blocking these pathways can be an effective anticancer treatment. Hormone therapy is used on its own or in multi-modality treatment regimens in the neo-adjuvant, adjuvant and palliative settings. Hormone therapy falls into two broad groups; (1) those that block the body's ability to produce hormones, and (2) those that interfere with how hormones behave in the body (Table 3).

Glucocorticoid steroidal hormones, such as prednisolone and dexamethasone are frequently incorporated into cytotoxic chemotherapy regimens for its anti-emetic and anti-inflammatory effects in managing chemotherapy toxicities. Steroids also have a direct anti-tumour effect in most lymphoid malignancies and reduce cancer-related inflammation.

These agents have a favourable therapeutic ratio causing typically mild toxicity; many hormone agents can cause menopausal-like side effects including weight gain and sarcopenic obesity, as well as gastrointestinal side effects such as diarrhoea and nausea.

Table 3 Classes of hormone therapies and their mechanism of action

Hormone modulation	Mechanism of action	Cancer type	Example agents
Gonadotrophin releasing hormone agonists	Interferes with pituitary gland stimulation of the ovaries and testicles to produce oestrogen or androgens respectively	Breast	Goserelin
		Prostate	Leuprolide
			Triptorelin
Aromatase inhibitors	Blocks non-ovarian production of oestrogen	Breast	Anastrozole
			Letrozole
			Exemestane
Oestrogen receptor blockers/ modulators	Interferes with oestrogen binding to its receptor on cancer cells	Breast	Tamoxifen
		Endometrial	Fulvestrant
Anti-androgens	Interferes with oestrogen binding to its receptor on cancer cells; or suppress androgen production	Prostate	Enzalutamide
			Bicalutamide
			Abiraterone
Synthetic progesterones	Stimulates progesterone receptor	Endometrial	Medroxyprogesterone
			Megestrol

Small Molecule Inhibitors and Monoclonal Antibodies

Targeted therapies interfere with molecular targets involved in the sustained proliferative signalling of cancer. This is in contrast to non-selective cytotoxic chemotherapy which targets all rapidly dividing cells. Many targeted agents have been developed via rational drug design where targets are selected and drugs designed based on their key role in inhibiting uncontrolled cancer growth. Targeted agents may be monoclonal antibodies targeting cell surface receptors or small molecules designed to bind and inhibit specific signalling proteins. Common targets of small molecule inhibitors are tyrosine kinases, hence the use of a broad class of agents called tyrosine kinase inhibitors (TKIs).

Small molecule inhibitors may focus on extracellular and intracellular targets as they are able to translocate through the cell membrane. Monoclonal antibodies are antibodies with antigen binding domains, which have been engineered to bind with high specificity to the target of interest, typically membrane receptors. Modern immunotherapy agents which affect the immune response to cancer (described further below) are predominantly monoclonal antibodies though small molecule inhibitors are in development. The complexity of the pathways involved in cancer initiation, survival and propagation is reflected by the increasing number of targeted agents that are clinically available, in clinical testing, or in development.

The mechanism of action of small molecule inhibitors and monoclonal antibodies is dependent upon the receptor targeted and the pathway in which that receptor has a function. The specificity of such targeted agents varies, therefore some agents may have more than one site of action. Figures 3 and 4 show the various targets of action of small molecule and monoclonal antibody on the epidermal growth factor receptor (EGFR) family and the vascular endothelial growth factor (VEGF) family respectively.

In addition to the EGFR and VEGFR pathways, there are a growing number of other classes of targeted monoclonal antibodies or small molecule inhibitors used in anti-cancer agents (Table 4).

Effect of Targeted Therapies on Gastrointestinal Tract

Despite their targeted action, monoclonal antibodies and small molecule inhibitors exhibit toxicities of the gastrointestinal tract as despite being "targeted", these agents often show activity on similar kinase classes on normal cells that express the target receptor. Table 5 shows common and uncommon gastrointestinal toxicities of targeted agents and their management. Below, two specific examples of toxicities are detailed, and the management explained.

Diarrhoea is a common side effect of many targeted agents, and frequently occurs within the first 2 weeks of commencing therapy [25]. Diarrhoea may be particularly severe in cases where targeted agents are combined with conventional chemotherapy. Anti EGFR family agents are commonly associated with diarrhoea. EGFR is expressed in the normal colonic mucosa, involved in regulation chloride secretion and sodium inhibition, and therefore EGFR inhibitors may result in secretory diarrhoea [26]. Other causes of diarrhoea should be excluded, including concurrent medications and infection (in particular *Clostridium difficile* infection). In addition to the impact on quality of life, diarrhoea may also lead to fluid and electrolyte loss, subsequent renal impairment, and malnutrition.

Management is dependent upon the Common Terminology Criteria for Adverse Events (CTCAE) grade [27].

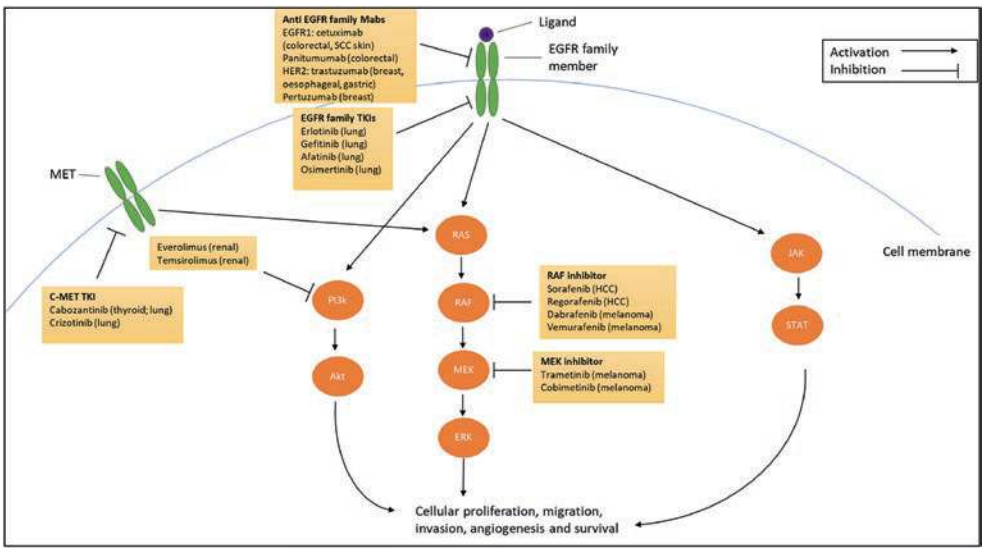

Fig. 3 Action of small molecule inhibitors and monoclonal antibodies targeting EFGR family, MET, and downstream cellular pathways, including example agents. Cancer sites agents used in shown in brackets. *Mab* monoclonal antibody, *TKI* tyrosine kinase receptor inhibitor, *HCC* hepatocellular carcinoma. (Adapted from Stone et al. [21])

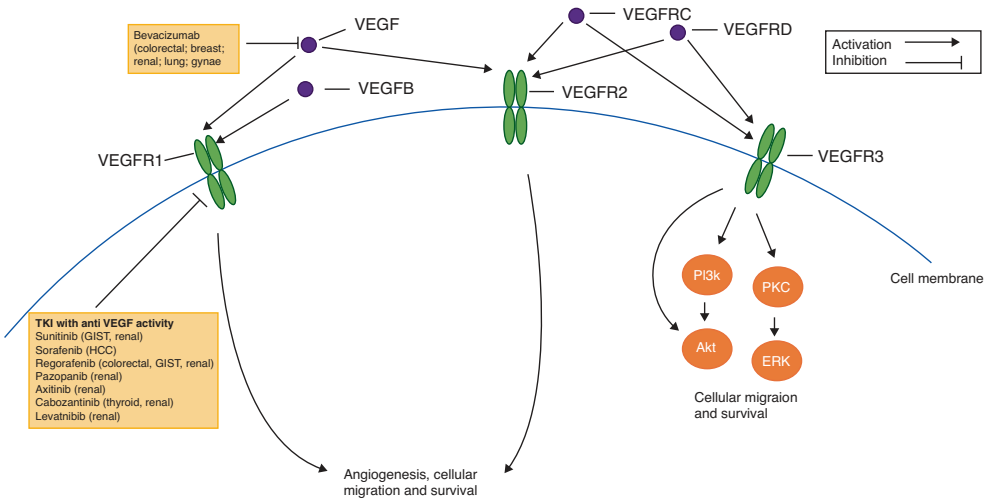

Fig. 4 Effect of on VEFG signaling pathways in cancer. Binding of VEGF ligands to VEGF receptors leads to downstream intracellular pathways resulting in angiogenesis, migration and survival. Cancer sites agents used in shown in brackets. *GIST* gastrointestinal stromal tumour; *HCC* hepatocellular carcinoma

Table 4 Targeted therapy classes with example target, cancer type this agent is used in and the potential gastrointestinal toxicities

Target pathway	Example agents	Example agent target	Cancer type	Gastrointestinal toxicities
DNA repair	Olaparib	PARP	Gynaecological cancers	Diarrhoea, nausea, vomiting, decreased appetite [22]
Cell signalling	Crizotinib, Alectinib	ALK and ROS1	ALK or ROS1 mutated non-small cell lung cancer	Diarrhoea, vomiting, constipation [23]
Cell cycle regulation	Palbociclib	CDK4 and CDK6	HER2 negative breast cancer	Nausea, diarrhoea [24]

Table 5 Gastrointestinal (GI) toxicities of small molecule inhibitors and monoclonal antibodies

	Targeted therapy class	
Gastrointestinal toxicity	Common toxicity	Uncommon toxicity
Diarrhoea	EGFR inhibitors	
Constipation	All	
Nausea and vomiting	All	
Abdominal pain	All	
Stomatitis	All	
Dyspepsia	All	
Gastrointestinal perforation	VEGF inhibitors	RAF inhibitors; temsirolimus; crizotinib
Gastrointestinal haemorrhage	VEGF inhibitors	
Fistula formation	VEGF inhibitors	
Pancreatitis		RAF inhibitors; VEGF inhibitors

Uncomplicated diarrhoea, that is patients with grade 1 or 2 diarrhoea, with no additional complications, may be managed conservatively with oral hydration and loperamide therapy in an outpatient setting. In cases of grade 3 or 4 diarrhoea fluid replacement should be via the intravenous route, which may include potassium replacement. Management is the same as previously described on chemotherapy induced diarrhoea [17].

A serious potential toxicity of anti-VEGF treatments is gastrointestinal perforation [28] most commonly bowel perforation. Bowel perforation may lead to peritonitis, fistula formation, abscess and sepsis. Management of bowel perforation should involve the multidisciplinary team including oncology, surgery, and radiology. Conservative, non-operative management options include bowel rest, antibiotics and parenteral feeding. The decision of whether or not to operate is complex, and such decision-making should take into account the severity and sequelae of the perforation, the patient's comorbidities, likely outcome of the operation, and the patient's wishes.

Immunotherapy

"Immunotherapy" is a broad term encompassing any therapy that up-regulates the immune system to target cancers. Over the years, various different methods of "switching on" the immune system have been used including vaccine therapies, intra-tumoral injections and cytokine therapies. This section focuses on the currently most commonly utilized immunotherapy; the family of drugs referred to as the immune checkpoint inhibitors (ICPIs). These drugs are monoclonal antibodies, which target the 'checkpoints' the immune system has in place to regulate autoimmunity. Examples of ICPIs include the anti-CTLA4 directed therapy (ipilimumab)

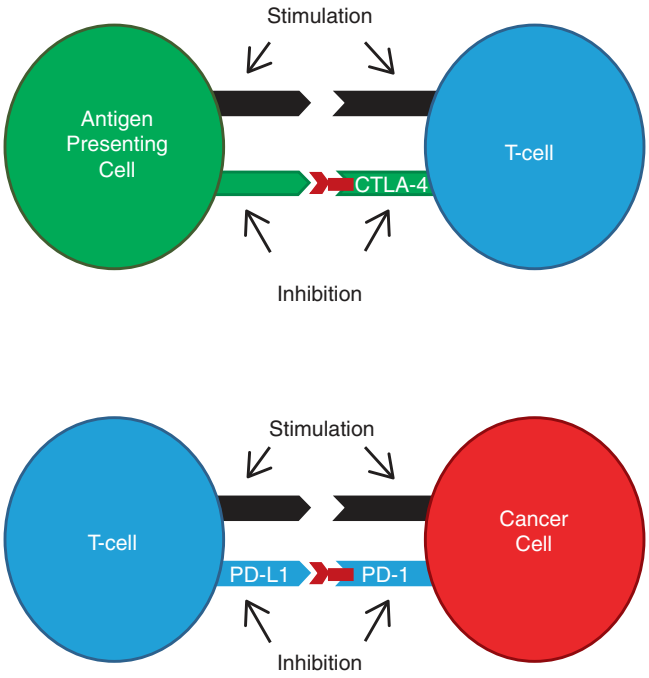

Fig. 5 Mechanism of Action of CTLA-4 and PD-1/PD-L1 inhibitors; adapted from [29]. For an immune reaction to take place there must be stimulation between a cell displaying abnormal proteins (either the antigen presenting cell or a tumour cell) and the T-cell via a receptor pathway (in black). The interaction between CTLA-4 (green pathway) and PD-1/L1 (blue pathway) blocks immune activation, which in normal cells prevent inappropriate immune activation but in cancer cells is used to evade immune destruction. When anti-CTLA-4 or anti-PD1/PD-L1 antibodies (dark red) are present, they block CTLA-4 or PD-1/L1 interaction respectively, thus allowing immune activation

or the anti-PD-1/PD-L1 directed therapies (e.g. pembrolizumab, nivolumab, atezolizumab and durvalumab).

The indications for checkpoint inhibitors are growing exponentially with ever increasing trials testing these agents in different cancers at different disease stages with different treatment objectives; given as monotherapy or in combination multi-modality treatment regimens. One of the hallmarks of cancer is the ability to evade detection by the immune system through these immune checkpoints. ICPIs are used to allow the immune system to 'recognize' cancers again (see Fig. 5). This can lead to dramatic responses of cancers to treatment and has revolutionized the treatment and survival of some cancers.

The side effects of ICPIs, however, are incredibly broad and either originate from the effect of having a systemic therapy (fatigue, nausea) or due to the effect of direct immune attack on specific organs of the body. ICPIs can lead to immune adverse effects on any organ; three of the commonly affected organ systems include the colon (colitis), liver (hepatitis) and endocrine organs including the thyroid and pancreas. Whilst this auto-inflammatory response can often be managed, this can require long-term use of high doses steroids or immunosuppressive agents, which themselves can cause long term side effects.

Effect of Immunotherapy on the Gastrointestinal Tract

ICPIs can impact the GI tract and nutrition in a multitude of actions, either through direct action on the mucosa itself, or by the effects on supporting organ systems or through toxicity from supportive agents. Table 6 gives a list of example toxicities:

Investigation and Management of Patients on ICPIs

The most important initial step is recognition that the presenting complaint could be secondary to the ICPI. This is often easy if the patient is still receiving the drug, however, toxicities of ICPIs can occur late even months following ces-

Table 6 Toxicities from ICPI and the effect on nutrition

Site/cause of toxicity (frequency)	Impact on nutrition
General drug adverse effects (very common)	Nausea is a common side effect of ICPI therapy and therefore can impact on nutritional intake
Immune-related colitis (common)	Diarrhoea, abdominal pain, bloating, urgency of defaecation and possible malabsorption. Can cause severe inflammation of the colon with a syndrome of symptoms similar to inflammatory bowel disease;
Immune-related enteritis (unknown)	Similar to colitis but with inflammation within the small bowel; can cause nausea/vomiting, bloating, malabsorption
Immune-related diabetes (uncommon)	Causing a syndrome similar clinically to type 1 diabetes mellitus; dysregulation of glucose homeostasis requiring management with insulin
Immune-related pancreatic insufficiency (uncommon)	Failure of the pancreas to produce enzymes to allow digestion of macronutrients; presents with diarrhoea, steatorrhoea, bloating, weight loss
Steroid-induced diabetes	Steroids cause altered glucose homeostasis which can cause a picture similar to type 2 diabetes, but patients can present acutely with hyperglycaemic hyperosmolar syndrome
GI infection	Either as an effect of the ICPI or secondary to immunosuppression, patients are at risk of GI infection; recent safety signals were released about the risk of reactivation of cytomegalovirus causing colitis with ICPIs [30].
Endocrine insufficiency (from common to uncommon)	Immune-related endocrine adverse effects are well recognized with ICPIs most commonly thyroid dysfunction. Less common conditions include hypopituitarism, and hypoadrenalism. Potential effects of these conditions include weight loss, nausea and anorexia.

sation of immunotherapy, which can make diagnosis difficult especially if patients did not present at an oncology unit.

There are published international guidelines (for example by the European Society of Medical Oncology [31]) on the management of ICPI-induced toxicity based on the severity of the toxicity using the Common Terminology Criteria for Adverse Events (CTCAE) grading system [27] to guide the subsequent requirement for admission, investigations for alternative causes and management options, typically the consideration of oral or intravenous steroids. In the event of lack of response to steroids, other forms of immunosuppression are then considered.

Specific Examples

Immune-Related Colitis

Patients on ICPI frequently present with diarrhoea or a change in bowel habit, often mild and relating to the consistency of stools. Presenting features are often similar to inflammatory bowel disease (IBD). For mild CTCAE grade 1 toxicity, treatment may involve just the use of simple anti-motility agents such as loperamide and exclusion of infection. In severe CTCAE grade 3+ toxicity, inpatient admission for high dose intravenous steroids and rapid further investigation including cross-sectional imaging, endoscopy and biopsy of the colon may be required. In patients with unresponsive severe symptoms, therapies often used in IBD are considered such as infliximab or vedolizumab. Specialist gastroenterology review is strongly recommended for these patients with severe toxicity. Early pre-treatment screening tests for eligibility for anti-TNF monoclonal antibody therapies (such as tuberculosis, viral hepatitis and HIV infections) should be considered for any patient presenting with severe immune-related colitis to allow prompt escalation of treatment.

Immune-checkpoint inhibitors are being used in an increasingly broad range of cancer therapies in both the adjuvant (following completion of definitive management, either surgical or concurrent chemo-radiotherapy) and metastatic setting with good outcomes and therefore these patients may have excellent survival outcomes from their cancer therapy however, the effect on quality of life in the long term due to immunotherapy can be profound. Prompt consideration and management of ICPI toxicity is therefore paramount.

Radiotherapy

Radiotherapy (RT) has been used in the management of malignant diseases for over a century. Conventional RT uses high energy X-rays or photons to cause ionization events (removal of orbiting electrons from atoms) within cells resulting in DNA damage and if unrepaired, initiating cell death pathways. RT ionization events and cancer cell death follow a probabilistic model, hence DNA damage (and cancer cell death) escalates with increasing RT dose. Thus, with high enough radiation doses, localized cancer eradication and cure can be achieved. However, in metastatic disease, RT has an important role in localized palliation of symptoms such as pain, obstruction and bleeding.

RT is becoming increasingly more targeted and sophisticated owing to significant developments in technology allowing the delivery of higher RT doses to cancers with improved cure rates while sparing normal tissue with reduced toxicity. RT continues to evolve with developments in particle therapy, such as proton therapy, which delivers radiation dose in a more confined manner compared to conventional photon RT, allowing greater sparing of normal tissue from low/intermediate doses especially to organs adjacent to the cancer, and potentially reducing long-term morbidity in some situations.

Effect of Radiotherapy on the Gastrointestinal Tract

Ionizing radiation beams travel in straight lines. Therefore, either on the way toward the tumour or after passing through it, radiation may damage the surrounding normal tissues of the body. This damage causes cessation of normal cellular functions and can cause death of the normal body tissues. This effect of radiation on normal structures causes both acute and late toxicity. It is important to note that the majority of curative RT regimens are often multi-modality, typically combined with concurrent chemotherapy as a radiosensitizer to improve cure rates but exacerbating acute RT toxicity onset and severity in addition to the chemotherapy-related toxicity.

Acute RT toxicities (those seen during a course of treatment or in the short weeks following completion) relate to the cell death of rapidly dividing cells (for example skin and mucosal surfaces) causing breakdown of epithelial surfaces. As the GI tract is lined by an epithelial membrane, any part of this receiving a dose of radiation can be affected. Acute toxicity typically subsides within a couple of months of treatment as normal tissue cells regrow and restoring the epithelial surfaces.

Late RT toxicities are related to multiple different factors including normal tissue hypoxia, inflammation, stem cell death, fibrosis and angiogenesis (formation of new vasculature). Its late onset is related to the cells of the stroma responding more slowly to radiotherapy damage. These processes can result in tissue necrosis (e.g. osteoradionecrosis of the mandible), stenosis (e.g. oesophageal strictures), telangiectasia (the development of new, fine fragile blood ves-

sels prone to bleeding), and functional changes in the gut, dependent on the site affected (e.g. bile acid diarrhoea when the terminal ileum is irradiated).

The most common cancer sites with likely acute and late effects of RT affecting gastrointestinal (GI) function include treatment for gynaecological organs (endometrium, cervix), lower GI (rectum, anus) and urology (bladder, prostate)—persistent symptoms have now been termed 'Pelvic Radiation Disease'. Other sites affected can be the pancreas, liver, oesophagus and head and neck. In addition to acute and late toxicity, due to the direct action of radiation on the gut, there are a multitude of other effects that RT has on intestinal function and nutrition. The supportive organs can also be affected; for example salivary glands, pancreas, liver or surrounding bloods vessels. In general, the effects of RT are localized to the area being treated (e.g. salivary glands affected in head and neck RT, oesophagitis in oesophageal or lung RT).

A common side effect of RT is nausea which is believed to be related to 5-hydroxytryptamine 3, neurokinin-1 (NK-1), and dopamine neurotransmitter release affecting the emetogenesis centres of the brain. RT induced nausea is most typically related to irradiation of the GI tract or brain. Management of RT induced nausea is as discussed earlier with chemotherapy induced nausea.

The acute and late toxicities affecting different regions of the GI tract are detailed in Tables 7 and 8.

Below are two examples of acute and late RT toxicities respectively.

Table 7 Acute toxicities of radiotherapy on gastrointestinal tract

Site of treatment	Effects on GI function/nutrition
Head and neck	Xerostomia, dysphagia potentially leading to aspiration, decreased enjoyment of food, alterations to consistency of the diet, mucositis/ulceration
Gustatory system (taste)	Change in tastes/cravings and decreased enjoyment leading to food avoidance
Oesophagus	Mucositis/oesophagitis, odynophagia, dyspepsia, gastro-oesophageal reflux, requirement for altered dietary consistency, dysphagia and risk of aspiration (in cervical oesophageal treatment). See worked example
Stomach	Nausea/vomiting, dyspepsia, early satiety, ulceration
Small intestine	Bloating, nausea/vomiting, borborygmi, pain/cramping, enteritis, poor absorption of nutrients, bacterial translocation, oedema leading to subacute obstruction
Large intestine	Diarrhoea, pain/cramping, dehydration, proctitis leading to food avoidance to reduce need to defaecate, oedema leading to subacute obstruction
Liver	Nausea/vomiting
Pancreas	Acute pancreatitis

Table 8 Late-effects of radiotherapy on gastrointestinal tract

Site of treatment	Effect on GI function/nutrition
Head and neck	Long term xerostomia—may affect choice of diet and fatigability of chewing, poor dentition
Oesophagus	Disordered motility, strictures
Small intestine	Bacterial overgrowth, bile acid diarrhoea, strictures
Large intestine	Proctopathy, radiation colopathy, rectal telangiectasia
Pancreas	Exocrine dysfunction, stricture of pancreatic ducts
Vascular system	Vessel damage, calcification, reduced splanchnic blood flow and reduced absorption.

Oropharyngeal/Oesophageal Mucositis

Patients receiving high RT doses to the oropharynx or oesophagus in head and neck, oesophageal and central lung cancers commonly develop acute mucositis of the oropharynx or oesophagus. It usually presents with odynophagia (pain on swallowing) and if uncontrolled, worsening dysphagia. Symptoms typically develop 2 weeks into RT treatment, progressing over the course of RT and peaking 1–2 weeks following completion of treatment.

Patients often require a change in diet to aid swallow function, changing from solid to a soft or liquid diet. The aim of treatment is supporting nutrition and controlling symptoms until recovery of the normal tissues and side-effect resolution, typically 4–6 weeks post treatment but can be up to several months with head and neck cancers.

Supportive medical therapies are focused on symptom control to aid swallowing and manage pain, for example topical lubricants (carboxymethylcellulose), oral coating solutions, oral local anaesthetics and analgesics with strong opiates often required. Active prevention and management of conditions likely to exacerbate mucositis recovery such as acid reflux (especially with concurrent chemotherapy-related emesis) with antacids and anti-emetics, and oropharyngeal/oesophageal candidiasis (due to loss of the protective mucosal surface from RT treatment and chemotherapy-related immunosuppression) with good oral hygiene and a low threshold to commence anti-fungal treatment.

If nutritional intake is inadequate, consideration has to be given to enteral feeding (typically nasogastric tube feeding). In high risk head and neck or oesophageal cancer patients, prophylactic percutaneous enteral tube insertion is often considered prior to commencing treatment. Multidisciplinary support of patients on treatment with specialist speech and language therapists and dietitians is vital to ensure weight loss is minimized due to its impact not just on patient malnutrition but also on RT treatment dosimetry and accuracy.

Pelvic Radiation Disease

Pelvic radiation disease can be defined as "transient or longer-term problems, ranging from mild to very severe, arising in non-cancerous tissues resulting from radiotherapy treatment to a tumour located in the pelvis" [32, 33]. This disease can present with multiple different GI symptoms and

can have a wide range of implicated aetiologies with the underlying cause often secondary to more than one diagnosis and may not directly relate to the effects of radiotherapy itself.

Diagnosis is often the first problem for patients, as the late GI effects of radiation are often underdiagnosed or perceived to be untreatable by healthcare professionals, or patients may not mention them, wrongly thinking they are expected to "just live with it". However, the underlying aetiologies are often treatable with good symptomatic benefit for patients. Referral to a radiotherapy late effects specialist team or gastroenterologist is recommended. For further guidance on the management of pelvic radiation disease, please refer to collaborative guidance by Andreyev et al. [34].

Effects of Chemotherapy on Radiation Toxicity

Chemotherapeutic agents are often given concurrently in curative radiotherapy regimens often as a radiosensitizer by binding to radiation-induced DNA damage and inhibiting DNA repair thus enhancing cancer cell kill [35]. Common concurrent chemoradiotherapy agents used include platinum agents, 5-fluorouracil, capecitabine and taxanes. However, radiosensitization from concurrent chemotherapy also impacts irradiated normal tissue with higher incidences of severe acute radiotherapy toxicity including acute gastrointestinal radiotherapy toxicities as listed previously in Table 6 [36].

Although enhancement of toxicity is greater when both chemotherapy and radiotherapy are given concomitantly, docetaxel, paclitaxel, gemcitabine, capecitabine and doxorubicin, and EGFR tyrosine kinase inhibitors have been reported to produce a 'radiation recall phenomenon' [37, 38]. This may occur at a site that has previously been irradiated when one of these drugs is given weeks or months later. Gastrointestinal tract recall phenomenon reported include mucositis, oesophagitis, gastritis and colitis reported.

Nutrition Support

Under-nutrition (protein–energy malnutrition) is a common issue in patients with malignancy, and studies have demonstrated a relationship between weight loss and a lower chance of responding to treatment [39, 40]. Malnutrition can contribute to morbidity in cancer patients by many mechanisms, including: increased infection risk, delayed wound healing, muscle weakness, depression, worse quality of life, reduced chemotherapy and radiotherapy response, increased surgical complications and worse survival rates [41]. Five-year survival rates may be up to 50% lower for patients with weight loss at the time of diagnosis compared with those who have retained their previous weight [42]. Cancer cachexia is not simply due to lack of adequate oral intake; rather, its pathophysiology is complex and includes a combination of systemic inflammation and hyper-metabolism alongside decreased intake.

Metabolic abnormalities in patients with cancer cachexia have been reported to include marked alterations of lipid, carbohydrate and protein metabolism [40]. Energy stores are diminished and total body water is increased. Of particular interest is the marked reduction of glutamine levels in patients with cancer cachexia [43]. Malignant cells extract glutamine with higher efficiency than any other cell in the body and this may affect normal protein synthesis. Recently, sarcopenia has been shown to be an important prognostic factor in cancer patients undergoing chemotherapy, with many recent studies showing that loss of lean body mass loss is an independent risk factor for chemotherapy toxicity, chemotherapy dose reductions, hospital admissions, and a decreased survival in these patients [44].

This evidence has emphasised a role for nutritional support in cancer patients to attempt to combat this reversible poor prognostic factor. This has been incorporated into many cancer therapy guidelines, with recent guidelines by the European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) having advocated increased attention to nutritional support in all patients with cancer [45] and United Kingdom National Institute for Clinical Excellence best practice guidelines advocating early nutritional screening to identify malnourished patients for consideration of interventions [46].

Nutrition support in cancer patients should always be dietetic-led. Initially oral nutrition should be optimised if possible. If this fails to meet nutrition requirements, supplementary nutrition can be offered to patients via the gut (enterally), or using intravenous (parenteral) nutrition (PN) in selected patients (Table 9).

Effect of Cancer on Nutritional Status

The presence of cancer can have a profound effect on nutritional status through its effect on nutrition impact symptoms, food intake and body composition. The term disease related malnutrition refers to malnutrition along with the activation of systemic inflammation by underlying disease. The resulting inflammatory response contributes to loss of appetite and has a metabolic impact on tissues and organs. It can result in a loss of body weight, changes in body composition with a loss of muscle mass and fat along with a deterioration in physical functioning or performance status [47]. Metabolic abnormalities in patients with cancer cachexia have been reported to include marked alterations of lipid, carbohydrate and protein metabolism. Energy stores are

Table 9 Reasons for giving parenteral nutrition to patients with malignancy (a predicted 'long' survival with a good quality of life is desirable before starting parenteral nutrition)

Indications for parenteral nutrition
Gastrointestinal toxicity (mucositis/enterocolitis)
Bowel obstruction
Prolonged ileus
High-output enterocutaneous fistula
Malabsorption
Graft-versus-host-disease (GVHD)

Table 10 Terminology used to describe physiological changes occurring in cancer

Term	Description
Cachexia	A multi-factorial wasting syndrome characterised by involuntary weight loss, loss of skeletal muscle mass and fat mass [51].
Pre-cachexia	Early clinical and metabolic signs which precede loss of body weight and muscle.
Refractory cachexia	Cancer cachexia which does not respond to conventional nutritional support [51]
Sarcopenia	Low skeletal muscle mass and low muscle function [52]. Fatigue is common and physical function is limited.
Sarcopenic obesity	Low skeletal muscle mass in obese individuals. Often overlooked as body weight may appear normal, overweight or obese. Associated with poorer outcomes in relation to systemic anti-cancer treatment as associated with increased risk of toxicity and potential dose reduction of treatment [53, 54]

diminished and total body water is increased. The metabolic changes are mediated by systemic and tumour related cytokines including tumour necrosis factor-α (TNF-α), interleukin 1 (IL-1) and IL-6. Cytokines can impact on the neuroendocrine control of appetite leading to anorexia, in addition to causing wasting of skeletal muscle and reduced performance status [47].

Cancer cachexia is often not diagnosed or mentioned in a full medical assessment as there is often confusion as to its definition [48]. Percentage weight loss over time is often the main criteria with more recent definitions including a combination of factors, for example, weight loss, a simple questionnaire of sarcopenia (SARC-F), Eastern Cooperative Oncology Group performance status, appetite loss and abnormal biochemistry [49]. The Glasgow Prognostic Score (GPS), based on serum albumin and levels of C-reactive protein are also predictive tools used for the assessment of inflammation in cancer which are associated with prognosis and mortality [50].

A number of terms are used to describe the physiological syndromes that occur and these are described in Table 10.

The prevalence of malnutrition in the people with cancer varies depending on tumour type, tumour stage and the person's age with increasing age conferring a greater risk. Cancers affecting the upper gastrointestinal tract, head and neck, pancreas and lung are associated with an increased risk of malnutrition. Overall the reported range is from about 20–70% [47, 55]. Nutritional screening should be mandatory at diagnosis and at key points during the treatment pathway using a validated screening tool [55]. As the weight of populations is increasing it is essential that a normal body mass index or weight to height ratio is not used as the only method of assessment. This can hide changes in weight, body composition and food intake. Anorexia and other nutrition impact symptoms are recognised as important early indicators as a risk of malnutrition [47].

Following nutrition screening those identified as having a moderate or high risk of malnutrition should be referred for specialist dietary advice with the aim of meeting estimated nutritional requirements.

Systemic Anti-Cancer Treatment and Nutritional Status

Tolerance to systemic anti-cancer treatment (SACT) is influenced by nutritional status and body composition. Early studies demonstrated that people who had lost weight generally experienced more side effects of chemotherapy during treatment [56, 57]. This association is now recognised to be closely linked with low lean mass. Calculation of dose of SACT is based on body surface area derived from measurement of body weight. This estimate does not take into account body composition and the amount of lean mass and fat mass. Studies have shown that people who have a low lean, as measured by dual-energy X-ray scans or measurement of muscle mass from computed tomography scans (CT) have a high risk of toxicity of treatment and dose adjustment of SACT [53, 58].

Nutrition Support During Systemic Anti-Cancer Treatment

Individualised dietary advice is required for anyone deemed to be at risk of malnutrition following a diagnosis of cancer. Continual and ongoing screening should identify people who develop toxicities of treatment that impact on their dietary intake or nutritional status. Nutritional support should be part of a comprehensive approach that provides supportive care in a holistic way (Table 11). This may include psychological support, pain control, symptom control, physical activity and other aspects of daily life identified by the person themselves [60]. Increasingly physical activity in the form of both aerobic and resistance exercise is recognised as an important strategy to improve upper and lower body muscle strength [61].

The European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) recommend the use of indirect calorimetry to predict resting energy expenditure; however, this is often not performed in routine clinical care [47]. In the absence of this measurement it is recommend to estimate energy requirements as 25–30 kcal/kg/day with 1.2–1.5 g protein/kg/day with higher

Table 11 Assessment for the provision of nutrition support [59]

Category	Examples
Anthropometry	Weight
	Height
	Body mass index
	Weight change—actual and percentage body weight from normal over 1, 3 or 6 months
	Mid upper arm circumference
Biochemistry	Electrolytes, Urea, Creatinine, Albumin and C-reactive protein (to determine modified Glasgow Prognostic Score)
Clinical	Type of SACT, expected side effects, patient reported symptoms preferably using validated symptom scores or scales.
Dietary intake	Current intake of food and fluid/nutritional intake
	Habitual food intake
	Meal pattern
	Texture of food consumed
	Foods not tolerated
	Dietary supplements consumed
Environment	Social circumstances
	Primary carer
	Arrangements for shopping, cooking
Behavioural	Food related behaviour, physical activity
Psychological	Self efficacy, self-management, mental health status
Health care utilisation	Hospitalisation, treatment planning

amounts of protein being required when depletion is severe [47]. Severely depleted patients should be managed with a slow, gradual introduction of nutrients with concurrent monitoring of electrolytes and tolerance to reduce the risk of refeeding syndrome [50].

Nutrition counselling is the first and most commonly utilised intervention for people with cancer who have a functioning gastrointestinal tract. This must include adequate symptom control particularly with respect to nausea and vomiting. Nutritional care should be undertaken within a framework of the nutrition care process taking into account multiple clinical, nutritional, sensory and social factors. For people who are struggling to maintain an adequate dietary intake, expertise from a Registered Dietitian has been shown to help improve intake of protein and energy intake [62, 63]. Some symptoms such as taste changes are particularly challenging to manage and can lead to a decrease in oral intake [64].

Oral nutritional supplements may also be appropriate to use and these have been demonstrated to improve protein and energy intake [65]. Although many trials on the use of nutritional support have not demonstrated a clear benefit for enteral nutrition in cancer patients, some of these have, unfortunately, been poorly designed. Increasingly studies are providing support for the early provision of dietary advice and nutrition support to influence the ability to withstand SACT [66].

More intensive nutrition support should be considered for patients with cachexia and increasing weight loss if aggressive therapy is to be offered [47]. For patients who are markedly malnourished and, as a result, are felt to be poor risks for chemotherapy, the use of enteral nutrition should be considered as the improvement in nutritional status may allow its subsequent use. Enteral nutrition is the preferred form of feeding if the gastrointestinal tract is functional and may be achieved by the use of nasogastric tubes or gastrostomy or jejunostomy feeding catheters if oral intake is insufficient or not possible due to tumour or the effect of treatment. Post pyloric feeding may be preferable in those who have ongoing or uncontrolled nausea and vomiting although placement and retention displacement of naso-jejunal feeding tubes may present a challenge in such cases. For longer-term EN support (particularly in patients with head and neck cancers undergoing radiotherapy) a gastrostomy tube (PEG or RIG) can be considered, often placed prophylactically prior to treatment.

Concomitant use of SACT and radiotherapy, for example in head and neck cancer, may exacerbate the toxicity of treatment. It is paramount that the provision of appropriate nutritional support is part of the treatment pathway to avoid delays in tube placement which in turn may influence ability to continue with treatment. The risks and benefits of appropriate feeding tubes should be discussed with people early in the treatment pathway enabling them to make an informed decision on the most suitable method of feeding.

Multi-Modal Interventions

Increasingly it is recognised that improvements in sarcopenia, cachexia and poor nutritional status require a multimodal approach that incorporates nutritional support and physical activity. The European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) (ESPEN) recommend maintenance or increased level of physical activity to support muscle mass, physical function and metabolic pattern [47]. The role of drugs such as non-steroidal anti-inflammatory drugs (NSAID) to increase body weight and androgens to increase muscle mass are not supported by a sufficient body of evidence to be used routinely in clinical practice. Appetite stimulants such as progestins and steroids have studies to demonstrate their efficacy; however, their use is associated with potentially serious side effects such as thromboembolism in the case of progestins [47].

It is hoped that this multi-modal approach early in the treatment pathway will support optimisation prior to and during SACT resulting in reduced toxicity of treatment and improved outcomes. This has yet to be demonstrated in clinical trials and requires appropriate planning and support rather than waiting to identify those who have become malnourished.

Specific Nutrients and Their Influence in Cancer

The use of specific nutrients to improve nutritional status have met with varying degrees of success. Amino acids have been studied to determine their ability to increase fat free mass, however, these studies have failed to demonstrate sufficient benefits to warrant their use in routine nutritional support. Fish oil derived eicosapentaenoic acid (EPA) has been administered for its anti-inflammatory properties with the purpose of dampening the inflammatory changes that occur in cachexia. Whilst some studies have failed to demonstrate a clinical benefit from their administration, others have reported improvements in appetite, energy intake, body weight, lean body mass and prognostic benefits from fish oil enriched nutrition [67, 68]. More definitive evidence is required before fish oils can be recommended for use during SACT.

The role of glutamine in cancer continues to be controversial. It has been suggested that glutamine is semi essential in catabolic states and that glutamine depletion is linked to cancer related fatigue, performance status, poor nutritional status and inflammation in patients with solid tumours [69]. Glutamine has also been trialled as a treatment for SACT induced mucositis although studies have not provided sufficient evidence for it to be recommended for this use [47].

Can Diet Influence Gastrointestinal Symptoms of SACT?

The effect of SACT on gut mucosa is well known with diarrhoea being a common side effect of treatment. It has also recognised that this may have temporary implications for digestion and absorption of nutrients, including lactose, vitamins and minerals. Lactose intolerance during chemotherapy has been demonstrated with the use of lactose hydrogen breath tests demonstrating a rate of lactose intolerance higher than the normal population [70]. However, it is important to note that not all patients were symptomatic from lactose intolerance and lactose restriction has not been shown to be an effective method for managing gastrointestinal symptoms caused by SACT. Dietary restrictions during acute toxicity should not be imposed without evidence that they are effective as they are likely to further exacerbate the risk of malnutrition during treatment.

Are Dietary Restrictions Required in SACT?

People undergoing SACT are more susceptible to infection and should be given advice to avoid foods that are a high risk of containing pathogenic organisms. These include pate (meat or vegetarian), cheese from unpasteurised milk, raw fish (for example sushi) and uncooked eggs. Good food hygiene is paramount and advice should be available to reinforce the importance of hand hygiene, appropriate storage and heating of food. There is an ongoing debate about further food restrictions that may be imposed for people who have neutrophil counts below 0.5 or 2.0×10^9/L and whether these are both necessary and effective at reducing food borne infections [71–73]. Increasingly hospitals are reviewing their policy and in many cases are relaxing the previous restrictions that were imposed.

Parenteral nutrition (PN) should only be used in people who have a non-functioning gastrointestinal (GI) tract or in whom it is not possible to access the GI tract. Some patients may develop diffuse intra-abdominal malignancy and this may cause malabsorption or obstruction. Use of PN should also be considered for people in whom enteral nutrition has been commenced but failed to become established (for example, in immunotherapy or graft versus host disease where symptoms and intestinal failure may result in reduced tolerance to enteral nutrition). PN may also be considered for patients whose severe cachexia is the primary reason for failure of restoration of performance status and in whom treatment-associated toxicities prevent the use of enteral nutrition. There should be a reasonable expectation that antitumour therapy will produce a response, improve survival and may reduce the severity of intestinal failure so that PN may be stopped.

Some patients may develop diffuse intra-abdominal malignancy, and this may cause malabsorption or obstruction, with death due to nutritional failure, rather than cancer progression. The decision to provide home PN for such patients depends primarily on the underlying tumour type and the likelihood of it responding to chemotherapy. Chemoresponsive diseases such as germ cell tumours, lymphomas and ovarian cancers may reduce rapidly in volume with chemotherapy, and recovery can be enhanced by a period of PN. Similarly, patients who have developed severe, prolonged mucositis and enterocolitis as a result of radiotherapy may benefit from support with PN. For patients who are markedly malnourished and, as a result, are felt to be poor risks for chemotherapy, the use of enteral nutrition should be considered as the improvement in nutritional status may allow its subsequent use.

The consideration of PN versus EN in cancer patients without one of the strong PN indications (Table 9) remains controversial with a recent review and meta-analysis of over 43 studies show that EN and PN are equal in terms of mortality and nutritional complications, with a slight increase in risk of infection for PN support [74]. The use of PN in the peri-operative setting has been examined in several studies and, again, conflicting results have been obtained. Patients seem to benefit from PN after the development of a prolonged ileus following an abdominal procedure: if the patient has been unable to resume oral intake 7 days after surgery, PN may be considered. Lean body mass may be maintained as a result, improving quality of life and allowing a more rapid return to normal activities [75]. Cancer patients who undergo multiple bowel resections may develop the prob-

lems of a short bowel. Prolonged home PN may be required for those patients who are potentially cured by their surgery.

A recent study has shown that although oncologists accept that nutritional status and intervention are important, they still struggle to identify patients at risk of malnutrition and to refer those who may benefit from early nutritional intervention [48]. The ability to provide good nutritional care in these complex patients requires a multi-disciplinary team approach, including surgeons, medical and clinical oncologists, nurses, speech and language therapists, physiotherapists, occupational therapists, pharmacists and the nutrition team. There is also a requirement for ongoing education around the role of nutrition and its importance to all involved in looking after cancer patients and to the patient themselves.

Summary

Gastrointestinal toxicity from chemotherapy, radiotherapy and newer targeted agents is common and some effect on nutritional balance is almost universal. Most oncologists are increasingly aware of the importance of this toxicity as a contributory factor to the reduced quality of life and, potentially, to the survival of their patients, but feel ill-equipped in the diagnosis and management of malnutrition. Cancer survivors also often present with late non-specific symptoms with wide ranging aetiologies which can include toxicities of prior treatments, cancer recurrence, a range of non-malignant causes and psychological overlay due to fear of cancer recurrence. It can often be difficult to differentiate the specific cause of symptoms and its relationship to prior cancer treatment. There is a need for increased access to multidisciplinary nutritional support for cancer patients on treatment, and the availability of specialist late effects teams to ensure appropriate investigation and management of late morbidity in cancer survivors.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.
2. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review (CSR) 1975-2016. Bethesda, MD: National Cancer Institute; 2019. https://seer.cancer.gov/csr/1975_2016/.
3. Denekamp J. Cell kinetics and radiation biology. Int J Radiat Biol Relat Stud Phys Chem Med. 1986;49(2):357–80.
4. Tannock IF. Experimental chemotherapy and concepts related to the cell cycle. Int J Radiat Biol Relat Stud Phys Chem Med. 1986;49(2):335–55.
5. Tarricone R, Ricca G, Nyanzi-Wakholi B, Medina-Lara A. Impact of cancer anorexia-cachexia syndrome on health-related quality of life and resource utilisation: a systematic review. Crit Rev Oncol Hematol. 2016;99:49–62.
6. Lin A, Jabbari S, Worden FP, Bradford CR, Chepeha DB, Teknos TN, et al. Metabolic abnormalities associated with weight loss during chemoirradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2005;63(5):1413–8.
7. Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management. Ther Adv Med Oncol. 2010;2(1):51–63.
8. Herrstedt J. Antiemetics: an update and the MASCC guidelines applied in clinical practice. Nat Clin Pract Oncol. 2008;5(1):32–43.
9. Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl J Med. 2008;358(23):2482–94.
10. Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM, et al. On the receiving end--patient perception of the side-effects of cancer chemotherapy. Eur J Cancer Clin Oncol. 1983;19(2):203–8.
11. Olver IN. Update on anti-emetics for chemotherapy-induced emesis. Intern Med J. 2005;35(8):478–81.
12. Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. Cancer. 1978;41(1):36–51.
13. Stoller RG, Hande KR, Jacobs SA, Rosenberg SA, Chabner BA. Use of plasma pharmacokinetics to predict and prevent methotrexate toxicity. N Engl J Med. 1977;297(12):630–4.
14. Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA, Fryer JG. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. J Clin Oncol. 1989;7(4):425–32.
15. Eras P, Goldstein MJ, Sherlock P. Candida infection of the gastrointestinal tract. Medicine (Baltimore). 1972;51(5):367–79.
16. Gibson RJ, Bowen JM, Inglis MR, Cummins AG, Keefe DM. Irinotecan causes severe small intestinal damage, as well as colonic damage, in the rat with implanted breast cancer. J Gastroenterol Hepatol. 2003;18(9):1095–100.
17. Bossi P, Antonuzzo A, Cherny NI, Rosengarten O, Pernot S, Trippa F, et al. Diarrhoea in adult cancer patients: ESMO clinical practice guidelines. Ann Oncol. 2018;29(Suppl 4):iv126–42.
18. Weiss HD, Walker MD, Wiernik PH. Neurotoxicity of commonly used antineoplastic agents (second of two parts). N Engl J Med. 1974;291(3):127–33.
19. Weiss HD, Walker MD, Wiernik PH. Neurotoxicity of commonly used antineoplastic agents (first of two parts). N Engl J Med. 1974;291(2):75–81.
20. McQuade RM, Stojanovska V, Abalo R, Bornstein JC, Nurgali K. Chemotherapy-induced constipation and diarrhea: pathophysiology, current and emerging treatments. Front Pharmacol. 2016;7:414.
21. Stone A, Harringaton K, Frakes M, Blank K, Rajanna S, Rastogi I, et al. EGFR and c-Met inhibitors are effective in reducing tumorigenicity in cancer. J Carcinog Mutagen. 2014;5:173.
22. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(9):1274–84.
23. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371(23):2167–77.
24. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016;375(20):1925–36.
25. Nakagawa K, Tamura T, Negoro S, Kudoh S, Yamamoto N, Yamamoto N, et al. Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Japanese patients with solid malignant tumors. Ann Oncol. 2003;14(6):922–30.

26. Asnacios A, Naveau S, Perlemuter G. Gastrointestinal toxicities of novel agents in cancer therapy. Eur J Cancer. 2009;45(Suppl 1):332–42.
27. National Cancer Institute. Common Terminology Criterial for Adverse Events (CTCAE). Version 5.0; 2017. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
28. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011;365(26):2484–96.
29. Godwin JL, Zibelman M, Plimack ER, Geynisman DM. Immune checkpoint blockade as a novel immunotherapeutic strategy for renal cell carcinoma: a review of clinical trials. Discov Med. 2014;18(101):341–50.
30. Medicines and Healthcare products Regulatory Agency. Nivolumab (Opdivo): reports of cytomegalovirus (CMV) gastrointestinal infection or reactivation; 2019. https://www.gov.uk/drug-safety-update/nivolumab-opdivo-reports-of-cytomegalovirus-cmv-gastrointestinal-infection-or-reactivation.
31. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(Suppl 4):iv119–42.
32. Andreyev HJ, Wotherspoon A, Denham JW, Hauer-Jensen M. "Pelvic radiation disease": new understanding and new solutions for a new disease in the era of cancer survivorship. Scand J Gastroenterol. 2011;46(4):389–97.
33. Teo MT, Sebag-Montefiore D, Donnellan CF. Prevention and management of radiation-induced late gastrointestinal toxicity. Clin Oncol (R Coll Radiol). 2015;27(11):656–67.
34. Andreyev HJ, Davidson SE, Gillespie C, Allum WH, Swarbrick E, British Society of G, et al. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut. 2012;61(2):179–92.
35. Seiwert TY, Salama JK, Vokes EE. The concurrent chemoradiation paradigm--general principles. Nat Clin Pract Oncol. 2007;4(2):86–100.
36. Datta NR, Stutz E, Liu M, Rogers S, Klingbiel D, Siebenhuner A, et al. Concurrent chemoradiotherapy vs. radiotherapy alone in locally advanced cervix cancer: a systematic review and meta-analysis. Gynecol Oncol. 2017;145(2):374–85.
37. Burris HA III, Hurtig J. Radiation recall with anticancer agents. Oncologist. 2010;15(11):1227–37.
38. Choi SJ, Kim HJ, Kim JS, Bak YT, Kim JS. Radiation recall gastritis secondary to combination of gemcitabine and erlotinib in pancreatic cancer and response to PPI - a case report. BMC Cancer. 2016;16:588.
39. Fearon KC, Hansell DT, Preston T, Plumb JA, Davies J, Shapiro D, et al. Influence of whole body protein turnover rate on resting energy expenditure in patients with cancer. Cancer Res. 1988;48(9):2590–5.
40. Bozzetti F, Arends J, Lundholm K, Micklewright A, Zurcher G, Muscaritoli M, et al. ESPEN guidelines on parenteral nutrition: non-surgical oncology. Clin Nutr. 2009;28(4):445–54.
41. Talwar B, Donnelly R, Skelly R, Donaldson M. Nutritional management in head and neck cancer: United Kingdom national multidisciplinary guidelines. J Laryngol Otol. 2016;130(S2):S32–40.
42. Yamada N, Koyama H, Hioki K, Yamada T, Yamamoto M. Effect of postoperative total parenteral nutrition (TPN) as an adjunct to gastrectomy for advanced gastric carcinoma. Br J Surg. 1983;70(5):267–74.
43. Kuhn KS, Muscaritoli M, Wischmeyer P, Stehle P. Glutamine as indispensable nutrient in oncology: experimental and clinical evidence. Eur J Nutr. 2010;49(4):197–210.
44. Blackwood HA, Hall CC, Balstad TR, Solheim TS, Fallon M, Haraldsdottir E, et al. A systematic review examining nutrition support interventions in patients with incurable cancer. Support Care Cancer. 2019;28:1877.
45. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11–48.
46. Excellence. NIfC. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition; 2017. https://www.nice.org.uk/guidance/cg32.
47. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, Fearon K, Hutterer E, Isenring E, Kaasa S, Krznaric Z, Laird B, Larsson M, Laviano A, Muhlebach S, Muscaritoli M, Oldervoll L, Ravasco P, Solheim T, Strasser F, de van der Schueren M, Preiser JC. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11–48.
48. Spiro A, Baldwin C, Patterson A, Thomas J, Andreyev HJ. The views and practice of oncologists towards nutritional support in patients receiving chemotherapy. Br J Cancer. 2006;95(4):431–4.
49. Zhou T, Wang B, Liu H, Yang K, Thapa S, Zhang H, Li L, Yu S. Development and validation of a clinically applicable score to classify cachexia stages in advanced cancer patients. J Cachexia Sarcopenia Muscle. 2018;9(2):306–14.
50. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, Erickson N, Laviano A, Lisanti MP, Lobo DN, McMillan DC, Muscaritoli M, Ockenga J, Pirlich M, Strasser F, de van der Schueren M, Van Gossum A, Vaupel P, Weimann A. ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr. 2017;36(5):1187–96.
51. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489–95.
52. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel J-P, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M, P. European Working Group on Sarcopenia in Older. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on sarcopenia in older people. Age Ageing. 2010;39(4):412–23.
53. Prado CMM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629–35.
54. Jung HW, Kim JW, Kim JY, Kim SW, Yang HK, Lee JW, Lee KW, Kim DW, Kang SB, Kim KI, Kim CH, Kim JH. Effect of muscle mass on toxicity and survival in patients with colon cancer undergoing adjuvant chemotherapy. Support Care Cancer. 2015;23(3):687–94.
55. Shaw C, Fleuret C, Pickard JM, Mohammed K, Black G, Wedlake L. Comparison of a novel, simple nutrition screening tool for adult oncology inpatients and the Malnutrition Screening Tool (MST) against the Patient-Generated Subjective Global Assessment (PG-SGA). Support Care Cancer. 2015;23(1):47–54.
56. Andreyev HJN, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? Eur J Cancer. 1998;34(4):503–9.
57. Ross PJ, Ashley S, Norton A, Priest K, Waters JS, Eisen T, Smith IE, O'Brien MER. Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? Br J Cancer. 2004;90(10):1905–11.
58. van den Berg M, Kok DE, Posthuma L, Kamps L, Kelfkens CS, Buist N, Geenen M, Haringhuizen A, Heijns JB, van Lieshout R, Los M, Sommeijer DW, Timmer-Bonte JNH, de Kruif A, van Laarhoven HWM, Kampman E, Winkels RM. Body composition is

associated with risk of toxicity-induced modifications of treatment in women with stage I-IIIB breast cancer receiving chemotherapy. Breast Cancer Res Treat. 2018;173:475.
59. British Dietetic Association. Model and process for nutrition and dietetic practice; 2016. https://www.bda.uk.com/publications/professional/model_and_process_for_nutrition_and_dietetic_practice.
60. Maddocks M, Hopkinson J, Conibear J, Reeves A, Shaw C, Fearon KCH. Practical multimodal care for cancer cachexia. Curre Opin Support Palliat Care. 2016;10(4):298–305.
61. Stene GB, Helbostad JL, Balstad TR, Riphagen II, Kaasa S, Oldervoll LM. Effect of physical exercise on muscle mass and strength in cancer patients during treatment--a systematic review. Crit Rev Oncol Hematol. 2013;88(3):573–93.
62. Uster A, Ruefenacht U, Ruehlin M, Pless M, Siano M, Haefner M, Imoberdorf R, Ballmer PE. Influence of a nutritional intervention on dietary intake and quality of life in cancer patients: a randomized controlled trial. Nutrition. 2013;29(11–12):1342–9.
63. Tanaka N, Takeda K, Kawasaki Y, Yamane K, Teruya Y, Kodani M, Igishi T, Yamasaki A. Early intensive nutrition intervention with dietary counseling and oral nutrition supplement prevents weight loss in patients with advanced lung cancer receiving chemotherapy: a clinical prospective study. Yonago Acta Med. 2018;61(4):204–12.
64. Hutton JL, Baracos VE, Wismer WV. Chemosensory dysfunction is a primary factor in the evolution of declining nutritional status and quality of life in patients with advanced cancer. J Pain Symptom Manag. 2007;33(2):156–65.
65. Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104:371–85.
66. Xie FL, Wang YQ, Peng LF, Lin FY, He YL, Jiang ZQ. Beneficial effect of educational and nutritional intervention on the nutritional status and compliance of gastric cancer patients undergoing chemotherapy: a randomized trial. Nutr Cancer. 2017;69(5):762–71.
67. Shirai Y, Okugawa Y, Hishida A, Ogawa A, Okamoto K, Shintani M, Morimoto Y, Nishikawa R, Yokoe T, Tanaka K, Urata H, Toiyama Y, Inoue Y, Tanaka M, Mohri Y, Goel A, Kusunoki M, McMillan DC, Miki C. Fish oil-enriched nutrition combined with systemic chemotherapy for gastrointestinal cancer patients with cancer cachexia. Sci Rep. 2017;7(1):4826.
68. Fearon KC, Von Meyenfeldt MF, Moses AG, Van Geenen R, Roy A, Gouma DJ, Giacosa A, Van Gossum A, Bauer J, Barber MD, Aaronson NK, Voss AC, Tisdale MJ. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. Gut. 2003;52(10):1479–86.
69. Schlemmer M, Suchner U, Schapers B, Duerr EM, Alteheld B, Zwingers T, Stehle P, Zimmer HG. Is glutamine deficiency the link between inflammation, malnutrition, and fatigue in cancer patients? Clin Nutr. 2015;34(6):1258–65.
70. Parnes HL, Fung E, Schiffer CA. Chemotherapy-induced lactose intolerance in adults. Cancer. 1994;74(5):1629–33.
71. Bloodwise. Eating well with neutropenia: a guide for people with blood cancer; 2017. https://bloodwise.org.uk/document/dietary-advice-patients-neutropenia.
72. Carr SE, Halliday V. Investigating the use of the neutropenic diet: a survey of U.K. dietitians. J Hum Nutr Diet. 2015;28(5):510–5.
73. Tramsen L, Salzmann-Manrique E, Bochennek K, Klingebiel T, Reinhardt D, Creutzig U, Sung L, Lehrnbecher T. Lack of effectiveness of neutropenic diet and social restrictions as anti-infective measures in children with acute myeloid leukemia: an analysis of the AML-BFM 2004 trial. J Clin Oncol. 2016;34(23):2776–83.
74. Chow R, Bruera E, Arends J, Walsh D, Strasser F, Isenring E, et al. Enteral and parenteral nutrition in cancer patients, a comparison of complication rates: an updated systematic review and (cumulative) meta-analysis. Support Care Cancer. 2019;
75. Valdivieso M, Frankmann C, Murphy WK, Benjamin RS, Barkley HT Jr, McMurtrey MJ, et al. Long-term effects of intravenous hyperalimentation administered during intensive chemotherapy for small cell bronchogenic carcinoma. Cancer. 1987;59(2):362–9.

Bacterial Overgrowth and Enteric Infections

Eamonn M. M. Quigley

Key Points

1. Small intestinal overgrowth (SIBO) can occur due to alterations in intestinal anatomy (including diverticula), gastrointestinal dysmotility, or a lack of gastric acid secretion.
2. Can cause steatorrhoea and B_{12} deficiency (folate may be high).
3. The diagnosis of SIBO is commonly made on the basis of an early rise in exhaled breath H_2 following the administration of an appropriate substrate (glucose or lactulose). Criteria for diagnosis vary and must take account of accelerated small intestinal transit. Alternatively, quantitative cultures of aspirated small bowel contents may be used to make the diagnosis.
4. In clinical practice, the diagnosis of SIBO is often assumed and empirical antibiotic treatment commenced and the effect carefully monitored.
5. Chronic SIBO may justify long-term rotating oral antibiotics (e.g. co-amoxyclav, rifaximin, ciprofloxacin, metronidazole, a tetracycline or a cephalosporin) given for 6 weeks before rotating with an intervening 1–2 weeks off antibiotics. There are many different regimens.

Small Intestinal Bacterial Overgrowth

The Gut Microbiota: A Key Player in Homeostasis

As one passes down the gastrointestinal (GI) tract from esophagus to rectum the numbers and diversity of bacteria increase dramatically. Though, not as previously considered, sterile, the esophagus and stomach contain relatively low numbers of bacteria but still feature quite a diversity of bacterial species. The most dramatic increase in diversity and population numbers occurs on crossing the ileo-cecal valve into the colon where over 10^{12} bacteria per mg of feces and up to a 1000 species will be encountered. It must be conceded, however, that the detailed composition of the gut microbiota (and not just bacteria but also archaea, viruses, fungi and protozoa) continues to be defined; it is evident that culture-based techniques had dramatically underestimated the size and diversity of microbial communities within the GI tract. As molecular techniques, such as shotgun sequencing, are applied to enteric communities, their full dimensions in health and disease will be appreciated [1–3]. The same applies to the definition of small intestinal bacterial overgrowth (SIBO); as we will see later, its definition has, to date, relied upon culture or indirect approaches, such as the analysis of exhaled gases—we await the systematic application of high-throughput sequencing, metagenomics and metabolomics to its assessment. The latter may prove to be especially important by identifying those bacterial products and metabolites that actually produce symptoms and injure the intestine in SIBO. In a similar vein, while a profile of bacterial numbers along the GI tract has been described based on cultures of luminal aspirates (and used as the benchmark for defining abnormality), data, derived from either sequencing or metagenomics on bacterial populations throughout the small intestine, in health or disease, is scanty and this remains a major obstacle to our understanding of SIBO [4]. While there have been many studies of the human gut microbiota in health and a variety of gastrointestinal diseases, most have been, for reasons of obvious logistical simplicity, based on the analysis of stool samples. While such studies have revealed many of the factors that influence the development and maintenance of the gut microbiota throughout life, they may be poorly reflective of those critical interactions that occur between bacteria and the host at, or close to, the epithelial surface [4].

We do know that enteric bacteria colonize the alimentary tract at and soon after birth. Thereafter, the infant's microbiota rapidly increases in numbers and diversity to reach adult

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proportions at about 2 years of age and then remains relatively constant throughout adulthood only to decline somewhat in later years [5]. These early years may be critical, not only to the development of the mature microbiome but also to shaping immunological and metabolic interactions with the host—interactions that may play a critical role in predisposing an individual to disease in adolescence and adulthood. The literature is now replete with examples of the sensitivity of the developing microbiota to various interventions (diet and antibiotics, for example) that presage later ill health. We also now have a reasonable understanding of some of the factors that shape the microbiota in adulthood—here again, diet and antibiotic use loom large with certain medications, ethnicity, host genetics, geographic location and disease itself appearing to exert impacts; ones that could readily confound the interpretation of microbiota data.

The four dominant bacterial phyla in the human GI tract are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Most bacteria belong to the genera *Bacteroides*, *Clostridium*, *Faecalibacterium*, *Eubacterium*, *Ruminococcus*, *Peptococcus*, *Peptostreptococcus*, and *Bifidobacterium*. Other genera, such as *Escherichia* and *Lactobacillus*, are present in lower numbers. It must be stressed that a number of fungal genera are normal inhabitants of the gut and include *Candida*, *Saccharomyces*, *Aspergillus*, *Penicillium*, *Rhodotorula*, *Trametes*, *Pleospora*, *Sclerotinia*, *Bullera*, and *Galactomyces*, among others. Archaea include important species such as the methane-producing (methanogenic) *Methanobrevibacter smithii.* Major differences in the distribution of bacterial taxa are evident as one moves in an aborad direction along the gut with lactobacilli, enterococci, oral streptococci and other gram-positive aerobic or facultative anaerobes reflecting the bacterial flora of the oropharynx dominating in the upper gut; for example, coliforms rarely exceed 10^3 colony forming units (cfu's)/mL of jejunal juice. The microbiology of the terminal ileum represents a transition zone between the jejunum, containing predominantly aerobic species, and the dense population of anaerobes found in the colon. On crossing into the colon, the concentration and variety of enteric flora changes dramatically with obligate anaerobes such as bacteroides, porphyromonas, bifidobacteria, lactobacilli and clostridia dominating and outnumbering aerobic bacteria by a factor of 100–1000:1.

The Gut Microbiota in Short Bowel and Intestinal Failure

There have been relatively few studies on the intestinal microbiota in SBS and/or IF. Bacterial diversity and acetate levels are markedly decreased and Proteobacteria (including pro-inflammatory Enterobacteriaceae) emerge as the predominant phylum, especially among those with type III SBS and with intestinal failure associated liver disease (IFALD) and central line-associated bloodstream infections (CLABSI) [6–9]. Lactobacilli may be increased [10]. In various studies, changes in the microbiota have also been linked to diarrhea, the need for parenteral nutrition, D-lactic acidosis, liver disease and growth failure [8–10]. The interpretation of all of these findings must remain guarded given the small sizes of the study populations and the multiple factors that may impact on the microbiota in these patients rendering it difficult to assign causality to any association between changes in the microbiota and a clinical finding.

Definition of SIBO

In its original usage the term small intestinal bacterial overgrowth (SIBO—sometimes referred to as "contamination") was introduced to describe a situation where an increase in the numbers and/or change in the type of bacteria in the small intestine resulted in clinical consequences and, specifically, those associated with malabsorption and maldigestion [11]. However, this rather narrow context has been radically expanded in recent years to encompass a broad spectrum of intestinal and extra-intestinal disorders often on the basis of imprecise methodology and/or limited data. Such studies have generated considerable controversy and thrown the definition of SIBO into sharp relief. Fortunately, a discussion of SIBO in the context of intestinal failure is largely concerned with SIBO as a contributor or exacerbator of maldigestion/malabsorption where the clinical presentation is related to effects of the contaminating organism on host morphology or function which, in turn, result in the clinical consequences typically associated with SIBO, such as steatorrhea, diarrhea, protein losing-enteropathy and/or specific deficiency states.

In this context, SIBO can be defined as "**clinical and/or laboratory evidence of maldigestion/malabsorption related to qualitative and/or quantitative alterations in the small intestinal microbiota**" [11]. Here the emphasis is on the clinical context and SIBO is incriminated, firstly, by documenting its presence, and, secondly, by demonstrating a clinical response to its eradication.

In IF, especial caution should be exercised in the diagnosis of SIBO and its treatment by antibiotics given that the use of antibiotics must be balanced against the benefits to the individual patient of energy salvage due to colonic bacterial metabolism of unabsorbed carbohydrate to short-chain fatty acids [12].

Pathogenesis of SIBO

An appreciation of the factors that protect against the development of SIBO in health helps to predict the likelihood of its occurrence in disease (Table 1). Of these, gastric acid and intestinal motor activity seem to be most important. In the stomach, acid kills and suppresses the growth of most organisms that enter from the oropharynx. In the small bowel, the cleansing action of aborad propulsive forces and, especially, phase III of the interdigestive migrating motor complex (MMC), limits the ability of bacteria to colonize the small intestine [13]. Other protective factors include the integrity of the intestinal mucosa, including its protective mucus layer and intrinsic anti-bacterial mechanisms, such as defensins and immunoglobulins; the enzymatic activities and bacteriostatic properties of intestinal, pancreatic and biliary secretions; the protective effects of the commensal flora; and the mechanical and physiological properties of the ileocecal valve [14]. One can readily appreciate that many of these protective factors may be missing or impaired in the individual with short bowel syndrome or intestinal failure. Let us now examine the contribution of these various factors to SIBO in the individual with intestinal failure (IF).

Dysmotility

Virtually every condition that has been linked to small intestinal dysmotility has been associated with SIBO with diabetic autonomic neuropathy and scleroderma being prominent examples of dysmotility-related SIBO [15–17]. In diabetes, SIBO is especially common among those with long standing, type I diabetes who exhibit other target organ pathologies, such as nephropathy, retinopathy and, most notably, autonomic neuropathy [15, 16]. Intestinal pseudo-obstruction, whether based on myogenic of neurogenic intestinal dysmotility, though an uncommon cause of SIBO, in general, looms large in any IF population [18]. Dysmotility may also be relevant to the pathogenesis of another rare cause of SIBO, jejunal diverticulosis. Morphological studies suggest that disorders of intestinal motility such as progressive systemic sclerosis, visceral myopathies and neuropathies play an important role in the formation of small bowel diverticula [19]. Disruption of the MMC appears to be an important factor leading to the development of SIBO in patients with radiation enteropathy; a not infrequent cause of IF [20].

Table 1 Factors involved in the pathogenesis of SIBO

• Dysmotility
– Intestinal pseudo-obstruction
– Scleroderma and related disorders
– Autonomic neuropathy
– Jejunal diverticulosis
– Radiation enteropathy
• Altered anatomy
– Blind loops
– Strictures
– Fistulae
– Entero-colonic anastomoses
– Loss of the ileo-cecal valve
• Hypochlorhydria
– Vagotomy
– Gastric resection
– Acid suppressive medications
• Immune deficiency
– Hypogammaglobulinemia
– Combined variable immune deficiency (CVID)
• Multifactorial
– Crohn's disease
– Radiation enteropathy
– Chronic pancreatitis
– Chronic liver disease
– Celiac disease

Altered Anatomy

A variety of surgical procedures that alter gastrointestinal anatomy have been associated with SIBO. A number of pathophysiological factors may be operative in this setting, including hypochlorhydria, formation of blind loops (depending on the nature of the surgical procedure), lack of contact between chyme and bile and/or digestive enzymes and disruption of intestinal motility. Stagnation and/or recirculation of intestinal contents resulting from strictures, fistulae, enterostomies and anastomoses also predispose to SIBO; all relevant to IF, in general, as well as to two common causes of IF, Crohn's disease and radiation enteropathy. Loss of the ileocolonic junctional region, as well as direct anastomoses between the proximal small intestine and colon, will also predispose to and promote SIBO in some IF subjects. The distinction between the ileocecal valve and the ileocolonic junctional region is important. While the ileocecal valve forms a physical barrier to reflux of colonic material from the colon into the small bowel, results from both experimental animal models and human studies have failed to identify a major effect on either bacterial translocation or SIBO following resection of just the valve [14]. These findings would lend support to the hypothesis that specialized motor patterns in the distal ileum, and not the valve itself, are the critical elements in sustaining the propulsive functions of this region [21].

Hypochlorhydria

Initially described in relation to surgical procedures that reduced gastric acid secretion, hypochlorhydria has, more recently, been invoked in the development of SIBO among individuals on long-term treatment with proton-pump inhibitors (PPIs). Though some studies suggested that long-term PPI therapy was associated with SIBO [22–24], others have failed to confirm this [25]. Furthermore, though their meta-

analysis revealed a pooled odds ratio of 2.82 for SIBO among PPI users versus non-users, Lo and Chan found that this association held true only for studies employing intestinal culture rather than breath tests for the diagnosis of SIBO [23]. Interestingly, Ratuapli and colleagues, who failed to identify a relationship between PPI use and SIBO, based their analysis on breath tests [25]. In IF it seems prudent to exert some caution in the use of PPIs.

Immune Deficiencies

SIBO has been described in association with hypogammaglobulinemia, both in inherited and acquired forms, as well as with disorders of cellular immunity, such as human immunodeficiency virus infection.

Impact of Co-morbidities

From the above it is clear that multiple factors will contribute to the pathogenesis of SIBO in IF. Diseases that may occur in the IF patient (such as Crohn's disease, radiation enteropathy [26] and diabetes, for example) may also predispose to SIBO. It is likely that multiple factors also contribute to the pathophysiology of SIBO associated with chronic renal failure, chronic pancreatitis and liver disease; all may occur in the IF patient. The cause of SIBO in chronic pancreatitis is multifactorial and includes the loss of pancreatic enzymes, a decrease in intestinal motility resulting from the inflammatory process, the effects of narcotics on gut motility and the presence, in some instances, of intestinal obstruction. Of these the association with chronic liver disease is, perhaps, the best documented. SIBO has also been frequently documented in association with liver disease and it is in this context that relationships between SIBO and systemic sepsis have been most extensively explored [27, 28]. In liver disease and of great relevance to IF, SIBO has been linked to systemic endotoxemia, spontaneous bacterial peritonitis and both overt hepatic encephalopathy and minimal hepatic encephalopathy [29–31]. Just as an altered intestinal microbiota has been linked to non-alcoholic fatty liver disease (NAFLD) [32], there is some evidence to link a disrupted microbiota, in IF, with, not only poor outcomes [10, 33], but also IFALD [6, 10, 34, 35].

SIBO: Consequences and Complications (Tables 2 and 3)

SIBO may influence gut function through direct and indirect mechanisms. Deconjugation of bile acids in the proximal small bowel will disrupt fat digestion and lead to the production of lithocholic acid, which is poorly absorbed and may be directly toxic to enterocytes. Carbohydrate malabsorption, due to SIBO, can contribute to diarrhea due to metabolism of malabsorbed carbohydrates by bacteria to form short-acid fatty acids that, in turn, increase the osmolarity of intestinal fluid and promote motility. Direct mucosal injury may also result from bacterial adherence or increased conversion, by enterotoxins, of the enzyme xanthine dehydrogenase to xanthine oxidase; indirectly, morphological changes may occur secondary to cobalamin deficiency. Regardless of mechanism, enterocyte injury leads to both a loss of activity of brush border disaccharidases and altered permeability, the later predisposing to the development, in the most severe cases, of a protein-losing enteropathy. The former will result in the presentation of more unabsorbed carbohydrates to intestinal bacteria for fermentation and could also contribute to lactose intolerance. Mucosal injury by bacterial toxins may also trigger an inflammatory response with the generation of inflammatory cytokines such as tumor necrosis factor α which may contribute to hepatic and systemic complications.

Bacterial digestion of luminal protein will leave the affected individual susceptible to malnutrition and will also contribute to hypoproteinemia and edema. Although some degree of hypoproteinemia is common, severe malnutrition is rare in SIBO. Bacterial metabolism of protein can also lead to the production of ammonia. In the context of an

Table 2 Consequences of SIBO

• Symptoms and signs
– Diarrhea
– Steatorrhea
– Edema
– Weight loss
– Malnutrition
– Anemia
– Encephalopathy
• Laboratory findings
– Steatorrhea
– Hypoproteinemia
– Anemia
– Vitamin B_{12} deficiency
– Elevated levels of Folic acid
– Elevated levels of Vitamin K
– Deficiency of other fat-soluble vitamins
– D-lactic acidosis
– Hyperammonemia

Table 3 Complications of SIBO

• Malnutrition
• Protein-losing enteropathy
• Mucosal injury
• Encephalopathy
– Hyperammonemia
– D-lactic acidosis
• Bacterial translocation
– Gut-derived sepsis
– CLABSI
• Liver disease

impaired mucosal barrier, encephalopathy may result. Moreover, short bowel syndrome patients, especially those with an intact colon, may suffer D-lactic academia and associated encephalopathy as a result of the production of D-lactic acid by certain Gram-positive anaerobes [36, 37].

A number of phenomena combine to make SIBO an important cause of B_{12} deficiency. These include the consumption of cobalamin by anaerobes, malabsorption of the vitamin as a result of competitive binding with cobalamin from bacterially-generated metabolites of cobalamin at the ileal receptor and, in instances of more severe overgrowth, actual mucosal damage involving the binding site. Bacterial utilization of vitamins, in SIBO, has also been invoked in the development of thiamine and nicotinamide deficiency.

Deconjugation of bile acids and consequent depletion of the bile acid pool will lead to maldigestion of fat and fat soluble vitamins. Here there is one particular paradox: bacterial production of vitamin K, combined with enhanced absorption of the vitamin, due to greater permeability, may serve not only to sustain but even increase vitamin K levels to a degree that warfarin dose may need to be adjusted to maintain therapeutic anticoagulation [38]. Bacterial synthesis of folic acid may result in the rather unusual combination of high folate and low B_{12} levels in the circulation.

Bacterial Translocation and Sepsis

The possible contribution of SIBO to bacterial translocation and sepsis is an important issue in intestinal failure, a disorder where sepsis is an important cause of morbidity and mortality. Bacterial translocation is defined as the passage of viable bacteria or bacterial products, such as lipopolysaccharide, from the gastrointestinal tract to extraintestinal sites, such as the mesenteric lymph node complex, liver, spleen, kidney, and bloodstream [39–41]. Experimental animal models have shown that bacterial translocation may be promoted by mucosal inflammation, intestinal obstruction, ischemia and hypo-perfusion injury, acute pancreatitis, liver disease, prematurity, burns and trauma. SIBO, increased intestinal permeability, and impaired host immune defense, are considered to be the primary mechanisms which promote bacterial translocation. Indeed, this model of an altered luminal microbiota, impaired gut barrier function ("the leaky gut") and bacterial translocation has been invoked to explain a host of hepatic and systemic disorders. However, it must be emphasized that while animal studies support this concept, it has been poorly documented in man [42, 43].

The term gut-derived sepsis is used to describe a state of systemic inflammation and organ dysfunction associated with severe catabolic stress; it has been hypothesized that this syndrome is initiated and perpetuated by the intestinal microbiota. Although the gut plays a role in the development of sepsis syndrome and multiple organ failure, recent studies have shown that gut-derived-bacteremia, even when due to potent nosocomial pathogens, is an event of low proinflammatory potential and, is of itself an insufficient stimulus for the systemic inflammatory response and organ failure state typically seen after severe and prolonged catabolic stress. It seems much more likely that alterations in the gut's immune function and interactions between the gut-associated immune tissue and the rest of the body form the basis for this syndrome.

Central venous infection is the most frequent complication during parenteral nutrition and in IF. Although catheter sepsis is often associated with enteric organisms, Reimund et al. found that, in their 42 adult patients, *Staphylococcus epidermidis* was detected in 51% [44]. Moreover, the presence of enteric organisms in the bloodstream does not necessarily mean bacterial translocation caused by bacterial overgrowth, because of diarrhea episodes, patients often have colonization of skin and their immediate environment with enteric flora.

Diagnosis of SIBO

Although aspiration and direct culture of jejunal contents are regarded by many as the gold standards for the diagnosis of SIBO, these methods have several limitations, such as the potential for contamination by oropharyngeal bacteria during intubation, and the fact that bacterial overgrowth may be patchy and thus missed by a single aspiration. Overall the reproducibility of jejunal aspiration and culture have been reported to be as low as 38% in comparison to 92% for breath tests. In addition, these methods may be regarded as cumbersome and invasive for patients who may require repeated testing.

For this reason, a variety of noninvasive diagnostic tests have been devised for the diagnosis of SIBO based on the excretion, in exhaled breath, of hydrogen generated by the metabolism of carbohydrate by luminal bacteria. In these breath tests, the diagnosis of SIBO is established when the exhaled breath H_2 increases by more than 20 parts per million (ppm) over baseline on two consecutive samplings within 90 min of substrate ingestion [45] (Fig. 1). If methane is measured, a rise of 10 ppm is considered diagnostic (Fig. 2). These criteria assume that the small intestine is anatomically intact and that small intestinal transit is normal. It has also been suggested that a fasting breath hydrogen level that exceeds 20 ppm is indicative of SIBO; in short bowel patients where the small bowel remnant is in continuity with a functioning colon, breath test interpretation may be difficult as the baseline breath H_2 level may be very high.

Even though double peaks (SIBO and colonic peaks) have previously been defined as representing an abnormal lactu-

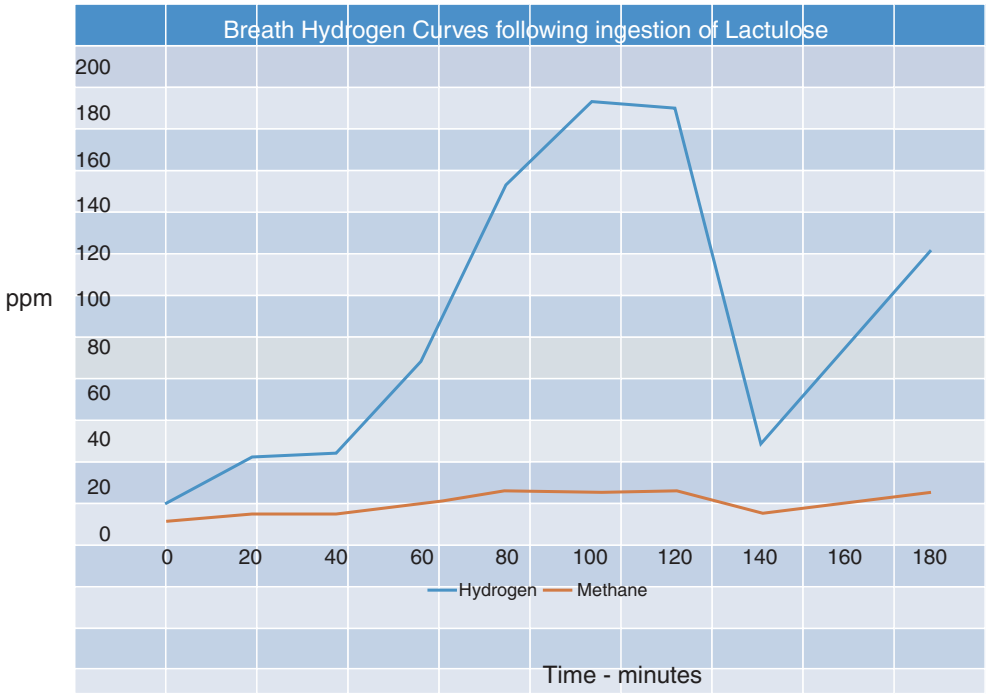

Fig. 1 Breath Hydrogen and Methane levels for 180 min following ingestion of lactulose (time 0). Note: early (>20 ppm) rise in breath hydrogen between 20 and 40 min illustrating an "early" peak and very suggestive of SIBO

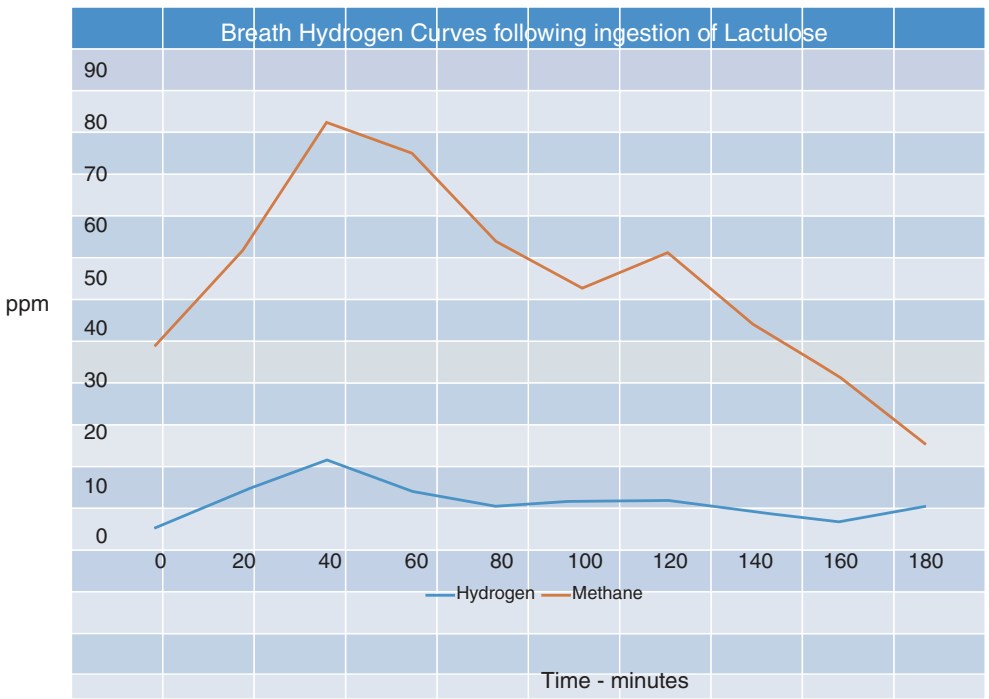

Fig. 2 Breath Hydrogen and Methane levels for 180 min following ingestion of lactulose (time 0). Note: "double peak" in methane excretion, the first at 40 min (indicative of SIBO) and the second at 120 min (consistent with arrival of the substrate in the colon)

lose breath test (Fig. 2), they may also result from rapid orocecal transit resulting in the premature delivery of fermentable substrate to cecal bacteria. Indeed, the reliability of these diagnostic techniques has been criticized in patients with intestinal failure, and especially those with short bowel syndrome, because of the rapid intestinal transit that accompanies these disorders. Interpretation of breath tests may also be complicated, in patients with short bowel syndrome, by carbohydrate malabsorption and a resultant increase in colonic fermentation. However, in support of a role for bacterial overgrowth in symptom pathogenesis, studies have reported a parallel improvement in gastrointestinal symptoms and breath tests after antibiotic therapy among intestinal failure patients with positive breath tests [46, 47]. It must also be borne in mind that false-negative or "flat" responses to lactulose administration may be found among those whose

bacterial flora has been altered by antibiotic therapy or diarrhea or in whom motility disorders coexist, situations commonly present in patients with intestinal failure. Finally, between 15% and 27% of the population do not generate hydrogen, following the ingestion of this substrate, but, rather produce methane (as illustrated in Fig. 2); the measurement of hydrogen alone will clearly underestimate the prevalence of SIBO among such individuals.

The diagnosis of SIBO remains problematic [48]. Jejunal aspiration is cumbersome and open to confounders while breath tests are fraught with problems of interpretation. We await the application of nucleic acid amplification techniques and metabolomics to SIBO; approaches that have revolutionized the study of the microbiota elsewhere.

In the IF patient, SIBO should be suspected based on the symptomatology described above but breath tests interpreted with caution. A therapeutic trial may also be considered but mindful of the negative aspects of indiscriminate antibiotic therapy.

Therapy of SIBO (Table 4)

SIBO should be suspected in patients with intestinal failure whenever they are not progressing in a normal manner, especially if patients require additional calories, lose weight, or regress in their growth. Control of SIBO can be expected to improve absorption when significant enteritis has occurred due to severe bacterial proliferation.

Surgery

Clearly, the primary goal should be the treatment or correction of any underlying disease on defect when possible. Unfortunately, several of the clinical conditions associated with SIBO, bacterial translocation and intestinal failure are not readily reversible. Nontransplantation surgical procedures and medical treatment have the same emphasis, which is to reduce the requirement for total parenteral nutrition and to reach a normal weight, height and lifestyle. Nontransplantation surgical approaches (see elsewhere in this volume) can improve intestinal function and increase nutrient and fluid absorption by either slowing intestinal transit or increasing intestinal absorption.

Table 4 Management of SIBO

• Correction of predisposing abnormalities
• Correction of nutritional deficiencies
• Prokinetics
• Antibiotics
– Rifaximin
– Norfloxacin
– Amoxicillin-clavulanic acid
– Co-trimoxazole
– Tetracycline
– Metronidazole
– Ciprofloxacin
Single course—7–14 days
Intermittent therapy
Rotating antibiotics (4–6 weeks on, 2 weeks off)
Continual

Nutrition

The nutritional support of the IF patient is dealt with extensively in this volume; if SIBO is present attention should be paid to the correction of deficiencies, such as hypoproteinemia and B_{12} deficiency resultant from, or exacerbated by, SIBO.

Prokinetics

Prokinetics that accelerate intestinal transit and improve postprandial small-intestinal motility may be attractive adjuvants to the treatment of SIBO and intestinal failure. In spite of this, there are few studies about the effect of prokinetics in this group of patients and the majority have been performed in gastrointestinal motility disorders *per se.* Options are limited; cisapride, perhaps the most extensively studie drug in this context, was withdrawn due to cardiovascular effects. Although new prokinetic drugs, without cardiovascular adverse effects, such as prucalopride [49], are now available in some countries, controlled studies are needed to establish the efficacy of these drugs in the treatment of SIBO.

Antibiotics

In most instances the therapy of SIBO rests exclusively on the use of antibiotics. The ESPEN guideline recommends "*that short bowel syndrome (SBS) patients who have motility disorders, including those with dilated segments of residual small bowel, blind loop etc., and who suffer from symptoms of bacterial overgrowth, benefit from occasional antibiotic treatment. (Grade of evidence: very low). We do not recommend the routine use of antibiotics in SBS patients with a preserved colon, given the benefit of the energy salvage due to colonic bacterial fermentation of malabsorbed carbohydrate to short-chain fatty acids, in spite of a potential reduction in the production of gases and consequent symptoms related to this fermentation. (Grade of evidence: very low)*" [12]. They concluded that very little is known about the pres-

ence of small bowel bacterial overgrowth in patients with SBS; a situation confounded by the aforementioned lack of consensus regarding its definition and the lack of consensus on indications for treatment.

The objective of antibiotics in SIBO should not be to eradicate the bacterial flora but to alter it in a way that leads to symptomatic improvement. Although, ideally, the choice of antimicrobial agents should reflect in vitro susceptibility testing, this is usually impractical as many different bacterial species with different antibiotic sensitivities typically coexist. Antibiotic treatment remains, therefore, primarily empirical. Effective antibiotic therapy must cover both aerobic and anaerobic enteric bacteria and different schedules have been suggested. Although in general, a short single (7- to 10-day) course of antibiotic may improve symptoms for up to several months in between 46% and 90% of patients with SIBO and render breath tests negative in 20–75%, patients with SIBO and intestinal failure due to short bowel syndrome and/or gastrointestinal disease are more refractory to antibiotic therapy and may require either repeated (e.g. the first 5–10 days out of every month) or continuous courses of antibiotic therapy. For the latter, rotating antibiotic regimens are recommended to prevent the development of resistance. Decisions on management should be individualized and consider such risks of long-term antibiotic therapy as diarrhea, Clostridium difficile infection, intolerance, bacterial resistance, and cost. In the past, antibiotics such as norfloxacin, amoxicillin-clavulanic acid, and metronidazole for 7 days were a good option. More recently and given its minimal systemic absorption and favorable safety profile, rifaximin has emerged as an important option [50]. Rotating regimens are especially valuable in patients with visceral myopathy, scleroderma and jejunal diverticulosis and commonly feature 4–6 weeks on one antibiotic followed by a 2 week "holiday" off antibiotic followed by 6 weeks with another antibiotic, and so on.

Prebiotics and Synbiotics

A prebiotic is defined as a substrate that is selectively utilized by host microorganisms conferring a health benefit [51]. They are, typically, non-digestible but fermentable food ingredients that selectively stimulate the growth and activity of one species or a limited number of species of bacteria in the colon. Though the science behind prebiotics continues to develop, there is less clinical data and little in relation to SIBO and IF. One study found that the addition of the prebiotic preparation guar gum enhanced the efficacy of rifaximin [52].

Probiotics

Probiotics, a word is derived from the Greek and meaning "for life", are defined as live organisms that, when ingested in adequate amounts, exert a health benefit on the host [53].

Several experimental studies have suggested that the mechanism of probiotic activity is likely multifactorial. Competitive metabolic interactions with pathogens, production of bacteriocins, inhibition of bacterial translocation, enhancement of mucosal barrier function, and signaling with the epithelium and immune system have been reported as possible modes of action of probiotics strains [54].

There is also a paucity of data on probiotics in SIBO related to IF. In an isolated case of D-lactic acidosis in a patient with short bowel syndrome and recurrent encephalopathy, Uchida et al. showed that a probiotic associated with oral kanamycin was effective in ameliorating these episodes [55]. While some lactobacilli can generate D-lactic acid, others do not and the latter have actually been used to treat D-lactic acidosis [37].

Vanderhoof and colleagues suggested that, in their children with bacterial overgrowth associated with short bowel syndrome, *Lactobacillus plantarum* 299v either prevented or delayed the recurrence of symptoms following antibiotic treatment [56]. In a randomized, double-blind trial, Gaon and colleagues found that, in their 12 patients with bacterial overgrowth-related chronic diarrhea, both *Lactobacillus casei* and *acidophilus* strains *cerela* were effective for bacterial overgrowth-related chronic diarrhea, and suggested that probiotics should be used continuously [57]. In contrast, *Saccharomyces boulardii* did not significantly influence the evolution of chronic diarrhea and breath test results [58]. Stotzer et al. showed that, in their patients with long-standing bacterial overgrowth, *Lactobacillus fermentum* did not benefit symptoms or normalize breath tests [59]. Data remains, therefore, inconclusive.

Enteric Infections and Intestinal Failure

Human Immunodeficiency Virus (HIV) Enteropathy

In the previous edition of this textbook an entire chapter was devoted to HIV infection; it is a testament to the dramatic progress in treatment of this once fatal condition that HIV enteropathy merits a mere footnote in this edition. Indeed, as the incidence of opportunistic enteric infections has decreased due to more effective anti-retroviral therapy (ART), the incidence of noninfectious diarrhea (such as that

occurring as an adverse consequence of therapy and HIV enteropathy) has increased [60, 61] While diarrhea remains common among those infected with HIV, intestinal failure should now be an extreme rarity among those who have access to effective anti-viral therapy [60, 61]. Once opportunistic infections have been excluded, therapy becomes primarily symptomatic and supportive with careful attention to choosing ART agents with minimal diarrheagenic effects. While a number of medications are used on an off-label basis, crofelemer is the only therapy currently approved in the US for symptomatic relief of non-infectious diarrhea in patients with HIV on ART.

Infections in Common Variable Immunodeficiency

In a manner similar to HIV, a variety of opportunistic enteric infections, such as giardiasis [62], have been reported among those who suffer from common variable immunodeficiency (CVID). CVID is diagnosed on the basis of levels of IgG and IgA more than two standard deviations below normal in the absence of any other cause for hypogammaglobulinemia. Though rarely meriting the diagnosis of intestinal failure, chronic diarrhea in CVID can result from chronic norovirus infection. Symptoms can last for years but clinical and histological remission can result from effective clearance of the virus with ribavirin [63]. Chronic norovirus infection has been reported to cause IF, however, in children who have undergone stem cell transplants [64].

Other Infections

The literature contains individual case reports of infections leading to IF—visceral leishmaniasis in a young immunocompetent patient [65], fatal gastrointestinal histoplasmosis in a liver transplant recipient [66], disseminated aspergillosis causing IF after colectomy [67] and *Clostridium difficile* causing multiple organ failure and enteritis [68]. There are also two reports of patients possessing the NOD2 mutation developing tuberculous lymphadenitis and intestinal failure requiring home parenteral nutrition [69].

References

1. Cho I, Blaser MJ. The human microbiome: at the interface of health and disease. Nat Rev Genet. 2012;13:260–70.
2. Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. Nat Rev Gastroenterol Hepatol. 2018;16:35.
3. Ventura M, O'Toole PW, de Vos WM, van Sinderen D. Selected aspects of the human gut microbiota. Cell Mol Life Sci. 2018;75:81–2.
4. Blaser MJ. The microbiome revolution. J Clin Invest. 2014;124:4162–5.
5. Quigley EM. Gut microbiome as a clinical tool in gastrointestinal disease management: are we there yet? Nat Rev Gastroenterol Hepatol. 2017;14:315–20.
6. Wang P, Wang Y, Lu L, Yan W, Tao Y, Zhou K, Jia J, Cai W. Alterations in intestinal microbiota relate to intestinal failure-associated liver disease and central line infections. J Pediatr Surg. 2017;52:1318–26.
7. Huang Y, Guo F, Li Y, Wang J, Li J. Fecal microbiota signatures of adult patients with different types of short bowel syndrome. J Gastroenterol Hepatol. 2017;32:1949–57.
8. Piper HG, Fan D, Coughlin LA, Ho EX, McDaniel MM, Channabasappa N, Kim J, Kim M, Zhan X, Xie Y, Koh AY. Severe gut microbiota dysbiosis is associated with poor growth in patients with short bowel syndrome. JPEN J Parenter Enteral Nutr. 2017;41:1202–12.
9. Davidovics ZH, Carter BA, Luna RA, Hollister EB, Shulman RJ, Versalovic J. The fecal microbiome in pediatric patients with short bowel syndrome. JPEN J Parenter Enteral Nutr. 2016;40:1106–13.
10. Neelis E, de Koning B, Rings E, Wijnen R, Nichols B, Hulst J, Gerasimidis K. The gut microbiome in patients with intestinal failure: current evidence and implications for clinical practice. JPEN J Parenter Enteral Nutr. 2018;43:194.
11. Quigley EMM. Bacterial overgrowth. In: Camilleri M, Fitz JG, Kalloo AN, Podolsky DK, Shanahan F, Wang TC, editors. Yamada's textbook of gastroenterology. 6th ed. Chichester: Wiley; 2016. p. 1294–304.
12. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, Joly F, Kelly D, Lal S, Staun M, Szczepanek K, Van Gossum A, Wanten G, Schneider SM, Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35:247–307.
13. Vantrappen G, Janssens J, Hellemans J, Ghoos Y. The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. J Clin Invest. 1977;59:1158–66.
14. Phillips SF, Quigley EM, Kumar D, Kamath PS. Motility of the ileocolonic junction. Gut. 1988;29:390–406.
15. Azpiroz F, Malagelada C. Diabetic neuropathy in the gut: pathogenesis and diagnosis. Diabetologia. 2016;59:404–8.
16. Gotfried J, Priest S, Schey R. Diabetes and the small intestine. Curr Treat Opt Gastroenterol. 2017;15:490–507.
17. Sakkas LI, Simopoulou T, Daoussis D, Liossis SN, Potamianos S. Intestinal involvement in systemic sclerosis: a clinical review. Dig Dis Sci. 2018;63:834–44.
18. Di Nardo G, Di Lorenzo C, Lauro A, Stanghellini V, Thapar N, Karunaratne TB, Volta U, De Giorgio R. Chronic intestinal pseudo-obstruction in children and adults: diagnosis and therapeutic options. Neurogastroenterol Motil. 2017;29(1):12945.
19. Krishnamurthy S, Kelly MM, Rohrmann CA, Schuffler MD. Jejunal diverticulosis: a heterogeneous disorder caused by a variety of abnormalities of smooth muscle or myenteric plexus. Gastroenterology. 1983;85:538–47.
20. Husebye E, Skar V, Hoverstad T, Iversen T, et al. Anormal intestinal motor patterns explain Enteric colonization with gram-negative bacilli in late radiation entrophaty. Gastroenterology. 1995;109:1078–89.
21. Quigley EMM, Borody TJ, Phillips SF, Wienbeck M, Tucker RL, Haddad A. Motility of the terminal ileum and ileocaecal sphincter in healthy man. Gastroenterology. 1984;87:857–66.
22. Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clin Gastroenterol Hepatol. 2010;8:504–8.

23. Lo WK, Chan WW. Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis. Clin Gastroenterol Hepatol. 2013;11:483–90.
24. Su T, Lai S, Lee A, He X, Chen S. Meta-analysis: proton pump inhibitors moderately increase the risk of small intestinal bacterial overgrowth. J Gastroenterol. 2018;53:27–36.
25. Ratuapli SK, Ellington TG, O'Neill MT, Umar SB, et al. Proton pump inhibitor therapy use does not predispose to small intestinal bacterial overgrowth. Am J Gastroenterol. 2012;107:730–5.
26. Harb AH, Abou Fadel C, Sharara AI. Radiation enteritis. Curr Gastroenterol Rep. 2014;16:383.
27. Quigley EM, Stanton C, Murphy EF. The gut microbiota and the liver. Pathophysiological and clinical implications. J Hepatol. 2013;58:1020–7.
28. Almeida J, Galhenage S, Yu J, Kurtovic J, et al. Gut flora and bacterial translocation in chronic liver disease. World J Gastroenterol. 2006;12:1493–502.
29. Bauer TM, Schwacha H, Steinbrückner B, Brinkmann FE, et al. Small intestinal bacterial overgrowth in human cirrhosis is associated with systemic endotoxemia. Am J Gastroenterol. 2002;97:2364–70.
30. Bauer T, Steinbrückner B, Brinkmann F, Ditzen AK, et al. Small intestinal bacterial overgrowth in patients with cirrhosis: prevalence and relation with spontaneous bacterial peritonitis. Am J Gastroenterol. 2001;96:2962–7.
31. Gupta A, Dhiman RK, Kumari S, Rana S, et al. Role of small intestinal bacterial overgrowth and delayed gastrointestinal transit time in cirrhotic patients with minimal hepatic encephalopathy. J Hepatol. 2010;53:849–55.
32. Quigley EM, Abu-Shanab A, Murphy EF, Stanton C, Monsour HP Jr. The metabolic role of the microbiome: implications for NAFLD and the metabolic syndrome. Semin Liver Dis. 2016;36:312–6.
33. Engstrand Lilja H, Wefer H, Nyström N, Finkel Y, Engstrand L. Intestinal dysbiosis in children with short bowel syndrome is associated with impaired outcome. Microbiome. 2015;3:18.
34. Lee WS, Sokol RJ. Intestinal microbiota, lipids, and the pathogenesis of intestinal failure-associated liver disease. J Pediatr. 2015;167:519–26.
35. Korpela K, Mutanen A, Salonen A, Savilahti E, de Vos WM, Pakarinen MP. Intestinal microbiota signatures associated with histological liver steatosis in pediatric-onset intestinal failure. JPEN J Parenter Enteral Nutr. 2017;41:238–48.
36. Bianchetti DGAM, Amelio GS, Lava SAG, Bianchetti MG, Simonetti GD, Agostoni C, Fossali EF, Milani GP. D-lactic acidosis in humans: systematic literature review. Pediatr Nephrol. 2018;33:673–81.
37. Yilmaz B, Schibli S, Macpherson AJ, Sokollik C. D-lactic acidosis: successful suppression of D-lactate-producing *Lactobacillus* by probiotics. Pediatrics. 2018;142:e20180337.
38. Giuliano V, Bassotti G, Mourvaki E, Castellani D, et al. Small intestinal bacterial overgrowth and warfarin dose requirement variability. Thromb Res. 2010;126:12–7.
39. Nagpal R, Yadav H. Bacterial translocation from the gut to the distant organs: an overview. Ann Nutr Metab. 2017;71(Suppl 1):11–6.
40. Kell DB, Pretorius E. On the translocation of bacteria and their lipopolysaccharides between blood and peripheral locations in chronic, inflammatory diseases: the central roles of LPS and LPS-induced cell death. Integr Biol (Camb). 2015;7:1339–77.
41. Giannelli V, Di Gregorio V, Iebba V, Giusto M, Schippa S, Merli M, Thalheimer U. Microbiota and the gut-liver axis: bacterial translocation, inflammation and infection in cirrhosis. World J Gastroenterol. 2014;20:16795–810.
42. Quigley E. Gut permeability in irritable bowel syndrome: more leaks add to slightly inflamed bowel syndrome conspiracy theory. Gastroenterology. 2009;137:728–30.
43. Quigley EM. Leaky gut - concept or clinical entity? Curr Opin Gastroenterol. 2016;32:74–9.
44. Reimund JM, Arondel Y, Finck G, Zimmermann F, Duclos B, Baumann R. Catheter-related infection in patients on home parenteral nutrition: results of a prospective survey. Clin Nutr. 2002;21:33–8.
45. Rezaie A, Buresi M, Lembo A, Lin H, McCallum R, Rao S, Schmulson M, Valdovinos M, Zakko S, Pimentel M. Hydrogen and methane-based breath testing in gastrointestinal disorders: the North American Consensus. Am J Gastroenterol. 2017;112:775–84.
46. Castiglione F, Del Vecchio Blanco G, Rispo A, et al. Orocecal transit time and bacterial overgrowth in patients with Crohn's disease. J Clin Gastroenterol. 2000;31:63–6.
47. Justino SR, Goncalves Dias NC, Maculevicius J, et al. Fasting breath hydrogen concentration in short bowel syndrome patients with colon incontinuity before and after antibiotic therapy. Nutrition. 2004;20:187–91.
48. Di Stefano M, Quigley EMM. The diagnosis of small intestinal bacterial overgrowth: two steps forward, one step backwards? Neurogastroenterol Motil. 2018;30:e13494.
49. Omer A, Quigley EMM. An update on prucalopride in the treatment of chronic constipation. Ther Adv Gastroenterol. 2017;10:877–87.
50. Ponziani FR, Gerardi V, Gasbarrini A. Diagnosis and treatment of small intestinal bacterial overgrowth. Exp Rev Gastroenterol Hepatol. 2016;10:215–27.
51. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, Verbeke K, Reid G. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol. 2017;14:491–502.
52. Lauritano EC, Gabrielli M, Scarpellini E, Lupascu A, et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. Am J Gastroenterol. 2008;103:2031–5.
53. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC, Sanders ME. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11:506–14.
54. Quigley EMM. Prebiotics and probiotics in digestive health. Clin Gastroenterol Hepatol. 2019;17:333.
55. Uchida H, Yamamoto H, Kisadi Y, et al. D-lactic acidosis in short bowel syndrome managed with antibiotics and probiotics. J Pediatr Surg. 2004;39:634–6.
56. Vanderhoof JA, Young RJ. Probiotic therapy in children with short bowel syndrome and bacterial overgrowth. Gastroenterology. 1997;112:A916.
57. Gaon D, Garmendia C, Murrielo NO. Effect of Lactobacillus strains (L. casei and L. acidophilus strains cereal) on bacterial overgrowth-related chronic diarrhea. Medicina (B Aires). 2002;62:159–63.
58. Attar A, Flourié B, Rambaud JC, Franchisseur C, Ruszniewski P, Bouhnik Y. Antibiotic efficacy in small intestinal bacterial overgrowth-related chronic diarrhea: a crossover, randomized trial. Gastroenterology. 1999;117:794–7.
59. Stotzer PO, Blomberg L, Conway PL, et al. Probiotic treatment of small intestinal bacterial overgrowth by lactobacillus fermetus KLD. Scand J Infect Dis. 1996;28:615–9.
60. Clay PG, Crutchley RD. Noninfectious diarrhea in HIV seropositive individuals: a review of prevalence rates, etiology, and management in the era of combination antiretroviral therapy. Infect Dis Ther. 2014;3:103–22.
61. Dikman AE, Schonfeld E, Srisarajivakul NC, Poles MA. Human immunodeficiency virus-associated diarrhea: still an issue in the era of antiretroviral therapy. Dig Dis Sci. 2015;60:2236–45.

62. Halliez MC, Buret AG. Extra-intestinal and long term consequences of Giardia duodenalis infections. World J Gastroenterol. 2013;19:8974–85.
63. Woodward J, Gkrania-Klotsas E, Kumararatne D. Chronic norovirus infection and common variable immunodeficiency. Clin Exp Immunol. 2017;188:363–70.
64. Saif MA, Bonney DK, Bigger B, Forsythe L, Williams N, Page J, Babiker ZO, Guiver M, Turner AJ, Hughes S, Wynn RF. Chronic norovirus infection in pediatric hematopoietic stem cell transplant recipients: a cause of prolonged intestinal failure requiring intensive nutritional support. Pediatr Transplant. 2011;15:505–9.
65. Hicks L, Kant P, Tay PH, Vincini V, Schuster H, Rotimi O, Maughan N, Jordan C, Moss S, Everett S, Hamlin PJ. Visceral Leishmaniasis presenting with intestinal failure: a case report and literature review. Eur J Gastroenterol Hepatol. 2009;21:117–22.
66. Agrawal N, Jones DE, Dyson JK, Hoare T, Melmore SA, Needham S, Thompson NP. Fatal gastrointestinal histoplasmosis 15 years after orthotopic liver transplantation. World J Gastroenterol. 2017;23:7807–12.
67. McElvanna K, Loughrey MB, Gillespie S, Gardiner KR. Disseminated aspergillosis causing intestinal failure following colectomy for perforated colitis. Frontl Gastroenterol. 2016;7:110–3.
68. Hariri S, Gouin P, Tuech JJ, Veber B, Dureuil B. Clostridium difficile infection causing multiple organ failure and small-bowel enteritis. Clin Res Hepatol Gastroenterol. 2011;35:142–4.
69. Schäffler H, Teufel M, Fleischer S, Hsieh CJ, Frick JS, Lamprecht G. Two patients with intestinal failure requiring home parenteral nutrition, a NOD2 mutation and tuberculous lymphadenitis. BMC Gastroenterol. 2014;14:43.

Extensive Mucosal Disease: Coeliac Disease and Eosinophilic Enteritis

Suzanne C. Donnelly

Key Points

1. Coeliac disease, the most common disease affecting the small intestine in the Western world, can be found in most countries
2. Coeliac disease is treated with a life-long gluten-free diet.
3. More severe metabolic complications of coeliac disease occur in refractory coeliac disease, ulcerative jejunitis and enteropathy-associated T-cell lymphoma
4. The development of treatment to allow gluten transgressions in coeliac disease is slow to come to market
5. Eosinophilic enteritis is a rare condition affecting the gastrointestinal tract
6. Treatment for eosinophilic enteritis currently involves oral corticosteroids

Introduction

The small intestine has a role in both secretion and absorption. Small intestinal disorders can be predominantly malabsorptive or secretory in nature but often the two co-exist with most small intestinal mucosal disease having malabsorption and excess secretions. Diarrhoea due to small intestinal disease is often non-inflammatory and of high output. The larger the surface area of small intestinal mucosa affected, the higher the outputs. Improvement of diarrhoea after fasting suggests an osmotic component to the diarrhoea and both may co-exist. Malabsorption symptoms include steatorrhoea, malodorous flatus, bloating and postprandial diarrhoea.

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Coeliac Disease

The most common cause in the Western world of small intestinal disease is coeliac disease which is also known as coeliac sprue or gluten-sensitive enteropathy. It is a small intestinal disorder caused by an inappropriate immune response to dietary gluten. Ingestion of wheat, rye or barley proteins in susceptible individuals triggers an inflammatory response particularly in the proximal small intestinal mucosa causing damage to the villous architecture. In a small minority of patients this also happens with oat proteins. The disease manifests itself as a generalised malabsorption which typically presents as weight loss, diarrhoea or disorders associated with specific nutrient deficiencies such as anaemia or osteoporosis. However, since the advent of highly sensitive serological screening tests, less well-defined forms of the disease are being increasingly recognised and the terminology has changed. Treatment, at present, is the life long, complete avoidance of gluten from the diet.

Epidemiology

Early estimations of the prevalence of coeliac disease indicated that it was an uncommon disorder. A study in 1950 estimated the incidence of coeliac disease to be 1:8000 in England and Wales and 1:4000 in Scotland [1]. Since then the diagnostic process has vastly improved with the advent of endoscopic small bowel biopsy in the 1960s and highly specific serological screening methods, such as the anti-endomysial or the tissue transglutaminase antibodies. This made it possible to evaluate the true prevalence of coeliac disease showing an unsuspected frequency of clinically atypical forms of coeliac disease. A UK study screened over 7000 serum samples for anti-endomysial antibody and found that, in England, undetected coeliac disease affects approximately 1% of the adults aged 45–76 years [2]. A large, international, multicentre study investigated a wide population

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sample in four different European countries [3]. On average the overall prevalence of coeliac disease was 1% with large variation between countries: 2% Finland, 1.2% Italy, 0.9% Northern Ireland, 0.3% Germany. This study also confirmed that many coeliac disease cases would be missed without active serological screening. Biagi et al. [4] cautioned that the prevalence of coeliac disease can be over-estimated if tissue transglutaminase is the only diagnostic tool.

Similar rates have been reported from the US population, 1:133 [5] and from developed countries mostly populated by individuals of European origin, Australia 1:251 [6] and New Zealand 1.2% [7]. The presence of coeliac disease is long established in many South American countries that are mostly populated by individuals of European origin. Among Brazilian blood donors, the prevalence of coeliac disease ranged between 1:681 [8] and 1:214 [9], however these may be artificially low as blood donors represent the "healthiest segment" of the population. In Argentina an overall prevalence of coeliac disease was found to be 1 in 167 in 2000 adults involved in a prenuptial examination [10].

Recent epidemiological studies performed in areas of the developing world show prevalence rates overlapping European figs [11, 12]. The prevalence of coeliac disease in North African countries was found to be 0.53% in Egypt [13], 0.79% in Libya [14] and 0.6% in Tunisia [15]. In the Middle East the prevalence was found to be 0.88% in Iran [16] and 0.47% in Turkey [17] while in India the rate was 0.7% [18].

This widespread diffusion is not surprising at all given that the causal factors, HLA predisposing genotypes (DQ2 and DQ8) and consumption of gluten containing cereals show a worldwide distribution [19].

The highest prevalence of coeliac disease is to be found in the Saharawi population of Arab-Berber origin living in Algeria and is 5.6% [20]. High levels of consanguinity, high frequencies of HLA-DQ2 [21] and heavy gluten ingestion are potential explanations for this phenomenon.

In the Far East, there are a few recent reports of coeliac disease where previously coeliac disease was thought not to exist. Coeliac disease was found in 14% of symptomatic children with diarrhoea in four major cities in China [22]. In another study, 2.6% of adults tested in the Jiangsu province, with high gluten ingestion, who had either type 1 diabetes mellitus or diarrhoea-predominant irritable bowel syndrome, had positive tissue transglutaminase serology. These adults declined endoscopy but improved symptomatically as well as clinically on a gluten-free diet. The HLA-DQ2 molecule was also found in 17% of the individuals tested [23]. With rising gluten consumption in China and a high level of consanguinity, increasing the prevalence of HLA-DQ2, in some of the population it may be that coeliac disease is more common than first thought [24]. Genetic screening of the HLA status of whole Chinese population may yield some interesting results.

There is no data about the prevalence of coeliac disease in Sub-Saharan Africa. There are however reasons to believe that coeliac disease is not common in these countries. Staple cereals such as millet and rice are mostly naturally gluten-free and the HLA-related predisposing genes DQ2 and DQ8 are much less frequent in these areas than Western countries. Coeliac disease is rare in individuals of Afro-Caribbean origin [25].

Evidence suggests that the pattern of disease is changing. A multicentre study found the average age of diagnosis in children had risen from two years in 1975 to four years in 1990 [26]. This probably reflects changes in feeding practices, for example, a prolonged breastfeeding period is highlighted by a well-documented phenomenon that occurred in Sweden in the mid-1980s. At this time there was a sharp increase in the incidence of symptomatic coeliac disease in children under two years of age [27]. Retrospective analysis of this epidemic found that there had been a two-fold increase in the average daily consumption of flour in formula feed. Furthermore, at this time only 50% of infants were breast-fed. The incidence rates fell in 1995. This coincided with an increase in the proportion of infants being breast fed at 6 months and lower quantities of flour in the formula feed. A study found breastfeeding to be protective against the onset of symptomatic coeliac disease [28]. The reason for this is unclear, although other studies have also shown a protective effect of breast-feeding against autoimmune diseases. However, a prolonged period of breastfeeding is not likely to prevent the later occurrence of coeliac disease in an individual who is genetically predisposed [29].

Manifestations of Coeliac Disease

The clinical manifestations of coeliac disease vary greatly and although this was perceived as a purely paediatric disease, the diagnosis is increasingly being made in adult life. The classical syndrome of diarrhoea, abdominal distension, muscle wasting and failure to thrive is usually seen in infants between the age of 9 and 18 months of age following the induction of gluten into their diet. Generally, the earlier introduction of gluten into the diet, the sooner the onset of symptoms, and therefore prolonged breastfeeding may postpone symptoms [30]. Anaemia is a common presenting feature of paediatric coeliac disease, and the disease can go undiagnosed where this is the only presenting feature [31]. Anorexia and vomiting are also common. Dental enamel defects have also been reported [32, 33]. Milder forms of the disease are becoming more common and children now tend to present at a later age and often with only minor symptoms [30].

In adults, coeliac disease can manifest as a variety of symptoms presenting to almost any hospital department. The presenting symptoms may be varied including gastrointestinal, metabolic, neurological or psychological. The most common presenting gastrointestinal symptom is diarrhoea which can be continuous, intermittent or alternated with periods of constipation. It may be accompanied by weight loss, bloating, anorexia or abdominal pain. Isolated increase in serum aminotransferase level caused by mild, non-progressive liver inflammation is also a common presentation [34].

Approximately 50% of coeliac patients do not have clinically significant diarrhoea and present with less severe symptoms such as lassitude, weakness or weight loss. Anaemia is a frequent finding in coeliac disease and may be the presenting feature [35]. Microcytic anaemia, secondary to iron deficiency anaemia is highly prevalent and is frequently the sole manifestation of the disease; oral iron supplementation will prove useless in these cases. Macrocytic anaemia may occur as a result of folate or B_{12} deficiency. This deficiency was previously thought to be unusual in coeliac disease because B_{12} is absorbed in the terminal ileum and coeliac pathology primarily occurs proximally. Studies have reported low serum vitamin B_{12} levels in untreated patients [36]. Low calcium and vitamin D absorption may give rise to osteomalacia and bone pain, with an increasing risk of developing osteoporosis.

Oslo Classification of Coeliac Disease

The true prevalence of coeliac disease within a population is difficult to estimate as many affected individuals will not display any symptoms; the disease is therefore undetected. Experts met, in Oslo, to agree nomenclature for the different forms of coeliac in Table 1 [37].

Table 1 Oslo nomenclature of coeliac disease

Term	Description
Classical coeliac disease	presents with signs and symptoms of malabsorption: diarrhoea, steatorrhoea, weight loss/growth failure
Non-classical coeliac disease	presents without signs and symptoms of malabsorption
Subclinical coeliac disease	is below the threshold of clinical detection. They have clinical or lab signs (IDA, enamel defects, osteoporosis, incidental VA) with no symptoms
Potential coeliac disease	normal small intestinal mucosa but increased risk of CD-positive serology
Coeliac disease autoimmunity	for those who have not had a biopsy but have at least two strongly positive tTG or EMA
Genetically at risk of coeliac disease	family members with CD that have HLA DQ2 or DQ8 positivity: 2–20% risk

Pathogenesis of Coeliac Disease

The pathophysiology of coeliac disease is not fully understood.

Coeliac disease occurs in genetically susceptible individuals in possession of particular human leucocyte antigen (HLA) class II molecules with approximately 95% of patients expressing HLA-DQ2 and the remainder HLA-DQ8 [38]. The HLA-DQ2 or DQ8 molecule is responsible for antigen recognition [39].

There are two mechanisms involved in the pathogenesis of coeliac that may be interlinked. What is not clear is the link between the epithelial response and the lamina propria response. There is an adaptive T cell response predominantly in the lamina propria as well as the innate response potentially driven by IL-15 and intraepithelial lymphocyte- enterocyte interaction. It is perhaps this response that is the initiator of the pathological process with the adaptive T cell response maintaining the inflammation. Pathological changes in the mucosa of coeliac individuals start to occur one hour after ingestion of gluten [40, 41] which is too early for an activated T cell response. Tissue transglutaminase is an intracellular enzyme that requires active secretion into the lamina propria to deamidate gluten peptides. The more peptides are deamidated the greater the available antigens for presentation to T cells. It may be that the innate response initiates the inflammatory cycle that is maintained by the adaptive T cell response.

Diagnosis of Coeliac Disease

Serology

The diagnosis of coeliac disease has changed recently in the paediatric population with the advent of improved coeliac immunological markers. Serum IgA and IgG antibodies against gliadin, reticulin, endomysium (components of connective tissue), tissue transglutaminase and deamidated gliadin peptides are detectable in individuals with coeliac disease. The expertise in immunofluorescence technique for EMA is being lost due to time constraints in modern immunology laboratories. The ease of using an ELISA based test means that IgG tissue transglutaminase antibodies are measured first line in individuals. Screening for serological markers is initially used for individuals who are at increased risk of coeliac disease: patients with non-specific symptoms; those with a family history of coeliac disease or patients with an associated condition such as Type 1 diabetes mellitus.

Approximately 2–3% of coeliac patients are IgA deficient [42] which can produce false negative EMA results. For this reason, it is recommended that serum IgA levels

be measured in those individuals at a higher risk of coeliac disease, those with symptoms or with a family history. IgA deficient individuals should be screened using an IgG based test.

Histology

The coeliac lesion predominantly affects the proximal small intestine with lessening damage occurring towards the distal small intestine. The pathology spans a spectrum of severity that has been classified into five stages by Marsh [43]: the pre-infiltrative, infiltrative, hyperplastic, destructive and hypoplastic (atrophic) lesions. These were subsequently modified by Oberhuber [44] to be able to use the classification for diagnostic purposes. The classification is summarised in Table 2. The parameters assessed in the diagnosis of coeliac disease on mucosal small bowel biopsy specimens include villous or crypt architectural changes as well as lamina propria cell density and intra-epithelial lymphocyte (IEL) cell counts.

These features form a continuum with normal mucosal architecture at one end and the classical flat lesion at the other end, which may take many years to develop. Marsh 1 is an increase in IELs counted per 100 enterocytes, the first and most sensitive index of the effects of gluten on the mucosa. Infiltration of gluten-dependent lymphocytes into the lamina propria is also seen. However, it is not pathognomonic for coeliac disease as they may be raised in infections for example. Marsh 1 is often seen in dermatitis herpetiformis, in treated coeliac disease, and in family members of those affected by coeliac disease. Figure 1 shows the histological changes of Marsh 3c lesion.

However, villous atrophy is not pathognomonic for coeliac disease as it can occur in the context of other disorders such as cow's milk allergy, giardiasis, rotavirus infection and autoimmune enteropathy [45].

Type 4 is a very rare hypoplastic lesion which is characterised by a flat mucosa but normal crypt depth and normal IEL count. It is probably a historic lesion seen in severely emaciated small children and most likely signifies malnutrition parallel findings in kwashiorkor [46].

Table 2 The modified Marsh classification

	Type 0	Type 1	Type 2	Type 3a	Type 3b	Type 3c
IEL/100 enterocytes	<40	>40	>40	>40	>40	>40
Crypts	normal	normal	hypertrophic	hypertrophic	hypertrophic	hypertrophic
Villi	normal	normal	normal	mild atrophy	marked atrophy	absent

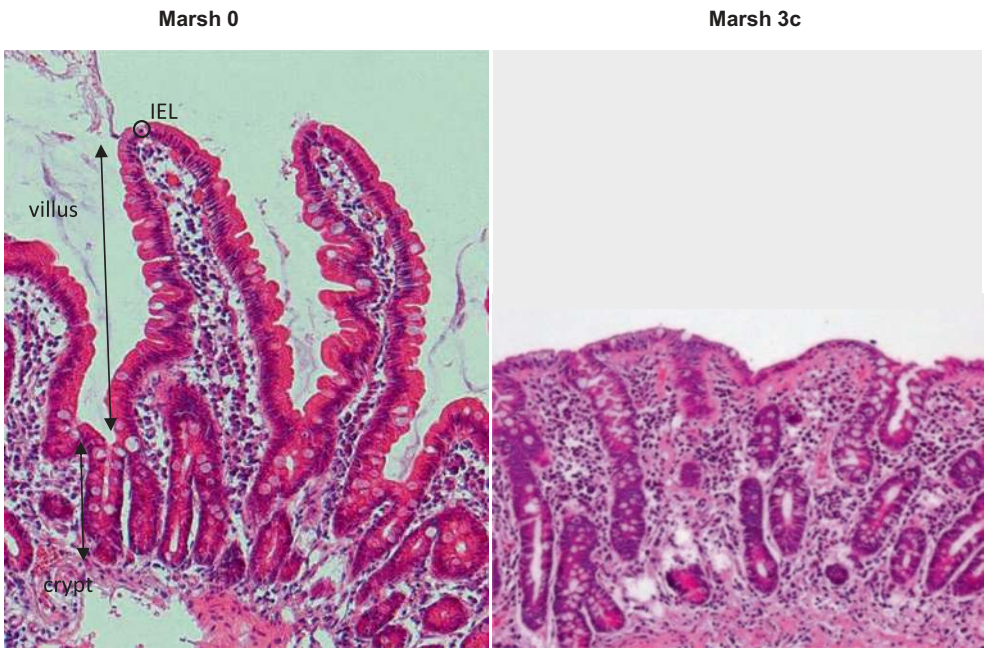

Fig. 1 Histological changes of coeliac disease. H + E stain second part of duodenum low power (×100) courtesy of Dr. Chang, St Thomas Hospital

Criteria for Diagnosis of Coeliac Disease

The required criteria for a diagnosis of coeliac disease were first proposed by the European Society of Paediatric Gastroenterology and Nutrition (ESPGHAN) in 1970 [47]. The original statement proposed that a diagnosis should be based on three criteria:

1. Structurally abnormal jejunal mucosa when taking a gluten-containing diet
2. Clear improvement of villous structure when taking a gluten-free diet
3. Deterioration of the mucosa as a result of a gluten challenge.

A patient underwent a minimum of three endoscopies for a definite diagnosis of coeliac disease. The criteria were revised in 1990 [48] after it was found that many gastroenterologists were not recommending a gluten challenge and a third biopsy. The revised criteria continue to emphasise that an initial biopsy is paramount. Histological examination showing the characteristic abnormalities, that is, lymphocytic infiltration, villous atrophy and crypt hyperplasia, on a gluten-containing diet provides the first step towards a diagnosis. In children under the age of 2 a gluten re-challenge and small intestinal biopsy is still required for the diagnosis of coeliac disease.

A definite symptomatic improvement within a few weeks of commencing a strict gluten-free diet would be consistent with a diagnosis of coeliac disease. A second biopsy may be carried out 3 to 6 months after commencement of the diet to confirm that there has been histological improvement as well as symptomatic relief [49]. If there is a symptomatic improvement but no histological recovery the gluten free diet should be verified and continued and a further biopsy taken after three months. It has been shown that complete mucosal recovery can take up to two years [50, 51]. Where there is still no histological response or symptomatic improvement it is recommended that patient compliance should be examined.

Those patients who do not respond to a strict diet may have refractory sprue, ulcerative jejunitis or intestinal lymphoma. A third endoscopy after gluten challenge is no longer a compulsory diagnostic step. It may be required however at a later date if the original diagnosis of coeliac disease is brought into question.

ESPGHAN decided in view of the improved serological testing available as well as the HLA DQ testing availability that there should be revised paediatric diagnostic criteria. This was precipitated by only 12% of paediatric gastroenterologists, who responded to a postal survey, adhered to the then current ESPGHAN guidelines [52]. The main transgression was the omission of gluten re-challenge in the under 2 age group. The algorithm proposed by the ESPGHAN working group on the diagnosis of coeliac disease is complicated but it aims to reduce the need for endoscopy which requires anaesthesia in the paediatric cohort. The new ESPGHAN diagnostic pathway in children who have classical symptoms of coeliac disease, with HLA-DQ2 or -DQ8, the genetic predisposition, and strongly positive tTG and EMA serology should not undergo endoscopic evaluation of the small intestine. Those who have the genetic predisposition and equivocal serology should proceed to a biopsy of the small intestine, as in those patients in whom the diagnosis in unclear [53].

Treatment

Gluten-Free Diet

Once a diagnosis of coeliac disease has been established, patients are advised to start a lifelong gluten-free diet. This involves the exclusion from the diet of any cereal that contains wheat gluten and prolamins from rye and barley or its derivatives, such as malt, or hybrid wheat varieties, such as spelt. The place of exclusion of oats from a gluten-free diet remains controversial. A typical gluten containing diet contains an estimated 10–20 g of gluten, derived from multiple sources and therefore a gluten free diet necessitates a calculated avoidance of many foods. A strict gluten-free diet is low in dietary fibre and folate, niacin and vitamin B_{12} [54–56]. Complying with a gluten-free diet is difficult for a number of reasons:

1. Gluten may contaminate food during harvesting, food preparation or processing [57, 58]
2. Gluten-free products are more expensive than gluten containing products and may be more difficult to source [59]
3. Dietary compliance is poor particularly in adolescents [60]
4. There is no agreed consensus on the minimal amount of gluten permitted in food: in Australia “no detectable gluten” is <5 mg/kg [61] whereas in Europe “gluten–free” is 20 mg/kg [62]
5. A wide variety of gluten sensitivities exist between patients: 50% of patients experience symptoms with an acute challenge whilst 50% do not
6. To improve palatability, many gluten-free products contain purified wheat starch which invariably contains residual gluten [57]
7. A gluten-free diet does not resolve the problems associated with the rare complication of refractory coeliac disease

Patients not adhering to a gluten-free diet are predisposed to numerous sequelae such as short stature [63], nutritional

deficiencies, early osteoporosis, secondary autoimmune disorders [64, 65], malignancies [66], infertility and poorer outcome of pregnancy [67]. However, a gluten-free diet has few side effects.

Naturally gluten–free cereals include rice, millet, maize and sorghum [68]. Quinoa, an Andean grain from Peru, has many benefits for a gluten-free diet as it is the only plant to have all essential amino acids as well as being high in minerals and vitamins. However, quinoa has similar prolamin content to wheat [69]. A recent study demonstrated that not all cultivars of quinoa are safe for coeliacs to eat as evidenced by T cell activation [70].

Products labelled as gluten-free have to adhere to strict permissible levels of gluten in Europe [62]. This standard was amended in 2008 to reduce permissible level of gluten in gluten-free foods. The change was ratified in January 2009 however manufacturers had until January 2012 to comply. Foods labelled as "gluten-free" must now contain no more than 20 mg/kg of gluten whereas foods labelled as "very low gluten" can contain between 21 to 100 mg/kg.

Oats in Gluten-Free Diet

Oats are more distantly related to wheat and are thought to be less toxic to coeliac patients. Several studies suggest that oats are safe for coeliac patients to eat [71–73] however, there are high dropout rates in both the Janatuinen studies [71, 72] in the oats group of patients. Janatuinen in his five year follow up study [72] only had 23 out of the original recruited 35 coeliac patients left, and in his study in 1995 [71] there was a 10% drop out rate in the group eating oats. Many commercially available oat products are contaminated with wheat, rye or barley [74]. Studies from Norway suggest that in a small minority of patients', non-contaminated oats are toxic [75, 76]. Avoidance of oats in the first year after diagnosis may help improve histology but an attempt should be made to reintroduce into the diet to help broaden the range of gluten-free foods.

Nutrient Replacement

Nutrient deficiencies should recede on commencement of gluten free diet but dietary supplements may be necessary. Recovery from anaemia can take between 6 and 12 months as intestinal mucosa reverts to normal [77]. After a diagnosis of CD patients should undergo a dual-emission x-ray absorptiometry scan to assess bone mineral density. Patients found to have a low BMD should be advised to strictly adhere to a gluten free diet, to avoid smoking and excessive alcohol intake, and take calcium and vitamin D supplements [78, 79].

Novel Therapies

A greater understanding of the pathogenesis of coeliac disease has allowed alternative treatments to be designed to act either as an adjuvant to a gluten-free diet, allowing for minor transgressions, or replace it all together through potential blocking of various postulated mechanisms [80]. The options include:

1. Modifying wheat in an attempt to reduce the toxic gluten epitope content
2. Degrading gluten to smaller peptides, not able to be presented to gluten-sensitive T cells, either *in vivo* or *in vitro*
3. Targeting tight junction proteins to ensure that they do not allow gluten to pass through
4. Tissue transglutaminase 2 blockade to reduce the deamidated peptides presented to gluten-sensitive T cells
5. Reducing HLA-DQ peptide presentation to gluten-sensitive T cells by amino acid substitution of gluten T cell stimulatory sequences
6. Immune system modification either by naturally occurring gluten peptide sequences or helminth infection
7. Targeting inflammatory cytokines with biological therapies, such as anti-IL15
8. Vaccination with gluten peptides in order to induce immune tolerance
9. Intra-nasal administration of T cell immunostimulatory gluten epitopes to induce tolerance

Many of the options above are a long way off from market as they are in the early stages of development and testing in animal or human subjects. However, this is a rapidly-expanding, market-driven, in part, by the wish of coeliac individuals for an alternative to a gluten-free diet. The main drawback facing researchers is that a gluten-free diet has few side effects. Therefore, for a treatment to be recommended in the treatment of coeliac disease, it has to have an acceptable low number of side effects.

Complications and Associations of Coeliac Disease

Non-responsive Coeliac Disease

Approximately 30% of individuals with coeliac disease fail to improve symptomatically with a gluten-free diet [81]. Non- responsive coeliac disease is defined as continued symptoms in patients on a gluten free diet. A study published demonstrated that 45% of non-responsive coeliac patients continued to ingest gluten, either inadvertently or deliberately. Eleven percent of non-responsive coeliac disease patients had concomitant microscopic colitis, 9% had small

bowel bacterial overgrowth (SBBO), 7% had evidence of inflammatory bowel disease as well as coeliac disease and 6% also had lactose deficiency. Some patients had more than one reason for continued symptoms. Eight out of 100 patients were found to have refractory coeliac disease (see Refractory coeliac disease below). Overall in 90% of non-responsive coeliac disease a remediable cause could be found [82].

Coeliac Disease and other Immunological Disorders

The raised prevalence of the DR3/DQ2 haplotype in patients with specific autoimmune disorders indicated a common genetic factor may confer a susceptibility to autoimmune disease. There is a well established association between coeliac disease and a number of autoimmune disorders, particularly type 1 diabetes mellitus (T1DM). 3–6% of the patients with T1DM have coexisting coeliac disease [83, 84] and share similar genetic variants [85]. Autoimmune thyroid disease (Grave's and Hashimoto's) and Sjögren's syndrome are also recognised associations. Evidence indicates that a gluten free diet may protect against the development of autoantibodies; adolescent patients not compliant with a gluten free diet have been found to have raised serum levels of antibodies against endocrine tissue [86]. A study in 1999 reported that a longer duration of exposure to gluten may give an increased risk of developing autoimmune disorders [87]. However, a subsequent study contradicted these findings [88]. This was a similar study but accounted for additional factors such as patient compliance to a gluten free diet. No correlation was found between duration of gluten exposure and onset of autoimmune disorders.

Neurological Manifestation

Neurological manifestations have been reported in coeliac patients for a number of years, but it is only recently that these neurological associations have been studied in depth. Peripheral neuropathy, myopathy, myelopathy, dementia, migrane and epilepsy are all associated with coeliac disease. A group in Sheffield, reported gluten sensitivity, based on the presence of anti-gliadin antibodies, in patients with neurological disorders of unknown cause. The majority of these patients had ataxia or peripheral neuropathy [89]. The terms gluten ataxia and gluten neuropathy have been coined to describe these disorders. Duodenal biopsy showed coeliac disease to be present in only a third of patients [90, 91]. The concept is still controversial as gluten sensitivity has also been found in hereditary ataxias, and response to a gluten-free diet in many patients is lacking [92]. Nevertheless, supporting evidence for idiopathic gluten ataxia continues to accumulate, such as the association with HLA-DQ2 and DQ8, the presence of circulating Purkinje cell antibodies and the presence of anti- tissue transglutaminase antibody in the gut and brain. Moreover, 60% of patients have evidence of cerebellar atrophy on MRI scanning and proton MR spectroscopy may also be abnormal, indicating abnormal cerebellar function [91]. The authors observed that improvement of these conditions may occur on a gluten-free diet.

The reason why some patients develop these neurological problems could revolve around a newly identified tissue transglutaminase, transglutaminase 6. Antibodies to tTG6 have been detected in a group of patients with idiopathic sporadic ataxia [93]. This work further extends the concept of gluten sensitivity beyond the bowel, coeliac disease, and the skin, dermatitis herpetiformis, to involve the nervous system.

Refractory Coeliac Disease

A rare complication of coeliac disease is refractory coeliac disease, when clinical symptoms and histological changes persist or recur after a good response to a gluten-free diet, after other causes of villous atrophy having been excluded. Intestinal mucosal recovery on commencement of a gluten free diet can take up to 2 years [50] and it may therefore be necessary to delay a diagnosis of refractory coeliac disease until at least one year on a gluten free diet.

Refractory coeliac disease can be classified according to the immunophenotype of intra-epithelial lymphocytes. Abnormal clonal lymphocytes with loss of surface markers CD8 and CD3 occur in type 2 RCD whereas in type I RCD the majority of lymphocytes have normal surface markers and T cell receptors are polyclonal [94]. Differentiation between the different types of refractory coeliac disease is important as the reported five-year survival rate varies between 40% and 58% for type 2 RCD [95–98], and 93% in type 1 RCD [97]. The main cause of death in type 2 RCD is progression to an enteropathy associated lymphoma with a 5-year survival rate of 8–20% [96, 99] as well as progressive malnutrition. Some of these patients are on parenteral nutrition to help with the management of their malnutrition and their small bowel histology do improve.

Ulcerative Jejunitis

Ulcerative jejunitis is another cause of non-responsive coeliac disease. It is a rare disorder characterised by ulceration of the jejunum and ileum. Scarring often occurs, leading to stricture formation with alternating areas of dilated small bowel. Ulcers can be of varying depth and can extend through the entire thickness of the bowel leading to perforation [100].

Like type 2 refractory coeliac disease, ulcerative jejunitis is characterised by non-lymphomatous monoclonal T cell population in the epithelium. These intraepithelial lymphocytes from Type 2 refractory coeliac disease and ulcerative jejunitis have been shown to share an identical aberrant immunophenotype to those found in enteropathy associated T cell lymphoma [101]. They are therefore considered to be part of a spectrum of neoplastic T cell disorders. As a result, the mortality is high due to obstruction, bleeding and perforation. Steroids are commonly used to treat the ulceration and a strict gluten-free diet is essential. In patients with ulcerative jejunitis, their small bowel often allows easy translocation of gut bacteria and sepsis is an early feature of this condition.

Malignancy

Early reports suggested a large increase in risk of gastrointestinal cancer in coeliac disease. With relative risk ration of 10 for oesophageal and 40 for non-Hodgkin's lymphoma, with a higher risk if non-compliant with a gluten-free diet [66]. Several other studies seemed to confirm the high relative risk of all site lymphoma in the range 30–100. Some of this data has managed to infiltrate and perpetuate itself in the literature. Most of the above data was based on cancer case-finding and inherently includes major acquisition bias. Later data suggests a more conservative doubling of risk for all cancers and, in particular, a relative risk of 6 for lymphoma [102]. Population-based studies have provided more convincing estimates of overall cancer risk and indicate only a small increase above the background population. This risk is negated if the first year after diagnosis of coeliac disease is excluded, which again accounts for a degree of acquisition bias.

The risk of both enteropathy associated T cell lymphoma and small bowel adenocarcinoma are elevated, the later many fold. A wealth of collected data exists as the incidence of cancer is one of the leading causes of concerns for coeliac patients as well as their gastroenterologists [64, 103–111].

The Italian Working Group on Coeliac Disease and Non-Hodgkin's lymphoma gathered data from 693 patients with Non-Hodgkin's lymphoma and found only 0.92% had a diagnosis of coeliac disease, with a calculated relative risk of 3 for Non-Hodgkin's lymphoma for coeliac patients, although the figure was 19 for EATL [105]. Mearin et al. [111] have reported on a prospective review in 10 European countries of 1446 Non-Hodgkin's lymphoma adults and matched controls, which indicated an odds ratio of 2.6 (1.4–4.9) for Non-Hodgkin's lymphoma. Importantly this risk was only significant for those diagnosed clinically prior to the study and not those with silent coeliac disease.

Survival from EATL is abysmal, with a five-year survival rate of 8–20% [96, 99]. As these cancers are particularly rare (0.5 to 1 in 1,000,000 annual incidence), their actual incidence in coeliac disease remains low, in the order of 1 case per 5500 patient years or less with a relative risk of 4.27 (2.36–7.74) [64]. EATL has a peak incidence in the jejunum in the sixth decade and is associated with refractory gastrointestinal symptoms, although it can present at extra-intestinal sites. It is probable that refractory coeliac disease and ulcerative jejunitis are the precursors to EATL with identical aberrant immunophenotype IELs [101]. Treatment options for these conditions are being evaluated to try to prevent progression to EATL.

Adenocarcinoma of the small intestine is a rare cancer, over represented in coeliac disease. In a British Society of Gastroenterology survey published in 2003, details of 175 cases of small bowel adenocarcinoma were collected over two years and 13% were found to be associated with coeliac disease, with two thirds presenting in diagnosed coeliac patients with a median length of diagnosis of 8 years. These patients had a 58% survival at 30 months, which equated to the absence of metastasis at presentation [107].

A recent publication suggests that patients with non-symptomatic coeliac disease have no increased risk of lymphoproliferative malignancy [112].

However, there can be some protective effects of coeliac disease. The reason behind a reduced risk of lung and breast cancers are not clear [64, 104, 113–116]. A population-based survey suggested that there are potentially adverse as well as favourable breast cancer risk profiles in coeliac disease compared to the general population [117].

Eosinophilic Enteritis

Eosinophilic enteritis is a rare primary eosinophilic gastrointestinal disorder of unknown aetiology which is characterised by the rich infiltrate of eosinophils on histological examination of the mucosa [118–120]. It is part of a group of eosinophilic disorders of gastrointestinal tract involving the oesophagus, small intestine and colon. Eosinophilic enteritis causes a wide array of symptoms such as abdominal pain, nausea, vomiting, diarrhoea, bloating or ascites. Table 3 shows the array of symptoms for each of the diseases. As these symptoms are non- specific, a high index of suspicion need to be maintained in order to diagnoses eosinophilic enteritis.

Table 3 Primary eosinophilic gastrointestinal disorders

	Eosinophillic oesophagitis	Eosinophillic enteritis	Eosinophillic colitis
Forms	Atopic Non-atopic Familial	Mucosal Muscular Subserosal	Atopic Non-atopic
Definition	Eosinophillic infiltration of the oesophageal mucosa without other intestinal segment involved	Gastrointestinal symptoms and eosinophilic infiltration of one or more intestinal segment	Children Eosinophillic infiltration of the colon Atopy or cow's milk protein allergy
Main clinical characteristics	Dysphagia Vomiting Food impaction	Abdominal pain Diarrhoea Obstruction Ascites	Diarrhoea Rectal bleeding

From ref. [121] Pineton et al

Diagnosis

Eosinophils normally reside in the lamina propria of the gut apart from the oesophagus. The eosinophil count of the lamina propria increased from duodenum to caecum and reduces from caecum to rectum. This means that the cut off values for the diagnosis rely on the accurate location of the tissue sample. In the duodenum, most studies quote a level of 20 eosinophils per high power field (×400) for the diagnosis of eosinophilic enteritis [122]. Apart from eosinophils in the lamina propria, other signs on histology in favour for eosinophilic enteritis are eosinophils in the epithelial or muscle layers, degranulation of eosinophils, villous atrophy, crypt hyperplasia or abscesses, and epithelial degenerative or regenerative changes.

The diagnosis of eosinophilic enteritis requires pathologic eosinophilic infiltration of at least one part of the intestinal wall and the exclusion of secondary eosinophilia. Eosinophils could be seen in any segment of the small intestine but were most commonly seen in the stomach and duodenum. They could also be seen in any layer within the small intestine: Klein et al. [119] described three anatomical variants based on the eosinophilic infiltration of the mucosa, intestinal muscle or. Thus, the diagnosis of eosinophilic enteritis requires the symptoms associated with a pathological eosinophilic infiltration of the small intestine with the exclusion of secondary causes of eosinophilia (in Table 4).

Table 4 Secondary causes of eosinophilia

Diagnosis	How to investigate
Hypereosinophilic syndrome Persistently elevated eosinophil count ≥1500 eosinophils/mm^3 for at least 6 months	• Clinical observation with testing for involvement of either the heart, nervous system or bone marrow • Testing for mutations involving the PDGFRA and FIP1L1 genes • T cell clonality
Gut infections	
Intestinal parasites Ascariasis, toxocariasis, trichinosis, schistosomiasis, teniasis, ankylostomiasis, trichuriasis, stronglyoidiasisenterobiasis	Patient medical history, stool parasite examination, serology (toxocariasis, trichinosis, schistosomiasis, teniasis), antiparasitic treatment
Helicobacter pylori, *Escherichia coli*, *Shigella*	Gastric biopsies, stool and blood cultures
Drugs and toxic substances Gold therapy, oral hypoglycaemiac agents, psychotropic drugs, antibiotics, NSAIDs	Patient medical history
Inflammatory bowel disease	Upper GI endoscopy and colonoscopy
Coeliac disease	Anti-tissue transglutaminase antibody and distal duodenal biopsy demonstrating villous atrophy
Vasculitis and autoimmune diseases Periarteritis nodosa, eosinophilic granulomatosis with polyangiitis, scleroderma	ANCA, anti-nuclear antibodies, vascular biopsies, clinical examination
Malignancy	Imaging studies, histology

Clinical Characteristics and Natural History of Patients with Eosinophilic Enteritis

Patients with eosinophilic enteritis can present with a variety of non-specific symptoms [122, 123]. Common symptoms would be abdominal pain, diarrhoea, bloating and nausea whereas jaundice, ascites, rectal bleeding and vomiting are less frequently seen. They often present with a complication of their disease as the index presentation [124]. The clinical presentation depends on the depth of intestinal wall involved. This was classified by Klein et al. [119] into three different forms of the disease according to the layer of intestinal wall involved:

- The mucosa form characterised by predominant mucosal inflammation causing diarrhoea, abdominal pain, signs of malabsorption or protein losing enteropathy

- The muscular form characterised by intestinal strictures with abdominal pain, nausea and vomiting which can lead to obstruction
- The subserosal form characterised by an eosinophilic-rich ascites with bloating and abdominal pain.

The occurrence of these forms varies in the literature, in part due to less surgical specimens being sent to help diagnose the muscular form of the disease [122, 125].

Patients with eosinophilic enteritis may vary in their presentation depending on how extensively the gut is involved. The most common sites to be involved would be the stomach and proximal small intestine, seen between 40–80% of patients with eosinophilic enteritis. The more extensive the disease the more likely to have protein losing enteropathy, malabsorption and iron deficiency anaemia. Biopsies of all parts of the gastrointestinal tracts are required to diagnose the enteritis.

An elevated peripheral eosinophil count can be seen [125]. More than 70% of patients with eosinophilic enteritis will have a transient high (>500/mm^3) eosinophil count during a flare. If the eosinophil count is >3000/mm^3, then the patient is likely to have predominantly subserosal involvement. An absence of peripheral eosinophilia should not exclude the diagnosis of eosinophilic enteritis.

Elevated IgE levels can also be seen in approximately 505 of patients. In eosinophilic patients with protein losing enteropathy, malabsorption or intestinal inflammation hypoalbuminaemia, iron deficiency, steatorrhoea and a high CRP can be seen [124].

Imaging studies are often non-specific and only intestinal biopsies will lead to the diagnosis. Upper gastrointestinal endoscopy and ileo-colonoscopy may be macroscopically normal or show slight erosions, oedema, erythema or nodules [126]. Capsule endoscopy can be used to examine the whole small intestine but does not allow biopsies of the areas [127].

The natural history of the disease follows three courses [125]:

- A single flare (42%)
- A recurring course with multiple flares and period of full remission from 2 months to several years (37%)
- A continuous course (21%)

Pineton de Chambrun et al. [125] found patients with predominantly mucosal disease accounted for 80% of patients with continuous course to their disease. Over 50% of the cases of patients with a single flare, without disease recurrence, had subserosal forms of the disease. There was also no occurrence of myeloproliferative disorders. Reed et al. [128] found that only a third of patients with eosinophilic enteritis remained in remission, with the many patients presenting with a persistent or progressive disease course.

Treatment

The treatment of eosinophilic enteritis can be challenging as there are no clear recommendations and very little evidence base in the literature [129]. Treatments which have been already used and evaluated are discussed below however, 40% of patients will have a spontaneous remission of eosinophilic enteritis.

Diet

Several dietary strategies have been proposed. If there is a clear and limited precipitant, identified on food allergen testing, then this should be avoided. When many or no allergens have been identified, a more aggressive empiric elimination diet or elemental diet can be tested. There is not enough evidence in the literature to recommend these in routine management.

Corticosteroids

The use of corticosteroids is one of the main treatments of the patients with eosinophilic enteritis [130, 131]. Most case series have reported good efficacy of corticosteroids with clinical remission achieved in 50–90% of patients with eosinophilic enteritis [128, 132].

Treatment should be started at 0.5 to 1 mg/kg for a few weeks before tapering the dose over 6 to 8 weeks [129]. After this approximately 20% of patients will have steroid dependency requiring low dose prednisolone to maintain clinical remission. To avoid the side effects of corticosteroids, Budesonide could also be used. Budesonide is effective at 9 mg per day for the induction and maintenance of clinical remission in patients with eosinophilic enteritis [133–140]. The dose can be tapered to 6 mg and then 3 mg per day for maintenance therapy, if required.

Azathioprine

Azathioprine can be used in patients with eosinophilic enteritis who are either refractory to or dependent on corticosteroids. The usual dose of eosinophilic enteritis patients is similar to the dose used in inflammatory disease patients at 2–2.5 mg/kg [141].

Biologics

There have been some reports of biological agents being used in eosinophilic enteritis. Mepolizumab, an anti-IL5 monoclonal antibody, having previously been used in eosinophilic oesophagitis, may be an alternative to patients with a complicated disease course. Mepolizumab was reported as having improved the tissue and peripheral eosinophilia in four patients with eosinophilic enteritis but it did not relieve symptoms [129]. Omalizumab, an anti IgE monoclonal antibody, has also been tested for the treatment of eosinophilic enteritis with improvement in histology [142]. Infliximab and adalimumab, two anti-tumour necrosis factor monoclonal antibodies, were reported as effective in inducing remission in refractory eosinophilic enteritis in some case reports [143].

Other Treatments

Other treatments used to treat patients with eosinophilic enteritis include antihistaminic drugs, montelukast and sodium cromoglycate [131]. Montelukast, a selective leukotriene inhibitor used to treat asthma, can be used at 5–10 mg per day [51–56]. Sodium cromoglycate, a mast cell stabiliser blocks the release of immune mediators and subsequent activation of eosinophils, has only had a few case reports [144]. Ketotifen, a second generation H1-antihistamine agent, is used to inhibit the release of mast cell mediators [145]. The results of these drugs in patients with eosinophilic enteritis are conflicting and need further larger, prospective studies.

References

1. Fasano A, Catassi C. Current approaches to diagnosis and treatment of coeliac disease: an evolving spectrum. Gastroenterology. 2001;120:636–51.
2. West J, Logan RFA, Hill PG, Lloyd A, Lewis S, Hubbard R, Reader R, Holmes GKT, Khaw K-T. Seroprevalence, correlates and characteristics of undetected coeliac disease in England. Gut. 2003;52:960–5.
3. Mustalahti K, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, Murray L, Metzger MH, Gasparin M, Bravi E, Mäki M, Coeliac EU Cluster, Project Epidemiology. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. Ann Med. 2010;42:587–95.
4. Biagi F, Klersy C, Balduzzi D, Corazza GR. Are we not overestimating the prevalence of coeliac disease in the general population? Ann Med. 2010;42:557–61.
5. Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, Elitsur Y, Green PH, Guandalini S, Hill ID, Pietzak M, Ventura A, Thorpe M, Kryszak D, Fornaroli F, Wasserman SS, Murray JA, Horvath K. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med. 2003;163:286–92.
6. Hovell CJ, Collett JA, Vautier G, Cheng AJ, Sutanto E, Mallon DF, Olynyk JK, Cullen DJ. High prevalence of coeliac disease in a population-based study from Western Australia: a case for screening? Med J Aust. 2001;175:247–50.
7. Cook HB, Burt MJ, Collett JA, Whitehead MR, Frampton CM, Chapman BA. Adult coeliac disease: prevalence and clinical significance. J Gastroenterol Hepatol. 2000;15:1032–6.
8. Gandolfi L, Pratesi R, Cordoba JC, Tauil PL, Gasparin M, Catassi C. Prevalence of celiac disease among blood donors in Brazil. Am J Gastroenterol. 2000;95:689–92.
9. Oliveira RP, Sdepanian VL, Barreto JA, Cortez AJ, Carvalho FO, Bordin JO, de Camargo Soares MA, da Silva Patrício FR, Kawakami E, de Morais MB, Fagundes-Neto U. High prevalence of celiac disease in Brazilian blood donor volunteers based on screening by IgA antitissue transglutaminase antibody. Eur J Gastroenterol Hepatol. 2007;19:43–9.
10. Gomez JC, Selvaggio GS, Viola M, Pizarro B, la Motta G, de Barrio S, Castelletto R, Echeverria R, Sugai E, Vazquez H, Maurino E, Bai JC. Prevalence of celiac disease in Argentina: screening of an adult population in La Plata area. Am J Gastroenterol. 2001;96:2700–4.
11. Barada K, Bitar A, Mokadem MA, Hashash JG, Green P. Celiac disease in Middle Eastern and North African countries: a new burden? World J Gastroenterol. 2010;16:1449–57.
12. Cataldo F, Montalto G. Celiac disease in the developing countries: a new and challenging public health problem. World J Gastroenterol. 2007;13:2153–9.
13. Abu-Zekry M, Kryszak D, Diab M, Catassi C, Fasano A. Prevalence of celiac disease in Egyptian children disputes the east-west agriculture-dependent spread of the disease. J Pediatr Gastroenterol Nutr. 2008;47:136–40.
14. Alarida K, Harown J, Ahmaida A, Marinelli L, Venturini C, Kodermaz G, Tozzoli R, Mandolesi A, Bearzi I, Catassi C. Coeliac disease in Libyan children: a screening study based on the rapid determination of anti-transglutaminase antibodies. Dig Liver Dis. 2011;43:688–91.
15. Ben Hariz M, Kallel-Sellami M, Kallel L, Lahmer A, Halioui S, Bouraoui S, Laater A, Sliti A, Mahjoub A, Zouari B, Makni S, Maherzi A. Prevalence of celiac disease in Tunisia: mass-screening study in schoolchildren. Eur J Gastroenterol Hepatol. 2007;19:687–94.
16. Imanzadeh F, Sayyari AA, Yaghoobi M, Akbari MR, Shafagh H, Farsar AR. Celiac disease in children with diarrhea is more frequent than previously suspected. J Pediatr Gastroenterol Nutr. 2005;40:309–11.
17. Dalgic B, Sari S, Basturk B, Ensari A, Egritas O, Bukulmez A, Baris Z. Prevalence of celiac disease in healthy Turkish school children. Am J Gastroenterol. 2011;106:1512–7.
18. Sood A, Midha V, Sood N, Avasthi G, Sehgal A. Prevalence of coeliac disease among school children in Punjab, North India. J Gastroenterol Hepatol. 2006;21:1622–5.
19. Catassi C, Cobellis G. Coeliac disease epidemiology is alive and kicking, especially in the developing world. Dig Liver Dis. 2007;39:908–10.
20. Catassi C, Rätsch IM, Gandolfi L, Pratesi R, Fabiani E, El Asmar R, Frijia M, Bearzi I, Vizzoni L. Why is coeliac disease endemic in the people of the Sahara? Lancet. 1999;54:647–8.
21. Catassi C, Doloretta Macis M, Rätsch IM, De Virgiliis S, Cucca F. The distribution of DQ genes in the Saharawi population provides only a partial explanation for the high celiac disease prevalence. Tissue Antigens. 2001;58:402–6.
22. Xin-Qiong W, Wei L, Chun-di X, Hong M, Yuan G, Han-Ming P, Lan Y, Jun-Jie X. Celiac Disease in Children with Diarrhea in four cities of China. J Pediatr Gastroenterol Nutr. 2011;53:368–70.

23. Wu J, Xia B, von Blomberg BM, Zhao C, Yang XW, Crusius JB, Peña AS. Coeliac disease in China, a field waiting for exploration. Rev Esp Enferm Dig. 2010;102:472–7.
24. Makharia GL. Celiac disease screening in Southern and East Asia. Dig Dis. 2015;33:167–74.
25. Brar P, Lee AR, Lewis SK, Bhagat G, Green PH. Celiac disease in African-Americans. Dig Dis Sci. 2006;51:1012–5.
26. Greco L, Mäki M, DiDonato F, Visakorpi JK. Epidemiology of coeliac disease in Europe and the Mediterranean area. In: Auricchio S, Visakorpi JK, editors. Common food intolerances 1: epidemiology of coeliac disease. Basel: Karger; 1992. p. 25–44.
27. Ivarsson A, Persson LA, Nystrom L, Asher H, Cavell B, Danielsson L, Dannaeus A, Lindberg T, Lindquist B, Stenhammar L, Hernell O. Epidemic of coeliac disease in Swedish children. Acta Paediatr. 2000;89:165–71.
28. Ivarsson A, Hernell O, Stenlund H, Persson LA. Breast-feeding protects against coeliac disease. Am J Clin Nutr. 2002;75:914–21.
29. Asher H. The role of quantity and quality in gluten-containing cereals in the epidemiology of coeliac disease. In: Mäki M, Collin P, Visakorpi JK, editors. Coeliac disease. Tampere: Coeliac Disease Study Group; 1997.
30. Mäki M, Kallonen K, Lahdeho ML, Visakorpi JK. Changing pattern of childhood coeliac disease in Finland. Acta Paediatr Scand. 1988;77:408–12.
31. Carroccio A, Iannitto E, Cavataio F, Montalto G, Tumminello M, Campagna P, Lipardi MG, Notarbartolo A, Iacono G. Sideropenic anemia and celiac disease: one study, two points of view. Dig Dis Sci. 1998;43:673–8.
32. Aine L, Mäki M, Colin P, Keyrilainen O. Dental enamel defects in celiac disease. J Oral Path Med. 1990;19:241–5.
33. Wierink CD, van Diermen DE, Aartman IH, Heymans HS. Dental enamel defects in children with coeliac disease. Acta Paediatr Dent. 2007;17:163–8.
34. Rubio-Tapia A, Murray JA. The liver in celiac disease. Hepatology. 2007;46:1650–8.
35. Halfdanarson TR, Litzow MR, Murray JA. Hematologic manifestations of celiac disease. Blood. 2007;109:412–21.
36. Dahele A, Ghosh S. Vitamin B_{12} deficiency in untreated celiac disease. Am J Gastroenterol. 2001;96:745–50.
37. Ludvigsin JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, Hadjivassiliou M, Kaukinen K, Kelly CP, Leonard JN, Lundin KE, Murray JA, Sanders DS, Walker MM, Zingone F, Ciacci C. The Oslo definitions for coeliac disease and related terms. Gut. 2013;62:43–52.
38. Sollid LM, Thorsby E. HLA susceptibility genes in celiac disease: genetic mapping and role in pathogenesis. Gastroenterology. 1993;105:910–22.
39. Sollid LM. Coeliac disease: dissecting a complex inflammatory disorder. Nat Rev Immunol. 2002;2:647–55.
40. Ciclitira PJ, Evans DJ, Fagg NL, Lennox ES, Dowling RH. Clinical testing of gliadin fractions in coeliac patients. Clin Sci. 1984;66:357–64.
41. Maiuri L, Picarelli A, Boirivant M, Coletta S, Mazzilli MC, De Vincenzi M, Londei M, Auricchio S. Definition of the initial immunologic modifications upon in vitro gliadin challenge in the small intestine of celiac patients. Gastroenterology. 1996;110:1368–78.
42. Cataldo F, Martino V, Ventura A, Bottaro G, Corazza GR. Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: an Italian multicentre study. Italian Society of Pediatric Gastroenterology and Hepatology (SIGEP) and "Club del Tenue" Working groups on Coeliac Disease. Gut. 1998;42:362–5.
43. Marsh NM. Gluten, Major Histocompatibility Complex and the small intestine: a molecular and immunologic approach to the spectrum of gluten-sensitivity ('celiac sprue'). Gastroenterology. 1992;102:330–54.
44. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. Eur J Gastroenterol Hepatol. 1999;11:1185–94.
45. Freeman HJ. Adult celiac disease and the severe "flat" small bowel biospy lesion. Dig Dis Sci. 2004;49:535–45.
46. Brunser O, Eidelman S, Klipstein FA. Intestinal morphology of rural Haitains. A comparison between overt tropical sprue and asymptomatic subjects. Gastroenterology. 1970;58:655–68.
47. Meeuwisse GW. Diagnostic criteria in celiac disease. Acta Paediatr Scand. 1970;59:461–3.
48. Walker-Smith JA, Guandalini S, Schmitz J, Shmerling DH, Visakorpi JK. Revised criteria for diagnosis of coeliac disease. Arch Dis Child. 1990;65:909–11.
49. Nice Guidelines. CG86 Coeliac disease: recognition and assessment of coeliac disease. 2009. http://www.nice.org.uk/nicemedia/live/12166/44356/44356.pdf (10.8.11).
50. Grefte JMM, Bouman JG, Ground J, Jansen W, Kleibeuker JH. Slow and incomplete recovery in adult gluten sensitive enteropathy. J Clin Path. 1988;41:886–91.
51. Wahab PJ, Meijer JWR, Mulder CJJ. Histologic follow-up of people with Celiac Disease on a Gluten Free Diet. Slow and incomplete recovery. Am J Clin Path. 2002;119:459–63.
52. Ribes-Koninckx C, Mearin M, Korponay-Szabó I, Shamir R, Husby S, Ventura A, Branski D, Catassi C, Koletzko S, Mäki M, Troncone R, Zimmer K, The ESPGHAN Working Group on Coeliac Disease Diagnosis. Coeliac disease diagnosis: ESPHGAN 1990 Criteria or need for a change? Results of a questionnaire. J Pediatr Gastroenterol Nutr. 2012, 54:15–9.
53. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, Troncone R, Giersiepen K, Branski D, Catassi C, Lelgeman M, Mäki M, Ribes-Koninckx C, Ventura A, Zimmer KP. (The ESPGHAN Working Group on Coeliac Disease Diagnosis). (2011) ESPGHAN guidelines for the diagnosis of coeliac disease in children and adolescents. J Paediatr Gastroenterol Nutr 2012;54:572.
54. Thompson T, Dennis M, Higgins LA, Lee AR, Sharrett MK. Gluten-free diet survey: are Americans with celiac disease consuming recommended amount of fibre, iron, calcium and grain foods? J Hum Nutr Diet. 2005;18:163–9.
55. Thompson T. Folate, iron and dietary fiber contents of the gluten-free diet. Am J Dietetic Assoc. 2000;100:1389–96.
56. Thompson T. Thiamin, riboflavin and niacin content of the gluten-free diet: is there cause for concern? Am J Dietetic Assoc. 1999;99:858–62.
57. Ellis HJ, Bermudo-Redondo MC, Butero ML, Šuligoj T, O'Sullivan CK, Ciclitira PJ. Measurement of gliadin alone cannot predict total gluten content of foods for coeliac disease sufferers. Gut. 2008;57(S1):A51 a134.
58. Henando A, Mujico JR, Mena MC, Lombardia M, Mendez E. Measurement of wheat gluten and barley hordeins in contaminated oats from Europe, the United States and Canada by Sandwich R5 ELISA. Eur J Gastroenterol Hepatol. 2008;20:545–54.
59. Singh J, Whelan K. (2011) Limited availability and higher cost of gluten-free foods. J Hum Nutr Diet. 2011;24:479–86.
60. Fabiani E, Taccari LM, Rätsch IM, Di Guiseppe S, Coppa GV. Catassi C Compliance with a gluten-free diet in adolescents with screening-detected celiac disease: a 5-year follow –up study. J Paediatr. 2000;136:841–3.
61. Australia and New Zealand Food Standards code. Standard 2.9.6: foods formulated for special diets. 2003. www.foodstandards.gov.au/foodstandards/foodstandardscode.cfm.
62. Codex Standards for "Foods for special dietary use for persons intolerant to gluten" Codex Stan 118-1979 (amended 1983 and 2015, revised 2008). 2015. http://www.codexalimentarius.net/web/more_info.jsp?id_sta=291.

63. Bonamico M, Sciré G, Mariani P, Pasquino AM, Triglione P, Scaccia S, Boscherini B. Short stature as the primary manifestation of mono symptomatic celiac disease. J Pediatr Gastroenterol Nutr. 1992;14:12–6.
64. West J, Logan RFA, Smith CJ, Hubbard RB, Card TR. Malignancy and mortality in people with Coeliac Disease: population based cohort study. BMJ. 2004;329:716–9.
65. Lewis NR, Holmes GK. Risk of morbidity in contemporary celiac disease. Expert Rev Gastroenterol Hepatol. 2010;4:767–80.
66. Holmes GKT, Prior P, Lane MR, Pope D, Allan RN. Malignancy in coeliac disease- effect of a gluten free diet. Gut. 1989;30:333–8.
67. Freeman HJ. Reproductive changes associated with celiac disease. World J Gastroenterol. 2010;16:5810–4.
68. Ellis HJ. Coeliac disease and other gluten sensitive disorders. In: Buttriss J, editor. Adverse reactions to food. Oxford: Blackwell Science Publications; 2002.
69. Vega-Gálvez A, Miranda M, Vergara J, Uribe E, Puente L, Martinez EA. Nutrition facts and functional potential of quinoa (Chenopodium quinoa willd.), an ancient Andean grain: a review. J Sci Food Agric. 2010;90:2541–7.
70. Zevalos VF, Herencia LI, Chang F, Donnelly S, Ellus HJ, Ciclitira PJ. Gastrointestinal effects of eating quinoa (Chenopodium quinoa Willd.) in celiac patients. Am J Gastroenterol. 2014;109:270–8.
71. Janatuinen EK, Pikkarainen PH, Kemppainen TA, Kosma VM, Jarvinen RM, Uusitupa MI, Julkunen RJ. A comparison of diets with and without oats in adults with celiac disease. N Engl J Med. 1995;333:1033–7.
72. Janatuinen EK, Kemppainen TA, Julkunen RJ, Kosma VM, Mäki M, Heikkien M, Uusitupa MI. No harm from five year ingestion of oats in coeliac disease. Am J Gastroenterol. 2002;98:1332–7.
73. Koskinen O, Villanen M, Korponay-Szabo I, Lindfors K, Mäki M, Kaukinen K. Oats do not induce systemic or mucosal autoantibody response in children with coeliac disease. JPGN. 2009;48:559–65.
74. Thompson T. Gluten contamination of commercial oat products in the United States. N Engl J Med. 2004;351:2021–2.
75. Lundin KEA, Nilsen EM, Scott HG, Løberg EM, Gøen A, Bratlie J, Skar V, Mendez E, Løvik A, Kett K. Oats induced villous atrophy in coeliac disease. Gut. 2003;52:1649–52.
76. Arentz-Hansen H, Fleckenstein B, Molberg Ø, Scott H, Koning F, Roepstorff P, Lundin KEA, Sollid LM. The molecular basis for oat intolerance in patients with coeliac disease. PLoS Med. 2004;1:84–92.
77. Annibale B, Severi C, Chistolini A, Antonelli G, Lahner E, Marcheggiano A, Iannoni C, Monarca B, Delle Fave G. Efficiency of a gluten-free diet alone on recovery from iron deficiency anaemia in celiac patients. Am J Gastroenterol. 2001;96:132–7.
78. Scott E, Gaywood I, Scott B. Guidelines for osteoporosis in coeliac disease and inflammatory bowel disease. Gut. 2000;46(Suppl 1):I1–8.
79. Ludvigson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, Green PHR, Hajjivassiliou M, Holdoway A, van Heel DA, Kaukinen K, Leffler DA, Leonard JN, Lundin KEA, Mcgough N, Davidson M, Murray JA, Swift GL, Walker MM, Zingzone F, Sanders DS. The diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut. 2014;63:1210–28.
80. Donnelly SC, Ellis HJ, Ciclitira PJ. Pharmacotherapy and management strategies for coeliac disease. Expert Opin Pharmacother. 2011;12:1731–44.
81. Pink IJ, Creamer B. Response to a gluten-free diet of patients with the coeliac syndrome. Lancet. 1967;1:300–4.
82. Dewar DH, Donnelly SC, McLaughlin SD, Johnson MW, Ellis HJ, Ciclitira PJ. Celiac disease: management of persistent symptoms in patients on a gluten-free diet. World J Gastroenterol. 2012;18:1348–56.
83. Schuppan D. Current concepts of coeliac disease pathogenesis. Gastroenterology. 2000;119:234–42.
84. Nehausen S, Steele L, Ryan S, Mousavi M, Pinto M, Osann K, Flodman P, Zone JJ. Co-occurrence of celiac disease and other autoimmune diseases in celiacs and their first-degree relatives. J Autoimmun. 2008;31:160–5.
85. Smyth DJ, Plagnol V, Walker NM, Cooper JD, Downes K, Yang JHM, Howson JMM, Stevens H, McManus R, Wijmenga C, Heap GA, Dubois PC, Clayton DG, Hunt KA, van Heel DA, Todd JA. Shared and distinct genetic variants in type 1 diabetes and celiac disease. NEJM. 2009;359:2767–77.
86. Toscano V, Conti FG, Anastasi E, Marianin P, Tiberti C, Poggi M, Montuori M, Monti S, Laureti S, Cipolletta E, Gemme G, Cariola S, Di Mario U, Bonamico M. Importance of gluten in the induction of endocrine autoantibodies and organ dysfunction in adolescent celiac patients. Am J Gastroenterol. 2000;95:1742–8.
87. Ventura A, Magazzu G. Greco L for the SIGPEP study group for autoimmune disorders in celiac disease. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. Gastroenterology. 1999;117:297–303.
88. Sategna Guidetti C, Solerio E, Saglione N, Aimo G, Mengozzi G. Duration of gluten exposure does not correlate with the risk of autoimmune disorders. Gut. 2001;49:502–5.
89. Hadjivassiliou M, Gibson A, Davies-Jones GA, Lobo A, Stephenson TJ, Milford-Ward A. Is cryptic gluten sensitivity an important cause of neurological illness? Lancet. 1996;347:369–71.
90. Hadjivassiliou M, Grünewald RA, Kandler RH, Chattopadhyay AK, Jarratt JA, Sanders DS, Sharrack B, Wharton SB, Davies-Jones GA. Neuropathy associated with gluten sensitivity. J Neurol Neurosurg Psychiatry. 2006;77:1262–6.
91. Hadjivassiliou M, Aeschlimann P, Strigun A, Sanders DS, Woodroofe N, Aeschlimann D. Autoantibodies in gluten ataxia recognise a novel neuronal transglutaminase. Ann Neurol. 2008;64:332–43.
92. Bushara KO, Goebel SU, Shill H, Goldfarb LG, Hallett M. Gluten sensitivity in sporadic and hereditary cerebellar ataxia. Ann Neurol. 2001;49:540–3.
93. Hadjivassiliou M, Aeschlimann P, Strigun A, Sanders DS, Woodroofe N, Aeschlimann D. Autoantibodies in gluten ataxia recognize a novel neuronal transglutaminase. Ann Neurol. 2008;64:332–43.
94. Ritter J, Zimmermann K, Jöhrens K, Mende S, Seegebath A, Seigmund B, Hennig S, Todorova K, Rosenwald A, Daum S, Hummel M, Schumen M. T-cell repertoires in refractory coeliac disease. Gut. 2018;67:644–53.
95. Mauriño E, Niveloni S, Cherñavsky AC, Sugai E, Váquez H, Pedreira S, Periolo N, Mazure R, Smecuol E, Moreno ML, Litwin N, Nachman F, Kogan Z, Bai JC. Clinical characteristics and long-term outcome of patients with refractory sprue diagnosed at a single institution. Acta Gastroenterol Latinam. 2006;36:10–22.
96. Al-Toma A, Verbeek WH, Hadathi M, von Blomberg BM, Mulder CJ. Survival in refractory celiac disease and enteropathy-associated T-cell lymphoma: retrospective evaluation of single-centre experience. Gut. 2007;56:1373–8.
97. Malamut G, Afchain P, Verkarre V, Lecomte T, Amiot A, Damotte D, Bouhnik Y, Colombel JF, Delchier JC, Allez M, Cosnes J, Lavergne-Slove A, Meresse B, Trinquart L, Macintyre E, Radford-Weiss I, Hermine O, Brousse N, Cerf-Bensussan N, Cellier C. Presentation and long-term follow-up of refractory celiac disease: comparison of type I with type II. Gastroenterology. 2009;136:81–90.
98. Rubio-Tapia A, Kelly DG, Lahr BD, Dogan A, Wu TT, Murray JA. Clinical staging and survival in refractory celiac disease: a single centre experience. Gastroenterology. 2009;136:99–107.
99. Gale J, Simmonds PD, Mead GM, Sweetenham JW, Wright DH. 2000 Enteropathy-type intestinal T-cell lymphoma: clinical fea-

tures and treatment of 31 patients in a single center. J Clin Oncol. 2000;18:795–803.
100. Bayless TM, Hendrix TR. Small intestinal ulcers and celiac disease. In: Booth CC, Dowling RH, editors. Proceedings of an International Conference held at the Royal Postgraduate Medical School, London. Churchill Livingstone; 1969.
101. Bagdi E, Diss TC, Munson P, Isaacson PG. Mucosal intra-epithelial lymphocytes in enteropathy-associated T-cell lymphoma, ulcerative jejunitis, and refractory celiac disease constitute a neoplastic population. Blood. 1999;94:260–4.
102. Corrao G, Corazza GR, Bagnardi V, Brusco G, Ciacci C, Cottone M, Sategna Guidetti C, Usai P, Cesari P, Pelli MA, Loperfido S, Volta U, Calabró A, Certo M, Club del Tenue Study Group. Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet. 2001;358:356–61.
103. Cellier C, Delabesse E, Helmer C, Patey N, Matuchansky C, Jabri B, Macintye E, Cerf-Bensussan N, Brousse N, French Coeliac Disease Study Group. Refractory sprue, coeliac disease and enteropathy-associated T-cell lymphoma. Lancet. 2000;356:203–8.
104. Askling J, Linet M, Grindley G, Halstensen TS, Ekström K, Ekbom A. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. Gastroenterology. 2002;123:1428–35.
105. Catassi C, Fabiani E, Corrao G, Barbato M, De Renzo A, Carella AM, Gabrielli A, Leoni P, Carroccio A, Baldassarre M, Bertolani P, Caramaschi P, Sozzi M, Guariso G, Volta U, Corazza GR. Risk of Non-Hodgkin lymphoma in celiac disease. JAMA. 2002;287:1413–9.
106. Green PH, Fleitschauer AT, Bhagat G, Goyal R, Jabri B, Neugut AI. Risk of malignancy in patients with celiac disease. Am J Med. 2003;115:191–5.
107. Howdle PD, Jalal PK, Holmes GK, Houlston RS. Primary small bowel malignancy in the UK and its association with coeliac disease. QJM. 2003;96:345–53.
108. Rampertab SD, Forde KA, Green PH. Small bowel neoplasia in coeliac disease. Gut. 2003;52:1211–4.
109. Green PH, Rampertab SD. Small bowel carcinoma and coeliac disease. Gut. 2004;53:774.
110. Smedby KE, Akerman M, Hildebrand H, Glimelius B, Ekbom A, Askling J. Malignant lymphomas in coeliac disease: evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. Gut. 2005;54:54–9.
111. Mearin ML, Catassi C, Brousse N, Brand R, Collin P, Fabiani E, Schweizer JJ, Abuzakouk M, Szajewska H, Hallert C, Farré Masip C, Holmes GK, Biomed Study Group on Coeliac Disease and Non-Hodgkin Lymphoma. European multi-centre study on coeliac disease and non-Hodgkin lymphoma. Eur J Gastroenterol Hepatol. 2006;18:187–94.
112. Elfström P, Granath F, Ekström Smedby K, Montgomery SM, Askling J, Ekbom A, Ludvigsson JF. Risk of lymphoproliferative malignancy in relation to small intestinal histopathology among patients with celiac disease. J Natl Cancer Inst. 2011;103:436–44.
113. Logan RF, Rifkind EA, Turner ID, Fergusson A. Mortality in celiac disease. Gastroenterology. 1989;97:265–71.
114. Card TR, West J, Holmes GK. Risk of malignancy in diagnosed coeliac disease: a 24-year prospective, population-based, cohort study. Aliment Pharmacol Ther. 2004;20:769–75.
115. Silano M, Volta U, Mecchia AM, Dessi M, Di Benedetto R, de Vincenzi M. Colborating centers of the Italian registry of the complications of coeliac disease. Delayed diagnosis of coeliac disease increases cancer risk. BMC Gastroenterol. 2007;7:8.
116. Solaymani-Dodaran M, West J, Logan RF. Long-term mortality in people with celiac disease diagnosed in childhood compared with adulthood: a population-based cohort study. Am J Gastroenterol. 2007;102:864–70.
117. Lewis NR, Logan RFA, Sanders DS, Holmes GKT, West J. Reproductive and hormonal factors for breast cancer among women with coeliac disease: a population-based questionnaire study. Gut. 2009;58(Suppl. 2):A413.
118. Mansoor E, Saleh MA, Cooper GS. Prevalence of eosinophilic gastroenteritis and colitis in a population based study from 2012 to 2017. Clin Gastroenterol Hepatol. 2017;15:1733–41.
119. Klein NC, Hargrove RL, Sleisenger MH, Jeffries GH. Eosinophillic gastroenteritis. Medicine (Baltimore). 1970;49:299–319.
120. Yam BM, Shaffer EA. Primary eosinophilic disorders of the gastrointestinal tract. Gut. 2009;58:721–32.
121. Pineton de Chambrun G, Desreumaux P, Cortot A. Eosinophillic enteritis. Dig Dis. 2015;33:183–9.
122. Talley NJ, Shorter RG, Philips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer and subserosal tissue. Gut. 1990;31:54–8.
123. Zhang L, Duan L, Ding S, Lu J, Jin Z, Cui R, McNutt M, Wang A. Eosinophilic gastroenteritis: clinical manifestations and morphological characteristics. A restrospective study of 42 patients. Scand J Gastroenterol. 2011;46:1074–80.
124. Coton T. Gastroentérite à éosinophils. Encyclopédie Médico-chirugicale. 2009;[9-089-C-40].
125. Pineton de Chambrun G, Gonzalez F, Canva JY, Gonzalez S, Houssin L, Desreumaux P, Cortot A, Colombel JF. Natural history of eosinophilic enteritis. Clin Gastroenterol Hepatol. 2011;9:950–6.
126. Navab F, Kleinman MS, Algazy K, Schenk E, Turner MD. Endoscopic diagnosis of eosinophilic gastritis. Gastrointest Endosc. 1972;19:67–9.
127. Endo H, Hosono K, Inamori M, Kato S, Uchiyama T, Lida H, et al. Capsule endoscopy evaluation of eosinophilic enteritis before and after treatment. Digestion. 2011;83:134–5.
128. Reed C, Woosley JT, Dellon ES. Clinical characteristics, treatment outcomes, and resource utilisation in children and adults with eosinophilic gastroenteritis. Dig Liver Dis. 2015;47:197–201.
129. Abou Rached A, el Hajj W. Eosinophilic gastroenteritis: approach to diagnosis and management. World J Gastrointest Pharmacol Ther. 2016;7:513–23.
130. Yan BM, Shaffer EA. Primary eosinophilic disorders of the gastrointestinal tract. Gut 2009;58:721-32, Khan S. Eosinophilic gastroenteritis. Best Pract Res Clin Gastroenterol. 2005;19:177–98.
131. Khan S. Eosinophilic gastroenteritis. Best Pract Res Clin Gastroenterol. 2005;19:177–98.
132. Chang JY, Choung RS, Lee RM, Locke JR 3rd, Schleck CD, Zinsmeister AP, Smyrk TC, Talley NJ. A shift in clinical spectrum of eosinophilic gastroenteritis toward the mucosal type. Clin Gastroenterol Hepatol. 2010;8:669–75.
133. Busoni VB, Lifschitz C, Christiansen S, GdD MT, Orsi M. Eosinophilic gastroenteropathy: a pediatric series. Arch Argent Pediatr. 2011;109:68–73.
134. Elsing C, Placke J, Gross-Weege W. Budesonide for the treatment of obstructive eosinophilic jejunitis. Z Gastroenterol. 2007;45:187–9.
135. Lombardi C, Salmi A, Passalacqua G. An adult case of eosinophilic pyloric stenosis maintained on remission with oral budesonide. Eur Ann Allergy Clin Immunol. 2011;43:29–30.
136. Lombardi C, Salmi A, Savio A, Passalacqua G. Localized eosinophilic ileitis with mastocytosis successfully treated with oral budesonide. Allergy. 2007;62:1343–5.
137. Russel MG, Zeijen RN, Brummer RJ, de Bruine AP, van Kroonenburgh MJ, Stockbrugger RW. Eosinophilic enterocolitis diagnosed by means of technetium-99m albumin scintigraphy and treated with budesonide (CIR). Gut. 1994;35:1490–2.
138. Shahzad G, Moise D, Lipka S, Rizvon K, Mustacchia PJ. Eosinophilic enterocolitis diagnosed by means of upper

endoscopy and colonoscopy with random biopsies treated with budenoside: a case report and review of the literature. ISRN Gastroenterol. 2011;2011:608901.
139. Siewert E, Lammert F, Koppitz P, Schmidt T, Matern S. Eosinophilic gastroenteritis with severe protein-losing enteropathy: successful treatment with budesonide. Dig Liver Dis. 2006;38:55–9.
140. Tan AC, Kruimel JW, Naber TH. Eosinophilic gastroenteritis treated with non-enteric-coated budesonide tablets. Eur J Gastroenterol Hepatol. 2001;13:425–7.
141. Netzer P, Gschossman JM, Straussmann A, Sendensky A, Weimann R, Schoepfer AM. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long term remission. Eur J Gastroenterolo Hepatol. 2007;19:865–9.
142. Foroughi S, Foster B, Kim N, Bernardino LB, Scott LM, Hamilton RG, Metcalfe DD, Mannon PJ, Prussin C. Anti-IgE treatment of eosinophil-associated gastrointestinal disorders. J Allergy Clin Immunol. 2007;120:594–601.
143. Turner D, Wolters VM, Russel RK, Shakhnovich V, Muise AM, Ledder O, Ngan B, Friesen C. Anti-TNF, infliximab and adalimumab can be effective in eosinophilic bowel disease. J Pediatr Gastroenterol Nutr. 2013;56:492–7.
144. Perez-Millan A, Martin-Lorente JL, Lopez-Morante A, Yuguero L, Saez-Royuela F. Subserosal eosinophilic gastroenteritis treated efficaciously with sodium cromoglycate. Dig Dis Sci. 1997;42:342–4.
145. Melamed I, Feanny SJ, Sherman PM, Roifman CM. Benefit of ketotifen in patients with eosinophilic gastroenteritis. Am J Med. 1991;90:310–4.

Intestinal Failure in Critical Care

Moran Hellerman Itzhaki and Pierre Singer

Key Points

1. Nutritional assessment and requirements on an intensive care unit (ICU) can be difficult to determine. Weight changes, indirect calorimetry (measuring CO_2 production) and a CT scan at L3 are helpful.
2. It is estimated that 1% muscle mass is lost per day on ICU.
3. In acute injury (trauma/major surgery) nutritional support aims to provide 70% of the nutritional target by day 3 and increase further in the post-acute phase.
4. Glutamine and Ω3 fatty acid supplements may be beneficial especially glutamine for burns (>20%) and trauma patients.
5. Relatively tight blood glucose control aims to keep the blood glucose to less than 10 mmol/L.
6. If there is a gastric aspirate of more than 500 ml at any time (often occurs with sepsis) then postpyloric feeding and prokinetic drugs should be considered.
7. Opiate drugs, cyclizine and many other drugs can inhibit gastrointestinal motility.
8. Enteral nutrition (EN) is preferred but if it fails to provide the target amount, supplementary parenteral nutrition may be given.

Introduction

Intestinal failure is a common condition in critically ill patients that may lead to severe morbidity or even death. Early diagnosis and proper treatment are mandatory to prevent such complications. This chapter will discuss the recognition of malnutrition and the complex planning nutritional support in the critically ill with emphasis on nutritional targets, macronutrients and the place of supplements in nutritional therapy. Specific populations, such as those with sarcopenia, diarrhea and the refeeding syndrome will be discussed in detail, along with current topics in intensive care such as COVID-19.

Definition and Etiology

Intestinal failure has been defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth. The reduction of gut absorptive function that doesn't require intravenous supplementation to maintain health and/or growth, can be considered as "intestinal insufficiency"" [1]. The estimated prevalence of acute intestinal failure in the acute hospital setting varies between 1.3% and 61% [2]. In the intensive care unit (ICU) about 8% of the patients suffer from intestinal failure [2]. Intestinal failure is classified into three types. Type 1 is an acute and self-limiting condition associated with critical illness or postoperative period. Type 2 is a less common form of acute intestinal failure following catastrophic abdominal events combined with sepsis and metabolic complications. It usually requires intense management with prolonged intravenous support. Type 3 is a chronic form of intestinal failure, either as a consequence of type 2 acute IF or of a chronic medical condition [1]. Acute IF in critically ill patients was graded by Blaser et al. according to severity of the symptoms and the interventions required (Table 1) [3]. The clinical manifestations of intestinal failure in critically ill patients vary according to specific pathophysiologic processes. The short bowel syndrome most commonly develops following extensive bowel resection, either as part of an acute exacerbation of a chronic disease or due to abdominal catastrophic events (trauma, ischemia, perforation, etc.). It will usually manifest as extensive intestinal loss of fluids and electrolytes. Intestinal fistu-

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Table 1 Classification of acute gastrointestinal injury (AGI)

AGI Grade	Definition	Clinical presentation
NO AGI	No GI malfunction	No GI symptoms
AGI grade 1	Risk for GI failure	• Nausea and/or vomiting (Post abdominal insult) • Absence of bowel sounds (following abdominal surgery, anesthetic or opioid therapy, shock) • Mild diarrhea • Abdominal distention
AGI grade 2	GI malfunction with symptoms requiring treatment	• Gastroparesis/large GRV • Severe diarrhea (causing fluid and electrolytes imbalance) • IAH (12–15 mmHg) • Visible GI bleeding
AGI grade 3	GI dysfunction progress despite treatment with systemic deterioration	• Large GRV/Vomiting/GI paralysis persist despite treatment • Severe IAH • Severe diarrhea • Abdominal sepsis • Ileus
AGI grade 4	Life threatening GI failure	• Bowel ischemia/necrosis • GI bleeding causing hemorrhagic shock • Acute colonic pseudo-obstruction • Abdominal compartment syndrome

Modified from Blaser et al. gastrointestinal failure in the ICU. Curr Opin Crit Care 2016; Apr 22(2):128–141
AGI acute gastrointestinal injury, *GI* gastrointestinal injury, *GRV* gastric residual volume, *IAH* intra-abdominal hypertension

lae may also occur as a complication of chronic inflammatory bowel disease, a persistent abdominal infection or a surgical complication. A fistula may cause a similar loss of fluid and electrolytes as well as a systemic metabolic response that is a part of sepsis. Chronic processes, such as intestinal tumors or chronic inflammation, are generally not acute in nature. However, the clinical implications of mechanical obstruction may be severe and life threatening, often requiring intensive care. Intestinal dysmotility is a common manifestation of IF in ICUs. Many factors are associated with its development, the most common being medications, systemic inflammation, post-operative states and metabolic disorders. It may then present as non-mechanical bowel obstruction (paralytic ileus) and delayed gastric empting (gastroparesis), both of which will be discussed later. Malabsorptive conditions often manifest as diarrhea. This is common in critically ill patients, are often secondary to medical treatments, infection or artificial nutrition, and may require close monitoring and nutritional supplementation [2].

Screening and Assessment of Malnutrition

In order to identify critically ill patients at risk of acute IF that may benefit from nutritional support, nutritional screening and assessment must be performed. Malnutrition is a common phenomenon, with reports of prevalence rates as high as 50% among hospitalized patients, depending on their clinical status, age and medical condition [4]. Critically ill patients are particularly vulnerable owing to the acute nature of their illness and co-morbidities potentially limiting their ability to eat and absorb food. There are many objective and subjective methods of assessing the risk of malnutrition in hospitalized patients, with the subjective global assessment (SGA) being one of the few tools validated in the ICU setting [5]. SGA includes five anamnestic components (weight changes, nutrition intake, gastrointestinal (GI) symptoms, functional capacity and metabolic stress) and two physical components (signs of muscle wasting and fluid balance). Laboratory parameters such as albumin and prealbumin levels are extremely affected by inflammation/saline administration and are therefore not useful for the diagnosis of malnutrition [6, 7]. Rattanachaiwong et al. compared several diagnostic tools for malnutrition in ICU patients and found the nutrition risk screening (NRS) to be more sensitive and specific than the SGA [8]. In 2019 the European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) (ESPEN) proposed the global leadership initiative on malnutrition (GLIM) criteria for the diagnosis of malnutrition. The GLIM criteria include phenotypic characteristics like unintentional weight loss, low basal metabolic index (BMI) and loss of muscle mass, and etiologies including reduced intake or absorption, inflammation and disease severity [9]. A paper published by Theilla et al. found that the GLIM criteria had a high sensitivity of 85% and specificity of 79% compared to the SGA, considered to be the gold standard in the ICU [10]. They concluded that the GLIM criteria are acceptable for use in the ICU. Reduced muscle mass is not only a phenotype of malnutrition but also a strong predictor of increased mortality, prolonged mechanical ventilation and a protracted hospitalization course [11, 12]. Assessment of body composition may provide insight into patient-specific characteristics of malnutrition. Body composition may be studied using several commercially available methods. Bioelectrical impedance is a quick, non-invasive, low-cost technique that does not expose the patient to radiation and is performed at the bedside. Bioimpedance uses low voltage electrical currents to identify different components of the body. Conduction alternation allows for the measurements of the fat mass and the fat free mass (FFM). FFM is mainly composed of water, proteins and carbohy-

drates [12]. A long-established method for assessing body composition is dual energy X ray absorptiometry (DXA). DXA was originally used to measure mineral bone density but now can be used to measure all three major tissue components of the body (fat mass, lean mass and bone mineral mass) [13] DXA is well validated and requires slight radiation exposure. However, it is rarely used in the ICU as it seldom available [12]. Computed tomography (CT) may be employed to assess body composition. It offers information on specific compartments, including dividing adipose tissue into visceral and subcutaneous and characterizing specific skeletal muscle groups. One technique is the use of single slice CT, usually at the level of L3, which provides information on several muscle groups, and correlate with whole body muscle mass [14]. In a retrospective study of 240 ICU patients, Weijs et al. examined the effect of low skeletal muscle area on mortality. A single slice CT scan showed reduced muscle area in 63% of the patients in both sex groups, with evidence of increased mortality compared to those with preserved muscle area (OR 3.86 [1.8–8.26]) [15]. A major disadvantage of this technique is the exposure to radiation, rendering it difficult to justify without other indications. The patient's clinical condition and the risk of mobilizing a patient outside of the ICU must be considered as well. Point of care ultrasound is an increasingly popular technique used in the ICU that provides the clinician with viable information at the bedside without radiation exposure. When ultrasound was studied for body composition assessment, it showed only moderate correlation with other modalities. The lack of consensus on the preferred site and method of measurement makes existing clinical data hard to compare [12].

Sarcopenic Obesity As previously mentioned, the risk of sarcopenia in the ICU is extremely high, with a prevalence of more than 90% and muscle mass loss of nearly 1% a day [16]. Accelerated catabolism, inadequate nutrition and immobilization are all major causes for sarcopenia in the critically ill. Obesity is another common condition in the ICU as worldwide prevalence increases. Although obesity holds an increased risk for co-morbidities and may limit treatment options, there is evidence for decreased ICU mortality in obese patients compared to non-obese, sometimes referred to as the obesity paradox [17]. Muscle mass in obese individuals is highly related to physical activity and age. In addition, characteristic muscle changes seen patients with obesity may impair muscle function. Given the impact of sarcopenic obesity on ICU patients' outcomes, specific measures should be taken to minimize it [4]. Other than intense physical therapy, personalized nutrition strategies are needed. Recent guidelines recognize the pitfall of using "ideal body weight" to calculate energy requirements in obese individuals as it neglects the metabolic demand of adipose tissue. It is therefore advocated by some to add a correction factor of 20–25% of excess weight (actual body weight - ideal body weight) to the ideal body weight [18]. Another strategy is to combine a relatively low number of calories with high protein intake (2–2.5 g/kg/day) [19].

Nutritional Targets

The importance of determining the proper nutritional targets for critically ill patients is well documented. In a large Cohort study, Zusman et al. showed a non-linear connection between the caloric intake of ICU patients and 60-day mortality. As caloric intake increased and reached 70% of resting energy expenditure (REE) assessment, mortality was reduced**.** On the other hand, mortality increased as caloric intake was above 100% of REE [20]. The clinical course of critical illness is divided in several phases. The hyperacute phase of hemodynamic instability often leading to ICU admission. The acute phase composed of the early period with marked catabolism and metabolic instability and the late period characterized by stabilization of metabolic disturbances and significant muscle wasting. This will be followed by the post-acute phase of persistent inflammation or rehabilitation [18]. In the acute phase there are alternation in hormone levels such as glucagon, cortisol and epinephrine increasing insulin resistance and gluconeogenesis. In addition, cytokines release including TNF-α, IL-1, IL-2 and IL-6 increases protein breakdown and insulin resistance. Increased glucose production, lipolysis and protein breakdown all lead to significant endogenous substrate production observed in early phases of acute illness [21]. In order to avoid overfeeding it is recommended to start nutritional support gradually with the nutritional target of 70% of REE in the first three days of ICU admission and gradually increase nutritional support upon patient's stabilization until reaching 80–100% of REE by day 5–7 [18]. Indirect calorimetry (IC) has been established as the gold standard for REE measurement [18, 22–24] and is considered the best strategy to reduce over/under feeding [18, 22]. Nevertheless, this technology is not available in all intensive care units and not applicable in clinical situations such as mechanical ventilation in high oxygen concentrations (FIO2 > 0.7), chest drains, and usage of nitric

oxide or helium. Predictive equation for REE estimation such as Harris-Benedict, Faisy-Fagon or Penn State have shown poor agreement with IC [25]. A recent large retrospective study by Zusman et al. demonstrated poor accuracy of the predictive equations [26]. An alternative method is to estimate energy expenditure from carbon dioxide production (VCO_2) values obtained from the ventilator in invasively ventilated patients [27]. Many respirators can measure VCO_2 and calculate REE by using the Weir formula and determining the respiratory quotient (RQ). This approach is controversial, as while some studies show high levels of accuracy, others show less encouraging results [28, 29]. One of the main limitations of measuring VCO_2 is the need for a predefined RQ. RQ, defined as the division of $VCO_2$by VO_2, is a constant influenced by many factors, including ventilator settings and acid-base balance, all of which are extremely dynamic in critically ill patients. In a retrospective study by Kagan et al., an RQ of 0.89 showed the best correlation between IC and VCO_2 measurement [30]. Nonetheless, it seems that the use of VCO2 measurement is the best alternative to IC if the latter is not available, with better accuracy than predictive equations. After determining the estimated energy expenditure, 70% of estimated needs should be prescribed in the first days of ICU admission and full nutritional support should be reached within three to seven days [18].

Non Nutritional Calories products that contain high caloric index and with little nutritional value are considered non nutritional calories (NNCs). In the intensive care these are mostly derived from the dextrose, citrate and the drug propofol. If nutritional plans do not take these "hidden" calories into account, the risk of overfeeding increases. Propofol is a general anesthetic commonly used in the ICU. It contains soybean oil, egg phospholipids and glycerol. Propofol contains 1.1 kcal/ml which translate into several hundred daily calories for the average sedated patient in the ICU [31]. 5% Dextrose contains 3.6 kcal/g, meaning a 1 liter infusion of 5% dextrose provides around 200 kcal of NNCs. Citrate is a regional anticoagulant used in continuous renal replacement therapy (CRRT). Its caloric value is difficult to calculate as it varies from between various preparations. It also depends on blood flow, infusion rate and filter characteristics of the CRRT circuit. Trisodium citrate, for example, contains 3 kcal/g [31]. A retrospective study examining the relevance of NNCs in the ICU revealed that in the first day of ICU admission about 31% of the patient's caloric intake were NNCs. By day 4 that number decreased to 6% [31]. It is important to know that on day 1 patients tend to receive a very little nutrition, largely precluding the risk of overfeeding.

Macronutrients

The nutritional composition of macronutrients require adaptations as the clinical condition changes. **Carbohydrate** absorption is delayed during critical illness. However, the glycemic response to carbohydrate ingestion is prolonged, in effect increasing the incidence of hyperglycemia [32]. Carbohydrates are essential in nutritional formulas in order to reach caloric targets, but the recommended upper limit for carbohydrates is 5 mg/kg body weight/min. Low carbohydrate enteral formulas were introduced in the past to critically ill patients in order to facilitate ventilator weaning. The hypothesis that low carbohydrate would lead to low carbondioxide production did not translate into clinical benefit [33]. Low carbohydrate formulas are mainly prescribed to diabetic patient for better glycemic control [34]. These formulas failed to show significant benefit in lowering glucose variability in the general ICU population [35]. As earlier parenteral nutrition formulas contained mostly carbohydrates, hyperglycemia posed a serious concern for patients receiving them. As technology progressed and lipids emulsions became more stable, the amount of carbohydrates in parenteral nutrition decreased and so did the prevalence of hyperglycemia. Glycemic control is still considered a crucial issue in the management of critically ill patients and it comprises not only controlling absolute glucose concentration but also glucose variability and time in optimal glucose range. In 2001 van den Berghe et al. examined the effect of tight glycemic control (glucose between 4.4 and 6.1 mmol/L) in critically ill surgical patients. Her group found that tight control led to improved mortality rates [36]. However, these results have not been reproduced. In the NICE-SUGAR 2009 study, intensive glycemic control led to increased hypoglycemic events and mortality. The authors suggested blood glucose level targets of 10 mmol/L or less, as they had better outcomes compared to lower values [37]. According to recent studies there is no optimal glucose value below 10 mmol/L that shows additional mortality benefit [38]. Several studies in critically ill patients have shown that high glucose variability increased mortality independently of mean glucose levels [39–41]. As previously mentioned, prognosis improved the longer patients spent within the proper glucose range, and those achieving good glycemic control for more than 80% of the time had better clinical outcomes [42, 43].

Lipids are another cornerstone of nutrition formulas. Enteral formulas are rich in lipids, either medium chain triglycerides (MCTs) or long chain triglycerides (LCTs). Fish oil is rich in the omega-3 (Ω-3) polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid

(DHA). These affect the inflammatory process, including in the immune response, coagulation, vasoactivity and bone metabolism. They are also essential for neuronal, behavioral and visual development [44, 45]. A recent systematic review showed the benefit of supplemental fish oil in patients with acute respiratory distress syndrome (ARDS), decreasing the length of ICU stay and increasing ventilator-free days, but had no effect on mortality. The authors noted these results should be interpreted with caution as the review was based on low quality trials [46]. ESPEN guidelines conclude that enteral formulas enriched with omega-3 fatty acid may be safely administered, while high dose omega-3 fatty acid preparations should be avoided [18]. Lipid emulsion designed for parenteral nutrition have been improved, starting from soybeans as a source for LCTs to MCT based emulsions, followed by olive oil based formulas and finally formulas enriched with fish oil. Soybean oil contains high levels of omega-6 (Ω-6). There is increased concern regarding the use of omega-6 fatty acids, specifically Linoleic Acid (LA) due to their pro-inflammatory and immunosuppressive effects [47, 48]. LA also suppresses the synthesis of EPA and DHA, potentially reducing their beneficial effects. Olive oil based formulas are considered good alternatives. In a meta-analysis by Dai et al., the authors concluded these formulas were safe, were associated with increased antioxidant levels as well as lower Ω-6 levels while not leading to significant differences in most liver enzymes [49]. Pradelli et al. performed a meta-analysis on the effects of Ω-3 enriched parenteral formulas and found their use was associated with lower infection rates, shorter ICU stays and non-significant trends for reduced mortality rates [50]. The ESPEN guideline authors conclude that lipid emulsions enriched with fish oil based fatty acids may be safely prescribed to patients receiving PN [18].

Protein intake is crucial for reducing muscle loss [51]. Protein and calorie targets may not always go hand in hand. The ESPEN guidelines advocate a protein target of 1.3 g/kg/day during critical illness [18]. The quality and origin of the proteins should also be taken into consideration. The amount of essential and non-essential amino acid, protein efficiency ratio, protein utilization and absorption make animal protein the optimal choice [52]. Nicolo et al. showed a reduction in mortality and length of stay when achieving more than 80% of desired protein intake [53]. Compher et al. showed similar results [54]. In a retrospective observational study of critically ill patients, Zusman et al. showed a linear association between protein intake and mortality [20]. For every gram of ingested protein there was a 1% reduction in mortality. However, the EAT-ICU prospective randomized trial compared standard nutritional care of 1.2 g/kg/day protein to a goal directed group based on indirect calorimetry and nitrogen balance measurements that received a minimum of 1.5 g/kg/day from day 1. There was no effect on morality, organ failure or infection rates [55]. In certain clinical situations such as burn victims, frail patients, cancer patients or patients suffering from acute kidney injury it is generally recommended to provide increased protein intake [56, 57]. It is still unclear whether the timing of protein administration affects patient outcomes. Bendavid et al. found early protein administration to be associated with increased survival (HR 0.83) in patients receiving protein>0.7 g/kg/day in the first 3 days following ICU admission [58]. On the other hand, Koekkoek et al. found that early high protein intake (>0.8 g/kg/day in the first 3–5 day of admission) was associated with higher 6 month mortality [59].

Amino-Acid Enriched Formulas Glutamine (GLN) is considered a non-essential amino acid as long as it is sufficiently synthetized by the skeletal muscle. In certain clinical conditions such as critical illness and burns, GLN levels decrease and mortality is increased [60] while the immune response is decreased [61]. In the REDOXS trial published in 2013, the administration of GLN supplements to critically ill patients with multi-organ failure was associated with higher mortality [62]. In another RCT from 2014 (the METAPLUS study), the prescription of an immune modulating nutrition that included GLN did not have any clinical beneficial effect and even led to an increase in 6 month mortality [63]. The ESPEN guidelines conclude that GLN supplementation should be administered in burn patients with burns >20% body surface area in the first 10–15 days of enteral nutrition and it may be considered in critically ill trauma patients in the first 5 days of enteral nutrition, perhaps longer if impaired wound healing is evident [18]. Other than these specific populations, GLN supplements are not recommended in the ICU. *β*-Hydroxy-*β*-methylbutyrate (HMB) is a metabolite of the amino acid Leucine and its positive effects on muscle mass by increasing protein synthesis and decreasing muscle catabolism have been well studied [64]. In a meta-analysis on the effect of HMB in clinical practice, results were conflicting. Only a small number of studies included critically ill patients, HMB was administered alongside GLN and arginine and it was used in different points along the hospitalization course [65]. In 2020 Nakamura et al. published a RCT examining the effect of HMB, GLN and arginine supplements on muscle loss in critically ill patients [66]. The study failed to show any decrease in muscle loss.

Micronutrients

Vitamins and trace elements are curial for proper function of metabolic processes and micronutrients deficiency can be life threatening [67]. Critically ill patients with decreased intake and increased catabolism are at additional risk to develop such deficiency. Trace elements are also known for their anti-oxidative properties and are sometimes given in higher doses in specific clinical conditions. Sepsis is one of the fields were high dose selenium have been studied [68]. In an RCT by Bloos et al. administrating high loading dose of selenium (1000 μg) followed by continues intravenous infusion of selenium to patients in septic shock or sever sepsis did not affect mortality [69]. In cardiac surgery Schmidt et al. showed significant decrease in the use of vasopressors by using high dose selenium preoperatively and during ICU stay but with effect of perioperative SOFA score. Patients with renal failure and renal replacement therapy suffer from Selenium and Zinc deficiency. Studies however have failed to normalize Selenium and Zinc level by intravenous supplements further highlighting the significant loss in these patients [70–72]. In burn victims there is substantial loss of trace elements especially Copper, Zinc and selenium and supplements of 5–8 times the recommended dietary intake is advised [73]. Finally, bariatric patients suffer from significant trace elements loss due to lack of absorption. This can lead to neuropathy, anemia, weakness etc.… resolution of symptoms may occur with intravenous supplementation [73].

The Best Route: Enteral Vs Parenteral Nutrition

When deciding on the best route to provide nutrition, a few factors must be taken into consideration. Enteral nutrition (EN) preserves intestinal function and it is the preferred option in a patient unable to consume sufficient oral intake [18]. It is however associated with more gastric and intestinal complications [74]. With Parenteral nutrition it is easier to reach caloric target [75] but some studies report higher rates of infectious complications [76]. In early studies comparing EN to PN there was significant reduction in infection rate however it was most prominent in subgroup of patients receiving significantly higher caloric intake resulting in more hyperglycemic events and liver function abnormalities. Also, studies conducted before the implementation of programs for the prevention catheter related blood stream infection, reveal a significantly higher rate of PN complications [77]. The CALORIES trail, an RCT comparing EN to PN in critically ill patients found no difference in mortality between the two groups. It is important to note that although in this study nutritional support was started early (within 36 h of admission), most patients did not reach the caloric target of 25 kcal/kg/day [78]. The NUTRIREA-2 study compared EN to PN in critically ill patients with shock that required mechanical ventilation with similar results, finding no difference in 28 day mortality or infection rates between the two groups. The risk of gut ischemia was significantly higher in the group of patients receiving EN [79]. In the clinical practice guidelines by the European society of intensive care medicine (ESICM), early EN was preferred over early PN. Their meta-analysis showed no benefit in mortality but did show a reduced infection rates in patients receiving EN. The same guidelines also recommend withholding enteral nutrition support in cases of upper GI bleeding, gastric residual volume >500 ml/6 h, bowel obstruction, bowel ischemia, abdominal compartment syndrome or high output fistula [80]. EN is not necessarily preferred over PN, and supplemental PN in patients receiving EN is in increased use. Heidegger et al. showed reduced infection rates when reaching 100% of target REE early (on day 4 of admission) compared to late (on day 8 of admission) using supplemental PN. The rates of nosocomial infections were significantly lower in the supplemental PN group, with a hazard ratio of 0.65 [81]. On the other hand, a large multi-center randomized controlled trial by Casaer et al. compared early (within 48 h of admission) to late supplemental PN (after 8 days of admission) in critically ill patients. Patients in the late supplemental PN group had significantly lower rates of infections, longer ICU and hospital stays and lower probabilities of prolonged mechanical ventilation and need for renal replacement therapy (RRT) [82]. ESPEN guidelines states that EN is preferred over PN in patients with intact GI tracts. However, PN is clearly indicated if caloric targets cannot be reached or if enteral feeding is not feasible [18].

Enteral Nutrition

There are many commercially available EN formulas. Most provide 100% of daily requirement of vitamins and trace elements when adequate calories are provided.

Timing A meta-analysis of randomized control trails compared early to late EN in critically ill patients and showed favorable outcomes in terms of mortality and the development of pneumonia in patients receiving early (within <24 h) enteral nutrition [83]. In the ESICM clinical practice guidelines early EN is preferred over delayed EN [71, 72]. ESPEN guidelines for clinical nutrition in the ICU recommend starting EN within 48 h of admission, aiming to provide 70% of REE and gradually increasing the caloric intake to no more than 100% of REE [18].

Continuous Versus Intermediate Feeding There is an ongoing debate whether to administer EN continuously or in intermittent boluses. Theoretically there are advantages for each method, but most studies fail to show significant differences. In artificially fed patients, muscle synthesis seems to come to a halt after 2–3 h despite continuous feeding. This "muscle full effect" may be due to the muscle inability to continuously absorb amino acids [84]. Even though bolus feeding helped to overcome that effect in healthy volunteers [85], a recent RCT comparing continuous to intermittent feeding early in the course of critical illness failed to show any effect on muscle loss [86]. It is not always feasible to reach caloric targets in ICU patients. Prolonged feeding cessations are common as patients are often sent to imaging studies or surgical procedures, experience high GRVs and there are many potential technical difficulties such as feeding tube removal or equipment failure, and feeding regimen progression is often lacking. Bolus feeding may potentially allow for better timing of nutritional support and help to overcome many of these technical difficulties [85]. McNelly et al. found that a larger percent of critically ill patients receiving bolus enteral feeding reached the 80% caloric target and 60% protein target [86]. On the other hand, an RCT by Chowdhury et al. found that bolus nasogastric feeding in healthy adults actually leads to higher GRVs and increased superior mesenteric artery blood volume [87]. Rhoney et al. showed similar results in brain injured patients [88]. In fact, many studies have shown no clinically relevant difference between the two modalities [89, 90]. Another emerging practice is deliberate intermittent fasting in order to induce ketogenesis and encourage autophagy [91]. Ketogenesis, ketogenic diets and ketone supplementation had some success in small animal and pediatric studies [92, 93] but RCTs are required in order to assess the clinical application. The ESPEN guidelines promote the use of continuous over bolus enteral feeding in critically ill patients [18].

Feeding Tube Placement EN can be delivered to the stomach (gastric feeding) or into the intestine (post pyloric feeding). Some studies have shown that post pyloric feeding was associated with lower rates of pneumonia [94] and better feeding tolerance [95], leading the American society of parenteral and enteral nutrition (ASPEN) and the society of critical care medicine (SCCM) to recommend the diversion of enteral infusion to the lower GI tract in patients who show signs of feeding intolerance or who are at high risk for aspiration [21]. When choosing feeding route one must consider that post pyloric tube placement requires skills, may cause feeding delays and is not without complications. Thus, most guidelines recommend that the majority of critically ill patients receive gastric feeding [18, 21].

Gastric Residual Volume Gastric intolerance can be assessed by measuring the GRV. Reignier et al. studied in a multicenter RCT the effect of not monitoring GRV on the risk of ventilator associated pneumonia in mechanically ventilated critically ill patients. Not measuring GRV was non inferior to routine (every 6 h) GRV measurements [96]. GRV measurements are currently not recommended as a routine monitoring tool but rather as means for diagnosing feeding intolerance if it is suspected. Large GRV (>500 ml/6 h) may signify feeding intolerance that requires action. Prokinetics, either erythromycin and/or metoclopramide, are recommended by most societies and the surviving sepsis campaign in cases of high GRV [21, 97]. In a meta-analysis by Singer et al., erythromycin had a clear advantage over metoclopramide and a treatment course of 48 h is recommended in patients with GRV > 500 ml [18]. If feeding intolerance persists, post pyloric feeding should be considered. Of note, although GRV > 500 ml is traditionally defined as a marker for feeding intolerance, studies have shown increased risk for mortality even in lower GRVs (>250 ml) [98, 99]. When dealing with a high GRV in a critically ill patient, contributing factors like the use of opiates, electrolyte abnormalities and hyperglycemia should be addressed [100].

Stress Ulcer Prophylaxis Stress gastritis in critically ill patients has been well documented for many years. Hemodynamic instability and coagulopathy can cause splanchnic hypoperfusion and gastric mucosa ischemia leading to significant complications [101]. The use of pharmacological stress ulcer prophylaxis has become the standard of care in ICUs but it is not clear whether they prevent clinically significant GI bleeding events [102]. In fact, studies have shown no added benefit to pharmacological prophylaxis over early enteral nutrition [103, 104].

Diarrhoea Diarrhoea is a common symptom in critically ill patients with an estimated prevalence of 14–21% [105]. Enteral feeding has long been considered a risk factor for diarrhea. A systemic review by Gramlich et al. did not find conclusive association between EN and diarrhea [106]. Thibault et al. found that EN was not a risk factor of diarrhea by itself, but when reaching >60% of caloric targets the risk of diarrhea increased by 1.75 (1.02–3.01) [107]. The use of antimicrobial treatment was also highly associated with diarrhea. It is essential to consider infectious causes in critically ill patients who develop diarrhea and treat accordingly. *Clostridium difficile* infections should be considered not only in patients receiving antibiotic therapy. Once infection has been ruled out, non-infectious etiologies should be raised. Non-infectious diarrhea may be a symptom of the pri-

mary disease such as pancreatic insufficiency, Intoxication or even lactose intolerance. In these cases, the trigger should always be treated first. Medication is another important cause for diarrhea in the critically ill. Laxatives and prokinetic drugs are obvious culprits, but antibiotics and antifungal medications must be considered as well. Diarrhea can also be related to the patient's specific diet. If this occurs in the orally fed patients, intake should consist of small meals with isotonic fluids, while in tube fed patients EN should be delivered continuously. If the diarrhea persists, consider changing enteral formula and reducing feeding rate [105].

Refeeding Syndrome Dramatic shifts in fluids and electrolytes can occur when feeding starts after prolonged starvation. This is referred to as refeeding syndrome and it can be lethal. Malnourished patients are particularly vulnerable, more so after initiation of artificial nutrition. This makes screening ICU patients for malnutrition crucial, as is continuous monitoring for its signs, namely hypophosphatemia. Diagnosing refeeding at its early stages is of key importance in order to prevent further complications. When refeeding is suspected or expected, slow progression in caloric intake is advised with close monitoring of electrolyte levels [18] (chapter "Refeeding Problems").

Parenteral Nutrition

PN provides intravenous nutrition to patients who are unable to tolerate EN or need supplemental nutrition to reach their caloric targets. As previously mentioned, in the case of a major GI failure (e.g. upper GI bleeding, bowel obstruction, bowel ischemia), PN should be used instead of EN [92]. Parenteral formulas contain carbohydrates, lipids, proteins, trace elements and vitamins, optimally in a composition suited to patient specific needs. In the past each of the elements were delivered separately but over time the three in one, or "All-in-one" (AIO) commercial admixtures where introduced. The use of AIO systems requires only one venous access, reducing infectious complications. They also save preparation time and prevent pharmacological mistakes [108–110]. Ready to use AIO commercial bags have become extremely common since they were first introduced, but personalized AIO compound bags are still an option when the clinical condition demands specific consideration [111].

Timing Doig et al. examined the effect of early PN (within 24 h of admission) compared to standard treatment in critically ill patients who had a contraindication for EN. No statistically significant different was found in mortality, infection rate and quality of life [112]. The optimal timing for nutritional support should be based on individual parameters. In the early stages of acute illness, large amounts of endogenous substrates are released from tissues and risk of overfeeding may increase [113].

Special Conditions

Shock Both ESICM clinical practice guidelines and ESPEN guidelines for nutrition in critically ill patients recommend delaying enteral nutrition in cases of uncontrolled shock and sever hemodynamic instability [18, 114]. Clinical studies are scarce but theoretically administering EN in uncontrolled shock may exacerbate splanchnic hypoperfusion and even lead to bowel ischemia. There is, however, evidence that early EN (<48 h) in patients receiving vasopressors at stable levels reduces mortality compared to delayed EN [115]. That is why the use of vasopressors does not necessarily defer EN.

Sepsis The catabolic nature of this acute illness makes septic patients highly prone to malnutrition. Septic patients are also likely to develop GI feeding intolerance subjecting them to increasing energy debt. On the other hand, in the early stages of acute illness endogenous substrate utilization supplies most of the patient's energetic needs, increasing the risk of overfeeding when delivering exogenous supplementation [18]. This phenomenon may explain the results of the aforementioned EPaNIC trial, where late initiation of PN decreased ICU mortality, hospital mortality, infection rates, mechanical ventilation days and the number of days on RRT [82]. A prospective large study by Weijs et al. found that septic patients did not benefit from early high protein intake (≥1.2 gr/kg) [116]. In contrast, non-septic patients receiving early high protein intake had a significant decrease in mortality (OR 0.42, 0.21–0.83). To summarize, nutrition in septic patients should be prescribed on a case-by-case basis after carefully evaluating patient's individual metabolic status.

Acute Kidney Injury and Renal Replacement Therapy Acute kidney injury (AKI) is a major health concern, with reported incidence of nearly 10% of hospitalized patients and 50% of ICU patients [117, 118]. Renal impairment negatively affects metabolic characteristics. Protein catabolism is enhanced, insulin resistance increases, lipolysis is reduced, fat clearance is impaired and the anti-oxidative system is suppressed owing to a pro-inflammatory status [119]. Hellerman et al. retrospectively examined substrate utilization in ICU patients with AKI. The study showed that patients with AKI consumed less carbohydrates and oxidized

much more lipids than expected [117]. Although commercial formulas contain mainly carbohydrates, the guidelines suggest increasing lipid intake while decreasing carbohydrate derived calories [119]. The same guidelines recommend patients with AKI and an acute/critical illness gradually receive 1.3 g/kg protein a day. Overall, there is no recommendation for a specific EN or PN formula for patients with AKI. However, if there are electrolyte abnormalities or significant fluid overload, concentrated, low electrolytes "renal" formulas should be preferred [119]. ICU patients who develop AKI are at increased risk for hospital mortality that may be as high as 50%. Moreover, about 5–6% of the patients will need renal replacement treatment (RRT) [120]. As in all ICU patients, patients requiring RRT should undergo IC to determine nutritional targets. Existing evidence suggests that the presence of RRT does not alter REE [121]. When prescribing a nutrition plan, additional calories from substrates like citrate, glucose or lactate provided in dialysate and replacement fluids should be taken into account. RRT can increase protein loss and therefore patients on intermittent hemodialysis (IHD) should receive 1.3–1.5 g/kg/day of protein and patients on CRRT should receive 1.5–1.7 g/kg/day [3]. Restricting protein intake during renal failure in order to postpone RRT may be considered, but only outside the acute illness scenario. Trace elements and vitamins require special consideration in patients undergoing CRRT, as they are lost on filter membranes. Monitoring and supplementing trace elements (especially selenium, zinc and copper) and vitamins (especially vitamin C, folic acid and thiamine) levels is advised [119].

COVID-19 Since the COVID-19 outbreak in 2020, there is an increasing number of ARDS patients in the ICU, experiencing prolonged hospitalizations and often recovering slowly time [122]. COVID-19 is characterized by an inflammatory burst (often referred to as "cytokine storm"), respiratory distress, hypercatabolism, reduced intake and prolonged immobilization, making patients extremely susceptible to malnutrition and muscle wasting [123]. Recent recommendations on nutrition in COVID-19 ICU patients emphasize a few practical aspects of treatment. Due to the workload during COVID-19 pandemic, often only vital procedures are performed, and the possible risk of viral spread during IC measurement may pose a threat to caregivers. Guidelines recommend the use of IC only after day 10 of hospitalization or in patients receiving full PN plan [124]. The significant energy deficit of COVID-19 patients before ICU admission makes them vulnerable to the refeeding syndrome, requiring careful electrolyte monitoring. The use of sedatives such as propofol in high doses increases the risk to develop the propofol infusion syndrome. Close monitoring of blood lactate levels, blood gases, creatinine phosphokinase (CPK) and triglycerides allows for early diagnosis [124]. EN is still the preferred route for feeding, even in patients in the prone position, despite the theoretical risk for gastroparesis and vomiting. A prospective study by Saez de la Fuente et al. found no significant difference in EN feeding intolerance, defined as high GRVs or frank vomiting, in patients in the prone position [125]. The same applies for the use of vasopressors or paralytic agents [124]. Special consideration should be made to nutritional support after liberation from mechanical ventilation. It is recommended to carefully evaluate extubated patients with suspected dysphagia and continue tube feeding if necessary. Upon initiation oral intake is rarely enough to reach nutritional targets and supplemental PN should be considered [124].

Extra Corporal Membrane Oxygenation (ECMO) ECMO is increasingly employed in ICUs, all the more so since the outbreak of the COVID-19 pandemic. ECMO patients are the most severely ill patients, very often experiencing multiorgan failure, long ICU and hospital stays and are predisposed to develop bacterial translocation and sepsis. That being said, early EN should still be administered if no other contraindication exists [18]. PN is also feasible in ECMO patients if so indicated, but lipid solutions must not be infused directly into the circuit to prevent lipid deposits and clotting [126]. The ECMO technique uses foreign materials that may aggravate the inflammatory response and induce significant loss of micro- and macronutrients [126]. A single dose ex-vivo study by Estensen et al. revealed a significant decrease in the levels of the amino acid isoleucine and of vitamins A and E [127]. This suggests some circuit loss as seen in other forms of extracorporeal life support systems [128]. On The other hand, Lindberg et al., in another ex-vivo study, found no difference in vitamin levels, lipid profile or total proteins [129]. Unlike RRT, there is no recommendation to provide ECMO patients with any additional micro- or macronutrient supplementation. Of note, the nutritional requirements during ECMO therapy are difficult to predict. These patients have an extremely dysregulated inflammatory response, are often septic and tend to require hemodynamic support. It is not currently feasible to measure REE in ECMO patients via IC and the use of the simple 25–30 kcal/kg/day is recommended, using the ideal body weight [21].

Monitoring

Patients in the ICU suffering from intestinal failure require intense monitoring to prevent complications, evaluate effectiveness of treatment and adjust nutrition plan. Table 2 sum-

Table 2 Assesment, nutritional targets and monitoring tools in patients in different stages of intestinal failure

	Acute	Post-acute	Chronic
Time	<1 week	1–3 weeks	>3 weeks
Assessment	GRV, diarrhea, stoma output	GRV, diarrhea, stoma output	Number of stools, consistency of stool, vomiting
Route	EN/PN	EN/PN	EN/PN
Energy	IC—70% of REE, trophic feeding	IC—100% of REE	IC—120% of REE
Protein	1 g/kg[a]	1.3 g/kg[a]	1.5 g/kg[a]
Monitoring	Nitrogen balance, urea, Electrolytes, fluid Balance, liver function tests[b]	Nitrogen balance, urea, electrolytes, fluid Balance, liver function tests[b]	Electrolytes, liver function tests, albumin, vit B1, Vit B12, Vit B6, selenium, zinc, vit D, DXA

GRV gastric residual volume, *EN* enteral nutrition, *PN* parenteral nutrition, *IC* indirect calorimetry, *REE* resting energy expenditure, *vit* vitamin

DEXA dual-energy X ray absorptiometry

[a]Ideal body weight

[b]*AST* aspartate transaminase, *ALT* alanine transaminase, Bilirubin, *GGT* gamma glutamyl transferase

marizes common monitoring tools in patients in different stages of intestinal failure. Physical examination is an essential part of the assessment. In the critically ill, especially those suffering from intestinal failure, special care must be taken to look for signs of muscle wasting, weight loss by daily weighing and the development of edema. Events of vomiting, bowel movement, complaints of abdominal pain and the presence of diarrhea should be documented. As mentioned, GRV measurements are not a part of routine patient monitoring, but it should be measured and accounted for when intestinal failure is suspected. Fluid status is important as it may require a change in nutrition plan along with other interventions. Laboratory tests should be obtained, including electrolytes levels (sodium, potassium, phosphate, magnesium) for nutritional adjustments and screening for the refeeding syndrome. Increased blood lactate levels may indicate intestinal ischemia and/or shock. Elevated Inflammatory markers such as white blood cell count or C-reactive protein may signify active inflammatory or infectious intestinal pathology. Indirect calorimetry should be a part of the evaluation of every ICU patient and should be repeated if the patient's clinical status changes. Finally, assessment of body composition should be performed by any of the common methods (Bioelectrical Impedance, DXA, CT, and ultrasound).

References

1. Pironi L, Arends J, Shaffer J, Home Artificial Nutrition and Chronic Intestinal Failure and the Acute Intestinal Failure Special Interest Groups of ESPEN. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34:171–80.
2. Blaser AR, Ploegmakers I, Benoit M, et al. Acute intestinal failure: international multicenter point-of-prevalence study. Clin Nutr. 2020;39:151–8.
3. Blaser AR, Jakob SM, Starkopt J. Gastrointestinal failure in the ICU. Cur Opin Crit Care. 2016;22:128–41.
4. Kaiser MJ, Bauer JM, Ramsch C, et al. Frequency of malnutrition in older adults: a multinational perspective using the mini nutritional assessment. J Am Geriatr Soc. 2010;58(9):1734–8.
5. Sheean PM, Peterson SJ, Chen Y, et al. Utilizing multiple methods to classify malnutrition among elderly patients admitted to the medical and surgical intensive care units (ICU). Clin Nutr. 2013;32:752–7.
6. Eckart A, Struja T, Schuetz P, et al. Relationship of nutritional status, inflammation, and serum albumin levels during acute illness: a prospective study. Am J Med. 2020;133(6):713–22e7.
7. Zhang Z, Pereira SL, Matheson EM, et al. Evaluation of blood biomarkers associated with risk of malnutrition in older adults: a systematic review and meta-analysis. Nutrients. 2017;9(8):829.
8. Rattanachaiwong S, Zribi B, Kagan I, et al. Comparison of nutritional screening and diagnostic tools in the diagnosis of severe malnutrition in critically ill patients. Clin Nutr. 2020;39(11):3419–25.
9. Cederholm T, Jensen GL, Correia MITD, et al. GLIM Criteria for the diagnosis of malnutrition – A consensus report from, the global clinical nutrition community. Clin Nutr. 2019;38:1–9.
10. Theilla M, Rattanachaiwong S, Singer P, et al. Validation of GLIM malnutrition criteria for diagnosis of malnutrition in ICU patients: an observational study. Clin Nutr. 2020;40:3578–84.
11. Vanhorebeek I, Latronico N, Van den Berghe G. ICU acquired weakness. Intensive Care Med. 2020;46(4):637–53.
12. Mundi MS, Patel JJ, Martindale R. Body composition technology: implication for the ICU. Nutr Clin Pract. 2019;34(1):48–58.
13. Gluer CC. 30 years of DXA technology innovations. Bone. 2017;104:7–12.
14. Shen W, Punyanitya M, Heshka S. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97:2333–8.
15. Weijs PJ, Looijaard WG, Dekker IM, et al. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. Crit Care. 2014;18:R12.
16. Ju S, Choi SM, Park YS, et al. Rapid muscle loss negatively impacts survival in critically ill patients with cirrhosis. J Intensive Care Med. 2020;35:663–71.
17. Tieland M, van Dronkelaar C, Boirie Y, et al. Sarcopenic obesity in the ICU. Curr Opin Clin Nutr Metab Care. 2019;22:162–6.
18. Singer P, Blaser AR, Bischoff SC. ESPEN guidelines on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38:48–79.
19. Dickerson RN. Hypocaloric, high-protein nutrition therapy for critically ill patients with obesity. Nutr Clin Pract. 2014;29:786e91.
20. Zusman O, Theilla M, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. Crit Care. 2016;20:367.
21. Tappy L, Chiolero R. Substrate utilization in sepsis and multiple organ failure. Crit Care Med. 2007;35(9):531–4.
22. McClave SA, Taylor BE, Braunschweig C. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and American society for parenteral and enteral nutrition (A.S.P.E.N.). J Parenter Enter Nutr. 2016;40(2):159e211.
23. Gomes F, Schuetz P, Cederholm T. ESPEN guidelines on nutritional support for polymorbid internal medicine patients. Clin Nutr. 2018;37(1):336–53.
24. Arends J, Bachmann P, Bozzetti F. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11–48.

25. Tatucu-Babet OA, Ridley EJ, Tierney AC. Prevalence of under prescription or overprescription of energy needs in critically ill mechanically ventilated adults as determined by indirect calorimetry: a systematic literature review. J Parenter Enter Nutr. 2016;40(2):212–25.
26. Zusman O, Kagan I, Singer P. Predictive equations versus measured energy expenditure by indirect calorimetry: a retrospective validation. Clin Nutr. 2019;38(3):1206–10.
27. Stapel SN, de Grooth HJ, Oudemans-van Straaten HM. Ventilator-derived carbon dioxide production to assess energy expenditure in critically ill patients: proof of concept. Crit Care. 2015;19:370.
28. Rousing ML, Hahn-Pedersen MH, Preiser JC. Energy expenditure in critically ill patients estimated by population-based equations, indirect calorimetry and CO2-based indirect calorimetry. Ann Intensive Care. 2016;6:16.
29. Oshima T, Graf S, Pichard C. Can calculation of energy expenditure based on CO2 measurements replace indirect calorimetry? Crit Care. 2017;21:13.
30. Kagan I, Zusman O, Singer P. Validation of carbon dioxide production (Vco2) as a tool to alculte resting energy expenditure (REE) in mechanically ventilated critically ill patients: a retrospective observational study. Crit Care. 2018;22:186.
31. Bousie E, Van Blokland D, Van Zanten ARH. Relevance of non-nutritional calories in mechanically ventilated critically ill patients. Eur J Clin Nutr. 2016;70:1443–50.
32. Deane AM, Summers MJ, Zaknic AV, et al. Glucose absorption and small intestinal transit in critical illness. Crit Care Med. 2011;39(6):1282–8.
33. Van den Berg B, Bogaard JM, Hop WC. High fat, low carbohydrate, enteral feeding in patients weaning from the ventilator. Int Care Med. 1994;20(7):470.
34. Alish CJ, Garvey WT, Maki KC. A diabetes-specific enteral formula improves glycemic variability in patients with type 2 diabetes. Diabetes Technol Ther. 2010;12(6):419–25.
35. Van Steen SC, Rijkenberg S, Van Der Voort PHJ. Glycemic effects of a low-carbohydrate enteral formula compared with an enteral formula of standard composition in critically ill patients: an open-label randomized controlled clinical trial. J Parenter Enter Nutr. 2018;42(6):1035–45.
36. Van Den Berghe G, Wouters P, Bouillon R. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.
37. The NICE STUDY Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
38. Yatabe T, Inoue S, Egi M. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. Intensive Care Med. 2017;43:16–28.
39. Egi M, Bellomo R, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology. 2006;105:244–52.
40. Ali NA, O'Brien JM Jr, Preiser JC. Glucose variability and mortality in patients with sepsis. Crit Care Med. 2008;36:2316–21.
41. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med. 2008;36:3008–13.
42. Krinsley JS, Preiser JC. Time in blood glucose range 70 to 140 mg/dL >80% is strongly associated with increased survival in non-diabetic patients. Crit Care Med. 2015;19:179.
43. Lanspa MJ, Krinsley JS, Hirshberg EL. Percentage of time in range 70 to 139 mg/dL is associated with reduced mortality among critically ill patients receiving insulin infusion. Chest. 2019;156:878–86.
44. Calder PC, Adolph M, Singer P. Lipid in the intensive care unit: recommendations from the ESPEN expert group. Clin Nutr. 2018;37:1–18.
45. Calder PC. Functional roll of fatty acids and their effect on human health. J Parenter Enter Nutr. 2015;39:18S–32S.
46. Koekkoek KW, Panteleon V, van Zanten AR. Current evidence on v-3 fatty acids in enteral nutrition in the critically ill: a systematic review and meta-analysis. Nutrition. 2019;59:56–68.
47. Battistella FD, Widergren JT, MacColl K. A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. J Trauma. 1997;43:52–8.
48. Furukawa K, Yamamori H, Tashiro T. Influences of soybean oil emulsion on stress response and cell mediated immune function in moderately or severely stressed patients. Nutrition. 2002;18:235–40.
49. Dai YJ, Sun LL, Wang W. Comparison of formulas based on lipid emulsions of olive oil, soybean oil, or several oils for parenteral nutrition: a systematic review and meta-analysis. Adv Nutr. 2016;15:279–86.
50. Pradelli L, Mayer K, Muscaritoli M. Ω-3 Fatty acid enriched parenteral nutrition in hospitalized patients: systematic review with meta-analysis and trial sequential analysis. J Parenter Enter Nutr. 2020;44:44–57.
51. Biolo G, Tipton KD, Kelin S, Wolfe RR. An abundant supply of amino acids enhances the metabolic effect of exercise on muscle protein. Am J Phys. 1997;273:E122–9.
52. Singer P, Glass YD, Kagan I. The best recipe: fat based, protein based, single amino acid? Curr Opin Crit Care. 2020;26(4):335–40.
53. Nicolo M, Heyland DK, Compher C. Clinical outcome related to protein delivery in the critically ill population: a multicenter, multinational observation study. J Parenter Enter Nutr. 2016;40:45–51.
54. Compher C, Chittams J, Heyland DK. Greater protein and energy intake may be associated with improved mortality in higher risk critically ill patients: a multicenter, multinational observational study. Crit Care Med. 2017;45:156–63.
55. Allingstrup MJ, Kondrup J, Wils J. Early goal directed nutrition versus standard of care in adult intensive patients: the single center, randomized, outcome assessor blinded EAT-ICU trail. Intensive Care Med. 2017;43:1637–47.
56. Arends J, Bodoky G, Znader A. ESPEN guidelines on enteral nutrition: non-surgical oncology. Clin Nutr. 2006;25:245–59.
57. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. Lancet. 2004;363:1895–902.
58. Bendavid I, Zusman O, Singer P, et al. Early adminestraion of protein in critically ill patients: a retrospective cohort study. Nut. 2019;11:106.
59. Koekkoek WAC, van Setten CH, van Zanten ARH, et al. Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENtilation: the PROTINVENT retrospective study. Clin Nutr. 2019;38:883–90.
60. Rodas PC, Rooyackers O, Wernerman J, et al. Glutamine and glutathione at ICU admission in relation to outcome. Clin Sci (Lond). 2012;122(12):591–7.
61. Oehler R, Pusch E, Dungel P, et al. Glutamine depletion impairs cellular stress response in human leucocytes. Br J Nutr. 2002;87:S17–21.
62. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368(16):1489–97.
63. van Zanten AR, Sztark F, Kaisers UX, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. JAMA. 2014;312(5):514–24.
64. Wilkinson DJ, Hossain T, Ashcroft S, et al. Impact of the calcium form of beta-hydroxy-beta-methylbutyrate upon human skeletal muscle protein metabolism. Clin Nutr. 2018;37:2068–75.

65. Bear DE, Langan A, Dimidi E, et al. b-Hydroxy-b-methylbutyrate and its impact on skeletal muscle mass and physical function in clinical practice: a systematic review and meta-analysis. Am J Clin Nutr. 2019;109:1119–32.
66. Nakamura K, Kihata A, Naraba H, et al. Morimura-b-hydroxy-b-methylbutyrate arginine, and glutamine complex on muscle volume loss in critically ill patients: a randomized control trial. JPEN J Parenter Enteral Nutr. 2020;44:205–12.
67. Vankrunkelsven W, Gunst J, Casaer MP. Monitoring and parenteral administration of micronutrients, phosphate and magnesium in critically ill patients: the VITA-TRACE survey. Clin Nutr. 2021;40(2):590–9.
68. Valenta J, Brodska H, Kazda A. High-dose selenium substitution in sepsis: a prospective randomized clinical trial. Int Care Med. 2011;37:808–15.
69. Bloos F, Trips E, Reinhart K. Effect of sodium selenite administration and procalcitonin-guided therapy on mortality in patients with severe sepsis or septic shock: a randomized clinical trial. JAMA Intern Med. 2016;176(9):1266–76.
70. Schmidt T, Pargger H, Seeberger E, Eckhart F, von Felten S, Haberthur C. Effect of high-dose sodium selenite in cardiac surgery patients: a randomized controlled bi-center trial. Clin Nutr. 2018;37(4):1172–80.
71. Tonelli M, Wiebe N, Thompson S, Kinniburgh D, Klarenbach SW, Walsh M, et al. Trace element supplementation in hemodialysis patients: a randomized controlled trial. BMC Nephrol. 2015;16:52.
72. Ben-Hamouda N, Charrière M, Voirol P, Berger MM. Massive copper and selenium losses cause life-threatening defciencies during prolonged continuous renal replacement. Nutrition. 2017;34:71–5.
73. Singer P, Manzanares W, Berger MM. What's new in trace elements? Int Care Med. 2018;44(5):643–5.
74. Gungabissoon U, Hacquoil K, Bains C. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. J Parenter Enter Nutr. 2015;39:441–8.
75. Ridley EJ, Daives AR, McGuinness S, for the Supplemental Parenteral Nutrition Clinical Investigators. Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomized control study. Crit Care. 2018;22:12.
76. Elke G, van Zanten ARH, Heyland DK. Enteral versus parenteral nutrition in critically ill patients: an updated systemic review and meta-analysis of randomized controlled trails. Crit Care. 2016;20:117.
77. Hellerman IM, Singer P. Advances in medical nutrition therapy: parenteral nutrition. Nutrients. 2020;12:717.
78. Harvey SE, Parrott F, Rowan KM, for the CALORIES Trail Investigators. Trail of the route of early nutritional support in critically ill adults. N Engl J Med. 2014;371:1673–84.
79. Reignier J, Boisrame-Helms J, Le Gouge A, for the NUTRIREA-2 Trail Investigators and the Clinical Research in Intensive Care and Sepsis (CRICS) Group. Enteral versus Parenteral early nutrition in ventilated adults with shock: a randomized, controlled, multicenter, open-label, parallel-group study (NUTRIREA-2). Lancet. 2018;391:133–43.
80. Blaser AR, Starkopf J. Alhazzani W and the ESICM working group on gastrointestinal function. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med. 2017;43:380–98.
81. Heidegger CP, Berger MM, Pichard C. Optimization of energy provision with supplemental parenteral nutrition in critically ill patients: a randomized controlled trial. Lancet. 2013;381:385–93.
82. Casaer MP, Messoten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults (EPaNIC). N Engl J Med. 2011;365:506–17.
83. Tian F, Heighes PT, Diog GS. Early enteral nutrition provided within 24 hours of ICU admission: a meta-analysis of randomized control trails. Crit Care Med. 2018;46(7):1049–56.
84. Atherton PJ, Etheridge T, Watt PW, et al. Muscle full effect after oral protein: time-dependent concordance and discordance between human muscle protein synthesis and mTORC1 signaling. Am J Clin Nutr. 2010;92:1080–8.
85. Puthucheary Z, Gunst J. Are periods of feeding and fasting protective during critical illness? Cur Opin Clin Nutr Metab Care. 2021;24:183–8.
86. McNelly AS, Bear DE, Connolly BA, et al. Effect of intermittent or continuous feed on muscle wasting in critical illness: a phase 2 clinical trial. Chest. 2020;158:183–94.
87. Chowdhury AH, Murray K, Lobo D, et al. Effects of bolus and continuous nasogastric feeding on gastric emptying, small bowel water content, superior mesenteric artery blood flow, and plasma hormone concentrations in healthy adults: a randomized crossover study. Ann Surg. 2016;263:450–7.
88. Rhoney DH, Parker D Jr, Coplin WM, et al. Tolerability of bolus versus continuous gastric feeding in brain-injured patients. Neurol Res. 2002;24:613–20.
89. Evans DC, Forbes R, Thongrong, et al. Continuous versus tube feeds: does modality affect glycemic variability, tube feeding volume, caloric intake or insulin utilization? Int J Crit Illness Inj Sci. 2016;6:9–15.
90. Argilera-Martinez R, Barrado-Narvion J, et al. Effectiveness of continuous enteral nutrition versus intermittent enteral nutrition in intensive care patients: a systematic review. JBI Database Syst Rev Implement Rep. 2014;12:281–317.
91. Gunset J, Casaer MP, Van Der Berghe G. Role of ketones, ketogenic diets and intermittent fasting in ICU. Curr Opin Crit Care. 2021;27:385–9.
92. Goossens C, Weckx R, Derde S, et al. Adipose tissue protects against sepsis-induced muscle weakness in mice: from lipolysis to ketones. Crit Care. 2019;23:236.
93. De Bruyn A, Gunst J, Goossens C, et al. Effect of withholding early parenteral nutrition in PICU on ketogenesis as potential mediator of its outcome benefit. Crit Care. 2020;24:536.
94. Acosta-Escribano J, Fernández-Vivas M, Menendez-Mainer A, et al. Gastric versus transpyloric feeding in severe traumatic brain injury: a prospective, randomized trial. Intensive Care Med. 2010;36:1532e9.
95. Davies AR, Morrison SS, Bailey MJ, Bellomo R, Doig GS, et al. A multicenter, randomized controlled trial comparing early nasojejunal with nasogastric nutrition in critical illness. Crit Care Med. 2012;40:2342–8.
96. Reigner J, Mercier E, Le Gouge A, Boulain T, Desachy A, Bellec E, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a controlled randomized trial. JAMA. 2013;209:249–56.
97. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis initiative. Intensive Care Med. 2017;43:304–77.
98. Blaser AR, Strakopf J, Deane AM. Definition, prevalence, and outcome of feeding intolerance in intensive care: a systematic review and meta-analysis. Acta Anaesthesiol Scand. 2014;58:914–22.
99. Heyland DK, Ortiz A, Day AG. Incidence, risk factors, and clinical consequence of enteral feeding intolerance in the mechanically ventilated critically ill: an analysis of a multicenter, multiyear database. Crit Care Med. 2021;49:49–59.
100. Sandoval AV, Ghamande S, Surani S. Critically ill patients and gut motility: are we addressing it? World J Gastrointest Pharmacol Ther. 2017;8:174–9.

101. Quenot JP, Thiery N, Barbar S. When should stress ulcer prophylaxis be used in the ICU? Curr Opin Crit Care. 2009;15(2):139–43.
102. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. Intensive Care Med. 2015;41(5):833–45.
103. Huang HB, Jiang W, Du B, et al. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: a systematic review and meta-analysis. Crit Care. 2018;22:20.
104. El-Kersh K, Jalil B, Saad M, et al. Enteral nutrition as stress ulcer prophylaxis in critically ill patients: a randomized controlled exploratory study. J Crit Care. 2018;43:108–13.
105. Reintam BA, Deane AM, Fruhwald S. Diarrhoea in the critically ill. Curr Opin Crit Care. 2015;21(2):142–53.
106. Gramlich L, Kichien K, Pinilla J, et al. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition. 2004;20:843–8.
107. Thibault R, Graf S, Delieuvin N, et al. Diarrhoea in the ICU: respective contribution of feeding and antibiotics. Crit Care. 2013;17:R153.
108. Alfonso JE, Berlana D, Boullata J. Clinical, Ergonomic and Economic outcomes with multichamber bags compared with (Hospital) Pharmacy compounded bags and multibottle systems: a systemic Literature review. J Parenter Enter Nutr. 2017;41:1162–77.
109. Schwarz G, Sierro C, Griffiths W. Convenience and cost-efficiency by the use of multicompartment bags for total parenteral nutrition. In: Proceedings of the XVIII ESPEN congress on clinical nutrition and metabolism. 1996.
110. Baras Z, Theilla M, Singer P. From compound to "ready to use" parenteral nutrition bags use in a tertiary medical center: an observational study. Clin Nutr. 2019;38(1):S270–1.
111. Hellerman MI, Singer P. Advances in medical nutrition therapy: parenteral nutrition. Nutrition. 2020;12:717.
112. Doig GS, Simpson F, Peake S, for the Early PN Investigators of the ANZICS Clinical Trials Group. Early parenteral nutrition in critically ill patients with short term relative contraindication to early enteral nutrition. A randomized controlled trail. JAMA. 2013;309:2130–8.
113. Blaser AR, Starkopf J, Oudemans-van Straaten HM, et al. Early enteral nutrition in critically ill patients: ESCIM clinical practice guidelines. Intensive Care Med. 2017;43:380–98.
114. Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. Am J Crit Care. 2010;19:261–8.
115. Oshima T, Berger MM, Pichard C. Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. Clin Nutr. 2017;36:651–62.
116. Weijs PJ, Looijaard WG, Oudemans-van Straaten HM, et al. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care. 2014;18:701.
117. Hellerman M, Sabatino A, Singer P, et al. Carbohydrate and lipid prescription, administration and oxidation in critically ill patients with acute kidney injury. A Post hoc analysis. J Ren Nutr. 2019;29:289–94.
118. Case J, Khan S, Khan A, et al. Epidemiology of acute kidney injury in the intensive care. Crit Care Res Pract. 2013;2013:479730.
119. Fiaccadori E, Sabatino A, Cuerda C. ESPEN guidlineson clinical nutrition in hospitalized patients with acute and chronic kidney disease. Clin Nut. 2021;40:1644–68.
120. Kam Tao Li P, Gurdmann EA, Mehta RL, et al. Acute kidney injury: global health alert. Kidney Inter. 2013;86:372–6.
121. de Oliveira MC, Bufarah MNB, Balbi AL, et al. Poor agreement between indirect calorimetry and predictive formula of rest energy expenditure in pre-dialytic and dialytic chronic kidney disease. Clin Nutr ESPEN. 2018;28:136.
122. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–81.
123. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
124. Thibault R, Seguin P, Singer P, et al. Nutrition in the COVID-19 patient in intensive care unit (ICU): a practical guidance. Crit Care. 2020;24:447.
125. Saez de la Fuente I, Saez de la Fuente J, Quintana Estelles MD, et al. Enteral nutrition in patients receiving mechanical ventilation in a prone position. J Parenter Enter Nutr. 2016;40:250–5.
126. Stoppe C, Nesterova E, Elke G. Nutritional support in patients with extracorporeal life support and ventricular assist devices. Curr Opin Crit Care. 2018;24:269–76.
127. Estensen K, Shekar K, Robins E, et al. Macronutrient and micronutrient disposition in an ex vivo model of extracorporeal membrane oxygenation. Intensive Care Med Exp. 2014;2:29.
128. Lumlertgul N, Bear DE, Ostermann M. Clearance of micronutrients during continuous renal replacement therapy. Crit Care. 2020;24:616.
129. Lindberg BR, Videm V, Thiara AS, et al. Influence of the ECMO circuit on the concentration of nutritional supplements. Sci Rep. 2020;10:19275.

Eating Disorders in Adults

Paul Robinson and David Russell

Key Points

1. Eating disorders are common and can appear in any medical context.
2. The main types involve weight loss, binge eating ad vomiting and intermediates occur.
3. Having an eating disorder is not a lifestyle choice. The patients are driven by extreme concerns about weight and shape that they cannot control.
4. Anorexia nervosa is the psychiatric disorder with the highest standardized mortality ratio
5. If you are a non-specialist and you meet an acutely ill patient with an eating disorder, look up "Medical emergencies in eating disorders (MEED)" guidelines 2022 which have replaced the senior and junior MARSIPAN ones and follow its advice.
6. The outcome for eating disorders is not that bad, but not good enough, with around half making a full recovery, more if the patient is young and has a short history.
7. The literature is large. We recommend The NICE guideline [1] and the MEED guidelines[1] [2]. Available on-line

Basic Information

Definitions: What are eating disorders?

And why are they of interest to general medical services?

Eating disorders originate in a conviction, shared by many in the West, especially females, that one's body weight is too high and body shape too large. Whereas most people with this conviction might moderately reduce their nutritional intake often with little long term impact on weight, patients with some eating disorders take these behaviours to extremes and add others. They may be successful in reducing weight and can end up profoundly malnourished or they may lose a smaller amount and proceed to overeating (binge eating) and compensatory behaviours such as vomiting or laxative abuse. This introduces two of the currently recognised eating disorders anorexia nervosa and bulimia nervosa. The difference between common dieting and an eating disorder is that the patient takes dieting to such an extreme that their life can be at risk [1–3]. The reasons they do that are not fully understood, but genetic, developmental, family, social and cultural factors are all believed to play a part [3].

Another presentation is that of the patient whose weight is in the obesity range and who engages in binge eating, sometimes following attempts to lose weight. In this case there are

[1] https://www.rcpsych.ac.uk/improving-care/campaigning-for-better-mental-health-policy/college-reports/2022-college-reports/cr233.

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no compensatory behaviours and the condition is called Binge Eating Disorder (Box 3) although this can occur at normal weight.

A fourth eating disorder associated with nutritional restriction but not body image disturbance is ARFID or avoidant restrictive food intake disorder.

All these eating disorders have been defined in the most recent version of the American Psychiatric Association classification, the DSM 5 [4] and the essentials of the three main conditions are listed in Boxes 1, 2, and 3. Pica, which is the consumption of non-nutritive substances, and Rumination Disorder, with recurrent regurgitation of gastric contents, have also been included under eating disorders in the DSM 5. Atypical eating disorders are now classed as Other Specific Feeding and Eating Disorder (OSFED) and Unspecified Feeding or Eating Disorder (UFED).

Box 1 DSM-5 Criteria for Anorexia Nervosa

According to the DSM-5 criteria, to be diagnosed as having Anorexia Nervosa a person must display:

- Persistent restriction of energy intake leading to significantly low body weight (in context of what is minimally expected for age, sex, developmental trajectory, and physical health).
- Either an intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain (even though significantly low weight).
- Disturbance in the way one's body weight or shape is experienced, undue influence of body shape and weight on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight

Subtypes: Restricting type and Binge-eating/purging type.

Box 2 DSM 5 Criteria for Bulimia Nervosa

According to the DSM-5 criteria, to be diagnosed as having Bulimia Nervosa a person must display:

- Recurrent episodes of binge eating. An episode of binge eating is characterised by both of the following:
  - Eating, in a discrete period of time (e.g. within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.
  - A sense of lack of control over eating during the episode (e.g. a feeling that one cannot stop eating or control what or how much one is eating).
- Recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, or other medications, fasting, or excessive exercise.
- The binge eating and inappropriate compensatory behaviours both occur, on average, at least once a week for three months.
- Self-evaluation is unduly influenced by body shape and weight.
- The disturbance does not occur exclusively during episodes of Anorexia Nervosa.

Box 3 DSM-5 Criteria for Binge Eating Disorder

According to the DSM-5 criteria, to be diagnosed as having Binge Eating Disorder a person must display:

- Recurrent episodes of binge eating. An episode of binge eating is characterised by both of the following:
  - eating, in a discrete period of time (e.g. within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.
  - a sense of lack of control over eating during the episode (e.g. a feeling that one cannot stop eating or control what or how much one is eating).
- The binge eating episodes are associated with three or more of the following:
  - eating much more rapidly than normal
  - eating until feeling uncomfortably full
  - eating large amounts of food when not feeling physically hungry
  - eating alone because of feeling embarrassed by how much one is eating
  - feeling disgusted with oneself, depressed or very guilty afterward
- Marked distress regarding binge eating is present
- Binge eating occurs, on average, at least once a week for three months
- Binge eating not associated with the recurrent use of inappropriate compensatory behaviours as in Bulimia Nervosa and does not occur exclusively during the course of Bulimia Nervosa, or Anorexia Nervosa methods to compensate for overeating, such as self-induced vomiting.

Definitions

The definitions of the main eating disorders as described in DSM5 are listed in Boxes 1, 2 and 3. Anorexia nervosa is characterised by self-induced low weight, avoidance of weight gain and a disturbance in body image. In bulimia nervosa the patient attempts to lose weight and may have some success, but then is overcome by urges to eat and suffers episodes of binge eating followed often by vomiting or laxative abuse. Binge eating and vomiting may also complicate low weight anorexia nervosa. In binge eating disorder distressing binge eating occurs unaccompanied by compensatory behaviours. This condition is often associated with obesity and is commonly seen in patients seeking bariatric surgery. Usually the diagnosis of an eating disorder is not difficult because of the weight loss, unexplained by other conditions, body image concerns, resistance to weight gain, binge eating, vomiting or laxative abuse. However, if the prevalence of eating disorders within a particular environment (e.g. a diabetic or gastroenterology clinic) is sought, clinicians may use the SCOFF questionnaire [5] which is very brief and has very high sensitivity (case detection) but a lower specificity (more false positives).

Epidemiology

Estimates vary in different studies but on average [6] the figures for prevalence in the West are 0.4% of young women for anorexia nervosa 1% for bulimia nervosa and 1–2% for binge eating disorder. Hence taking AN and BN together the prevalence of an eating disorder among young women the prevalence of eating disorders is about 3–4%. Men also suffer from anorexia and bulimia nervosa at 10–30% of the female data and for binge eating the sex ratio is about 3 men to 5 women. Hence eating disorders are sufficiently common for all doctors to be liable to see an affected patient in the course of his or her practice.

Different Presentations of Eating Disorders

Sir William Osler, one of the founders of the Johns Hopkins Medical School coined the term "The great imitator" when describing syphilis and its multifarious manifestations. These days several diseases compete for this description and eating disorders have a good case. Because eating disorders appear (whether or not the physician is aware) in almost every medical clinic, the most important clinical presentations will be described in turn.

Acute Nutritional Deficiency

This is one of the most alarming presentations in clinical medicine. The front-line doctor will usually consult Wikipedia (check "Anorexia Nervosa", "Admission to hospital"), even though respectable publications do not allow their articles in a reference list. The patient is usually but not always a young female and the history may be fairly brief with two or three months of severe dietary restriction sometimes with vomiting or laxative abuse, or the patient may have well established anorexia nervosa of several years duration. She may be carried into the emergency room or brought in on a wheelchair. She will show severe muscle wasting and her appearance may be reminiscent of a concentration camp survivor. In contrast with her emaciated appearance, she may be alert and bright although she may equally be cognitively impaired with slurred speech, depending on central nervous system nutrition. The assessing doctor in the emergency room may suspect a malignancy or other wasting condition. However, an eating disorder should be suspected from the age and gender of the patient, and confirmed as in the following conversation in which the patient is concealing some of her symptoms:

Doctor: You seem to have lost a lot of weight. Can you tell me how this happened?

Patient 1 (female age 19): I don't know, it just went down without me noticing.

Doctor: How do you feel about the weight loss?

Patient 1: I don't mind it really. I still feel that I could lose just a little more. Although I don't mind if it stays like this. I feel so weak. Can you help me?

Doctor: Well, starting to increase your food would really help that.

Patient 1: Can we do that later? I don't feel ready just now.

The doctor will be highly suspicious that anorexia nervosa might be the diagnosis, and attempt to contact a relative to obtain further information that might indicate recent food refusal, body image preoccupation or evidence of vomiting. If tests are required to exclude other disorders which might present in this way such as Addison's Disease or tuberculosis, they should be done quickly and management of the malnutrition, with a probable diagnosis of anorexia nervosa, should begin.

In the history, ask about recent nutrition, excess water drinking, a history of fractures and muscle weakening, with difficulty climbing stairs, overeating and vomiting. Ask if others have noticed and expressed concern about weight loss and whether anyone (relative, doctor) has mentioned anorexia. What does the patient think might be wrong?

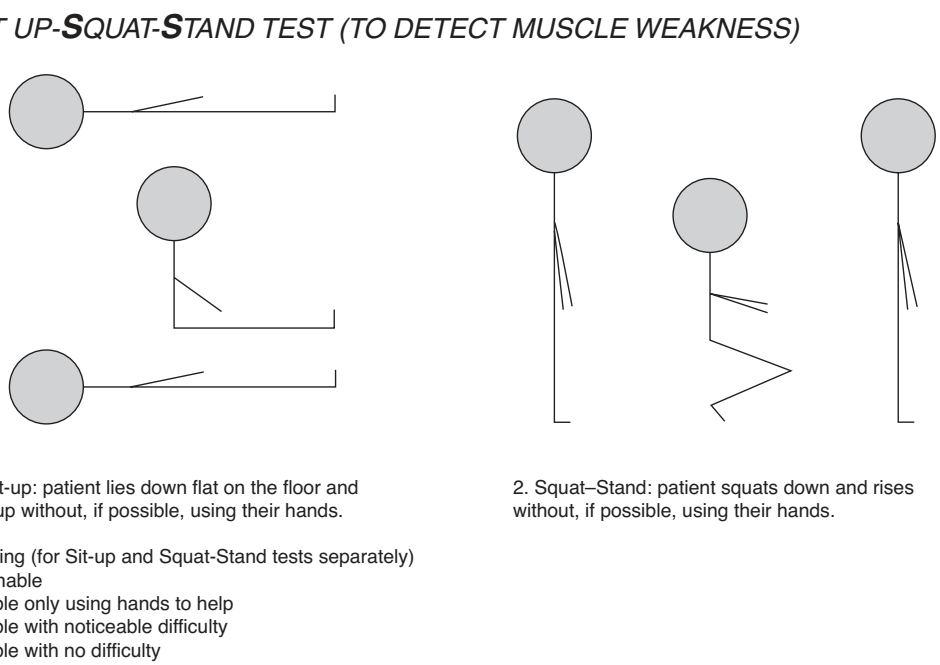

Fig. 1 The SUSS test (Royal College of Psychiatrists. With permission) [7]

Continuing with physical examination, look for swelling of the parotid glands (bingeing and vomiting), lanugo hair (fine downy hair on the back, face and elsewhere) and muscle atrophy. Check the dorsa of the dominant hands for calluses due to induced vomiting (Russell's sign). If the patient is not obviously weak, ask her to do the SUSS test (Sit Up Squat Stand) (Fig. 1). This is a reliable test of muscle power with the following scale: 0: unable to rise from squatting or sit up from lying flat, 1: Able to rise or sit up only by using hands to help, 2: Able to rise or sit up but with noticeable difficulty, 3: able to rise or sit up with no difficulty.

Check the pulse which may be under 50 or less at low weight, and see if the patient gets dizzy on standing. Check the lying and standing BP and see if the difference is >20 mm Hg. Measure the core temperature. Hypothermia occurs in malnourished patients who sometimes deliberately expose themselves to cold in order to shiver and hence lose more weight.

The pathophysiological changes attribute to starvation are summarised in Box 4. The clinically significant ("red flag") manifestations of these pathophysiological changes on anorexia nervosa are summarised in Box 5.

The investigations that apply specifically to an eating disorder are urea and electrolytes, liver function tests, calcium, phosphate, magnesium and electrocardiogram. Hypokalaemia suggests vomiting or laxative abuse, hyponatraemia may indicate excess water drinking, sometimes to conceal weight loss when on the scale and raised urea and creatinine may indicate dehydration or, sometimes, renal insufficiency. Raised transaminase levels are common and appear to be related to malnutrition. They may increase transiently during refeeding but then go back to normal. There is almost never an indication for liver biopsy. Blood glucose can fall as metabolism moves from carbohydrate based to fat based when glycogen stores have become exhausted. The patient may be alert because the brain is using fatty acids for energy. She may however require glucose and hypoglycae-

Box 4 Pathophysiological Changes of Starvation

Starvation

- Reduced carbohydrate fuel source leads to increase: (1) Ketosis (2) Proteolysis
- Loss of lean body mass affects major organs
- Atrophy of the myocardium → poor contractility and ↓ Cardiac Output Thiamine deficiency
- Gastrointestinal atrophy → malabsorption and dysmotility

(1) Translocation bacteria (2) Gastroparesis

- Pancytopenia – increase in infection
- Intracellular loss of electrolytes—(K^+/PO_4^{--}) and intracellular water
- Micronutrient Deficiency-trace elements and vitamins
- Insulin secretion, GH release and thyroid function are all diminished → the basal metabolic rate slows down to 20% to 25% to conserve energy
- Consequently, the body becomes bradycardic, hypothermic, and hypotensive

Box 5 Red Flag Findings in Severe Eating Disorders (See MEED [2])

System	RED Finding	Note
BMI	<13	BMI can be higher if weight loss rapid
Weight loss	>1 kg per week	
CVS	HR < 40 bpm	
	Standing SBP < 90 mm Hg with syncope	
Dehydration	Clinically present	
Core temperature	<35 °C	
Muscle strength	SUSS test (Fig. 1) score < 2	Or use Hand Grip Strength
Comorbidities	Sepsis, bleeding	
	Diabetes Mellitus: HbA1C > 10%	
ECG	Any significant abnormality	Bradycardia, T wave changes
	Prolonged QTc	
Biochemistry	Na K P. Ca	Reduced P, K, Mg suggest refeeding syndrome. Reduced Na suggests water loading and reduced K suggests vomiting or laxative abuse
	Low Glu (<3mmol/L) or if diabetic HbA1C>10%	
	Transaminases up to 3× ULN	
Haematology	Reduced WBC Rarely pancytopenia	
Food refusal	<500 kcal per day	
Activity	Compulsive exercise	
Purging	Self induced vomiting, Laxative abuse	
Self harm, suicide	Self poisoning, suicidal thoughts/ intent	

mia should not be neglected. The blood count may show mild anaemia, usually of mixed origin (mostly iron deficiency and marrow hypoplasia) and platelets can be low in extreme malnutrition and accompanied by a purpuric thrombocytopaenic rash and pancytopenia in gelatinous transformation of the marrow [8]. The ECG can show almost any abnormality with ST and T changes which suggest ischaemia, but which probably indicate reduced energy delivery to the heart, and prolonged QTc (>450 ms) which is thought to predict serious cardiac arrhythmias.

The nutritional management of a patient such as the one described comprises three phases: resuscitation, repair and repletion [9]. The role of the emergency department is to resuscitate and perhaps begin the other phases. A detailed guide to managing this clinical situation is provided in the MEED guidelines and textbook [2, 7, 10] which readers are advised to consult. A broad outline will be provided here. The MEED guideline, are accompanied by the MeeD checklist (Fig. 2) applicable to all ages and this will be described in order to highlight the essential clinical approaches in this very difficult situation.

The first column covers assessment: 1. Does the patient have anorexia nervosa? The diagnosis may be apparent either from information from the patient or relative as described above. If there is doubt, and this will be unusual, ask the opinion of the on-call psychiatrist. 2. Are there significant risk factors? a. Low BMI, <13 in adults indicate high risk. b. Rate of weight loss: has weight been lost at over 1 kg per week for two consecutive weeks? c. Little or no nutrition for >5 days. This predisposes to refeeding syndrome. d. Abnormalities on examination, in blood tests and ECG all contribute to risk.

The middle column is concerned with refeeding. 1. Is the patient so ill that intensive care is required? 2. Are there risk factors for refeeding syndrome (RFS)? This is dealt with elsewhere in this book. Here it should be mentioned that in anorexia nervosa, abnormal electrolytes, very low BMI, and significant co-morbidities (see checklist) all increase the risk of RFS. Advice is given to begin refeeding at low rates if the risk of RFS is vey high, but to build up quickly in order to avoid the equally dangerous underfeeding syndrome (UFS) in which too few calories are provided with sometimes fatal results. 3. If the risk of RFS is not too high, begin with higher rates of refeeding and 4. Give thiamine and 5. Monitor closely.

The right hand column is for general management. 1. Are medics and psychs collaborating closely? This is very important. It is not acceptable for the psychiatrists to leave the scene until the patient is better. Equally, physicians must make sure that the mental health staff, who could be from an eating disorder service (best) or from a liaison or general psychiatry service, are called and involved in treatment planning and staff support. 2. Are the staff trained? Usually not. The senior staff must make sure that staff on every shift, especially if from an agency, are familiar with the patient's symptoms, likely behaviour and potential problems and their management. A one side sheet of paper detailing the treatment plan and what to do if things go wrong should be given to all staff working directly with the patient. 3. Are there psychological factors that increase risk? Falsifying weight is common in patients with anorexia nervosa who are afraid that weight loss or failure to gain weight might lead clinicians to increase their calories, begin tube feeding, arrange admission to an eating disorders inpatient unit, or begin proceedings to force nutrition under the Mental Health Act. Methods vary and test the powers of observation and deduction of the clinician.

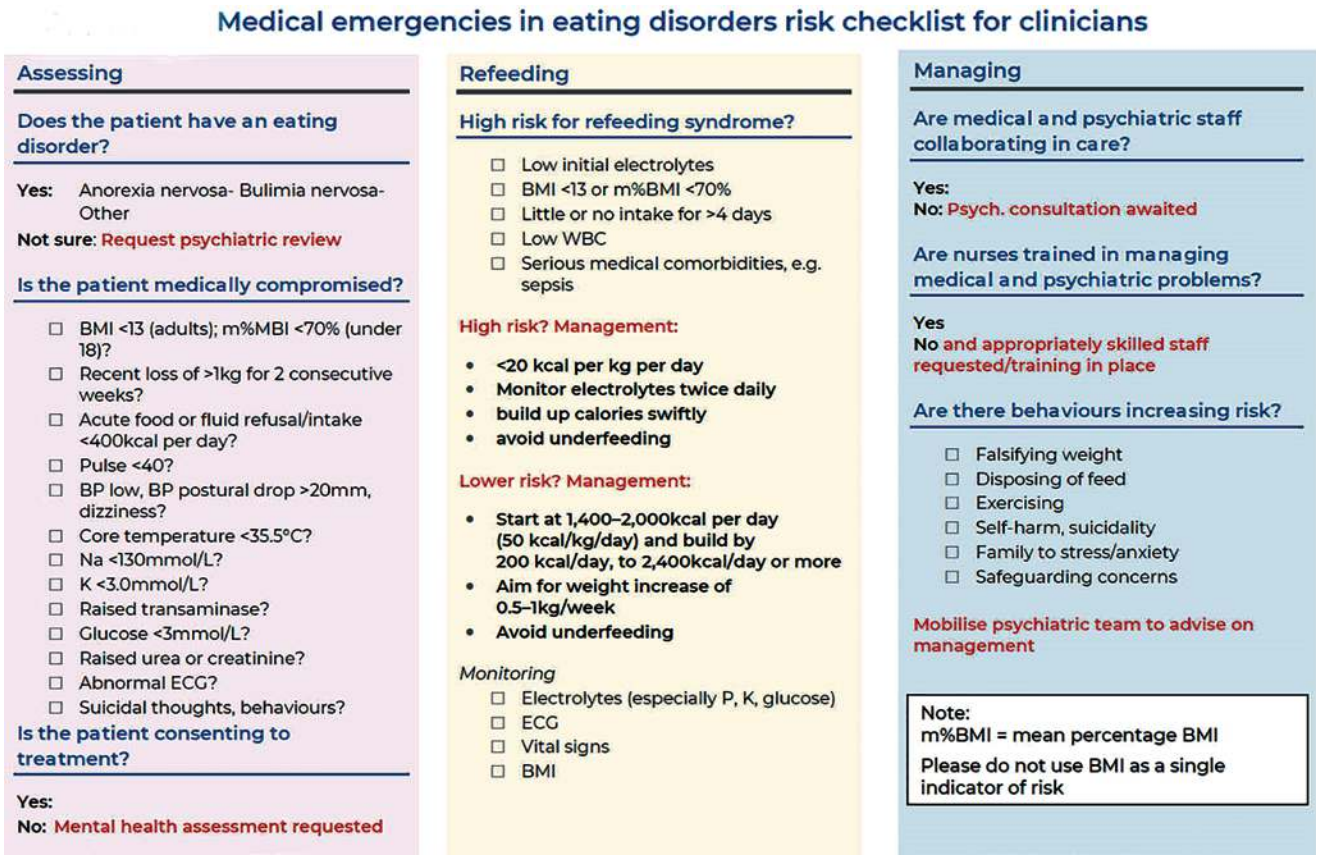

Fig. 2 The MEED Checklist (Royal College of Psychiatrists. With permission)

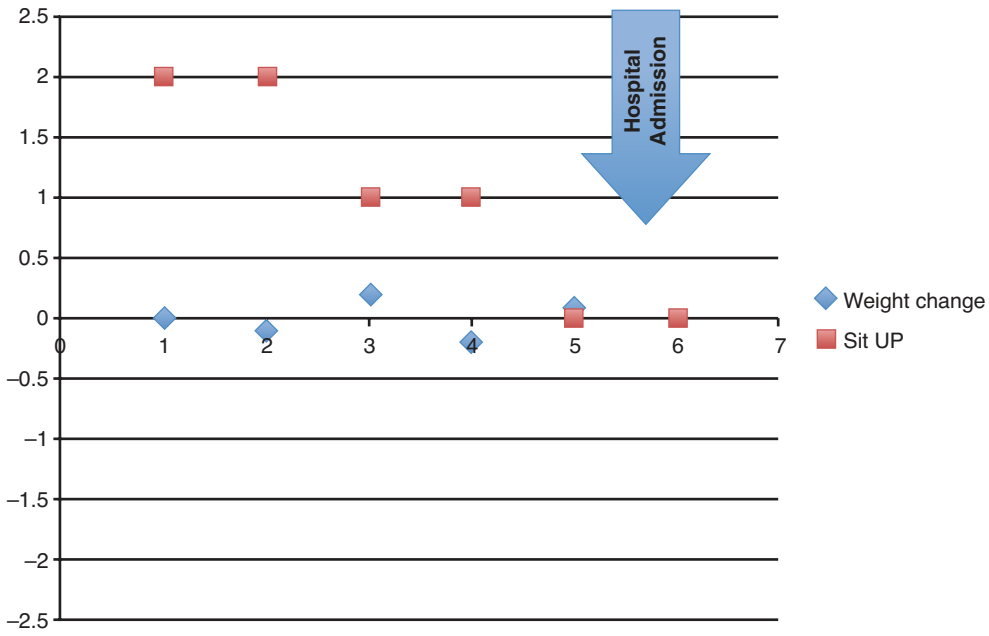

Fig. 3 A graph of weight change in kg (diamonds, from 37.5 kg) each week and the Sit Up test on the same day (squares). The weight stays stable but the Sit Up scores decline. The patient is admitted (down arrow) and weight immediately falls by 2 kg

Patient 2 was being seen in the outpatients' department for severe anorexia nervosa. Her weight was 37.5 kg and her BMI 13.5. Every week she was seen in the clinic she was weighed and the SUSS test (see above and [7]) was performed. Her weight appeared to be stable and her BMI was above the high risk range (<13). However, her Sit Up test declined and on the basis the consultant decided to admit her to hospital against her wishes. After admission her weight immediately fell to 35.5 kg, BMI 12.8. Her comment was "Doctor, I'm so glad you admitted me. I couldn't have

managed to drink any more water." She was drinking 2 litres of water whenever she was weighed prior to admission. (See Fig. 3*).*

Patient 3: This patient was being seen by a therapist in an outpatient clinic and being weighed weekly. Her BMI was 15.5 (weight 41.7 kg) so she was not regarded as very high risk. However, her therapist that she thought that the patient was looking thinner. Two days later the patient was admitted to a medical ward in status epilepticus. She was treated and woke up from the fit 24 h later. Her sodium on admission was 119 mmol/L (normal range 135–145) and two days later she weighed 35.1 kg (BMI 13). She admitted to massive water loading prior to her therapy for fear of admission. When asked how she managed to "gain" 8 kg she said that she would go into the shower, place the shower rose in her mouth and turn on the water.

Disposing of food: This is a common practice in hospital and at home and is sometimes evidenced by the family cat becoming obese! In hospital, patients have been known to dispose of nasogastric feed in the sink, the toilet and even into a pillow into which a hole has been drilled.

Patient 4: A patient with anorexia nervosa and a borderline personality disorder was admitted to a general psychiatric ward with a BMI of 13. She spent four weeks there and appeared to be eating well. However her weight stayed exactly the same and eventually she was discharged because of lack of progress. After she left a smell was noticed in her en-suite bathroom. Investigation revealed a large amount of rotting food when the side panel of her bath was unscrewed.

Secretive exercise: This is also common. Many acute hospitals have signs encouraging staff and others to use the stairs rather than the lifts. Our patients need no second invitation. Because they are often not confined to the ward, even though they should probably be confined to bed, the patients use the stairs as an indoor gym, sometimes with 12 floors to run up. Other common forms of exercise are less obvious. Micro-exercising means the use of small muscles to increase calorie consumption and patients will be noticed to be wiggling their toes or fingers or, sometimes knitting furiously. Standing is another variant and some patients refuse to sit, knowing that maintaining the erect posture increases calorie use. Lastly, wearing inadequate clothing in cold weather is a form of micro-exercise because the patient is aware that if she shivers she will use more energy.

Managing exercise and micro-exercise can be a challenge. The patient can be strongly advised not to leave the ward, and to stay in bed until her BMI has improved and this approach will work for some patients. However, keeping a reluctant patient on the ward when she is not detained under the Mental Health Act is not legally defensible and if it is thought that exercise is adversely affecting her recovery and she is in a dangerously poor state of nutrition, a discussion with the psychiatrist about the Mental Health Act may be justified. Even if a patient is on a "section" and is kept on the ward, it is very difficult to prevent micro-exercise. Initially, advice from a nurse who may be observing the patient one to one can be helpful, but a determined patient may continue. Again, if it is thought to be impairing her response to nutrition, it may be justified to use small doses of a benzodiazepine such as Lorazepam [7]. This can be hazardous, however, because of the potential for hypotension these drugs bring, in a patient who may already be hypotensive. There has been some interest in the use of Olanzapine [11] in the treatment of anorexia nervosa at a dose of around 5 mg. It may have some effect on weight, although this is disputed and being further investigated, but the drug may also have a beneficial effect on agitation and it would not be unreasonable to use it in patients with micro-exercising.

Suicidal Behaviour and Self-Harm

This is a large and very important subject and can only be dealt with cursorily here. A proportion of patients with eating disorders express suicidal thoughts and some even see starvation as a more acceptable way to die (e.g. for their families) than other methods. 20% of patients with anorexia nervosa who die do so by suicide [12]. Patient should be asked about suicidal ideation and psychiatric assistance obtained for patients with suicidal ideas. Self harm is characteristic in patients with eating disorders who also suffer from borderline personality disorder, but it also occurs in a proportion of patients who do not fulfil criteria for BPD [13]. Self harm can be very difficult to deal with on a medical ward, especially if the patient is resistant to attempts to improve nutrition. A meeting between the medical and the psychiatric team is essential and a clear management plan developed. Sometimes patients, usually female, may cut or burn a part of the body that they find most unacceptable, such as the stomach. A real danger with such a patient is the possibility of escalating levels of observation so the patient can find herself with one or two special nurses, sometimes with restraints on one or both wrists. Such treatment naturally requires a compulsory order, but even then it can be hard to justify continuing it for days or even months which has occurred in some cases. Escalating treatment can seem to be a motivating factor as in the following patient who was interviewed in an inpatient unit for eating disorders:

Doctor: How is it that you came to need two nurses looking after you?

Patient 5: Well I noticed that Jenny got her own nurse when she started cutting, so I did the same. Then when Jenny started cutting the other arm, so did I and I've now got two special nurses, like her, although I don't like it because I have hardly any freedom and both my wrists are bandaged to the bed.

Family Distress and Anxiety

When a patient is admitted for care to an inpatient bed, especially in a medical unit, the family members are well aware that their loved one is in a very dangerous medical state. They may also realise that eating disorders are not very well understood on the unit, and that experts in the subject may not be on the scene. Their anxiety is at very high levels, and is increased by shortage of information. The combination of fear for their loved one's survival, concern about competence and lack of information can lead to behaviour which may seem irrational. One family arranged for an uncle, a retired anaesthetist, to come and provide a second opinion which conflicted with the views of the consultant, leading to much heat and little light. In another case, the mother became convinced that the nurses were sexually interfering with her son who was on the ward with extreme malnutrition and a paranoid psychosis, probably of nutritional origin.

Such incidents are more easily prevented than stopped, and a number of principles can be suggested for managing the relationship with relatives.

1. Include at least one relative in discussions about the patient's care. Most patients over 18 will agree to their relatives being involved in treatment decisions.
2. Rather than deal with all members of the family, it is useful to ask them to nominate one member as the family representative, both for meetings and phone calls.
3. Make sure that information is available regularly; say every few days, so that the family's knowledge is up to date.
4. When there is clear distress which is not satisfactorily dealt with by the above measures, designate a sensitive and experienced team member to meet with the relative and attempt to resolve issues by providing support and information.
5. Because complaints are not unknown, staff should make sure that they document and justify their treatment decisions in case they are later examined.
6. As long as the collaboration between medical and psychiatric personnel is occurring as advised above, relatives can be reassured that experts in both the psychological and medical aspects of the condition are working together, and be invited to meet both sides, preferably together.

Safeguarding Concerns

Safeguarding for adults at risk because of mental disorder refers to the responsibility of staff looking after them to make sure they are not subject to abuse or neglect. The inpatient medical setting does not often provide examples of such abuse or neglect by carers or relatives of patients with eating disorders, although in some cases laxatives have been smuggled into the ward at the request of the patient and this could fall under safeguarding. On discharge home, staff must be clear that care is appropriate and as helpful as possible, which it almost always is, so that neglect or abuse does not take place after discharge.

In general, the MEED recommendations are designed to facilitate joint work between psychiatric and medical experts, and when there is doubt, the last recommendation in the right hand column should always be enacted "Mobilise psych team to advise on management".

Electrolyte and Micronutrient Imbalance

Hypokalaemia

Patient 6: A primary care physician referred a male patient of 32 to the emergency department. He was underweight, had been vomiting regularly for several years and had recently fainted. A serum potassium level was 1.9 mmol/L (normal range 3.5–5 mmol/L). The doctor in the emergency department noticed that his teeth were almost all worn away, with some fillings "standing proud".

Low potassium occurs quite commonly in the course of eating disorders. Self induced vomiting as a form of weight control occurs in bulimia nervosa and also in the bulimic form of anorexia nervosa. Among atypical eating disorders, patients of normal weight who purge without binge eating (termed "Purging disorder") are also at risk. The patient may or may not have relevant symptoms and although some patients describe muscle cramps or episodes of loss of consciousness consistent with cardiac arrhythmia, the problem is most often identified in a routine blood test. Low potassium can also occur after loss of the ion in diarrhoea, induced by extreme laxative abuse, and also sometimes because of very low intake in anorexia nervosa, restricting subtype. Examination may not be instructive, but the ECG may show U waves and other abnormalities (Fig. 4).

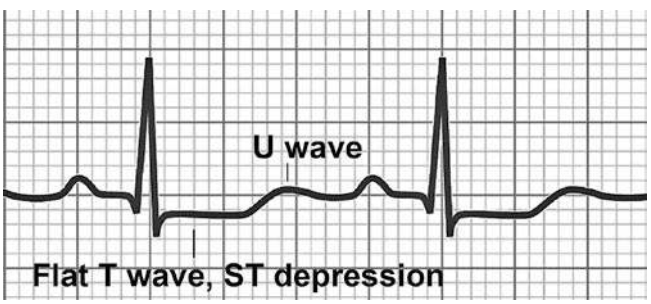

Fig. 4 ECG characteristics in hypokalaemia showing ST depression, T flattening and a U wave

The cause of hypokalaemia in eating disorders varies with the patient's behaviour. In the above case, the problem was repeated self induced vomiting over many years. Vomitus does not contain much potassium, and the mechanism of hypokalaemia appears to be mediated by loss of hydrogen ions from gastric juice, leading to a metabolic alkalosis. The attempt to correct this and restore body pH to normal, results in H+ being retained and K+ lost and this increases renal excretion of potassium and leads to hypokalaemia. However, the process can continue for some time while potassium, which is primarily intracellular, leaks out of the cells and maintains serum potassium levels. Only when total body depletion of potassium is substantial does hypokalaemia show itself.

In other situations, such as laxative abuse, the cause of hypokalaemia is loss of potassium in the stool, whereas in restrictive anorexia nervosa, the most likely cause is chronic under-ingestion of potassium. Lastly, patients with eating disorders, some of them doctors, nurses and pharmacists, may abuse diuretics in an attempt to reduce body water and achieve weight loss, which of course does not reflect any change in fat mass. The action of diuretics, especially the more powerful ones such as furosemide, is to stimulate the loss of sodium and potassium, and hypokalaemia can be the result. The metabolic effects of hypokalaemia are widespread and are serious and if unrecognised can be fatal.

Box 6 Consequences of Hypokalaemia
Sequelae of Hypokalemia

- Cardiac
  - Arrhythmias, cardiac arrest, increased digitalis sensitivity, orthostatic hypotension, EKG changes (T wave flattening or inversion, U waves, ST segment depression)
- Gastrointestinal
  - Constipation, ileus, exacerbation of hepatic encephalopathy
- Metabolic
  - Glucose intolerance, hypokalemic metabolic alkalosis
- Neuromuscular
  - Areflexia, hyporeflexia, paralysis, parenthesis, respiratory depression, rhabdomyolysis, weakness
- Renal
  - Decreased urinary concentrating ability, polyuria and polydipsia, nephropathy with decreased glomerular filtration rate, myoglobinuria (secondary to rhabdomyolysis)

Managing Hypokalaemia

The physician can safely assume that loss of potassium (K), whatever the route is likely to continue. Change in attitude to body image takes time and therapy and in the short term is unlikely. There have been reported cases of patients with hypokalaemia due to bulimia being given an intravenous infusion of potassium chloride until the serum potassium is in the normal range and then sent home with no follow up. This is a very dangerous practice and can result in the death of the patient. At the very least the patient requires regular and frequent (every few days) blood tests to monitor electrolytes, as well as support and therapy from an expert eating disorders practitioner. Secondly, considering that there is a large total body deficit of potassium, an infusion for a day is unlikely to replenish it, and longer treatment is required.

Intravenous potassium chloride is certainly an appropriate lifesaving intervention if potassium levels are very low. This can be followed by oral potassium chloride tablets to continue the process of repletion, bearing in mind that the patient may have resumed vomiting and potassium loss may therefore have resumed. Monitoring should take place every few days to detect recurrent low levels of potassium. In clinics without access to intravenous infusion (such as outpatient eating disorders clinics) the following schedule can be followed:

9 am: Blood test for potassium level
10 am–4 pm: If hypokalaemic perform ECG and give potassium chloride tablets every 2–4 h
4 pm: Repeat Blood test for K level
Send home if level > 3.5 mmol/L
Subsequent days: Repeat Blood test for K level
Send home if level > 3.5 mmol. Continue to monitor K.
If still hypokalaemic refer to emergency dept.

Another approach which is theoretically interesting is to give the patient (with intractable hypokalaemia due to vomiting) a proton pump inhibitor drug such as Lansoprazole [14]. The theory is that if the stomach can be prevented from secreting acid then vomiting should not lead to alkalosis, and so potassium does not need to be exchanged for hydrogen in order to keep the body's pH normal.

Hypoglycaemia

Low blood sugar is frequently observed in patients with low weight due to anorexia nervosa. The carbohydrate stores of the body, glycogen in muscle and liver, have often been exhausted as a result of a low calorie, especially a low carbohydrate, diet, and sometimes by exercise, either overt or "micro". In complete starvation glycogen is exhausted by

24–48 h [15]. At that point energy delivery to essential organs (brain and heart) is continued by switching to triglycerides and ketones produced by the liver and by day 3 some 30% of energy needs are provided in this way. Fat cannot be transformed to glucose, but protein can, through gluconeogenesis, although the amounts are limited and protein breakdown occurs, for example in muscle.

Hence, the hypoglycaemia seen in severe anorexia nervosa may not have the same clinical impact as the same low level of glucose seen after, for example, an overdose of insulin. The patient may be alert and functioning, because the brain is being fed with energy through ketones.

Patient 7: A young woman with anorexia nervosa was an inpatient on a medical ward. Her blood glucose, by finger-prick, was low at 2.5 mmol/L. At around midnight the on-call doctor rang the senior physician to report that the blood glucose machine was recording a level of zero. The physician asked if the patient was conscious and was assured that she was in animated conversation with nurses and other patients. The physician concluded that the machine must be faulty. The patient was found dead in the morning. The glucose monitoring machine was found to be functioning normally.

Hence, in spite of very low blood glucose the patient may be deceptively well. The management of this situation demands good clinical judgement. The low glucose can, as seen above, be fatal. However, the body has shown major adaptation to lack of carbohydrate and the amount of glucose required may be less than is given in an insulin overdose. It is probably safe to provide enough glucose to maintain serum levels within the normal range, with a combination of oral, bolus and intravenous glucose, but each case needs careful thought and closely monitored treatment. Glucose refeeding can induce acute thiamine deficiency in patients with severe malnutrition. Prophylactic intravenous thiamine is strongly recommended prior to giving any oral or intravenous glucose.

Other major electrolyte disturbances that can occur due to severe starvation or as a result of refeeding are hypophosphatemia and hypomagnesemia. The clinical manifestations are summarised in Boxes 7 and 8.

Box 7 Sequelae of Hypophosphatemia

- Decreased cardiac ATP
→ CCF
→ arrythmias
- CNS
  - Delirium
  - Seizures
  - paraesthesia
- Muscular skeletal
  - Rhabdomyolysis
  - Diaphragm dysfunction
- Haematological
  - Reduced RBC 2-3 DPG – oxygen dissociation curve to the left
  - Haemolysis
  - Reduced WCC function

Box 8 Sequelae of Hypomagnesemia

- Cardiac
  - Arrythmias, tachycardia, torsade de pointes
- Gastrointestinal
  - Abdominal pain, anorexia, diarrhea, constipation
- Neuromuscular
  - Ataxia, confusion, fasciculations, hyporeflexia, irritability, muscle tremors, painful paresthesias, personality changes, positive Trouseau's sign, seizures, tetany, vertigo, weakness

Renal Insufficiency

Eating disorders can cause renal failure by different mechanisms. Many patients with anorexia nervosa restrict not only calories, but also water and after months of such deprivation, the kidneys can be severely damaged.

Patient 8: A woman of 19 who had withdrawn from treatment the year before contacted one of the authors by email as follows: "Dear Dr, I think I need help. Maybe something can be done? Signed x". An urgent appointment was arranged and the history obtained that for the previous year, she had consumed, every day, only a small pie and half a glass of water. She was severely underweight and tests showed that she was in acute renal failure. She was admitted to a medical ward and a glucose infusion was set up, in order to encourage her kidneys to begin functioning again. She noticed that the infusion contained glucose, ie calories, and switched it off during the night. The nurses noticed what she had done and restarted the drip. However, she died a few hours later.

Apart from fluid restriction, the most common metabolic problem affecting renal function is hypokalaemia, discussed above. Patients who maintain very low levels of serum potassium for long periods may sustain progressive renal tubular damage and the result can be end stage renal failure, requiring dialysis sometimes followed by transplantation.

Refeeding Syndrome

Refeeding syndrome (RFS) is covered in chapter "Refeeding Problems". In eating disorders patients there are a few points worth noting (Figs. 5 and 6).

1. In discussions between physicians and psychiatrists during the MEED consultations, it was clear that RFS was more commonly seen by the physicians than the psychiatrists. The reasons for this are not readily apparent, but differences in practice did emerge, with patients in medical beds being given initial rates of feeding well below those admitted to eating disorder specialist beds. One likely explanation is that patients admitted medically may have had more major medical co-morbidities such as infection and cardiac problems and to be fed nasogastrically, than those admitted to eating disorder services. They may also have had lower BMI levels, simply because they had waited for treatment longer, become more ill and hence had required an emergency medical bed rather than a psychiatric admission. There may also have been differences in attitude between the two types of specialist, with physicians having had more experience of severe RFS than psychiatrists and hence being more cautious. In the end, the advice in MEED provides for lower initial kilocalorie provision for patients with the highest risk of RFS, and higher provision for the rest. However, it was stressed that to avoid Under Feeding Syndrome, calories should be increased rapidly while monitoring for the emergence of RFS.
2. Refeeding syndrome is more likely to occur in admitted patients, especially when enteral feeding is given. However, RFS has been described in a patient with anorexia nervosa who, during admission, began binge-eating [16]. This complication has also been observed in outpatients and the need for moderation in refeeding should also be conveyed to community patients with anorexia nervosa undergoing nutritional treatment in outpatients or day care. In practice, most patients' reluctance to eat and gain weight makes the emergence of RFS in patients on oral refeeding rather uncommon.

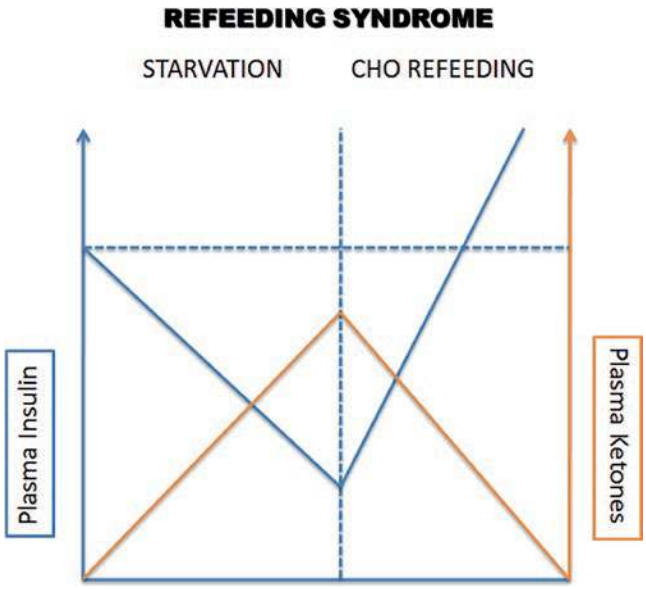

Fig. 5 Metabolic changes in starvation and carbohydrate refeeding

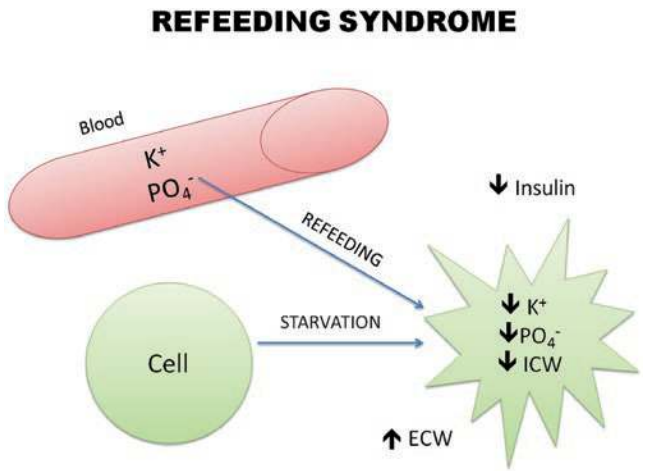

Fig. 6 Electrolyte and body water (Intracellular and extracellular) changes in starvation and refeeding

Fractures

The presence of fractures in a young person not associated with major trauma should alert the physician to the possibility of an eating disorder. The context can be the emergency department, where a patient may present with fracture of any bone, and the fracture may have occurred after relatively minor trauma. Patients with eating disorders who exercise by walking for hours may present with fractures in the foot ("march fractures") which seem to be the result of repeated minor trauma in a patient with osteoporosis. Other medical services including primary care can be consulted as a result of bone or joint pain, fractures or loss of height.

Patient 9: The man of 37 had suffered from anorexia nervosa since his teens with chronically low weight and frequent admissions. He was known to have severe osteoporosis. He was seen in an outpatients clinic and proudly announced that his anorexia had recovered. He explained that he had worked out his Body Mass Index and found that it had risen to 19. Further enquiry and examination demonstrated that his weight had remained the same, 45 kg, but his height had reduced from 1.74 m (BMI 14.9) to 1.54 m (BMI 19) over the previous 3 years as a result of spinal vertebral collapse fractures causing a kyphosis. The patient was advised to use his former height in order to work out his BMI.

Bone involvement in anorexia nervosa is progressive as long as weight is low. Within a year or two of onset, many patients are found to have osteopenia on the Bone Mineral Density "Dexa" scan. The T score in the spine and hip will be between <1 and <2.5. As years go by osteoporosis in more frequently observed (T score ≤2.5) and the rate of fractures increases. The aetiology of osteopenia in anorexia nervosa is complex. Unlike post-menopausal osteopenia, bone loss cannot be slowed using sex hormones [17]. The exception to this rule is that in adolescents with anorexia nervosa bone loss may be reduced by physiological doses of oestrogen delivered transdermally [18]. Sex hormones may therefore play a part in aetiology. Other hormones such as cortisol, which is increased in anorexia nervosa and which can reduce bone density may be relevant while the reduction in stress on bones which accompanies chronically low weight, in a process analogous to the osteopenia experienced by astronauts during periods of weightlessness may also be important. Nutritionally determined lack of calcium, vitamin D and protein are also candidates. Weight loss does seem to be the key factor, because restoration of weight leads to a reliable improvement in bone density [19] although it is not clear that complete bone recovery can occur.

Treatment with bisphosphonate drugs such as alendronate has been suggested as treatment for osteoporosis associated with anorexia nervosa. There effectiveness is in doubt [17, 20]. However, they have very long half lives in the body as they are bound to bone tissue (example half life 10.9 years for Alendronate) and treatment of a patient who may later become pregnant is controversial. One approach would be to restrict the use of bisphosphonates to patients with anorexia nervosa and severe osteoporosis in men and in women after childbearing age.

Gastrointestinal Symptoms

Many symptoms of eating disorders involve the gastrointestinal tract. It is therefore not unexpected that gastrointestinal disturbances can present to different physicians at varying levels of acuteness. Self-induced vomiting, which often accompanies anorexia nervosa and bulimia nervosa as well as an atypical eating disorder, purging disorder, which is mainly characterised by vomiting as a method of weight control. Enlargement of the parotids occurs in patients who vomit and also in those who binge-eat without vomiting. The parotids are usually non-tender and the occasional histological examination [21] has shown sialadenosis (non-inflammatory enlargement). Sore throat, sometimes with scratches on the pharyngeal mucosa, may accompany self-induced vomiting, and haematemesis due to oesophagitis related to reflux, or occasionally an oesophageal tear (Mallory-Weiss syndrome) in which case the bleeding may be massive and the patient gravely ill, have been described [22]. Patients with anorexia nervosa have delayed gastric emptying probably related to undereating and starvation [23, 24] and this can predispose to early satiety and, if large quantities of food are consumed, a danger of acute gastric dilatation and rarely perforation [25]. Occasionally oesophageal perforation has been reported in anorexia nervosa [26]. In patients with laxative abuse, very large doses of stimulant laxatives may be taken daily, initially in an attempt to speed calories through the gut, but later in response to increasing constipation and tolerance to the effects of laxatives. The patient may complain of diarrhoea, but in more chronic cases, constipation is seen and this may be resistant to laxative treatment. In a few instances, a "floppy colon" is seen, with severe constipation and rectal prolapse [27] which may require surgical treatment and sometimes colonic resection and a colostomy.

Acute abdominal pain in a very underweight patient with anorexia nervosa can be caused by pressure of the superior mesenteric artery on the duodenum (superior mesenteric artery syndrome, [28]) and requires urgent surgical treatment. Recurrent abdominal pain and colonic symptoms may be diagnosed as being due to Irritable Bowel Syndrome. The possibility of an eating disorder should be borne in mind before this conclusion is reached, although the conditions can co-exist.

Amenorrhoea and Infertility

Loss of weight usually leads to amenorrhoea and the association of low BMI and amenorrhoea should signal the possibility of an eating disorder, usually anorexia nervosa. Amenorrhoea is also common in patients with binge eating [29] and many patients with bulimia nervosa are found to have polycystic ovaries on ultrasound [30]. The association is not understood but women with bulimia nervosa in the latter study who had recovered showed normal ovarian morphology suggesting an effect of symptoms on the ovaries. Some patients with bulimia nervosa have lost significant amounts of weight, even though they are within the normal weight range, and this might contribute to amenorrhoea.

All patients referred for or applying for infertility treatment should be screened for eating disorder symptoms. Providing, for example, in-vitro fertilization to a woman who is seriously underweight as a result of anorexia nervosa [31] provides an ethical dilemma, because of the increased risk of pregnancy complications [32] and risks to the nutrition of the infant and child [33]. In the view of the authors, such patients should receive psychological and nutritional treatment for their eating disorder before embarking on infertility treatment.

Psychiatric Symptoms

Eating disorder symptoms such as food restriction, binge eating, vomiting and laxative abuse are of course psychiatric symptoms. However, here we draw attention to the comorbid symptoms such as depression, suicidality and self-harm which often accompany eating disorders and which may present to primary and secondary care and to emergency services. The mortality rate for patients with anorexia nervosa is one of the highest of all psychiatric conditions and a substantial percentage of those deaths are by suicide [12]. Hence, any patient with an eating disorder should be asked about suicidal thoughts and intentions and appropriate referrals considered if they are present. Moreover, a substantial proportion of patients with eating disorders [13] present with deliberate self harm, which may be part of a borderline personality disorder. The combination of an eating disorder and a borderline personality disorder requires complex treatment so that both conditions are taken into account. Drug and alcohol misuse can further complicate the picture and may require attention in their own right. Recognition of these interacting problems, which are sometimes the long term sequelae of childhood sexual abuse, in primary and secondary medical care, can be very helpful in triggering appropriate referral and reducing the rate of hospitalization and increasing symptoms that can otherwise occur [34].

Eating Disorders in the Clinic: Summary and Concluding Remarks

From the above review, which has been far from exhaustive, it can be seen that patients with eating disorders can turn up in almost any clinic in a health system. Acuteness of presentation varies from the cachectic patient near death carried into the emergency department, to the chronically ill patient with SEED (Severe and Enduring Eating Disorder, [35] presenting with symptoms due to osteoporosis, laxative abuse or social isolation, amongst many others. The task of the non-psychiatrist is to recognise the eating disorder and to treat the medical complications bearing in mind that eating disorder symptoms often make treatment, especially if it leads to improved nutrition, very difficult. There is no doubt that some clinical staff in all areas of work, faced with a patient who is obviously in need of treatment, but who is doing her best to avoid and sabotage that treatment, may lose sympathy for the patient, and that can affect the patient's care. Our advice is to try and view the patients as in the grip of a process that they cannot control, which leads to these sabotaging behaviour, and to avoid blaming the patient. In addition to the belief that the patient is to blame for the symptoms "doing it to herself", there is also a widespread belief that there is not very much hope for these patients and this also can affect staff reactions to them. In fact the eating disorders have a recovery rate of around 50% and that improves as patients with shorter illnesses are treated. There is evidence, for example in anorexia nervosa, that treatment within 3 years of onset can substantially improve prognosis [36].

Treatment of eating disorders follows, in general a bio-psycho-social model of care. Bio: The "bio" part of this triad involves assessment of general medical state, of risk to health and life and treatment of those medical problems, some of which have been discussed here. This includes resuscitation of a patient in an extreme state of nutritional deficiency or electrolyte imbalance, managing refeeding safely and monitoring and treating some of the chronic sequelae of eating disorders such as osteoporosis and infertility. Under the "bio" heading we also have physical treatments for psychological disorder. In eating disorders, treatment of undernutrition can be seen as such an intervention and this includes offering and supervising meals and occasionally, if life is at risk, imposing nutrition by oral or nasogastric feeding under the Mental Health Act.[2] There are many drug treatments in psychiatry and most of them have been tried in eating disorders. Antidepressants which are effective in many patients with depressive illness seem much less effective when weight is low [37] perhaps because of the neuro-transmitter changes that may occur at low weight. In bulimia nervosa however, antidepressants, such as Fluoxetine 20-60 mg daily, have been found to have a significant impact on bulimic symptoms and are recommended in NICE for eating disorders [1, 38]. They are less effective than psychological treatments and the patient may relapse when the drug is withdrawn, and it seems to the present authors that the role of antidepressants in bulimia nervosa should probably be restricted to patients who remain unwell after a course of psychological treatment such as cognitive behavioural therapy. This approach has been tested and found to give better results than treatment with either method separately [39]. Neuroleptic drugs such as Olanzapine [40] have been used in anorexia nervosa on the basis that they cause weight gain in patients with schizophrenia. They may have an effect on BMI, fear of weight gain and general anxiety in anorexia nervosa but the treatment remains controversial and large randomised trials are awaited. On an even more experimental basis, brain treatments such as repetitive transcranial magnetic stimulation (rTMS) [41] and deep brain stimulation (DBS) [42] have both been tested in trials with some encouraging but not conclusive results in patients with severe intractable anorexia nervosa.

The main treatments in eating disorders are psychological. These include assessment of motivation to change using the methods developed in the treatment of alcohol misuse

[2] https://www.gov.uk/government/publications/code-of-practice-mental-health-act-1983.

Table 1 The 6 phases of motivation

Level of motivation	Description	Typical statement
Pre-contemplation	Denial	There's nothing wrong with me. It's everyone else's problem. They need to change
Contemplation	Acceptance there might be a problem, but not acting to change it	I think my eating is problematic, and maybe my weight, but I can handle it and don't need to change it just yet.
Preparation	Preparing to take action to address the problem	This problem is affecting my life seriously. I'm planning to get help to address it
Action	Acting to alleviate the problem	I'm now in treatment and am struggling to deal with the problem
Maintenance	Taking steps to reduce the risk of relapse	I'm a lot better and need to remain alert to the possibility of relapse
Relapse management	Re-establishing control during a relapse	My symptoms came back and I'm putting a lot of effort into getting them under control again

[43]. This essentially involves interviewing the patient in a way that elicits his or her attitude to the illness, its negative (and positive) aspects, and the pros and cons of change. The patient may be asked to write a letter to "My eating disorder as my friend" and "My eating disorder as my enemy" in order the make explicit the ambivalence about change that is often present in patients with eating disorders, in preparation for a discussion with the patient about change, including how much change and at what rate. The different levels of motivation are illustrated in Table 1.

The motivational sequence, which can also be seen as a cycle, can be applied to any problem in which behaviour can affect health adversely including weight loss in obesity, diabetic control, dietary approaches to hypertension and renal disease, as well as misuse substances such as alcohol and other drugs. In eating disorders treatment, elements of motivational enhancement can be found in many approaches and rather than a stand-alone therapy it is probably better seen as an important component of treatment. The main psychological treatment that has been found to be effective in controlled trials in eating disorders is cognitive behaviour therapy for bulimia nervosa (CBT-BN) [44]. This approach initially concentrated on the behaviours which lead to eating disorder problems (such as restriction, binge eating and vomiting) and on the cognitions, such as body image disturbance and low self esteem, underlying such behaviours. More recently there has been a recognition that emotional dysregulation (inability to control or manage unpleasant feelings such as depression, anxiety or anger) have an important role in eating disorders and treatment of those problems has been included in CBT-BN. CBT has been extended (CBT-E) to include other eating disorders such as anorexia nervosa [44] and trials are awaited. Other therapies have been used which primarily address emotional and relational problems (Interpersonal therapy [45] and mentalization based therapy [46]) and one approach, Cognitive Remediation Therapy, [47] has been introduced which addresses the detail focus and cognitive rigidity that particularly occurs in low weight patients.

Social: This is a big area and includes family based therapy, sometimes provided in multiple family groups which is particularly indicated for younger patients with anorexia suffering from a relatively short (<3 years) illness [48], support and education for carers and families of patients with eating disorders [49], and attention to the major social and occupational problems encountered by patients with eating disorder, especially after several years of illness [50].

Should the health worker, whether doctor, dietitian, nurse or psychologist, be a generalist or a specialist? As in most areas of health, the more you know about a subject the better the likely deal is for the patient. Thus, initial treatment of a diagnosed eating disorder should, we believe, be from a specialist in the field, or a generalist who is working closely with a specialist, for example as supervisor or collaborator. This may be in a specialist outpatient, day patient or inpatient setting. When non-specialists are involved because of specific circumstances, as in the case of the patient admitted via the emergency department to a medical bed, we recommend that the medical team involves the eating disorder specialist or liaison psychiatrist as soon as feasible, and that care is shared with frequent joint review and consultation, as recommended in MEED. In non-emergency cases, as long as the patient has been assessed and treated by a specialist team, follow up can reasonably come from primary care or another non-specialist health worker. It is in the early cases (less than 3–5 years from onset) that we have evidence that specialist care can make the greatest difference to prognosis. After that the evidence is not so strong. It should also be emphasised that however long the history, complete recovery, although less likely, is never impossible and all of us in the field have seen patients recover completely after 20 or 25 years of continuous illness, sometimes for reasons that we cannot fathom.

References

1. NICE—National Institute for Health and Care Excellence. Eating disorders: recognition and treatment: NICE guideline NG69. 2017 [cited 2018 26/4/18]; Available from: https://www.nice.org.uk/guidance/ng69.
2. Royal College of Psychiatrists. Medical emergencies in eating disorders: guidance on recognition and management. London: Royal College of Psychiatrists; 2022.

3. Schmidt U. Aetiology of eating disorders in the 21(st) century: new answers to old questions. Eur Child Adolesc Psychiatry. 2003;12(Suppl 1):30–7.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
5. Morgan JF, Reid F, Lacey JH. The SCOFF questionnaire: assessment of a new screening tool for eating disorders. BMJ. 1999;319(7223):1467–8.
6. Smink FR, van Hoeken D, Hoek HW. Epidemiology, course, and outcome of eating disorders. Curr Opin Psychiatry. 2013;26(6):543–8.
7. Royal College of Psychiatrists. MARSIPAN: management of really sick patients with anorexia nervosa. 2nd ed; 2014.
8. Westmoreland P, Krantz MJ, Mehler PS. Medical complications of anorexia nervosa and bulimia. Am J Med. 2016;129(1):30–7.
9. Royal_College_of_Psychiatrists, CR130. Guidelines for the nutritional management of anorexia nervosa. London: Royal_College_of_Psychiatrists; 2004.
10. Robinson PH, Nicholls D, editors. Critical care for anorexia nervosa. The MARSIPAN guidelines in practice. Cham: Springer; 2015.
11. Norris ML, Spettigue W, Buchholz A, Henderson KA, Gomez R, Maras D, Gaboury I, Ni A. Olanzapine use for the adjunctive treatment of adolescents with anorexia nervosa. J Child Adolesc Psychopharmacol. 2011;21(3):213–20.
12. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. Arch Gen Psychiatry. 2011;68(7):724–31.
13. Claes L, Muehlenkamp JJ. Non-suicidal self-injury in eating disorders. Heidelberg: Springer; 2014.
14. Eiro M, Katoh T, Watanabe T. Use of a proton-pump inhibitor for metabolic disturbances associated with anorexia nervosa. N Engl J Med. 2002;346(2):140.
15. Berg JM, Tymoczko J, Stryer L. Biochemistry. 5th ed. New York: W H Freeman; 2002.
16. Kaysar N, Kronenberg J, Polliack M, Gaoni B. Severe hypophosphataemia during binge eating in anorexia nervosa. Arch Dis Child. 1991;66(1):138–9.
17. Mehler PS, MacKenzie TD. Treatment of osteopenia and osteoporosis in anorexia nervosa: a systematic review of the literature. Int J Eat Disord. 2009;42(3):195–201.
18. Misra M, Katzman D, Miller KK, Mendes N, Snelgrove D, Russell M, Goldstein MA, Ebrahimi S, Clauss L, Weigel T, Mickley D, Schoenfeld DA, Herzog DB, Klibanski A. Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. J Bone Miner Res. 2011;26(10):2430–8.
19. Zipfel S, Seibel MJ, Lowe B, Beumont PJ, Kasperk C, Herzog W. Osteoporosis in eating disorders: a follow-up study of patients with anorexia and bulimia nervosa. J Clin Endocrinol Metab. 2001;86(11):5227–33.
20. Robinson L, Aldridge V, Clark EM, Misra M, Micali N. A systematic review and meta-analysis of the association between eating disorders and bone density. Osteoporos Int. 2016;27(6):1953–66.
21. Vavrina J, Muller W, Gebbers JO. Enlargement of salivary glands in bulimia. J Laryngol Otol. 1994;108(6):516–8.
22. Robinson P. The gastrointestinal tract in eating disorders. Eur Eat Disord Rev. 2000;8(2):88–97.
23. Robinson PH, Clarke M, Barrett J. Determinants of delayed gastric emptying in anorexia nervosa and bulimia nervosa. Gut. 1988;29(4):458–64.
24. Russell DM, Freedman ML, Feiglin DH, Jeejeebhoy KN, Swinson RP, Garfinkel PE. Delayed gastric emptying and improvement with domperidone in a patient with anorexia nervosa. Am J Psychiatry. 1983;140(9):1235–6.
25. Mishima T, Kohara N, Tajima Y, Maeda J, Inoue K, Ohno T, Kitasato A, Watanabe T, Irie J, Adachi T, Kuroki T, Eguchi S, Kanematsu T. Gastric rupture with necrosis following acute gastric dilatation: report of a case. Surg Today. 2012;42(10):997–1000.
26. Schechter J, Altemus M Greenfeld DG. Food Bingeing and Esophageal Perforation in Anorexia Nervosa. Hospital and Community Psychiatry 1986;37(5):507–8.
27. Norris ML, Harrison ME, Isserlin L, Robinson A, Feder S, Sampson M. Gastrointestinal complications associated with anorexia nervosa: a systematic review. Int J Eat Disord. 2016;49(3):216–37.
28. Adson DE, Mitchell JE, Trenkner SW. The superior mesenteric artery syndrome and acute gastric dilatation in eating disorders: a report of two cases and a review of the literature. Int J Eat Disord. 1997;21(2):103–14.
29. Algars M, Huang L, Von Holle AF, Peat CM, Thornton LM, Lichtenstein P, Bulik CM. Binge eating and menstrual dysfunction. J Psychosom Res. 2014;76(1):19–22.
30. Morgan JF, McCluskey SE, Brunton JN, Hubert Lacey J. Polycystic ovarian morphology and bulimia nervosa: a 9-year follow-up study. Fertil Steril. 2002;77(5):928–31.
31. Nillius SJ, Wide L. Gonadotrophin-releasing hormone treatment for induction of follicular maturation and ovulation in amenorrhoeic women with anorexia nervosa. Br Med J. 1975;3(5980):405–8.
32. Micali N, Treasure J. Biological effects of a maternal ED on pregnancy and foetal development: a review. Eur Eat Disord Rev. 2009;17(6):448–54.
33. Stein A, Woolley H, Cooper S, Winterbottom J, Fairburn CG, Cortina-Borja M. Eating habits and attitudes among 10-year-old children of mothers with eating disorders: longitudinal study. Br J Psychiatry. 2006;189:324–9.
34. Bateman AW, Fonagy P. Handbook of mentalizing in mental health practice. Arlington, VA: American Psychiatric Publishing Inc; 2012.
35. Robinson P. Severe and enduring eating disorder (SEED): management of complex presentations of anorexia and bulimia nervosa. Wiley; 2009. p. 184.
36. Treasure J, Russell G. The case for early intervention in anorexia nervosa: theoretical exploration of maintaining factors. Br J Psychiatry. 2011;199(1):5–7.
37. Claudino AM, Hay P, Lima MS, Bacaltchuk J, Schmidt U, Treasure J. Antidepressants for anorexia nervosa. Cochrane Database Syst Rev. 2006;1:CD004365.
38. Shapiro JR, Berkman ND, Brownley KA, Sedway JA, Lohr KN, Bulik CM. Bulimia nervosa treatment: a systematic review of randomized controlled trials. Int J Eat Disord. 2007;40(4):321–36.
39. Mitchell JE, Agras S, Crow S, Halmi K, Fairburn CG, Bryson S, Kraemer H. Stepped care and cognitive-behavioural therapy for bulimia nervosa: randomised trial. Br J Psychiatry. 2011;198(5):391–7.
40. Attia E, Kaplan AS, Walsh BT, Gershkovich M, Yilmaz Z, Musante D, Wang Y. Olanzapine versus placebo for out-patients with anorexia nervosa. Psychol Med. 2011;41(10):2177–82.
41. Bainbridge K, Brown A. rTMS as a treatment for anorexia nervosa. Brain Stimul. 2014;7(1):149–50.
42. Treasure J, Schmidt U. DBS for treatment-refractory anorexia nervosa. Lancet. 2013;381(9875):1338–9.
43. Macdonald P, Hibbs R, Corfield F, Treasure J. The use of motivational interviewing in eating disorders: a systematic review. Psychiatry Res. 2012;200(1):1–11.
44. Fairburn CG. Cognitive therapy and eating disorders. New York: Guilford Press; 2008.
45. Agras WS, Walsh T, Fairburn CG, Wilson GT, Kraemer HC. A multicenter comparison of cognitive-behavioral therapy and interpersonal psychotherapy for bulimia nervosa. Arch Gen Psychiatry. 2000;57(5):459–66.
46. Robinson P, Hellier J, Barrett B, Barzdaitiene D, Bateman A, Bogaardt A, Clare A, Somers N, O'Callaghan A, Goldsmith K, Kern N, Schmidt U, Morando S, Ouellet-Courtois C, Roberts A, Skarderud F, Fonagy P. The NOURISHED randomised controlled

trial comparing mentalisation-based treatment for eating disorders (MBT-ED) with specialist supportive clinical management (SSCM-ED) for patients with eating disorders and symptoms of borderline personality disorder. Trials. 2016;17(1):549.
47. Tchanturia K, Doris E, Fleming C. Effectiveness of cognitive remediation and emotion skills training (CREST) for anorexia nervosa in group format: a naturalistic pilot study. Eur Eat Disord Rev. 2014;22(3):200–5.
48. Eisler I, Simic M, Hodsoll J, Asen E, Berelowitz M, Connan F, Ellis G, Hugo P, Schmidt U, Treasure J, Yi I, Landau S. A pragmatic randomised multi-centre trial of multifamily and single family therapy for adolescent anorexia nervosa. BMC Psychiatry. 2016;16(1):422.
49. Treasure J, Whitaker W, Todd G, Whitney J. A description of multiple family workshops for carers of people with anorexia nervosa. Eur Eat Disord Rev. 2012;20(1):e17–22.
50. Robinson PH, Kukucska R, Guidetti G, Leavey G. Severe and enduring anorexia nervosa (SEED-AN): a qualitative study of patients with 20+ years of anorexia nervosa. Eur Eat Disord Rev. 2015;23(4):318–26.

Intestinal Failure in Children: A Paediatric Surgical Perspective

Alexander L. Macdonald, Hannah Thompson, and Mark Davenport

Key Points

1. 'Surgical' short bowel whether congenital or acquired, is the commonest cause of intestinal failure in infancy and childhood
2. Remaining intestinal length is more meaningful when expressed as a percentage of the normal expected intestinal length for the infant's age/weight
3. Initial surgical management should adhere to the principles of preservation of enteral mass and continuity by distal refeeding and avoidance/early closure of stomas
4. Autologous intestinal reconstruction (AIR) has potential to deliver enteral autonomy.
5. Longitudinal Intestinal Lengthening and Tailoring (LILT) and Serial Transverse EnteroPlasty (STEP) represent the mainstay of contemporary AIR and combine increasing length and improving propulsive proficiency in a single procedure

Introduction

Intestinal failure in neonates and infants primarily results from insufficient intestinal mass—i.e. a 'short bowel' which is insufficient to maintain adequate nutrition to support normal physiology and growth. Consequent long-term dependency upon parenteral nutrition (PN) may result in significant morbidity and mortality from intestinal failure associated liver disease (IFALD); catheter related bloodstream infections (CRBSI); and metabolic and renal disease. Early adoption of synergistic medical and surgical strategies to augment the natural physiological process of adaption and maximise the potential for enteral autonomy are critical to long-term survival in this population.

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Definition

Normal small bowel length in term infants (derived from autopsy and multi-visceral transplant donor studies and measured un-stretched at the anti-mesenteric border) is typically considered to be 300 cm with potential to reach 600 cm by adulthood [1, 2]. Traditionally the actual length of the remaining bowel has been used for prognosis though agreement and consensus on what constituted "short" was seldom achieved. A more recent trend has been to express the remaining functioning intestinal length in terms of a percentage of the *expected normal length* for an infant of that age or weight. This distinction is particularly important in pre-term infants as in this population bowel lengths will more than double in late gestation from normal physiological growth alone (e.g. 'normal' length between 19–28 weeks gestation is observed to be 142 ± 22 cm increasing to 304 ± 44 cm by 35 weeks [1]). This makes the finding of 20 cm of remaining small intestine in a 27-week premature infant perhaps less concerning than the same finding in a term infant as it still has considerable functional reserve. So where to draw the line? Recent work has suggested that infants with <10% of the expected length have demonstrably poorer outcomes [3] and certainly those with less than 40 cm remaining are likely to require long-term PN as well as adjuvant medical and surgical strategies to promote enteral autonomy.

Aetiology of Short Bowel

Figure 1 illustrates the leading causes of surgical short bowel in the paediatric age-group. There are two equally prevalent causes in infancy with completely different characteristics: necrotising enterocolitis (NEC) and gastroschisis. The former is almost invariably found in the preterm infant—particularly those <30 weeks gestation—with multiple other co-morbidities (e.g. cerebral haemorrhage), whilst the latter are usually isolated anomalies in otherwise normal term infants. The usual reason for intestinal loss in gastroschisis is

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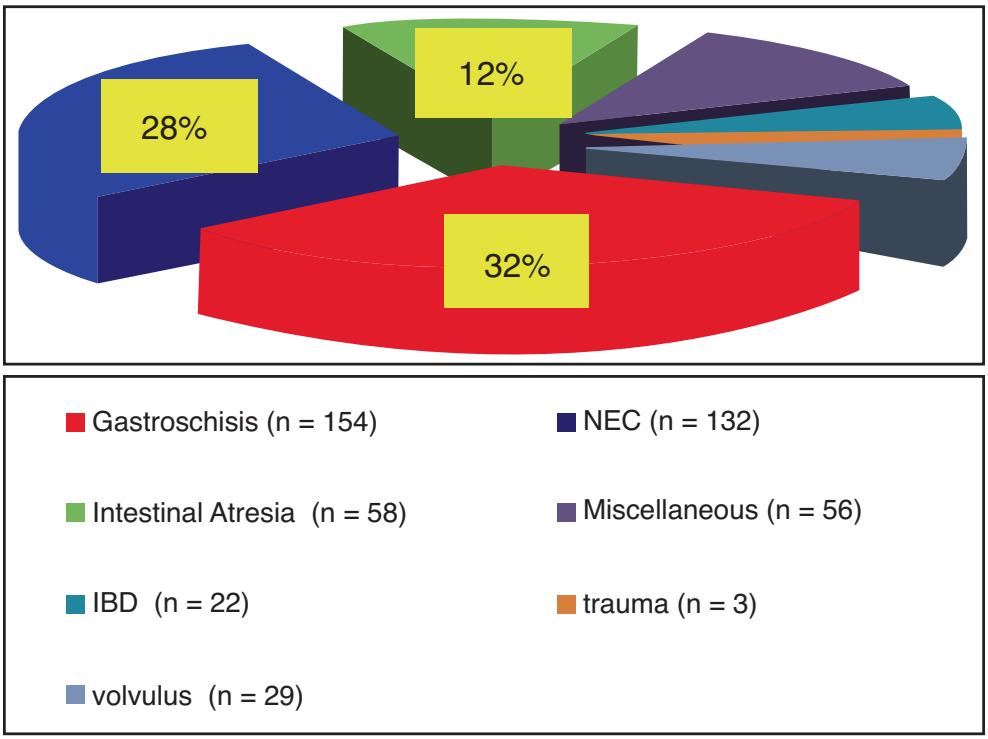

Fig. 1 Aetiology of short bowel syndrome (n = 477). Data are taken from the British Intestinal Failure Survey (BIFS) (2005–2013)—and defined by need for parenteral nutrition beyond 28 days. Abbreviations: NEC necrotising enterocolitis; IBD inflammatory bowel disease

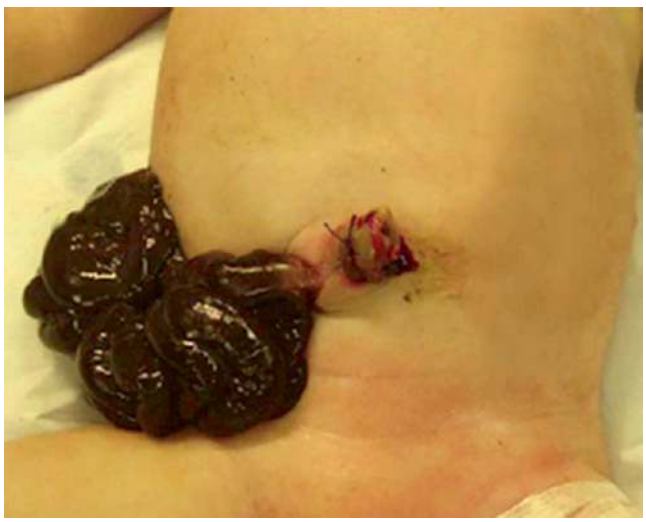

Fig. 2 Closed Gastroschisis. Necrotic midgut and typically the only viable residual bowel is an intraabdominal consisting of a short length of jejunal atresia and a corresponding segment of colon distal to the exit colon atresia. (Reprinted with permission from [4])

due to in-utero closure of the defect with resultant ischaemic compromise of the entire extra-abdominal midgut (known as a 'closed' or 'closing' gastroschisis [4]) (Fig. 2). The third most common cause of short bowel is due to a congenital intestinal atresia—typically jejunal atresia—which is associated with distal intestinal loss and gross dilatation of the remaining proximal bowel [5]. While the limited enterocyte mass is clearly important in short bowel sometimes dysmotility may also lead to major difficulties in achieving enteral autonomy. The residual bowel in gastroschisis and intestinal atresia seem particularly affected by this functional deficit.

Initial Medical Management

Initial surgical intervention should seek to minimise disruption to physiological intestinal adaptation and further surgical intervention is indicated when medically augmented adaptation fails to achieve enteral autonomy. It is thus important to understand both the physiology of adaptation and to appreciate what constitutes optimal medical augmentation.

Adaptation is the physiological process by which the remaining intestine increases its absorptive capacity following resection. The capacity for adaptation is dependent upon the type of bowel remaining. Loss of ileum represents the more significant insult as ileum has the greatest potential for compensation. Ileum is essential for the secretion of cholecystokinin and secretin as well as the resorption of bile acids. Resection of ileum thus leads to increased gastric acid secretion (as a consequence of loss of hormonal secretion) and osmotic diarrhoea (as a consequence of bile salts entering the colon) [6].

In promoting maximal potential for adaptation medical management seeks to; augment the physiology of adaptation; deliver safe parenteral nutrition; and minimise the complications of short bowel.

Enhancing the Physiology of Adaptation

Intestinal adaptation is stimulated by enteral nutrients and consequently a mainstay of promoting adaptation is the early introduction of enteral feeding regardless of the remaining intestinal length. Breast milk contains gastrointestinal hormones, immunogenic factors and amino acids, however it has a high lactose content the absorption of which may be hindered by the reduced surface area and enzyme activity that is inherit with short bowel. An extensively hydrolysed formula with a higher proportion of glucose polymers is thus an acceptable alternative. Bolus feeding is often poorly tolerated in short bowel and continuous feeding has the advantages of increased transit time, increased absorption and a lower risk of osmotic diarrhoea. The increased rate of oral aversion in tube-fed infants should be recognised and proactive strategies (such as "tasters" and trophic oral feeds) should be employed to minimise the long-term impact.

Adaptation may be pharmacologically stimulated by administration of exogenous trophic hormones. Human growth hormone (hGH) combined with the amino acid glutamine has been show to enhance adaptation and absorption improving both weight gain and lean body mass. However in the majority of published trials the effects are short-lived with a return to baseline shortly after cessation of therapy. At present there is insufficient evidence to support routine use of hGH and glutamine regimens in children with short bowel [7].

The proteinogenic amnio acid glucagon-like peptide-2 (GLP-2) analogue teduglutide acts to promote growth of intestinal mucosa and has regulatory approval for use in children >1 year. In open-label trials, teduglutide (0.025 or 0.05 mg/kg/d) was associated with trends toward reduction in PN requirements with the higher dose resulting in a 52% reduction in PN calorie requirement [8]. Reported disadvantages include: its high cost (£260 per 1.25 mg vial—price valid in 2017); reversal of effect on discontinuation of treatment; and concerns regarding malignancy with long-term use in children [3].

Short chain fatty acids (SCFAs) are the breakdown products of carbohydrates and are mediators of GLP-2 release. SCFAs can enhance absorption by up-regulating the glucose transporter proteins GLUT2 and SGLT-1 [9] and the addition of SCFAs to PN has been demonstrated—in animal models—to both prevent TPN-associated mucosal atrophy and enhance intestinal adaptation [10].

Delivering Safe Parental Nutrition

Delivery of parenteral nutrition must be both safe—minimising PN associated complications—and sustainable through preservation of venous access routes.

Liver Disease

Long-term use of TPN in infants can result in a subtype of cholestatic liver disease latterly termed Intestinal Failure Associated Liver Disease (IFALD). This in itself is probably the single most important reason for mortality in the paediatric age-group and causes cholestasis and steatosis leading to macrophage activation, liver fibrosis and ultimately liver failure. IFALD is related to the duration of PN with a fivefold increase observed per week of PN administration [11] and the 'immaturity' of the liver when the PN starts. Sepsis may also have a profound detrimental effect on worsening IFALD. The key preventative strategy is to establish enteral autonomy but it may also be minimised using 'hepatoprotective' PN formulations and specifically lipid emulsions derived from fish-oil (Omegaven®) or a mixture of fish oil, olive oil and soybean (Smoflipid®) that are less inflammatory and cholestatic [12–14].

Catheter Related Bloodstream Infections (CRBSIs)

PN is delivered via a single lumen cuffed tunnelled venous catheter of an appropriate size for the infant (suitable catheters are available in sizes of 2.7Fr upwards). Nowadays, lines should probably be inserted using percutaneous image-guided techniques as this is associated with lower rates of infection and critically—in infants that may have limited viable access routes—allows for considerably more uses of a given vessel [15, 16].

Short bowel patients are particularly susceptible to sepsis with rates as high as 68% [17]. Multiple factors contribute to this including; reliance on central venous catheters; concurrent presence of stomas; a more permeable GI epithelial barrier with consequent bacterial translocation [18] and a general paucity of physiological reserve. CRBSIs result in sepsis, thrombosis and loss of vascular access routes. The risk of CRBSIs is increased by frequent access to the catheter for administration of IV fluids or blood sampling and poor aseptic technique when inserting, changing and accessing catheters.

A systematic focus on aseptic techniques enshrined in so-called 'enhanced catheter care bundles' minimises the incidence of CRBSIs. Comprehensive bundles comprise; the use of chlorhexidine-impregnated patches at exit sites; daily bathing; ethanol line locks; two nurses for catheter care in a distraction-free environment; peripheral phlebotomy; the bundling of routine blood tests; and changing PN administra-

tion sets every 24 h. Successful implementation can lead to dramatic (85%) reductions in CRBSI rates [19] and incidences as low as 0.42 CRBSIs per 1000 catheter days are achievable [20].

Managing the Complications of Short Bowel

Disruption to Enterohepatic Circulation of Bile Acids

Loss of ileum disrupts the enterohepatic circulation of bile acids [21]. These unabsorbed bile acids irritate colonic mucosa resulting in a secretory diarrhea. Bile acids may be bound by cholestyramine and exogenous administration of the bile acid ursodeoxycholic acid (UCDA) may be utilised to improve the enterohepatic circulation by exchanging hydrophobic for hydrophilic bile acids improving bile flow and reducing cholestasis [22, 23].

In PN dependent infants with evidence of significant cholestasis UCDA has been demonstrated to shorten the duration of cholestasis and reduce peak bilirubin levels with effects seen within 1–2 weeks. However discontinuation of UCDA results in relapse [24].

Bacterial Overgrowth

Stasis resulting from dilatation and sumping produces an environment for bacterial overgrowth which is measurably present in up to 60% of surgical short bowel patients [25]. This can lead to; bacterial consumption of enteral nutrients and vitamins; de-conjugation of bile acids; accumulation of toxic metabolites (such as D-lactate); bacterial translocation and subsequent septicaemia. Clinically overgrowth is manifest as abdominal pain, anorexia, vomiting, diarrhea, cramps, and a metabolic acidosis from the accumulation of D-lactic acid which can lead to the significant complication of D-lactate encephalopathy. D-lactic acidosis may be avoided by judicious management of carbohydrate intake and enteral antibiotics. However overzealous management of symptoms with antibiotics can contribute to further overgrowth and appropriate stewardship through antibiotic-free period and cycling of agents is important. An alternative strategy is probiotic therapy with non-D-lactate producing bacteria [26].

Rapid Intestinal Transit

Where transit is rapid the judicious use of agents such as loperamide to reduce peristalsis can delay transit times and increase absorptive potential by increasing the duration of exposure of nutrients to the available mucosal surface area [27].

Hyperacidity

Increased gastrin levels due to loss of the gastrin-metabolising function of the bowel results in increased gastric acid production in up to half of infants with short bowel. Hyperacidity may result in: peptic injury to the stomach and small bowel; systemic acid-base imbalance; and inactivation of pancreatic enzymes with consequent malabsorption [28]. Acid suppression with agents such as the proton pump inhibitor, omeprazole, may mitigate these sequelae.

Surgical Management

The surgeon has a critical role to play both at the time of the initial finding of short bowel in an infant (the initial laparotomy) and in the weeks to follow.

The principles of initial surgical management (Box 1) comprise:

1. Comprehensive documentation of the findings at laparotomy
2. Preservation of intestinal mass
3. Facilitation of post-operative refeeding
4. Early establishment of intestinal continuity
5. Autologous intestinal reconstruction (AIR)

Box 1 Initial Principles in the Surgical Management of Short Bowel

Initial surgical principles
• Document length, quality and type of remaining bowel
• Preserve continuity and intestinal mass where possible
• Undertake distal refeeding and early closure of stomas
• Facilitate the creation of proximal dilatation when future AIR is thought to be likely necessary

The Initial Laparotomy

The length, type and quality of remaining bowel should be clearly recorded. Where viability is in question, a second look laparotomy at 24–48 h should be planned to minimise the requirement for resection. The length of bowel and the degree of dilatation present is key to both prognosis and the planning of future surgical interventions and so must be accurately measured and documented. It is also important to note the presence or absence of the ileocaecal valve (ICV) as its loss has been identified by some authors as an independent risk factor for requirement for future AIR. However it simply may indicate loss of a significant part of the colon in the pathology and the true significance remains controversial [29, 30].

At initial laparotomy the advantages and disadvantages of the creation of defunctioning stomas as against preservation of enteral continuity must be carefully weighed. Anastomosis

and preservation of continuity increases the potential for early enteral adaptation by maximising the absorptive surface available and prolonging transit times [31]. Preservation of intestinal continuity should thus be aimed for as the primary surgical strategy. This is particularly important in infants with >40 cm of small bowel and an intact ICV as this particular group is likely to achieve enteral autonomy by adaption alone [32]. However in those with shorter remaining bowel lengths early continuity is likely to result in high stool output and significant perianal excoriation [3]. If a stoma is chosen then it is important to bring out the distal bowel as a mucous fistula in order to gain the post-operative possibility of content re-feeding.

Necrotising Enterocolitis

In the context of neonatal acquired short bowel, necrotising enterocolitis (NEC) represents a unique surgical scenario. Unlike congenital short bowel (e.g. intestinal atresias) the remaining bowel isn't prone to significant dilatation and dysmotility [33]. Consequently outcomes are potentially relatively favourable but only if measures are taken to preserve intestinal mass from the outset. To this end when faced with the neonate with extensive and/or multifocal disease at the initial laparotomy the surgeon should consider either forming a high de-functioning jejunostomy (up to 10 cm from the duodenal-jejunal flexure) or undertaking a 'clip and drop-back' procedure [34, 35]. With the clip and drop-back technique any clearly necrotic bowel is excised but segments that are of questionable viability are initially retained by oversewing their ends/sealing them with LIGACLIP®s and dropping them back into the abdomen. With both approaches the diseased bowel is initially left in situ and whilst this may place a significant septic burden on the neonate it allows for the possibility of the recovery of a meaningful proportion of the intestine. In the clip and drop-back technique the abdomen is re-entered within 48–72 h, whereas when a high jejunostomy has been created re-laparotomy is typically postponed for 4–6 weeks.

Refeeding

Where stomas have been created at the initial laparotomy distal refeeding should be instituted as early as possible (Fig. 3). Refeeding is undertaken by regularly recycling the proximal effluent into the distal stoma under gravity via a soft catheter (e.g. a Jacques catheter) [32]. In addition to 'priming' the distal bowel prior to closure of the stomas, refeeding provides an additional source of calories through the colonic absorption of short chain fatty acids [3]. In situations where either the viability of the distal bowel is questionable or the development of a distal stricture is considered possible (e.g. in NEC) a distal contrast 'loopogram' should be performed with a water-soluble contrast agent prior to commencement of refeeding.

Fig. 3 Refeeding. Luminal content is aspirated and then slowly reinfused using a soft catheter into the distal mucus fistula

Autologous Intestinal Reconstruction

Following the initial laparotomy a significant proportion of infants will undergo successful enteral adaptation and achieve enteral autonomy without the need for further intervention. However for those infants who fail to achieve enteral autonomy despite optimal medical strategies to promote adaptation further surgical intervention in the form of autologous intestinal reconstruction (AIR) should be considered.

Aims of AIR

Intestinal dilatation which occurs as part of intestinal adaptation leads to stasis and secondary dysmotility resulting in bacterial overgrowth, increased risk of translocation and consequently sepsis. Indeed the presence of dilatation has been identified as an independent risk factor for prolonged PN requirement and decreased survival [33]. While AIR can-

not increase absolute enterocyte mass it can increase available bowel length and reduce the luminal dimeter. This results in an increase in transit times and perhaps an increase in mucosal surface area exposed to luminal contents facilitating absorption. The bowel length achieved post-AIR has been shown to correlate significantly with the percentage requirement for PN in the first post-operative year [36]. The reduction in the luminal diameter improves the efficacy of peristalsis reducing stasis and the associated bacterial overgrowth that results in complications of translocation, sepsis and malabsorption.

AIR should thus be considered in the setting of any infant who fails to achieve EA despite optimal medical management necessitating prolonged continuation of PN or in those infants thought unlikely to ever achieve EA by adaptation and conservative means alone. Additionally AIR should be considered in the presence of intestinal dilatation of a degree that is likely to be resulting in stasis/dysmotility (Box 2).

Box 2 Indications for and Contraindications to AIR in Children

Indications for AIR
• Failure to achieve enteral autonomy
• Intestinal dilatation
Relative contraindications to AIR
• Significant IFALD
– portal hypertension
– thrombocytopaenia and coagulopathy
– cirrhosis
• Ultrashort bowel length (<10 cm)
– probably futile

AIR is however contraindicated in certain scenarios and particularly in the presence of significant IFALD manifest as high-grade fibrosis and/or the presence of portal hypertension). In this context consideration should be given to liver or combined liver and small bowel transplantation the specifics of which are out-with the scope of this chapter. AIR may still have a role in this population as a bridge to transplant for those infants too young/small to receive organs. Typically the youngest recipient would be older than 2 years of age.

Intestinal dilatation is the *sine qua non* of autologous reconstruction. Typically dilatation of a segment/segments of bowel greater than 4 cm or more than twice the normal luminal diameter for age are quoted as necessary to undertake successful AIR [37].

One has to be realistic about the prospects of significant benefit in infants with ultra-short bowel. Clearly in a scenario where the remaining intestinal length is 10 cm or less, then even achieving a doubling of this length following successful AIR is unlikely to afford a significant nutritional benefit.

Timing of AIR

Intestinal adaptation typically starts within 48 h of the original insult/bowel resection and whilst it occurs most rapidly in the first year it is a continuous process that can take up to two years to complete [38, 39]. As a general principle AIR should be undertaken at the point where the child has shown a plateaux in their capacity to tolerate advancement of enteral nutrition. However, clearly there is a balance to be struck between postponing AIR for a sufficient enough period of time as to allow medically augmented adaptation to occur and minimising the time for which the child is dependent on PN (and exposed to its associated complications). AIR has been reported to have been undertaken as early as the first day of life [40] and as late as 15 years [41] but generally techniques such as the LILT and STEP are undertaken in infancy at around 2–3 years of age. However some would now advocate that when the future need for AIR is considered inevitable then earlier intervention should be undertaken—e.g. within the first year of life—to take advantage of the normal rapid growth and development that occurs in this period [42]. In predicting the eventual need for AIR the underlying aetiology of the infants short bowel should be taken into consideration. Certain pathologies like small bowel atresia have been reported as being a 13-fold more likely to require AIR whereas others like NEC are eightfold less likely to require AIR [33].

AIR Procedures

A variety of procedures fall under the umbrella term autologous intestinal reconstruction. These include: intestinal tapering; segmental reversal of the small bowel (SRSB); colonic interposition; the Iowa procedure; the longitudinal intestinal lengthening technique (LILT); serial transverse Enteroplasty (STEP) and spiral intestinal lengthening and tailoring (SILT).

Intestinal tapering [43] is relatively straightforward way of correcting a dilated segment and facilitating anastomosis. As it means discarding at least some mucosa it tends to be reserved for situations where bowel length is not critical. Imbrication may achieve the same effect but needs to be done with non-absorbable sutures otherwise it tends to come apart with time.

Segmental Reversal of the Small Bowel (SRSB) [31] refers to a procedure in which a segment (typically 3 cm) of small bowel is interposed distally in an antiperistaltic orientation. This acts to slow transit time, prolonging contact time with nutrients and increasing absorptive potential. This procedure may also be used as a means to produce the proximal dilation necessary for other AIR procedures. A segment of colon may also be interposed in in an antiperistaltic orien-

tation to achieve a similar effect without the need to resect small bowel. Alternatively, the colon may be interposed in an isoperistaltic orientation and the colon's generally slower motility and greater capacity to absorb fluid and electrolytes is relied upon to improve enteral tolerance [44].

The Iowa procedure was described by Ken Kimura in 1992 [45] and is a two-stage procedure whereby a dilated loop is split longitudinally and the antimesenteric segment is attached to an autologous host organ (e.g. liver) allowing for the generation of a collateral blood supply. At a subsequent laparotomy this bowel is reincorporated in an isoperistaltic manner as a 'new' loop. There is very little evidence of its practical use.

Aside from tapering, most of these procedures have failed to find a role and are now predominately only of historical interest. At present this leaves the LILT and STEP procedures as the mainstay of contemporary AIR surgery in children, together with the newly introduced technique of SILT.

Longitudinal Intestinal Lengthening Technique

The principle of the longitudinal intestinal lengthening technique (LILT) was first proposed by the Maltese paediatric surgeon Adrian Bianchi while working in Manchester, UK in the 1980s [46]; initially using an experimental animal model of short bowel and then first undertaken that same year on a 4 year old with 40 cm of small bowel, PN dependence and limited venous access [47]. The child achieved EA within 10 weeks and the procedure has gone on to gain widespread acceptance. LILT takes advantage of the anatomical observation that the small intestinal blood supply separates within the mesentery to one side or the other someway short of the actual bowel wall. This allows the bowel to be divided along its axis and at 180^0 anti-mesenterically with complete vascular preservation (Fig. 4a). The two intestinal "halves" are then tubularised and isoperistaltic continuity restored (Figs. 4b–d, and 5a, b).

Serial Transverse EnteroPlasty

The serial transverse enteroplasty (STEP) procedure was first described by Kim et al. in Boston, USA in 2003 (initially on a porcine model and then on a 2 year old boy) [48]. Owing largely to its ease of application it has gone on to achieve widespread adoption and to date numerous centres participate in an international registry. Firstly small mesenteric "windows "are created, then a GIA stapler is fired part way across the bowel diameter. This is repeated at equal intervals and from alternate sides (Fig. 6a) to create a zig-zag channel of about 1–2 cm diameter (Fig. 6b). The STEP can be undertaken as a primary procedure or applied to a segment of bowel previously lengthened by the LILT. Additionally STEP may be reapplied to bowel previously lengthened by STEP which has re-dilated in what is termed the ReSTEP procedure [49].

Spiral Intestinal Lengthening and Tailoring

Spiral intestinal lengthening and tailoring (SILT) was described by Cserni in Debrecen first on a synthetic bowel simulator in 2011 [50] and then in 2014 on a 3 year old girl with 15 cm of jejunum following a midgut volvulus [51], this represents the most recent of the reported AIR techniques in children (Fig. 7). Continuous spiral lines are marked between the mesenteric and antimesenteric border of the bowel at 45–60° to the longitudinal axis of a loop. These lines are incised and the bowel is stretched over a catheter and the edges sutured in a continuous fashion to produce a tube of longer length but narrower diameter. Its proposed advantages are that it involves minimal handling of the mesentery and—unlike STEP—does not disrupt the orientation of the bowel's muscle fibres. To date the reported experience of this technique is limited to case reports and small case series [52].

Outcomes of AIR and Choice of Technique

LILT and STEP represent the mainstay of AIR in children. Both techniques are attractive as they are single stage procedures that result in both a lengthening of the intestine and a reduction in calibre without requiring sacrifice of intestinal mass. Meaningful comparison of the outcomes of these two procedures (Table 1) is hindered by small numbers; heterogenous patient populations and a paucity of comparable long-term follow-up data (owing in part to the more recent inception of STEP in 2003 vs 1980 for the LILT). Thus any direct comparison should be interpreted with caution. However published outcome data to date would suggest that whilst LILT would appear to result in a greater proportion of infants successfully weaning from PN it is associated with a higher transplant rate [37]. This seemingly conflicting data is likely in part a consequence of the availability of longer-term follow-up data for the LILT.

LILT is a technically more challenging undertaking but certainly not beyond the reach of most neonatal surgeons. STEP however is relatively straightforward if one can get one's hands on a linear stapler (preferably an EndoGIA™) and is perhaps more versatile and may be applied to any length of dilated bowel including the duodenum [53]. Intestinal re-dilatation occurs following STEP at a greater rate than is reported following LILT [37], however unlike the LILT (which cannot be repeated on the same segment of bowel as the mesentery has already been split) STEP may be repeated as a ReSTEP procedure [49]. Complications arising from STEP include bleeding from staple-line ulcers (which can be life-threatening [54]), perforation and fistula formation.

Ultimately the choice of the most appropriate AIR procedure ought to be a combination of the surgeon's experience/familiarity with a particular procedure and the infants age

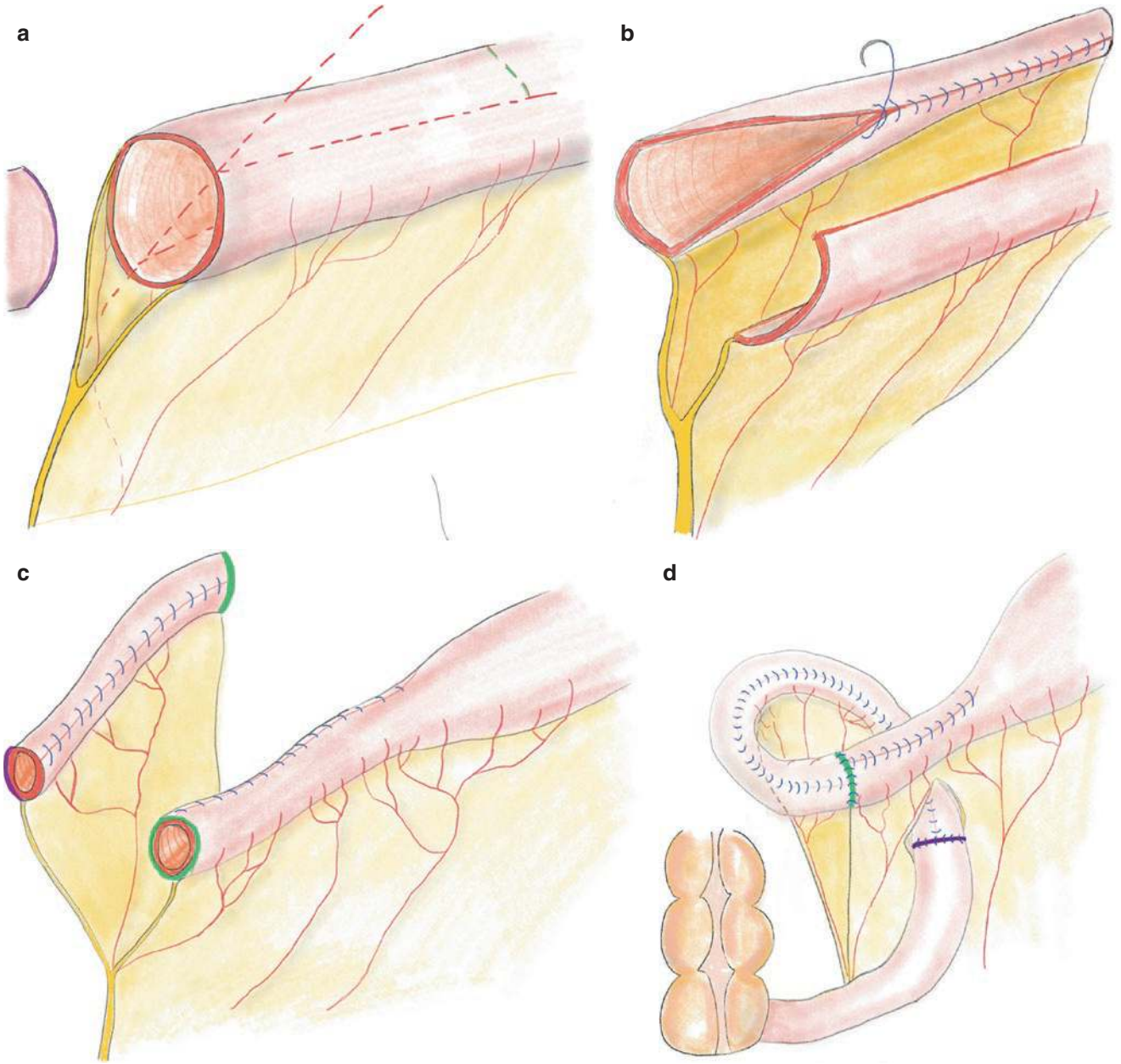

Fig. 4 Longitudinal intestinal lengthening technique (LILT). (**a**) The bowel is divided antimestenterically along its axis at 180° (red dashed lines) splitting the mesentery. (**b**) The two intestinal 'halves' are then tubularised with each relying on half of the original mesenteric blood supply. (**c**, **d**) Continuity is restored by anastomosing (green and purple lines) and reincorporating the 'new' loop in an isoperistaltic manner

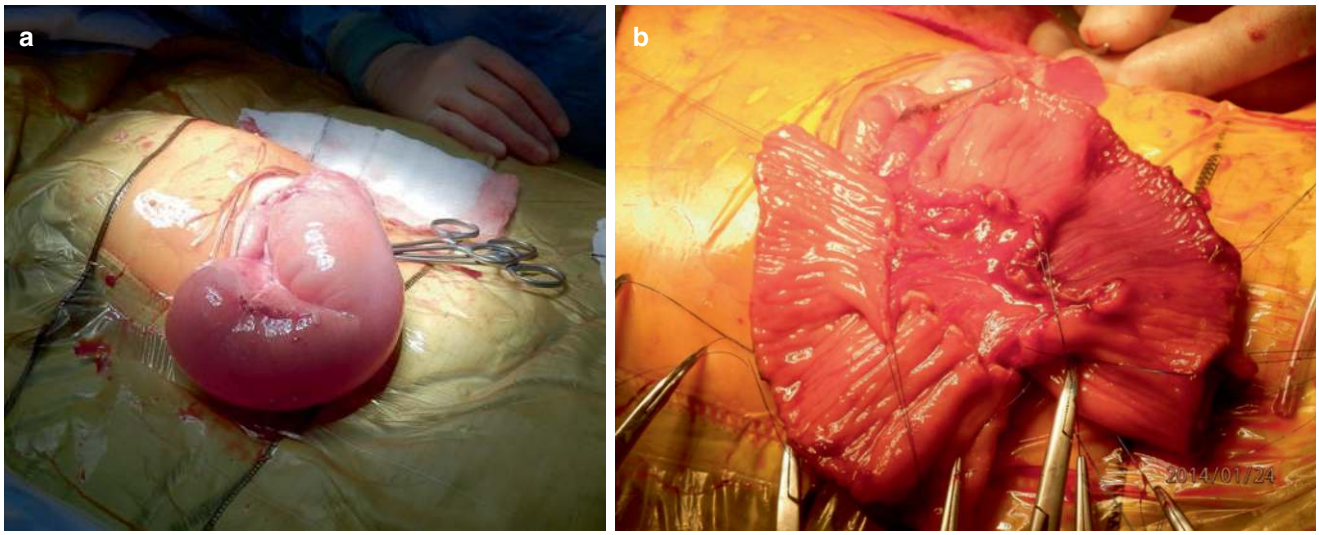

Fig. 5 LILT—operative picture after division of dilated jejunum. (**a**) Case of closed gastroschisis with grossly dilated jejunal atresia and an initial measured length of 20 cm. (**b**) Post-division of jejunum showing two independently vascularised intestinal strips prior to re-tubularisation

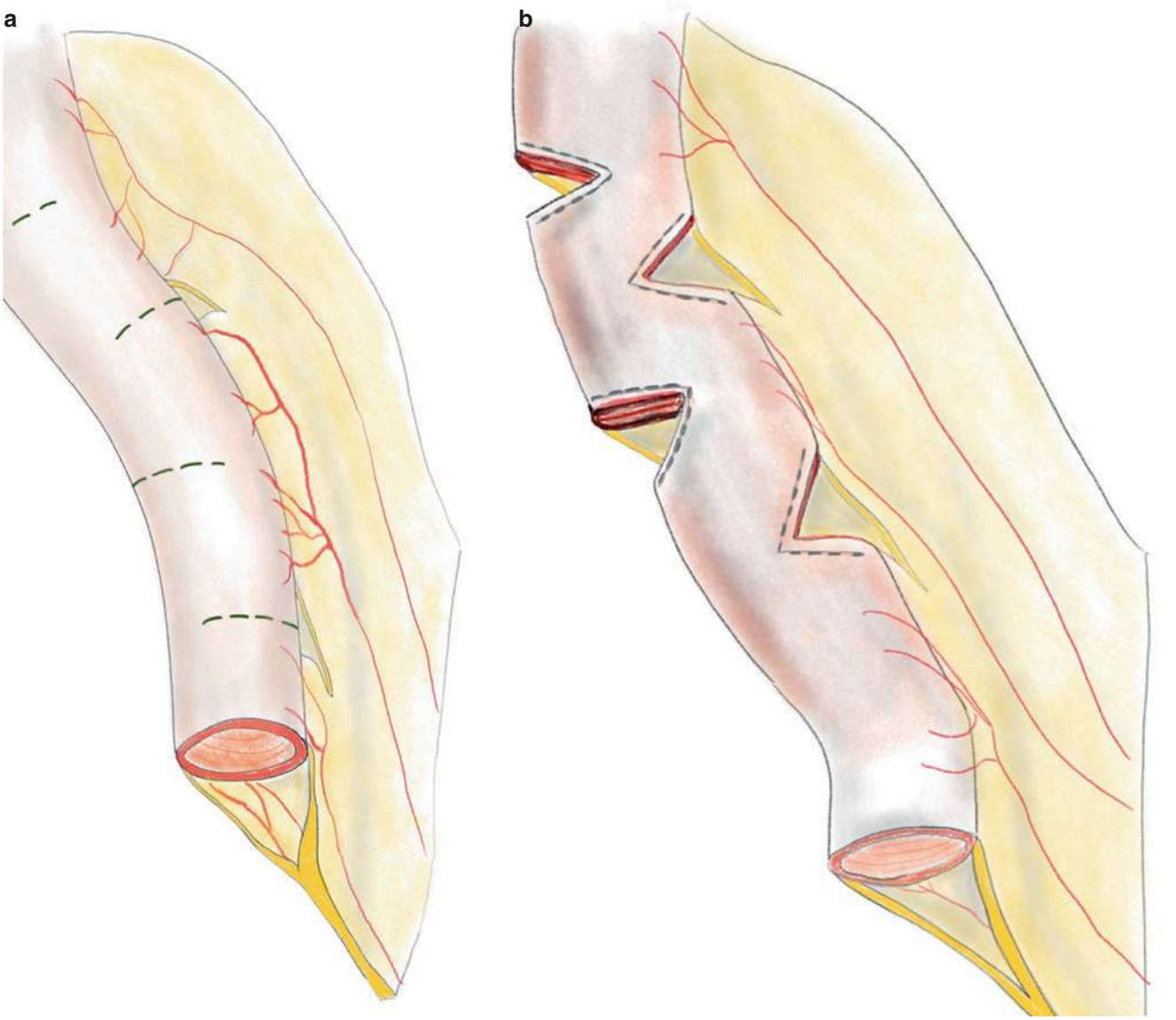

Fig. 6 Serial Transverse Enteroplasty (STEP). (**a**) Small mesenteric 'windows' are created so that a GIA stapler may be fired part way across the bowel diameter (dashed lines). (**b**) GIA firings are repeated at equal intervals and from alternate sides to create a zig-zag channel of about 1–2 cm diameter

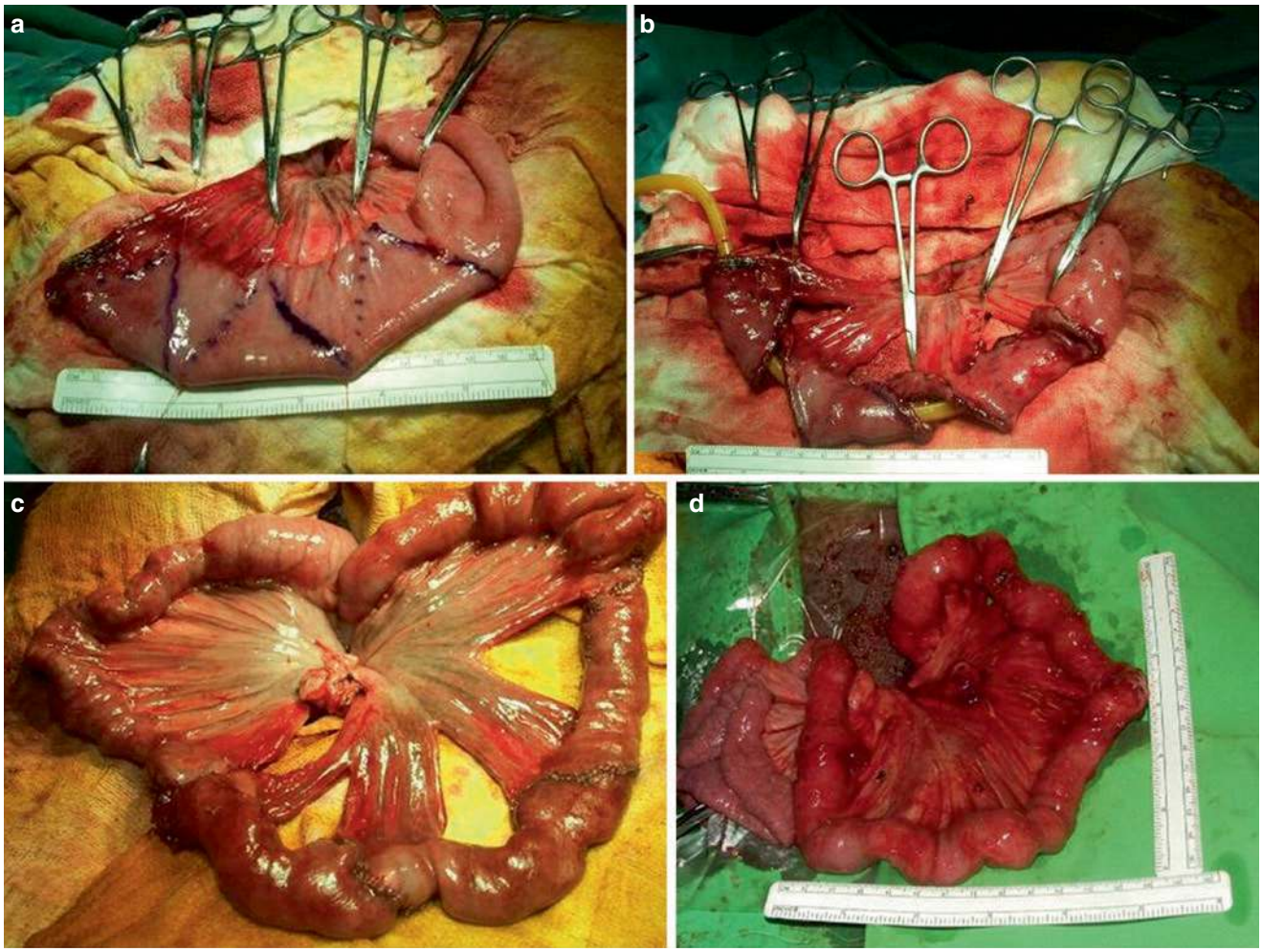

Fig. 7 Spiral Intestinal Longitudinal Intestinal and Tailoring (SILT): experimental model in minipigs. (**a**) Incision line marked on the dilated segment (dotted line: incision on the posterior wall). The scale is 15 cm. (**b**) After spiral incision. (**c**) End result of SILT.(**d**) Lengthened segment 5 weeks postoperatively is viable, with normal calibre and remains long. (Reprinted with permission from [50])

Table 1 Comparison of the Longitudinal Intestinal Lengthening Technique (LILT) and Serial Transverse Enteroplasty (STEP)

	LILT	STEP
First reported	1980	2003
Rate of successful PN weaning	70% (4–100%) at a mean of 10.3 months (5–21 months)	58.1% (20–100%) at a mean of 9.4 months (6–16 months)
Learning curve	Technically challenging requiring dissection of mesentery and long hand-sewn anastomoses	Undertaken with GIA stapler without disturbing mesenteric vessels
Limitations	Minimum of >20 cm of dilated bowel required Cannot be reapplied	Can be applied to any dilated bowel (including duodenum) though arguably of limited use Can be reapplied as ReSTEP
Complications	Re-dilatation, leak, stricture and necrosis	Re-dilatation, leak, stricture and bleeding
Reported mortality	30%[a]	14%

Reference: Frongia G, Kessler M, Weih S, Nickkholgh A, Mehrabi A, Holland-Cunz S (2013) Comparison of LILT and STEP procedures in children with short bowel syndrome—A systematic review of the literature. J Pediatr Surg 48:1794–1805

[a]The reported series of LILT are much older and reflect the limited options available for end-stage liver disease in previous eras

and anatomy. Ideally units undertaking AIR should be able to offer both procedures, but for those establishing an initial practice STEP would appear to be the more versatile, reproducible and straightforward procedure to adopt.

Controlled Intestinal Expansion

Actual enterocyte mucosal tissue expansion appears to be feasible, simply by increasing intraluminal pressure. This may be an exciting alternative pioneered in Manchester and Toronto for infants with ultra-short bowel due to closed gastroschisis or intestinal atresia and seemingly destined for life-time PN or intestinal transplant.

There are two methods which have been used to achieve what is effectively controlled proximal jejunal obstruction.

The Manchester method is to form a tube jejunostomy with a soft catheter (e.g. Malecot or Foley) constrained by purse-string sutures. This is then periodically obstructed over a period of time (e.g. 20–24 weeks) for progressively longer and longer periods to create proximal dilatation. This process—combined with ongoing distal refeeding—is termed the ‘controllable expansion recycle’ technique [55].

The Toronto approach entails the creation of a Stamm gastrostomy and a distal sigmoid colostomy at the initial laparotomy. Oral sham feeds are commenced post-operatively and the gastrostomy tube is intermittently clamped/unclamped to create proximal dilatation. When sufficient (>5 cm) dilatation is achieved a STEP is performed and intestinal continuity is restored [56].

Summary

Short bowel syndrome is the commonest cause of intestinal failure in infants and arises either as a result of congenital malformations such as small bowel atresia and gastroschisis or is acquired as a consequence of intestinal loss following acute pathology such as NEC or malrotation volvulus [57].

In the management of short bowel in childhood the paediatric surgeon is a key member of the MDT from the outset. Adopting a considered and structured approach to the initial surgical management of these infants can minimise the loss of intestinal mass, maximise the potential for enteral absorption and aid the creation of anatomy upon which future AIR is then feasible. When adequate adaption cannot be achieved by conservative means alone then the timely undertaking of AIR may deliver enteral autonomy or at least reduce the burden of PN.

References

1. Touloukian RJ, Smith GJW. Normal intestinal length in preterm infants. J Pediatr Surg. 1983;18:720–3.
2. Delrivière L, Muiesan P, Marshall M, Davenport M, Dhawan A, Kane P, Karani J, Rela M, Heaton N. Size reduction of small bowels from adult cadaveric donors to alleviate the scarcity of pediatric size-matched organs: an anatomical and feasibility study. Transplantation. 2000;69:1392–6.
3. Batra A, Keys SC, Johnson MJ, Wheeler RA, Beattie RM. Epidemiology, management and outcome of ultrashort bowel syndrome in infancy. Arch Dis Child Fetal Neonatal Ed. 2017;102:F551–6.
4. Houben C, Davenport M, Ade-Ajayi N, Flack N, Patel S. Closing gastroschisis: diagnosis, management, and outcomes. J Pediatr Surg. 2009;44:343–7.
5. Grosfeld JL, Ballantine TVN, Shoemaker R. Operative management of intestinal atresia and stenosis based on pathologic findings. J Pediatr Surg. 1979;14:368–75.
6. Finkle Y, Puntis J, Goulet O. Walker’s pediatric gastrointestinal disease. 2018.
7. Wales PW, Nasr A, de Silva N, Yamada J. Human growth hormone and glutamine for patients with short bowel syndrome. Cochrane Database Syst Rev. 2010;(6):CD006321.
8. Carter BA, Cohran VC, Cole CR. Outcomes from a 12-week, open-label, multicenter clinical trial of teduglutide in pediatric short bowel syndrome. J Pediatr. 2017;181:102–111.e5.
9. Tappenden KA, McBurney MI. Systemic short-chain fatty acids rapidly alter gastrointestinal structure, function, and expression of early response genes. Dig Dis Sci. 1998;43:1526–36.
10. Tappenden KA, Albin DM, Bartholome AL, Mangian HF. Glucagon-like peptide-2 and short-chain fatty acids: a new twist to an old story. J Nutr. 2003;133:3717–20.
11. Duro D, Mitchell PD, Kalish LA. Risk factors for parenteral nutrition–associated liver disease following surgical therapy for necrotizing enterocolitis. J Pediatr Gastroenterol Nutr. 2011;52:595–600.

12. Belza C, Thompson R, Somers GR, de Silva N, Fitzgerald K, Steinberg K, Courtney-Martin G, Wales PW, Avitzur Y. Persistence of hepatic fibrosis in pediatric intestinal failure patients treated with intravenous fish oil lipid emulsion. J Pediatr Surg. 2017;52:795–801.
13. Ventro GJ, Yang Y, Chen M, Harmon CM. The molecular impact of omega 3 fatty acids on hepatic pro-inflammatory cytokine signaling. J Pediatr Surg. 2017;52:1020–5.
14. Lam HS, Tam YH, Poon TCW, Cheung HM, Yu X, Chan BPL, Lee KH, Lee BSC, Ng PC. A double-blind randomised controlled trial of fish oil-based versus soy-based lipid preparations in the treatment of infants with parenteral nutrition-associated cholestasis. Neonatology. 2014;105:290–6.
15. Wragg RC, Blundell S, Bader M, Sharif B, Bennett J, Jester I, Bromley P, Arul GS. Patency of neck veins following ultrasound-guided percutaneous Hickman line insertion. Pediatr Surg Int. 2014;30:301–4.
16. Basford TJ, Poenaru D, Silva M. Comparison of delayed complications of central venous catheters placed surgically or radiologically in pediatric oncology patients. J Pediatr Surg. 2003;38:788–92.
17. Pichler J, Horn V, MacDonald S, Hill S. Sepsis and its etiology among hospitalized children less than 1 year of age with intestinal failure on parenteral nutrition. Transplant Proc. 2010;42:24–5.
18. Cole CR, Frem JC, Schmotzer B, Gewirtz AT, Meddings JB, Gold BD, Ziegler TR. The rate of bloodstream infection is high in infants with short bowel syndrome: relationship with small bowel bacterial overgrowth, enteral feeding, and inflammatory and immune responses. J Pediatr. 2010;156:941–947.e1.
19. Ormsby JA, Bukoye B, Lajoie D. Enhanced central venous catheter bundle for pediatric parenteral-dependent intestinal failure. Am J Infect Control. 2018;46:1284–9.
20. Ardura MI, Lewis J, Tansmore JL, Harp PL, Dienhart MC, Balint JP. Central catheter–associated bloodstream infection reduction with ethanol lock prophylaxis in pediatric intestinal failure. JAMA Pediatr. 2015;169:324.
21. Sinha L, Liston R, Testa HJ, Moriarty KJ. Idiopathic bile acid malabsorption: qualitative and quantitative clinical features and response to cholestyramine. Aliment Pharmacol Ther. 1998;12:839–44.
22. Raphael B, Duggan C. Prevention and treatment of intestinal failure-associated liver disease in children. Semin Liver Dis. 2013;32:341–7.
23. De Marco G, Sordino D, Bruzzese E, Di Caro S, Mambretti D, Tramontano A, Colombo C, Simoni P, Guarino A. Early treatment with ursodeoxycholic acid for cholestasis in children on parenteral nutrition because of primary intestinal failure. Aliment Pharmacol Ther. 2006;24:387–94.
24. Spagnuolo MI, Iorio R, Vegnente A, Guarino A. Ursodeoxycholic acid for treatment of cholestasis in children on long-term total parenteral nutrition: a pilot study. Gastroenterology. 1996;111:716–9.
25. Gutierrez IM, Kang KH, Jaksic T. Neonatal short bowel syndrome. Semin Fetal Neonatal Med. 2011;16:157–63.
26. Yilmaz B, Schibli S, Macpherson AJ, Sokollik C. D-lactic acidosis: successful suppression of D-lactate--lactobacillus producing. Pediatrics. 2018;142:1–5.
27. Coletta R, Khalil BA, Morabito A. Short bowel syndrome in children: surgical and medical perspectives. Semin Pediatr Surg. 2014;23:291–7.
28. Hyman PE, Everett SL, Harada T. Gastric acid hypersecretion in short bowel syndrome in infants: association with extent of resection and enteral feeding. J Pediatr Gastroenterol Nutr. 1986;5:191–7.
29. Demehri FR, Stephens L, Herrman E, West B, Mehringer A, Arnold MA, Brown PI, Teitelbaum DH. Enteral autonomy in pediatric short bowel syndrome: predictive factors one year after diagnosis. J Pediatr Surg. 2015;50:131–5.
30. Coran AG, Spivak D, Teitelbaum DH. An analysis of the morbidity and mortality of short-bowel syndrome in the pediatric age group. Eur J Pediatr Surg. 1999;9:228–30.
31. Chandra R, Kesavan A. Current treatment paradigms in pediatric short bowel syndrome. Clin J Gastroenterol. 2018;11:103–12.
32. Ba'ath ME, Almond S, King B, Bianchi A, Khalil BA, Morabito A. Short bowel syndrome: a practical pathway leading to successful enteral autonomy. World J Surg. 2012;36:1044–8.
33. Hukkinen M, Kivisaari R, Koivusalo A, Pakarinen MP. Risk factors and outcomes of tapering surgery for small intestinal dilatation in pediatric short bowel syndrome. J Pediatr Surg. 2017;52:1121–7.
34. Thyoka M, Eaton S, Kiely EM, Curry JI, Drake DP, Cross KMK, Hall NJ, Khoo AK, De Coppi P, Pierro A. Outcomes of diverting jejunostomy for severe necrotizing enterocolitis. J Pediatr Surg. 2011;46:1041–4.
35. Vaughan WG, Grosfeld JL, West K, Scherer LR, Villamizar E, Rescorla FJ. Avoidance of stomas and delayed anastomosis for bowel necrosis: the "clip and drop-back" technique. J Pediatr Surg. 1996;31(4):542–5.
36. Bonnard A, Staub G, Segura JF, Malbezin S, Dorgeret S, Aigrain Y, De Lagausie P. Evaluation of intestinal absorption after longitudinal intestinal lengthening for short bowel syndrome. J Pediatr Surg. 2005;40:1587–91.
37. Frongia G, Kessler M, Weih S, Nickkholgh A, Mehrabi A, Holland-Cunz S. Comparison of LILT and STEP procedures in children with short bowel syndrome - a systematic review of the literature. J Pediatr Surg. 2013;48:1794–805.
38. Williamson RCN. Intestinal adaptation. N Engl J Med. 1978;298:1393–402.
39. Bianchi A. Autologous gastrointestinal reconstruction for short bowel syndrome. Br J Hosp Med. 2007;68:24–7.
40. Cowles RA, Lobritto SJ, Stylianos S, Brodlie S, Smith LJ, Jan D. Serial transverse enteroplasty in a newborn patient. J Pediatr Gastroenterol Nutr. 2007;45:257–60.
41. Masumoto K, Souzaki R, Nagata K, Uesugi T, Nishimoto Y, Taguchi T. Improvement in the quality of life using both Bianchi's procedure and the closure of a jejunostomy in a case with short bowel syndrome. Pediatr Surg Int. 2007;23:285–8.
42. Wood SJ, Khalil B, Fusaro F, Folaranmi SE, Sparks SA, Morabito A. Early structured surgical management plan for neonates with short bowel syndrome may improve outcomes. World J Surg. 2013;37:1714–7.
43. Höllwarth ME. Surgical strategies in short bowel syndrome. Pediatr Surg Int. 2017;33:413–9.
44. Hutcher NE, Mendez-Picon G, Salzberg AM. Prejejunal transposition of colon to prevent the development of short bowel syndrome in puppies with 90 per cent small intestine resection. J Pediatr Surg. 1973;8:771–7.
45. Kimura K, Soper RT. A new bowel elongation technique for the short-bowel syndrome using the isolated bowel segment iowa models. J Pediatr Surg. 1993;28:792–4.
46. Bianchi A. Intestinal loop lengthening-A technique for increasing small intestinal length. J Pediatr Surg. 1980;15:145–51.
47. Bianchi A. Intestinal lengthening: an experimental and clinical review. J R Soc Med. 1984;77:35–41.
48. Kim HB, Lee PW, Garza J, Duggan C, Fauza D, Jaksic T. Serial transverse enteroplasty for short bowel syndrome: a case report. J Pediatr Surg. 2003;38:881–5.
49. Barrett M, Demehri FR, Ives GC, Schaedig K, Arnold MA, Teitelbaum DH. Taking a STEP back: assessing the outcomes of multiple STEP procedures. J Pediatr Surg. 2017;52:69–73.
50. Cserni T, Varga G, Erces D, Kaszaki J, et al. Spiral intestinal lengthening and tailoring — first in vivo study. J Pediatric Surg. 2013;48:1907–1913T.
51. Cserni T, Biszku B, Guthy I, Dicso F, Szaloki L, Folaranmi S, Murphy F, Rakoczy G, Bianchi A, Morabito A. The first clinical application of the spiral intestinal lengthening and tailoring (silt) in extreme short bowel syndrome. J Gastrointest Surg. 2014;18:1852–7.

52. Coletta R, Aldeiri B, Morabito A. Institutional experience with spiral intestinal lengthening and tailoring. Eur J Pediatr Surg. 2018;29(5):412–6. https://doi.org/10.1055/s-0038-1660850.
53. Bueno J, Redecillas S, García L, Lara A, Giné C, Molino JA, Broto J, Segarra O. Duodenal lengthening in short bowel with dilated duodenum. J Pediatr Surg. 2015;50:493–6.
54. Bogue CO, Alzahrani AI, Wales PW, John PR, Amaral JG. Delayed, life-threatening lower gastrointestinal hemorrhage in an infant after serial transverse enteroplasty: treatment with transcatheter n-butyl-2-cyanoacrylate embolization. Pediatr Radiol. 2009;39:1098–101.
55. Khalil BA, Ba'ath ME, Aziz A, Forsythe L, Gozzini S, Murphy F, Carlson G, Bianchi A, Morabito A. Intestinal rehabilitation and bowel reconstructive surgery: improved outcomes in children with short bowel syndrome. J Pediatr Gastroenterol Nutr. 2012;54:505–9.
56. Wales PW, Jancelewicz T, Romao RL, Piper HG, De Silva NT, Avitzur Y. Delayed primary serial transverse enteroplasty as a novel management strategy for infants with congenital ultra-short bowel syndrome. J Pediatr Surg. 2013;48:993–9.
57. Squires RH, Duggan C, Teitelbaum DH. Natural history of pediatric intestinal failure: initial report from the pediatric intestinal failure consortium. J Pediatr. 2012;161:723–728.e2.

Part III

Chronic (Long-Term) Intestinal Failure

Physiology and Problems of a Short Bowel

Jeremy M.D. Nightingale

Key Points

1. A short bowel occurs when there is an insufficient length of small intestine to absorb enough nutrition/fluid to maintain health/growth.
2. Due to large range of "normal" small intestinal length, it is important to refer to the remaining length of small bowel rather than the length resected.
3. There are two common types of patient with a short bowel. Those with jejunum anastomosed to colon (jejunum-colon or type 2) and patients with an end jejunostomy (type 1). A third less common group have had a predominantly jejunal resection [jejunum–ileum. (Type 3)], and have more than 10 cm of terminal ileum remaining, their problems are similar to the jejunum-colon patients.
4. Patients with a jejunostomy have high stomal losses of water and sodium and often have hypomagnesaemia. Fluid balance dominates their management.
5. Patients with a jejuno-colic anastomosis do not generally have fluid balance problems and the colon salvages energy from colonic fermentation. However they have a high prevalence of calcium oxalate renal stones.
6. All patient types have a high prevalence of calcium bilirubinate gallstones.
7. The absorption in patients with a preserved functioning colon improves with time; this does not occur in patients with a jejunostomy.

Background

In 1880, Koberle performed the first reported successful small intestinal resection of more than 200 cm on a 22-year-old girl with multiple intestinal strictures [1]. At the beginning of the twentieth century, a resection of more than 200 cm of small intestine, thought to be a third of the total small intestinal length, was referred to as an 'extensive' intestinal resection and was thought to be the maximum length of small intestine that could be removed and for the patient to survive [2]. In 1935, Haymond used the term 'massive' in preference to 'extensive' intestinal resection when he reviewed the literature of 257 patients, most of whom had had a resection for an intestinal volvulus (Table 1); he noted an overall survival of 67% [3].

In the 1960s, as an awareness developed that the outcome from an intestinal resection depended upon the length of small bowel remaining rather than the length resected, so the term 'short bowel syndrome' came into use. The syndrome was characterized by 'intractable diarrhoea with impaired absorption of fats, vitamins, and other nutrients, ultimately leading to malnutrition, anaemia, and continued weight loss' [4]. This description implies a slow chronic illness and is adequate to describe most patients who have a short bowel and retained functioning colon; it does not describe the acute fluid balance problems experienced by patients with a jejunostomy (end-jejunostomy syndrome). The first report of a patient surviving with a jejunostomy, 120 cm from the duodeno-jejunal flexure, was in 1963 [5].

Early work was on physiology first in animals after a large predominantly jejunal resection then work in man was initially in those with a jejunocolic anastomosis. Later work was with patients with a jejunostomy and a high output

Table 1 Reasons for a 'massive' intestinal resection in adults as published in 1935 [3]

	$n = 257$
Volvulus	76
Strangulated hernia	45
Mesenteric thrombosis	34
Tuberculosis	16
Mesenteric tumours	14
Uterine perforation	11
Adhesions/bands	7
Other	54

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stoma. The studies to understand the physiological changes in the 1990s were about motility and gastrointestinal hormones. Research since the millennium has concentrated on peptide growth factors, new hormones and the microbiome.

Length of Small Intestine

The length of the adult intestine, measured surgically, radiologically or at autopsy from the duodeno-jejunal flexure, ranges from about 275 to 1510 cm and tends to be shorter in women than in men (chapter "Normal Intestinal Anatomy and Physiology"). Congenital cases of a short bowel have been reported and are usually associated with malrotation of the gut [6, 7]. Patients who have a small intestinal length at or below the lower end of the normal range may develop the problems associated with a short bowel after relatively little small intestine has been removed. In a study of 11 patients with Crohn's disease and less than 200 cm small bowel remaining, the median original small bowel length was calculated from the lengths resected and remaining to be 240 cm (range 205–315 cm), indicating a short small bowel length before any resections [8]. A further study has confirmed that patients with Crohn's disease have a shorter total small intestinal length than controls (mean length at laparotomy in 279 Crohn's disease patients 460 cm vs. 564 cm in 77 non-inflammatory bowel disease patients) [9].

The large range of normal human small intestinal length means that it is more important to refer to the length of small bowel remaining rather than to the length removed. The term ultrashort bowel is occasionally used to refer to patients who have less than 20 or 30 cm small bowel remaining and are thus unlikely to absorb any macro or micronutrients.

Assessment of Residual Small Intestine

Anatomical Length

The remaining small bowel length is ideally assessed at surgery by measuring 10–30 cm segments of bowel along the antimesenteric border, taking great care not to over-stretch the bowel. If there is no surgical measurement available and radiographic films are available, the bowel can be measured using an opisometer, a device used for measuring distances on maps. It traces the long axis of the small bowel on a small bowel meal radiograph. This technique is relatively accurate if the total small intestinal length is less than 200 cm and if the entire small bowel is shown on one film [9, 10]. As most films are saved on a computer the small bowel length (on contrast follow through, computerized tomographic enterography [11] or magnetic resonance scans [12]) can be measured in short segments and give an a moderately accurate estimate of the remaining small bowel length. This is easier to estimate if the total small bowel length is less than 200–300 cm.

Functional Length

Citrulline is a non-essential amino acid that is almost exclusively synthesized in the enterocyte by pyrolline-5-carboxylase-synthase from glutamine. It is not derived from food or proteolysis and is not incorporated into body proteins. Some of the citrulline made by the enterocyte passes to the liver, where it is an important intermediate in the urea cycle (urea made from ammonia) and some passes into the systemic circulation. All the citrulline in the systemic circulation is derived from small intestinal enterocytes, thus plasma levels of citrulline are related to the length of the remaining functional small bowel (Fig. 1) [13–16].

Apolipoprotein AIV (Apo AIV) may be an equally effective marker of functional enterocyte mass; it is exclusively synthesized by enterocytes. Its concentration in plasma, like citrulline, mainly depends on production in the small intestine and is not affected by first-pass metabolism. Apo AIV is incorporated into the surface of nascent chylomicrons. Upon entering the blood circulation, it is rapidly dissociated from the chylomicrons and predominates in the plasma as a lipoprotein-free fraction. It shows no circadian rhythm and maintains stable physiological plasma levels. It has the advantage over citrulline of being easier to measure (smaller sample, simpler equipment and faster results) [17].

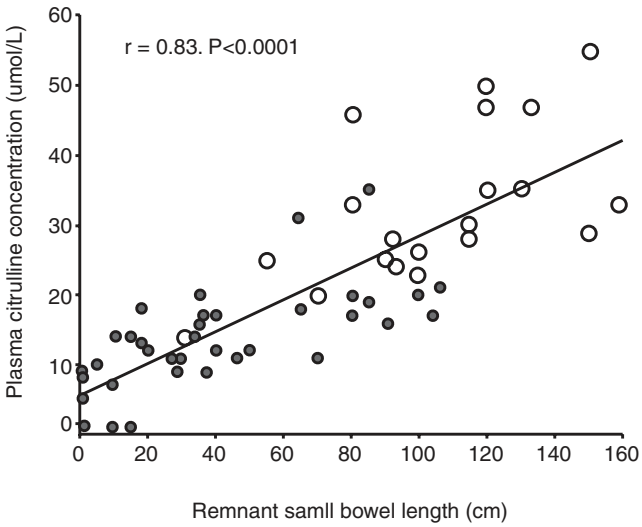

Fig. 1 Fasting plasma citrulline level and remaining small bowel length. (With permission [13])

Anatomical Considerations of Remaining Bowel

Ileum or Jejunum

A jejunal resection is better tolerated than an ileal resection. Ileal mucosa, in contrast to the jejunal mucosa, has tight intercellular junctions and thus can concentrate its contents. Gastrointestinal transit is naturally slower in the ileum than jejunum, so allowing more time for absorption [18, 19]. The terminal ileum absorbs vitamin B_{12} [20, 21] and bile salts. Ileum remaining after a small bowel resection can adapt in both structure and function to increase absorption [22–24], while the jejunum can only adapt functionally if some distal bowel remains (chapter "Intestinal Adaptation").

Ileocaecal Valve

It is traditionally considered that preservation of the ileocaecal valve is beneficial as it may slow transit and prevent reflux of colonic contents into the small bowel; however, studies of ileocaecal valve excision show no evidence that it slows transit, and small bowel peristalsis probably prevents reflux from the colon into the small bowel [18, 25] (chapter "Normal Intestinal Anatomy and Physiology").

Some reports suggest that conservation of the ileocaecal valve in children is beneficial in terms of survival and the need for parenteral nutrition [26, 27]; others show no such benefits [28, 29]. The reports proposing benefit of ileocaecal valve preservation in adults may reflect preservation of a significant length of terminal ileum.

Colon

Conservation of the colon is beneficial because it absorbs water, sodium [30–34], calcium [35] and short- and medium-chain fatty acids [36–38]; it also slows gastrointestinal transit [39], stimulates small intestinal hyperplasia [40] and its bacteria manufacture some amino acids and vitamins (e.g. vitamin K, biotin, folic acid and thiamine) which can then be absorbed in the colon. Patients with an entero-colic anastomosis may survive without parenteral support with a very short [41, 42] or even no remaining jejunum [43]. Patients with a preserved functioning colon rarely need regular water and sodium supplements [32–34]. In terms of the need for parenteral nutrients, preservation of at least half of the colon after a jejuno-ileal resection is equivalent to about 50 cm of small intestine [34].

Causes of a Short Bowel

The four most common reasons for patients to have less than 200 cm of small bowel are superior mesenteric artery thrombosis, Crohn's disease, irradiation damage and surgical complications [10, 34, 44] (Tables 2, 3 and 4). Resection of an ischaemic small intestine ultimately results in colonic pres-

Table 2 Reasons for a short bowel in adults in 1969 [44] (less than 120 cm small bowel remaining; almost all patients had a remaining functional colon)

	n = 123
Superior mesenteric artery thrombosis/embolus	49
Volvulus	24
Superior mesenteric vein thrombosis	10
Tumours	10
Non-occlusive gangrene	10
Strangulated herniae	5
Regional enteritis	1
Other	14

Table 3 Reasons for a short bowel in adults in 1992 (less than 200 cm small bowel remaining) [34]

	Jejunum–colon	Jejunostomy
Total (sex)	38 (26 F)[a]	46 (31 F)
Age (range)	46 (7–70)	42 (16–68)
Median jejunal length (cm)	90 (0–190)	115 (20–190)
Diagnosis		
Crohn's disease	16	33
Ischaemia	6	2
Irradiation	5	3
Ulcerative colitis	–	5
Volvulus	5	–
Adhesions	4	1
Diverticular disease	1	1
Desmoid tumour	1	1

[a]7 had an ileocaecal valve and 31 a jejuno-colic anastomosis

Table 4 Characteristics of 268 adult patients receiving HPN for non-malignant short bowel (less than 150 cm small bowel) from 1980 to 2006 [45]

Total (sex)	268 (139 F)
Age [mean (range)]	52.5 (18–89)
Diagnosis	
Mesenteric infarction	115 (43)[a]
Irradiation	61 (23)
Surgical complications	33 (12)
Soft tissue tumour	16 (6)
Crohn's disease	15 (6)
Volvulus and trauma	14 (5)
Chronic intestinal pseudo-obstruction	11 (4)
Other	3 (1)

[a]93 arterial and 22 venous infarction

ervation (75%) and affects an older age group (median age 57 years) [34]. Patients with Crohn's disease and jejunum in continuity with a functioning colon had undergone a median of 3 small intestinal resections (range 2–6) over a median of 14 years (range 0–29), compared with 4 resections (range 1–12) over a median of 11 years (range 1–26) in those with a jejunostomy [34]. The median time from irradiation to having a small intestinal length of less than 200 cm in 8 patients with irradiation damage (5 gynaecological cancers, 2 carcinomas of the colon and 1 seminoma) was 5 years (range 1–16) [34].

A short bowel occurs more commonly in women (67%) than in men [34, 45]; this may be because women start with a shorter length of small intestine than men.

The more recent causes of a short bowel in adults are derived from the reported aetiology of patients receiving parenteral support and additionally from those taking part in peptide growth hormone studies. There are no studies since 1992 of patients with a short bowel and not receiving HPS. The number of patients with a short bowel and Crohn's disease has reduced while the number following surgical resections, with mesenteric ischaemia and malignancy have all increased [46].

The causes of a short bowel arising in childhood and infancy usually result in colonic preservation. In infancy the causes include necrotizing enterocolitis, multiple jejuno-ileal atresia, gastroschisis, mid-gut volvulus and congenital [26–29, 46–49] (chapters "Peritoneal Adhesions and Encapsulating Peritoneal Sclerosis" and "Acid-Base Disturbances in Intestinal Failure"). In children trauma, post-operative complications, cancer and motility disorders dominate [46]. As the management and thus the survival of these children improves [27–29], they are being cared for as adults.

Types of Patient with a Short Bowel

There are three types of patient with a short bowel (Fig. 2):

1. *Jejunum–colon*. (Type 2) Patients in whom the ileum has been removed, often with the ileocaecal valve, to leave a jejuno-colic anastomosis (jejunum–colon); patients who have less than 10 cm of terminal ileum are included in this group.
2. *Jejunostomy*. (Type 1) Patients in whom some jejunum, the ileum and colon have been removed, so they are left with an end-jejunostomy.
3. *Jejunum–ileum*. (Type 3) Patients who have had a predominantly jejunal resection, and have more than 10 cm of terminal ileum and the colon remaining (jejuno-ileal) [10, 34, 50]. This last group is not common (2 of 86 patients [34]); since the residual ileum can adapt both structurally and functionally, these patients rarely have major problems and they are not specifically discussed in this chapter.

Patients with a jejunostomy can be classified according to the results of balance studies as net 'absorbers' or net 'secretors'. The 'absorbers' in general have more than 100 cm of residual jejunum and absorb more water and sodium from their diet than they take orally (usual daily jejunostomy output about 2 kg); they can therefore be managed with oral sodium and water supplements, and parenteral fluids are not needed. The 'secretors' usually have less than 100 cm residual jejunum and lose more water and sodium from their stoma than they take by mouth (the usual daily stomal output may be 4–8 kg). 'Secretors' cannot convert from negative to positive water and sodium balance by taking more orally, and so they need long-term parenteral supplements [51]. These requirements change very little with time [34]. The jejunostomy output from a net 'secretor' increases during the daytime in response to food and decreases at night; any drug therapy that aims to reduce the output is therefore given prior to food. The change from a net secretory state, in terms of water and sodium balance, to a net absorptive state occurs at a jejunal length of about 100 cm (chapter "Management of a High Output Stoma, Jejunotomy or Uncomplicated Enterocutaneous Fistula").

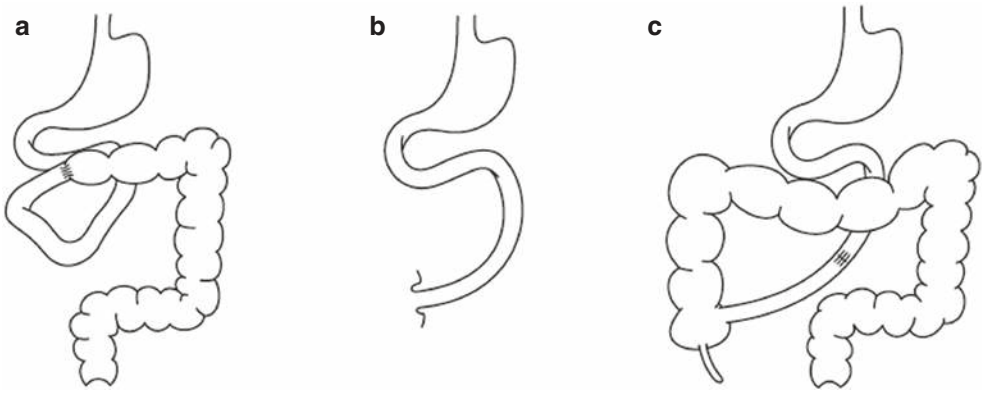

Fig. 2 The three types of patient with a short bowel. Patients with a jejuno-colic anastomosis or a jejunostomy are most commonly encountered. (**a**) Jejuno-colic anastomosis; (**b**) Jejunostomy; (**c**) Jejuno-ileal anastomosis

Bowel Length and Fluid/Nutritional Support

- *Jejunum–colon*. While it is possible for a patient with no remaining jejunum to survive without parenteral nutrition, quality of life is poor [42]. A patient with 100–200 cm of normally functioning jejunum in continuity with a functioning colon may need oral nutrient supplements for a few months but in the long-term would not be expected to need any supplements unless the remaining bowel was diseased. When the jejunal length is between 50 and 100 cm, some patients will need long-term parenteral nutrition (PN), if it is between 30 and 50 cm most will do so, and if it is less than 30 cm almost all patients will need PN [34, 50] (Fig. 3). Sometimes parenteral

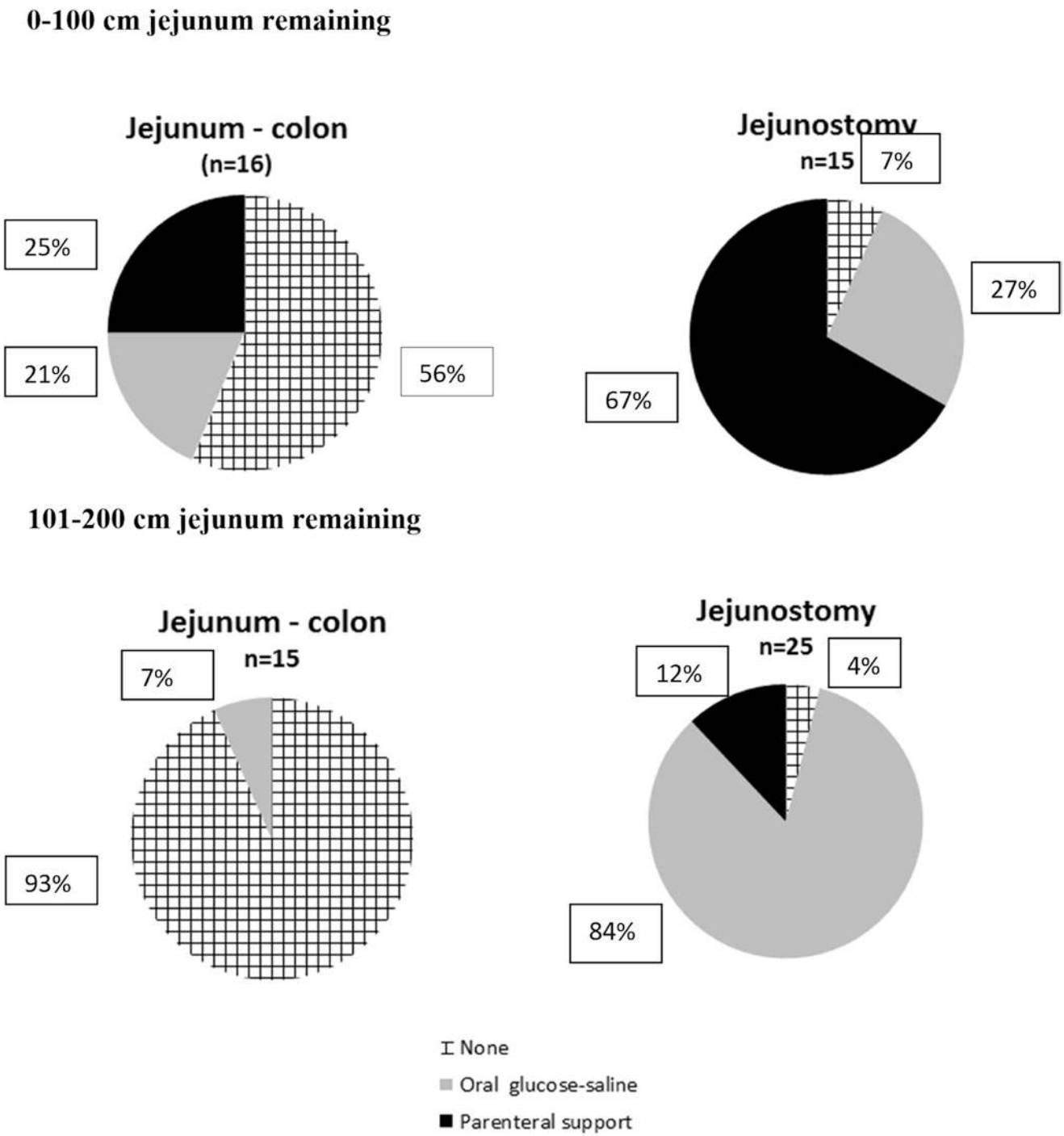

Fig. 3 Pie chart showing the parenteral and enteral sodium and water supplements given to 71 stable patients with less than 200 cm jejunum remaining. Few patients with a colon were receiving oral or parenteral sodium and water supplements, but almost all jejunostomy patients were receiving them [34]

nutrition is needed not to maintain nutritional status but to prevent the severe diarrhoea associated with eating.

- *Jejunostomy*. The survival of patients with a jejunostomy has improved since 1963 [5, 52]. If 100–200 cm normally functioning jejunum remains, oral sodium supplements (glucose–saline solution or sodium chloride tablets) are likely to be needed, often with oral nutrient solutions to which sodium chloride has been added [34, 50, 51, 53]. A patient with a jejunostomy and less than 100 cm jejunum remaining would be expected to need long-term parenteral saline. If less than 85 cm jejunum remains, long-term parenteral nutrition is likely to be required in addition to the saline. Patients usually need long-term parenteral nutrition when they absorb less than a third of their oral energy intake [51, 54].

Physiological Changes

Of the physiological changes observed after a small intestinal resection, some reflect normal and some altered physiology. Most experimental work in animals involves a predominantly jejunal resection (jejuno-ileal anastomosis); this has a better prognosis but is not a common situation in humans, in whom an ileal resection with or without a colectomy is most common.

Gastrointestinal Motility

Gastric Emptying

There are mechanisms (brakes) in the jejunum, ileum and colon that slow gastric emptying (chapter "Normal Intestinal Anatomy and Physiology"). In addition, events external to the bowel can affect gastric emptying; for example, malnutrition and many drugs (e.g. cyclizine and opiates) delay gastric emptying and parenteral nutrition delays the gastric emptying of solids [55]. Studies in animals have shown that gastric emptying of liquid is normal after a jejunal resection [56, 57].

- *Jejunum–colon*. Gastric emptying of liquids is normal in patients who have had a distal small intestinal resection that does not result in a short bowel [58]. Studies in which a dual isotope meal (liquid and solid components of the meal are labelled with different isotopes) has been given to patients with a jejuno-colic anastomosis have shown that some liquid leaves the stomach rapidly and travels quickly through the short length of remaining jejunum to reach the colon. In the colon, by a neural or hormonal mechanism, the liquid meal activates a colonic braking mechanism by which subsequent gastric emptying is slowed and overall measurements of liquid and solid gastric emptying are normal [39]. This colonic braking mechanism may be caused by the release of peptide YY from the colon [59] (Fig. 4). Infusions of peptide YY that achieve similar levels in normal subjects delay the gastric emptying of liquid [60].

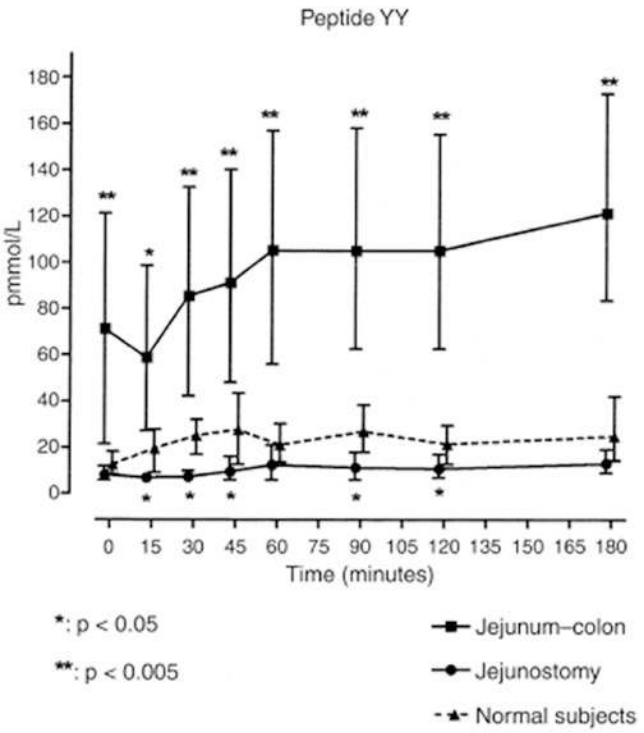

Fig. 4 Median peptide YY levels with interquartile range for 6 jejunum–colon patients, 7 jejunostomy patients and 12 normal subjects after a pancake and orange juice meal [59]

- *Jejunostomy*. The rate of gastric emptying of solids is normal in patients who do not have a short bowel but have had a proctocolectomy and distal ileal resection [61]. In patients with a jejunostomy, barium taken orally has been observed to pass rapidly into the jejunostomy bag. Dual radio-isotope studies have shown that the early rate of liquid gastric emptying is rapid and that this tends to correlate inversely with the remaining length of jejunum [39]. This is probably caused by the loss of cells secreting peptide YY in the terminal ileum and colon, and the consequent low plasma levels [59].

Small Bowel Transit

As there is normally faster transit of chyme through the jejunum than ileum [18, 19, 23, 61], it is not unexpected that small bowel transit has been shown to be fast after an ileal and slow after a jejunal resection [56, 57, 62].

- *Jejunum–colon*. The first part of a liquid meal travels rapidly from the stomach to the colon, reflecting both the

normal faster jejunal transit and the short distance it has to travel. The transit rate for solid is normal, however, suggesting that jejunal transit has been slowed by the colonic brake already activated by the prior arrival of some liquid in the colon. This effect may have been mediated by peptide YY.

- In the fasting state, in patients with a short bowel and a retained colon, the interdigestive migrating motor complex (MMC) occurs more frequently but for a shorter total time than in normal subjects, and phase 2 activity is of a shorter duration [63, 64]. The frequency and amplitude of jejunal contraction is unaffected [64].
- *Jejunostomy*. The rate of liquid and solid small bowel transit is rapid in patients with a jejunostomy. This may be due to low peptide YY levels. Six hours after a meal there is still some meal residue within the stomach, and this may result from a disorder of the MMC [39].

Gastrointestinal Secretions

Salivary Secretion

The volume of saliva produced at rest was significantly less in 7 jejunostomy patients (median 0.6 g/5 min, range 0.0–1.4) than in 13 normal subjects (median 2.2 g/5 min, range 0.9–8.7, $p < 0.005$). After stimulation of salivary flow by chewing paraffin wax for 5 min, the volume of saliva was significantly less in jejunostomy patients (median 4.6 g/5 min, range 2.2–8.2) than in normal subjects (median 9.7 g/5 min, range 7.0–20.5, $p < 0.005$). These observations are likely to reflect altered physiology, but a degree of dehydration was not excluded [65].

Gastric Secretion

In 1914, Stassoff [66] performed experiments on six dogs in which he demonstrated that if the distal half of the small intestine was removed, the chyme that emerged from a duodenal fistula was more liquid and had left the stomach more quickly than before the resection. Many studies in dogs with denervated Heidenhain pouches [67–82] and in some with innervated Pavlov pouches [76] have shown hypersecretion of gastric acid. In most studies, the colon has been retained, though in one a colectomy alone caused gastric acid hypersecretion [83]. The larger the intestinal resection, the greater is the postoperative gastric acid hypersecretion [70, 84]. The greatest rises in acid output are produced by jejunal rather than ileal resection [75, 81, 84] (with the exception of one study [72]) and by defunctioning bowel [69, 74] rather than resecting it. The increased secretion is prevented by antrectomy [74, 79, 81, 82] but not by a vagotomy and pyloroplasty [79, 82].

Fielding and Cooke showed an 8% incidence of peptic ulcer among 300 patients with Crohn's disease and they noted that resections of 60 cm or more of the small bowel caused an increase in basal and pentagastrin-stimulated acid output [85]. They related this increased gastric acid output to a previous terminal ileal resection rather than to active disease [86].

In humans, the survival of some patients with a very short bowel has been attributed to their previous gastric surgery [70, 87, 88]. The evidence for gastric acid hypersecretion in the long term in patients with a retained colon is not good. Miura et al. reported three of seven patients with a short gut and a retained colon who developed duodenal ulcers [89]. Windsor et al. described 19 patients in whom more than 300 cm of small intestine had been resected and noted in 8 patients large postoperative aspirates of gastric juice of more than 1.5 L daily which lasted for less than 14 days. The volume of aspirate did not correlate with the remaining length of small intestine. In 6 of the 19 patients the increased secretion was attributed to impaired liver function, which these researchers postulated might increase circulating histamine levels [78].

One patient with a jejunostomy 90 cm from the duodenojejunal flexure following surgery for Crohn's disease had an acidic (pH 1–6) jejunostomy output of 4.8 L daily that was reduced by gastric irradiation [72]. O'Keefe et al. showed normal pentagastrin-stimulated gastric acid secretion in nine patients with a jejunostomy (jejunal length 25–200 cm) more than a year after surgery [90].

High gastrin levels have been observed [59, 91, 92] and may result from a reduced length of small bowel being available to catabolize gastrin [93, 94]. However, gastrin may not be of major physiological importance as studies in the Rhesus monkey have shown that, 6 months after a distal small intestinal resection, basal and histamine-induced acid secretion are at their highest levels, yet serum gastrin levels have returned to normal [95]. Another reason for gastric acid hypersecretion may be the loss of a normal inhibitor of gastric acid secretion, such as neurotensin or peptide YY, from the distal small bowel/colon. In an extensive review in 1974, Buxton suggested that stasis in remaining bowel segments allowed bacterial colonization; these bacteria then either deconjugate bile salts or degrade 'protein' which directly or indirectly causes the release of gastrin or a gastrin-like hormone that causes increased gastric acid secretion [96].

Excess gastric acid in the duodenum, in addition to increasing the incidence of peptic ulceration, causes bile salt precipitation [97], reduced pancreatic enzyme function and increased jejunal motility; all of which impair nutrient absorption.

The evidence indicates that gastric acid hypersecretion, after a small intestinal resection, occurs in dogs with denervated gastric pouches and colons left in situ. It may be present for the first 2 weeks after a small bowel resection in humans, but there is no good evidence that it occurs in the

long term in patients with a short bowel with or without a colon, even though high gastrin levels are observed.

Pancreatico-biliary Secretions

If a person is undernourished [98], or if no food passes through the gut [99], pancreatic function is reduced. In seven well-nourished patients who had a mean small bowel resection of 164 cm (leaving colon) and were taking an oral diet, the post-prandial secretion of trypsin and bilirubin (measured by jejunal aspiration after a liquid meal) was the same as in normal healthy individuals [100]. However, another study in children showed reduced pancreatic volume and enzyme secretion, after an injection of secretin and cholecystokinin, in two of five patients; both of these had most of their colon remaining [101].

When more than 100 cm of terminal ileum has been resected the increased hepatic synthesis of bile salts cannot keep pace with the stool or stomal losses and thus fat malabsorption results [102]. The greatest lipid malabsorption (steatorrhoea) occurs in patients with a jejunostomy: partly because of a very reduced bile salt pool, partly due to rapid transit, and, in a few cases, due to bacterial overgrowth in the remaining bowel [103]. It has not been determined if changes occur in the volume of bile produced each day after an intestinal resection.

Gastrointestinal Hormones

There are differences in the systemic plasma gastrointestinal hormone profiles after a meal in patients with a short bowel compared to normal subjects. However, it is only as studies are performed in these patients, using the hormones, specific agonists or antagonists, that the physiological importance of the observations can be understood; until then the significance of many observations remains a matter for speculation.

Parenteral nutrition itself does not affect the gastrointestinal hormone response to food [104]. The levels of some plasma hormones (e.g. enteroglucagon, pancreatic polypeptide and somatostatin and gastric inhibitory polypeptide) before and after a meal in patients with a short bowel (with or without a colon) are the same as in normal subjects. Plasma levels of vasoactive intestinal peptide in patients with a colon were normal in one study [105], but high in another [106]. High plasma gastrin and cholecystokinin levels and low plasma neurotensin, GLP-1 and insulin levels occur in both types of patient. The plasma neurotensin levels correlate with the length of residual jejunum [59]. The high plasma cholecystokinin levels could cause satiety in some patients with a very short gut [59]. Ghrelin (the "hunger" hormone) levels have been found to be low in patients following a substantial resection (60–80% of total length) of small intestine [107].

There are differences between the two types of patient, the most significant ones being in the plasma levels of two hormones produced by the terminal ileum and colon, namely peptide YY [59, 105] (Fig. 3) and GLP-2 [108, 109] (Fig. 5). Peptide YY slows gastrointestinal transit and GLP-2 stimulates small bowel villus growth (chapter "Normal Intestinal Anatomy and Physiology"). Patients with a colon have high fasting plasma peptide YY and GLP-2 levels, and both hormone levels are low in patients with a jejunostomy [59, 108–110]. Low plasma peptide YY levels also occur in ileostomy patients who have had a colectomy [110]. High plasma motilin levels occur in patients with a jejunostomy, but this is unlikely to be of physiological importance as the highest levels occur in those with the longest lengths of jejunum remaining who do not have rapid intestinal transit [59].

Changes in Intestinal Microbiome

The faecal microbiome is becoming an increasingly researched and thus increasingly understood. Unabsorbed nutrients (especially polysaccharides) within the colon are metabolised by bacteria to form short chain fatty acids (chapter "Normal Intestinal Anatomy and Physiology") which in turn may enhance mineral absorption, promote enteroendocrine secretions, stimulate epithelial cell growth and differentiation in the small and large intestine and may also promote the motility across the ileocaecal junction [111]. Additionally the colonic microbiome manufactures (in addition to short chain fatty acids) some amino acids (especially when undernourished), micronutrients (e.g. vitamins: folate, K, biotin, thiamine, riboflavin and panthothenic acid). It may detoxify some chemicals and manufacture others that are important for messaging/that aid absorption and it may help regulate the immune system and promote intestinal adaptation [112].

The faecal bacteria composition is different from healthy individuals in that anaerobic bacteria are reduced (e.g. bacteroidetes). Firmicutes (includes the lactobacillus and chlostridium geni) are the most abundant phylum, Proteobacteria is second, followed by Bacteroidetes, and lastly by Actinobacteria (includes bifibacterium). The lactobacilli are the largest genus and are responsible for manufacturing L and D lactic acid which in some patients may accumulate in the stool. This may be promoted by lactate-consuming bacteria (Veillonellaceae, Bacteroidaceae, Sutterellaceae, and Acidaminococcacea) being under-represented [113, 114]. When the D isomer dominates then D-lactic acidosis can result. Healthy individuals do not accumulate faecal lactate as it is readily absorbed or metabolised by other commensal

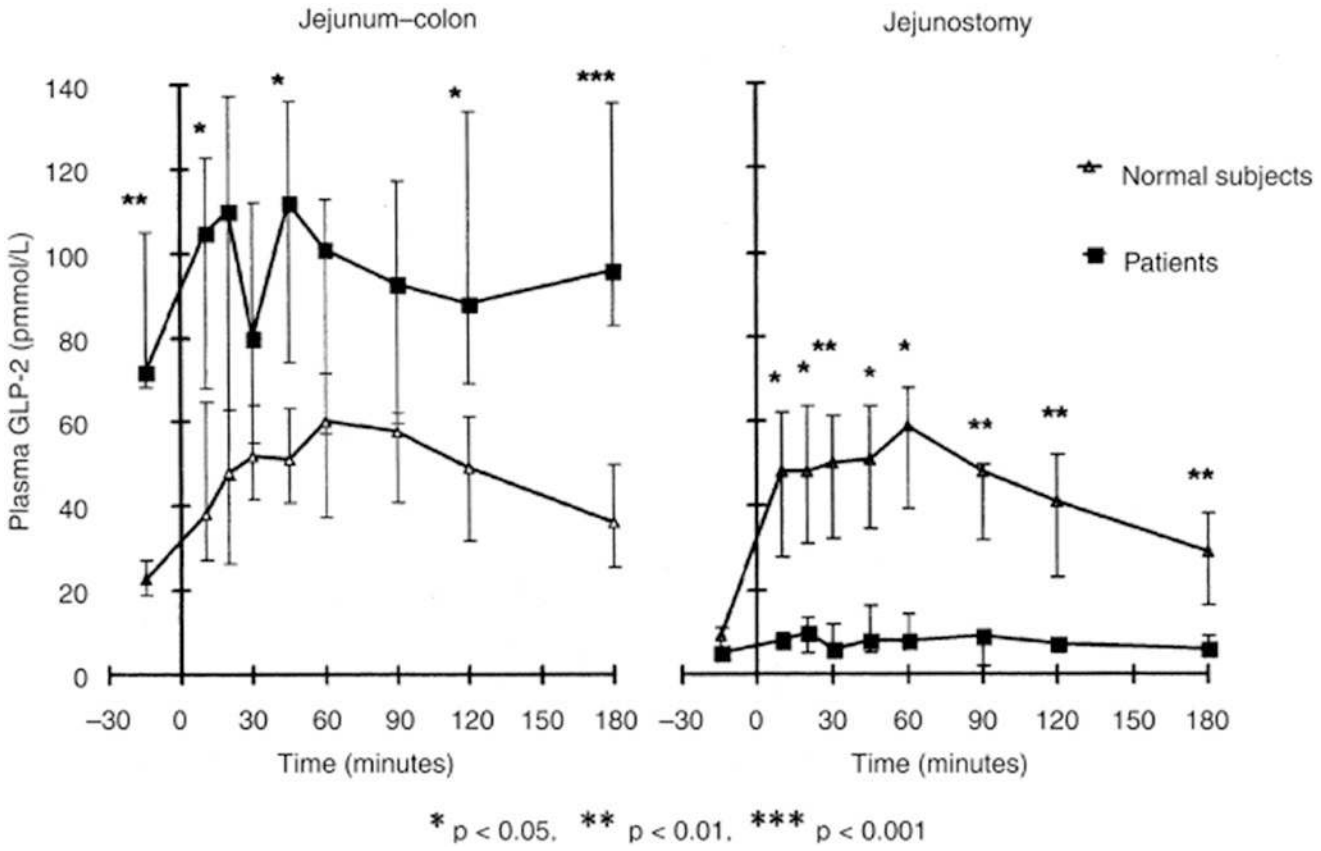

Fig. 5 Median GLP-2 levels with interquartile range in 7 jejunum–colon patients, 7 jejunostomy patients and 7 normal subjects after a continental breakfast [108, 109]. Courtesy of P. Jeppesen and P.B. Mortensen

bacteria or converted to other metabolites (e.g. SCFAs) [115]. It has been suggested that patients with jejuno-colonic anastomosis are stratified according to the presence or absence of lactate in their faeces [114].

A lack or reduction of the Gram-negative anaerobic bacterium *Oxalobacter formigenes* which both interacts with the *colonic mucosa* to induce active secretion of endogenously produced oxalate and also degrades oxalate in the intestinal tract may be partly responsible for the high prevalence of calcium oxalate renal stones in patients with a short bowel and a retained colon [116, 117] (chapter "Nephrolithiasis and Nephrocalcinosis").

The changes in bacterial content of patients with a jejunostomy or indeed an ileostomy are poorly investigated and due to a fast transit time may not be of major significance.

Changes in Absorption

In addition to absorption of nutrients, there are some specialist functions that are particular to the ileum. The ileum has the unique functions of absorbing vitamin B_{12} and bile salts. Vitamin B_{12} deficiency is likely to occur if more than 60 cm of terminal ileum has been resected [20, 62]. If more than 100 cm ileum has been removed, the enterohepatic circulation will be disrupted and diarrhoea is likely to be due to steatorrhoea [102]. If less than 100 cm has been resected, diarrhoea may result from unabsorbed deoxybile salts (secondary bile acids) causing colonic sodium and water secretion [102].

Clinical Problems and Their Treatment

The problems experienced by patients with a short bowel depend upon the type and length of remaining small bowel and the presence or absence of a functioning colon (Table 5). Most of these problems are dealt with in specific chapters and only a brief summary follows here.

Presentation

The presentation and long-term outcome from a resection can be predicted from knowledge of the remaining small bowel length and the presence or absence of a functioning colon. In both types of patient, treatment is aimed first at maintaining fluid balance. Nutritional supplements are usu-

Table 5 Problems of a short bowel

	Jejunum–colon	Jejunostomy
Presentation	Gradual, diarrhoea and undernutrition	Acute fluid losses
Water, sodium and magnesium depletion	Uncommon (in the long-term)	Common
Nutrient malabsorption	Common[a]	Very common
D(-) lactic acidosis	Occasionally	None
Renal stones (calcium oxalate)	25%	None
Gallstones (pigment)	45%	45%
Adaptation	Functional adaptation	No evidence
Social problems	Diarrhoea	High stomal output
		Dehydration
		Dependency on treatment

[a] Bacterial fermentation of carbohydrate salvages some energy, but D(-) lactic acidosis can occur if the diet is high in mono- and oligosaccharides

ally started 24–48 h after the surgery, to prevent loss of lean body mass. This may entail a period of parenteral nutrition, which is gradually reduced as the patient takes more food orally.

- *Jejunum–colon*. These patients are often deceptively well after the resection except for diarrhoea/steatorrhoea, but in the succeeding months they may lose weight and present as severely undernourished (classical 'short bowel syndrome').
- *Jejunostomy*. These patients have immediate problems after surgery due to the large volume of stomal output, which increases with food and drink. This high-volume output results in patients rapidly becoming depleted in water and sodium. Recognition of this high output means that clinicians are often aware that nutritional problems will follow; hence nutritional care is often addressed at a much earlier stage than in patients with a retained colon. Jejunostomy patients are highly dependent on treatments to compensate for water and sodium losses. If they miss their treatment for 1 day they are likely to become unwell from sodium and water depletion. Their requirements for water and sodium supplements change little with time (chapter "Intestinal Adaptation").

Undernutrition

Loss of muscle leads to weakness and early fatigue. Loss of body fat results in feeling cold, a gaunt facial appearance, dry and wrinkled skin, and dull hair. These features, together with a stooped posture, give an impression of premature ageing. Patients may dislike looking in the mirror and weighing themselves, and may avoid company because they are selfconscious about their wasted appearance. Apathy, depression and irritability associated with undernutrition may stop the patient from being motivated to recover (chapter "Consequences of undernutrition and dehydration"). Short bowel patients who can be maintained on an oral diet need to consume more energy than normal subjects because as much as 50% of the energy from the diet may be malabsorbed. Patients can achieve this by eating more high-energy food, having oral sip-feeds, or receiving high-energy enteral feeds at night through a nasogastric or gastrostomy tube. Once weight is regained, the daily energy requirements may decrease, especially in those with a retained colon. Only if these measures fail and the patient continues to lose weight, or fails to regain lost weight, is parenteral nutrition given. Even then, parenteral supplements may be needed for only a limited period of weeks or months, and thereafter oral supplements may be adequate.

In the long term, parenteral nutrition is needed if a patient absorbs less than one-third of the oral energy intake [51, 54], if there are high energy requirements and absorption is about 30–60%, or if increasing the oral/enteral nutrient intake causes a socially unacceptably large volume of stomal output or diarrhoea. In addition to consumption of a high-energy diet, the dietary advice given to the two types of patient is different (chapter "Dietary Treatment of Patients with a Short Bowel").

- *Jejunum–colon*. In order to increase energy absorption and to reduce the risk of renal stones, patients with a retained colon need a large total energy intake with a diet high in carbohydrate (polysaccharides) [37] but not increased in fat (long-chain triglycerides); the diet should also be low in oxalate. D(-) Lactic acidosis may occur if a diet is high in monosaccharides [118]. If oxalate is not reduced there is a 25% chance of the patient developing symptomatic calcium oxalate renal stones [34] (chapter "Nephrolithiasis and Nephrocalcinosis"). Long-term parenteral nutrition is likely to be needed if less than 50 cm jejunum remains [34].
- *Jejunostomy*. Jejunostomy patients need a diet high in energy. It does not matter whether this is as carbohydrate or lipid so long as the osmolality is kept low by using large molecules (polysaccharides, protein and triglycerides) [119, 120] and thus allowing extra sodium chloride to be added to give the meal/liquid feed a total sodium concentration of 90–120 mmol/L and an osmolality of about 300 mOsm/kg. An elemental diet has a high osmolality and little sodium and should therefore be avoided as it may increase water and sodium losses. A high-lipid diet may increase stomal calcium and magnesium losses (chapter "Dietary Treatment of Patients with a Short Bowel").

Water and Sodium Losses

Clinical Assessment/Monitoring

Deficiencies of water and sodium (most common in those without a retained colon) are common and result in a loss of extracellular fluid volume, hypotension and, if severe, prerenal failure. Daily body weight and an accurate fluid balance (to include stomal effluent) are essential measurements during the initial stages of management. Acute sodium and water deficiencies are detected by a rapid fall in body weight, postural hypotension, low urine volume and, if very severe, by a rising serum creatinine and urea. A useful guide to sodium depletion is measurement of sodium concentration in a random urine sample: lack of body sodium is suggested by a concentration of only 0–5 mmol/L. It is ideal, though not always possible, to achieve a daily urine volume of at least 800 mL with a sodium concentration greater than 20 mmol/L. In addition to relatively normal haematological and biochemical measurements, it is desirable (though again not always possible with oral medication) to have a plasma magnesium level greater than 0.6 mmol/L (chapter "Management of a High Output Stoma, Jejunotomy or Uncomplicated Enterocutaneous Fistula").

- *Jejunum–colon*. The colon has a large capacity to absorb sodium and water; thus patients with a short bowel and a preserved colon are rarely in negative water and sodium balance and rarely need water or sodium supplements [31, 34]. If sodium deficiency does develop, a glucose–saline drink can be sipped during the day, as for patients with a jejunostomy. Although the colon secretes potassium, a low serum potassium level is rare [34]. There is an exchange mechanism of chloride absorption/bicarbonate secretion in the colon; thus, if much sodium chloride is consumed, bicarbonate may be lost in the stools and give rise to a metabolic acidosis similar to that occurring in patients who have an ileo-conduit following a cystectomy.
- *Jejunostomy*. Patients with a jejunostomy have a large volume of stomal output that is greater after eating or drinking. Each litre of jejunostomy fluid contains about 100 mmol/L of sodium [51]. This high-volume output is mainly the result of loss of the normal daily secretions produced in response to food and drink (about 4 L/day) although gastric acid hypersecretion and rapid liquid gastric emptying and small bowel transit may contribute.

The effluent from a jejunostomy or ileostomy contains relatively little potassium (about 15 mmol/L) [32, 51]. Potassium balance is not often a problem, and net loss through the stoma occurs only when less than 50 cm jejunum remains [51]. A low serum potassium level may be caused by sodium depletion with secondary hyperaldosteronism and thus greater than normal urinary losses of potassium [32] or by magnesium depletion [121] (chapter "Dietary Treatment of Patients with a Short Bowel").

Treatment of Water and Sodium Depletion

Jejunostomy. Intravenous fluid is given initially while the patient takes no oral food or fluid. This will reduce the high output dramatically; food is then gradually reintroduced. Parenteral nutrition/saline is likely to be needed in the long term if less than 100 cm jejunum remains. Oral hypotonic fluids are restricted and a glucose–saline solution (sodium concentration 90–120 mmol/L) is given to sip during the day. Some clinicians suggest that liquid and solids be taken at different times although there is no published evidence that this reduces stool/stomal output [122]. Drugs that reduce gastrointestinal secretions or motility may be used; often both types of drug are administered. In general, patients who are net 'secretors' have the greatest reduction in their stomal output when drugs that predominantly reduce gastrointestinal secretions are given, for example omeprazole 40 mg daily, ranitidine 300 mg twice daily, cimetidine 200 mg every 6 h or 300 mg continuously over 6 h or, if there is insufficient gut to absorb these (less than 50 cm), subcutaneous or intravenous octreotide 50 μg twice a day. However, these treatments rarely completely alleviate the need for parenteral supplements. Patients who are net 'absorbers' have the greatest reduction when drugs that predominantly reduce gastrointestinal motility (e.g. loperamide 4 mg four times a day and codeine phosphate 60 mg four times a day) are given half an hour before food (chapter "Management of a High Output Stoma, Jejunotomy or Uncomplicated Enterocutaneous Fistula").

Magnesium and Other Micronutrients

The clinical syndrome of magnesium deficiency in man was described in 1960 [123, 124] and in the same year was reported as occurring after a massive intestinal resection [125]. It has subsequently been reported after jejuno-ileal bypass for obesity [126] and after ileal resections of more than 75 cm [127]. Its features include fatigue, depression, jerky and weak muscles, ataxia, athetoid movements, cardiac arrhythmias and, if severe, convulsions [123, 124, 128, 129]. Carpopedal spasm and positive Chvostek and Trousseau signs generally occur if there is a concomitant hypocalcaemia [124, 128, 130].

Low serum magnesium levels are more common in patients with a jejunostomy than in patients with a retained colon. Of short bowel patients who were not receiving parenteral nutrition, 11 of 27 (41%) of those with a colon were receiving magnesium or had low serum magnesium levels, compared with 19 of 28 (68%) with a jejunostomy [34].

Patients with a preserved colon require less magnesium and have higher serum values than those without a retained colon. This, together with reports that magnesium poisoning can occur after a magnesium sulphate enema, provides further evidence that the colon absorbs magnesium [131].

Most clinicians use a serum magnesium measurement of less than 0.6 mmol/L as their guide to magnesium depletion; however, urine, skeletal muscle, mononuclear cell or ionized magnesium levels [129] are more sensitive indicators.

There are several reasons for magnesium deficiency. Magnesium is normally absorbed by passive diffusion in the distal small bowel and colon. Bowel resections reduce the absorptive area and may increase stool losses [132]; however, this does not occur in an easily predictable manner and balance studies have shown that magnesium balance does not relate to the length of small bowel remaining [65]. The composition of the diet consumed may be another cause of stool losses of magnesium. Fatty acids, derived either from digestion of dietary fat or from bacterial fermentation of malabsorbed carbohydrate, combine with magnesium, calcium and zinc and prevent their absorption, increasing faecal or stomal losses [133]. A third reason, occurring particularly in patients with a jejunostomy, is stool/stomal loss of salt and water and the consequent secondary hyperaldosteronism. Aldosterone increases renal excretion of magnesium in rats and man and the faecal excretion of magnesium in rats [134, 135].

A low serum magnesium level reduces both the secretion and function of parathormone [136]. Thus parathormone cannot promote magnesium absorption in the ascending limb of the loop of Henle or activate renal 1α-hydroxylase to make 1,25-hydroxycholecalciferol. The failure to make 1,25-hydroxycholecalciferol results in reduced magnesium and calcium absorption from the gut [137]. Na^+/K^+-ATPase activity, which normally keeps potassium within a cell and sodium out, depends upon magnesium. When the serum magnesium level is low, activity of this enzyme is impaired. Potassium is therefore lost from cells and renal potassium excretion is increased, resulting overall in hypokalaemia. This hypokalaemia may not respond to the administration of oral or intravenous potassium, but does to magnesium supplementation [138].

The treatment of hypomagnesaemia is outlined in Table 6. Patient hydration and, thus, secondary hyperaldosteronism must first be corrected. Serum magnesium levels can usually be improved by oral supplements, however the data on magnesium absorption from different preparations are often derived from normal volunteer studies. Tablet dissolution and magnesium availability may be different in patients with a short bowel. Various magnesium salts have been given as oral treatment including magnesium sulphate, chloride, hydroxide, acetate, carbonate, gluconate, lactate, citrate, aspartate, pyroglutamate, oxide (magnesia) and diglycinate.

Table 6 Treatment of hypomagnesaemia

1. Correct water and sodium depletion (and thus secondary hyperaldosteronism)
2. Give oral magnesium preparation (e.g. 12 mmol magnesium oxide or 10 mmol magnesium aspartate at night)
3. Reduce lipid in diet
4. Give 1α-cholecalciferol (1–9 μg daily)
5. Give intravenous magnesium (occasionally subcutaneous or intramuscular magnesium sulphate)

Most magnesium salts are poorly absorbed and may worsen diarrhoea/stomal output. Magnesium acetate causes less diarrhoea than magnesium gluconate [139]. Magnesium oxide is commonly given and contains more elemental magnesium than the other salts. It is insoluble in water and alcohol but soluble in dilute acid. In the stomach it is converted to magnesium chloride. It is given as gelatine capsules of 4 mmol magnesium oxide (160 mg of MgO) to a total of 12–24 mmol daily or magnesium aspartate 10 mmol daily. Magnesium diglycinate (chelate) is absorbed as well as magnesium oxide as an intact dipeptide in the proximal jejunum and after an ileal resection it results in the passage of fewer stools than magnesium oxide [140]. Oral magnesium treatment is usually given at night when intestinal transit is assumed to be slowest and there is more time for absorption. This regimen does not appear to increase stomal or stool output. Magnesium may also be given as a topical spray [141]. A low-fat diet decreases stool/stomal magnesium losses, especially in patients with a retained colon [133]. If oral magnesium supplements, dietary advice and correction of water and sodium depletion do not bring the magnesium level into the normal range, oral 1α-hydroxycholecalciferol in a dose of 1–9 μg daily may improve magnesium balance [142, 143]. It may exert its effect by increasing both intestinal and renal magnesium absorption [143].

Magnesium can occasionally be given as a subcutaneous injection of 4 mmol magnesium sulphate every 2 or more days, but can cause skin ulceration. Intramuscular injection of 10 mmol/L is an alternative, but is painful. Regular intravenous infusions of 12 mmol or more can be given, usually in a litre of saline over 1–2 h, but can cause flushing.

Selenium

Patients receiving parenteral nutrition are commonly deficient in selenium [144–146] and need larger amounts of selenium than are required in the diet of normal subjects [146]. This suggests a loss of selenium from the gastrointestinal secretions. Patients with a jejunostomy also have a reduction in selenium absorption, the amount by which absorption is reduced correlating with residual jejunal length [147]. The kidney can conserve selenium but often not to a sufficient extent. Selenium deficiency is therefore common and may cause weak muscles, a tendency to infections, a dilated car-

diomyopathy and symptoms of hypothyroidism (it is a cofactor for the conversion of thyroxine to the more active triiodothyronine) [148].

Vitamin B_{12} Deficiency

Both groups of patients have had more than 60 cm of the terminal ileum removed and need long-term hydroxycobalamin injections, Traditionally 1 mg intra-muscularly every 3 months though may be longer depending on serum levels [20, 62].

Other Vitamin and Mineral Deficiencies

There may be impairment of absorption of the fat-soluble vitamins A, D, E and K and essential fatty acids. Essential fatty acid deficiency may be treated by rubbing sunflower oil into the skin [149]. Zinc deficiency is not common unless stool volumes are large, when zinc sulphate may be given (15–45 mg orally one to three times a day) [150]. In patients receiving parenteral nutrition the deficiencies depend on the regimen used, but deficiencies of iron, vitamin D and biotin [151–153] occurred with some regimens in the 1990s.

Diarrhoea (Jejunum–Colon Patients)

The oral intake determines the amount of stool passed. Diarrhoea may severely limit a patient's lifestyle; limiting food intake can reduce diarrhoea but may increase the problems of undernutrition. Rarely, a patient requires parenteral nutrition to allow him or her to eat less and so reduce the diarrhoea.

Diarrhoea may be treated with loperamide, 2–8 mg, given half an hour before food. Loperamide is usually given in preference to codeine phosphate (30–60 mg half an hour before food), as it is non-sedative and non-addictive; occasionally, however, both are needed. If tablets/capsules emerge unchanged in stool/stomal output, they can be crushed, opened, mixed with water or put on food. If less than 100 cm of terminal ileum has been resected, bile salt malabsorption may contribute to the diarrhoea. This may be helped by cholestyramine (or colesevelam) which has the additional advantage of reducing oxalate absorption but may be detrimental by reducing fat absorption and by further reducing the bile salt pool [102]. Gastric anti-secretory drugs may reduce diarrhoea shortly after surgery but are not usually effective in the long term.

Confusion

In addition to the many common general medical causes of confusion (e.g. hypoxia, hepatic, renal or cardiac failure, sepsis, hypoglycaemia, thiamine deficiency, alcohol or other drugs), other specific causes should be sought in a patient with a short bowel. Hypomagnesaemia may cause mild confusion. In patients with a preserved colon, severe confusion can result from D-lactic acidosis (in lactate accumulators), in which a metabolic acidosis with a high anion gap will be observed (chapter "Dietary Treatment of Patients with a Short Bowel"). Hyperammonaemia may cause confusion in both types of patients with a short bowel because ammonia cannot be detoxified. The small amount of intestine remaining cannot manufacture adequate citrulline to detoxify the ammonia created in the urea cycle. If there is concomitant renal impairment, the increase in blood ammonia causes a problem as the kidney will not be able to excrete the excess ammonia. Hyperammonaemia can be corrected by giving arginine (an intermediary in the urea cycle) [154, 155].

Drug Absorption

Drug absorption can be predicted from knowing the time to peak levels and the biopharmaceutical classification (chapter "Drug Absorption in the Short Bowel"). Omeprazole can be absorbed in the duodenum and upper jejunum; problems are likely to occur only if less than 50 cm jejunum remains. Warfarin [156] and thyroxine may need to be given orally in high doses. Loperamide circulates in the enterohepatic circulation, which is disrupted, and higher doses than usual may need to be given (chapter "Management of a High Output Stoma, Jejunotomy or Uncomplicated Enterocutaneous Fistula").

Adaptation

Intestinal adaptation (chapter "Intestinal Adaptation") is the process, following intestinal resection, that attempts restore total gut absorption of macronutrients, macrominerals and water to that occurring before the intestinal resection (chapter "Intestinal Adaptation").

In a classical paper in 1959, Pullan described three phases that related to the changing situations in patients after a 'massive intestinal resection' leaving a functioning colon in situ (i.e. 'short bowel syndrome') [157]. These changes reflect structural and functional adaptation.

- *Stage 1*. As intestinal motility returns in the first few days after the resection, profuse diarrhoea occurs and is maximal for the first 2–3 weeks. During this stage there may be large losses of fluid and electrolytes (up to 10 L/day). These losses have been attributed to gastric acid hypersecretion.

- Large volumes of saline (sometimes with magnesium) may be needed to maintain fluid balance, especially when the patient first starts to eat. A protein pump inhibitor or H_2 antagonist, loperamide and often codeine phosphate are empirically given. If the residual bowel length is less than 100 cm, parenteral nutrition may be started on the second postoperative day. Anal soreness and excoriations may be a problem. This phase ends as the diarrhoea lessens.
- *Stage 2*. The problem changes from that of fluid and electrolyte balance to that of progressive undernutrition requiring nutrition support. If untreated, the patient may rapidly lose weight and, despite a large oral energy intake, not absorb enough to maintain weight. Fat malabsorption is much more significant than that of carbohydrate and protein. Deficiencies of the fat-soluble vitamins A, D, E and K may occur, causing night blindness, bone pains, ataxia and bleeding respectively. Vitamin B and C deficiencies sometimes occur and cause glossitis, angular stomatitis, pellagra, psychotic changes and bleeding. Anaemia and hypoproteinaemia are rare after an uncomplicated resection.
- The patient may complain of abdominal cramps, distension and nausea. During this time the gastrointestinal transit rate slows, although a large volume of fatty stool is still passed. Carbohydrate and protein are better absorbed and a state of equilibrium is reached after 3–6 months.
- *Stage 3*. In the final stage relative equilibrium has been reached and minor adjustments are made. The dietary regimen tries to limit the lipid intake. Long-term parenteral nutrition is unlikely to be needed unless less than 50 cm jejunum remains. The beneficial effects of a proton pump inhibitor may have ceased by the end of the first year and the drug can be stopped.
- After a large resection of small intestine, improvement in absorption of macronutrients, macrominerals and water may occur by:
  - The patient eating more food than normal (hyperphagia);
  - The remaining bowel increasing in size and absorptive area (structural adaptation); and
  - Reduction in bowel transit rate to allow more time for absorption (functional adaptation).

An increased oral intake has been observed [158]. After a jejunal resection in animals, the ileal remnant undergoes structural changes which include elongation of villi, deepening of crypts, and an increase in the number of absorptive cells in a given length of villus. After a jejuno-ileal resection in man to leave a jejunocolic anastomosis, no structural adaptation (except possibly hyperplasia) has been demonstrated even though high GLP-2 levels are observed [109]. A degree of functional adaptation with slowing of liquid gastric emptying and solid small bowel transit has been demonstrated [39] and is likely to be caused by high peptide YY levels. Functional adaptation does occur, as demonstrated by the findings that there is a small reduction in faecal weight in the 3 months after a small bowel resection [159], and that there is increased jejunal absorption of water and sodium [160, 161], glucose [162] and calcium [163] with time. The intestinal calcium absorption may continue to increase for more than 2 years after a resection [163]. Restoring bowel continuity after a mesenteric infarction resulted in cessation of home parenteral nutrition in 77% within 5 years (Fig. 6) [164].

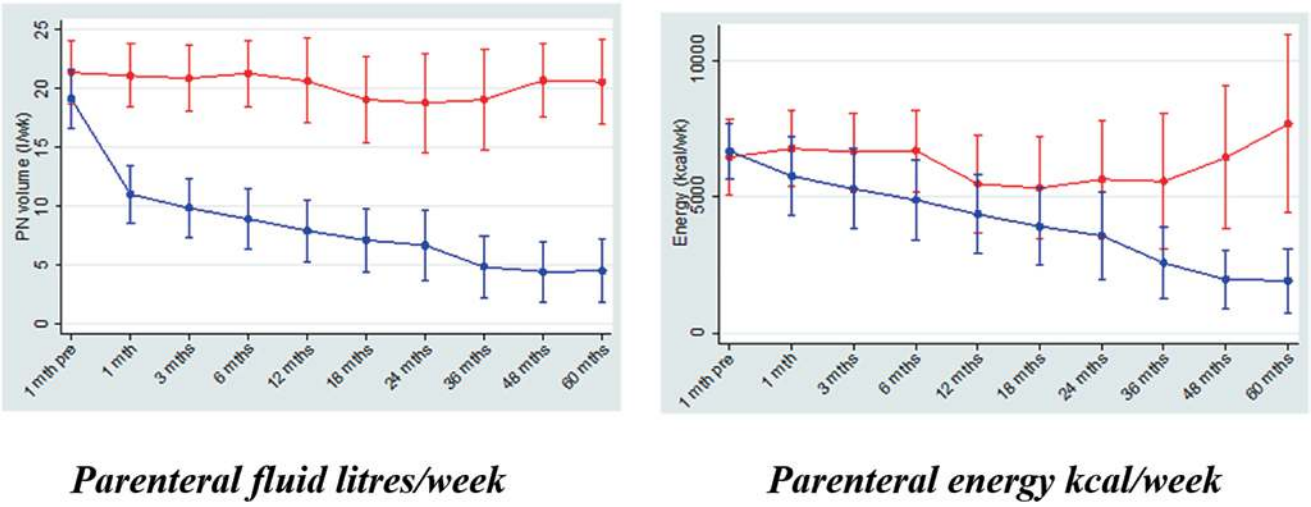

Fig. 6 Parenteral support after mesenteric infarction in patients with jejunostomy and in those following an anastomosis bringing the colon back into continuity [164]. Red top line Jejunostomy ($n = 29$) and lower blue line Jejunum-colon (re-anastomosis) ($n = 57$). There is a reduction in the need for parenteral fluid and nutrition in the 36 months (3 years) after the re-anastomosis

- Although adaptation occurs in the months after the creation of an ileostomy, there is no evidence for any structural [90] or functional [34, 165] adaptation at any time in patients with a jejunostomy.

Gallstones

Gallstones are common (45%) in both types of patient and are more common in men [34] (chapter "Gallstones in Intestinal Failure"). It was originally thought that gallstones in this circumstance resulted from deposition of cholesterol because of a depleted bile-salt pool. However, the gallstones tend to contain calcium bilirubinate. Such stones probably result from gallbladder stasis: biliary sludge develops and this subsequently forms calcium bilirubinate stones which often appear calcified on abdominal radiographs [166]. Calcium bilirubinate crystals within biliary sludge are more commonly found in men than in women [167]. Cholecystokinin injections have been used to prevent gallbladder stasis [168] and some units have advocated a prophylactic cholecystectomy [169, 170] (chapter "Gallstones in Intestinal Failure").

Social Problems

Most long-term patients with a short bowel have a body mass index within the normal range, and most are in full-time work or look after the home and family unaided [34]. Both groups of patients may have diarrhoea, which causes problems, especially if housing conditions are poor. In those with a colon the diarrhoea is malodorous and bulky due to steatorrhoea.

The effluent from a small-bowel stoma, unlike that from a colostomy, is not offensive. The large volume of fluid that emerges, however, may trouble the patient; sometimes 3 or more litres in 24 h may be passed from the stoma. The bag then has to be emptied frequently and, if it becomes overfull, the adhesive flange may separate from the skin with embarrassing leakage of fluid and with the likelihood of skin soreness.

Other and Future Treatments

New treatments are likely to be aimed at increasing the absorptive function of the remaining gut. Most are currently directed at inducing structural adaptation, for example GLP-1 or 2 analogues [171], epidermal growth factor [172, 173], colostrums or aminoguanidine [174]. Studies using growth hormone, glutamine and fibre have been disappointing [175–178]. Studies that use analogues of peptide YY have yet to be tried [179]. Cholylsarcosine is a synthetic bile acid resistant to bacterial deconjugation and dehydroxylation, that does not itself cause colonic secretion and thus diarrhoea, but does result in a variable improvement in fat and calcium absorption in patients with a short bowel, with or without a retained functioning colon [180, 181]. Attempts to replace colonic mucosa with small intestinal mucosa to increase absorption have not proved successful [182]. Tissue engineering to make small intestine over a scaffold (decellularized organ or synthetic biodegradable matrix) is difficult due to the complex structure of the small intestine (includes nerves, blood vessels, muscle and mucosa) and having to achieve a secretory, absorptive, propulsive and barrier function [183]. Another area of importance is the prevention of gallstones after an intestinal resection: trials using prophylactic antibiotics, ursodeoxycholic acid and cholecystokinin may be performed. An oral nutrient solution containing 100 mmol/L sodium and having an osmolality of 300 mOsm/kg has yet to be commercially manufactured as an ideal nutrient solution to give to patients with a jejunostomy or high-output ileostomy.

Small bowel transplantation is becoming more safe (chapter "Intestinal Transplantation") and the outcome in selected patients may be as good as that of prolonged parenteral nutrition though one set of problems may be changed for another (e.g. high output stoma, dependency on HPS for rejection/complications of immunosuppressive drugs).

Preventative Measures

Post-operative monitoring of Crohn's disease to ensure mucosal healing along with smoking cessation, immunosuppressive therapy (e.g. azathioprine, 6-mercaptopurine and methotrexate), and/or biological medication (e.g. anti-tumour necrosis factor antibodies) and balloon dilatation of strictures may reduce the need for repeated or major resections of Crohn's disease and thus the chance of developing a short bowel [184].

A small bowel embolus/venous infarction may be prevented by identification of risk factors such as atrial fibrillation, a poorly functioning myocardium, recent myocardial infarction, coagulation abnormalities or a period of hypotension. Anticoagulation therapy may be given to a patient in whom a potential source of emboli is identified. The diagnosis of a small bowel infarction can be difficult but needs to be made soon after the event. Clues to the diagnosis include the presence of the risk factors above, pain (usually of sudden onset and continuous), and usually a rise in the white cell count, amylase, phosphate, lactate and D-Dimers [185]. Ideally, contrast-enhanced computed tomography (CT) should be performed within 2–3 h of the onset of pain especially if a plain abdominal radiograph has shown no obvious abnormality [186]. If there is partial occlusive

obstruction to the mesenteric artery then percutaneous transluminal angioplasty or a surgical revascularization procedure can be performed (chapter "Mesenteric Ischaemia"). If clot is shown in the superior mesenteric artery or vein and bowel necrosis has not occurred, a bolus of a vasodilator (e.g. papaverine 60 mg or tolazoline 25 mg, phenoxybenzamine, adenosine triphosphate, glucagon or prostaglandin E) may be given into the superior mesenteric artery. If this is unsuccessful, surgery may be needed but papaverine can continue to be infused at a rate of 30–60 mg/h (1 mg/mL) [186]. Thrombolytic drugs, heparin and low molecular weight dextran may all be infused into the superior mesenteric artery or peripherally to try and halt and/or reverse the progression of the infarction or ischaemia. The outcome is best if there are no signs of peritonitis at the onset of treatment [186]. In addition nitrates, calcium antagonists or octreotide [187], may be given to try and reduce the chance of a small bowel infarction.

Experimentally, the most severe problems occur after ischaemic bowel is reperfused as the resultant toxins and cytokines can cause liver and multi-organ failure. Other drugs that may be of benefit include free-radical scavengers (e.g. superoxide dismutase, 5-aminosalicylate) or xanthine oxidase inhibitors (e.g. allopurinol) and antibiotics [188, 189]. Prostacyclin analogues may be useful when bowel is reperfused as they produce vasodilatation, reduce white cell and platelet aggregation and protect ischaemic tissues. If bowel is resected, a primary anastomosis is avoided and a temporary stoma created; often there is an elective re-exploration of the abdomen the following day and any further ischaemic bowel is resected [188, 190].

The techniques used to deliver abdominal radiotherapy have improved, with avoidance of the parallel opposed fields technique and the administration of glutamine and sucralfate (chapter "Pelvic Radiation Disease and the GI Tract"), so radiation damage may become uncommon.

Survival

The survival of patients with a short bowel is good, though there is only data on those requiring HPN in whom there is an over 50% survival at 10 years for non-malignant aetiologies [34, 45, 191–196] (chapter "Home Parenteral Support for Adults").

References

1. Koberle E. Resection de deux metres d'intestin grele. Bull Acad Med. 1881;4:128–31.
2. Flint JM. The effect of extensive resections of the small intestine. Bull Johns Hopkins Hosp. 1912;23:127–44.
3. Haymond HE. Massive resection of the small intestine. An analysis of 257 collected cases. Surg Gynecol Obstet. 1935;61:693–705.
4. Conn JH, Chavez CM, Fain WR. The short bowel syndrome. Ann Surg. 1972;175:803–14.
5. Mayo HW Jr, Duggan JJ. Post colectomy enteritis: survival after extensive small bowel resection complicated by magnesium deficiency. Case report. Ann Surg. 1963;157:92–6.
6. Wu T-J, Teng R-J, Chang M-H, Chen C-C. Congenital short bowel syndrome: report of a case treated with home central parenteral nutrition. J Formosan Med Assoc. 1992;91:470–2.
7. Schalamon J, Schober PH, Gallippi P, Matthyssens L, Hollwarth ME. Congenital short-bowel; a case study and review of the literature. Eur J Pediatr Surg. 1999;9:248–50.
8. Nightingale JMD, Lennard-Jones JE. Patients with a short bowel due to Crohn's disease often start with a short normal bowel. Eur J Gastroenterol Hepatol. 1995;7:989–91.
9. Nightingale JMD, Bartram CI, Lennard-Jones JE. Length of residual small bowel after partial resection: correlation between radiographic and surgical measurements. Gastrointest Radiol. 1991;16:305–6.
10. Carbonnel F, Cosnes J, Chevret S, et al. The role of anatomic factors in nutritional autonomy after extensive small bowel resection. J Parenter Enter Nutr. 1996;20:275–80.
11. Cheng W, Zhang S, Wang J, Zhou C, Li Y, Li J. Three-dimensional CT enterography versus barium follow-through examination in measurement of remnant small intestinal length in short bowel syndrome patients. Abdom Radiol (NY). 2018;43(11):2955–62.
12. Sinha R, Trivedi D, Murphy PD, Fallis S. Small-intestinal length measurement on MR enterography: comparison with in vivo surgical measurement. AJR Am J Roentgenol. 2014;203(3):W274–9.
13. Crenn P, Coudray-Lucas C, Thullier F, Cynober L, Messing B. Post-absorptive plasma citrulline concentration is a marker of absorptive enterocyte mass and intestinal failure in humans. Gastroenterology. 2000;119:1496–505.
14. Luo M, Fernandez-Estivariz C, Manatunga AK, Bazargan N, Gu LH, Jones DP, et al. Are plasma citrulline and glutamine biomarkers of intestinal absorptive function in patients with short bowel syndrome? JPEN J Parenter Enteral Nutr. 2007;31(1):1–7.
15. Papadia C, Sherwood RA, Kalantzis C, Wallis K, Volta U, Fiorini E, et al. Plasma citrulline concentration: a reliable marker of small bowel absorptive capacity independent of intestinal inflammation. Am J Gastroenterol. 2007;102(7):1474–82.
16. Bailly-Botuha C, Colomb V, Thioulouse E, Berthe MC, Garcette K, Dubern B, et al. Plasma citrulline concentration reflects enterocyte mass in children with short bowel syndrome. Pediatr Res. 2009;65(5):559–63.
17. López-Tejero MD, Virgili N, Targarona J, Ruiz J, García N, Oró D, García-Villoria J, Creus G, Pita AM. Apo AIV and citrulline plasma concentrations in short bowel syndrome patients: the influence of short bowel anatomy. PLoS One. 2016;11(9):e0163762.
18. Singleton AO, Redmond DC, McMurray JE. Ileocecal resection and small bowel transit and absorption. Ann Surg. 1964;159:690–4.
19. Summers RW, Kent TH, Osbourne JW. Effects of drugs, ileal obstruction and irradiation on rat gastrointestinal propulsion. Gastroenterology. 1970;59:731–9.
20. Booth CC, Mollin DL. The site of absorption of vitamin B_{12} in man. Lancet. 1959;1:18–21.
21. Thompson WG, Wrathell E. The relation between ileal resection and vitamin B_{12} absorption. Can J Surg. 1977;20:461–4.
22. Nygaard K. Resection of the small intestine in rats. III. Morphological changes in the intestinal tract. Acta Chir Scand. 1967;133:233–348.
23. Nygaard K. Resection of the small intestine in rats. IV. Adaptation of gastrointestinal motility. Acta Chir Scand. 1967;133:407–16.
24. Dowling RH, Booth CC. Structural and functional changes following small intestinal resection in the rat. Clin Sci. 1967;32:139–49.

25. Fich A, Steadman CJ, Phillips SF, Camilleri M, Brown ML, Haddad AC, Thomforde GM. Ileocolonic transit does not change after right hemicolectomy. Gastroenterology. 1992;103:794–9.
26. Wilmore D. Factors correlating with a successful outcome following extensive intestinal resection in newborn infants. J Pediatr. 1972;80:88–95.
27. Galea MH, Holliday H, Carachi R, Kapila L. Short-bowel syndrome: a collective review. J Pediatr Surg. 1992;27:592–6.
28. Goulet OJ, Revillon Y, Dominique J, et al. Neonatal short bowel syndrome. J Pediatr. 1991;119:18–23.
29. Weber TR, Tracy T Jr, Connors RH. Short-bowel syndrome in children. Quality of life in an era of improved survival. Arch Surg. 1991;126:841–6.
30. Philips SF, Giller J. The contribution of the colon to electrolyte and water conservation in man. J Lab Clin Med. 1973;81:733–46.
31. Debongnie JC, Phillips SF. Capacity of the colon to absorb fluid. Gastroenterology. 1978;74:698–703.
32. Ladefoged K, Ølgaard K. Fluid and electrolyte absorption and renin–angiotensin–aldosterone axis in patients with severe short-bowel syndrome. Scand J Gastroenterol. 1979;14:729–35.
33. Ladefoged K, Ølgaard K. Sodium homeostasis after small-bowel resection. Scand J Gastroenterol. 1985;20:361–9.
34. Nightingale JMD, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces the need for parenteral therapy, increases the incidence of renal stones but does not change the high prevalence of gallstones in patients with a short bowel. Gut. 1992;33:1493–7.
35. Hylander E, Ladefoged K, Jarnum S. Calcium absorption after intestinal resection. The importance of a preserved colon. Scand J Gastroenterol. 1990;25:705–10.
36. Ruppin H, Bar-Meir S, Soergel KH, Wood CM, Schmitt MG Jr. Absorption of short chain fatty acids by the colon. Gastroenterology. 1980;78:1500–7.
37. Nordgaard I, Hansen BS, Mortensen PB. Colon as a digestive organ in patients with short bowel. Lancet. 1994;343:373–6.
38. Jeppesen PB, Mortensen PB. The influence of a preserved colon on the absorption of medium chain fat in patients with small bowel resection. Gut. 1998;43:478–83.
39. Nightingale JMD, Kamm MA, van der Sijp JRM, et al. Disturbed gastric emptying in the short bowel syndrome. Evidence for a 'colonic brake'. Gut. 1993;34:1171–6.
40. Miazza BM, Al-Mukhtar MYT, Salmeron M, et al. Hyperenteroglucagonaemia and small intestinal mucosal growth after colonic perfusion of glucose in rats. Gut. 1985;26:518–24.
41. Jordan PH, Stuart JR, Briggs JD. Radical small bowel resection. Report of two cases. Am J Dig Dis. 1958;3:823–43.
42. Anderson CM. Long-term survival with six inches of small intestine. Br Med J. 1965;1:419–22.
43. Kinney JM, Goldwyn RM, Barr JS Jr, Moore FD. Loss of the entire jejunum and ileum, and the ascending colon: management of a patient. JAMA. 1962;179:529–32.
44. Simons BE, Jordan GL. Massive bowel resection. Am J Surg. 1969;118:953–9.
45. Amiot A, Messing B, Corcos O, Panis Y, Joly F. Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome. Clin Nutr. 2013;32(3):368–74.
46. Thompson JS. Short bowel syndrome and malabsorption—causes and prevention. Viszeralmedizin. 2014;30(3):174–8.
47. Pilling GP, Cresson SL. Massive resection of the small intestine in the neonatal period. Pediatrics. 1957;19:940–8.
48. Grosfeld JL, Rescoria FJ, West KW. Short bowel syndrome in infancy and childhood. Analysis of survival in 60 patients. Am J Surg. 1986;151:41–6.
49. Grosfeld JL, Rescoria FJ. Current management of short bowel syndrome in children. J Arkansas Med Soc. 1987;84:243–9.
50. Gouttebel MC, Saint-Aubert B, Astre C, Joyeux H. Total parenteral nutrition needs in different types of short bowel syndrome. Dig Dis Sci. 1986;31:718–23.
51. Nightingale JMD, Lennard-Jones JE, Walker ER, Farthing MG. Jejunal efflux in short bowel syndrome. Lancet. 1990;336:765–8.
52. Simko V, Linscheer WG. Absorption of different elemental diets in a short-bowel syndrome lasting 15 years. Dig Dis. 1976;21:419–25.
53. Nightingale JMD. How to manage a high-output stoma. Front Gastroenterol. 2021;13(2):140–51. https://doi.org/10.1136/flgastro-2018-101108.
54. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJG. Energy absorption as a measure of intestinal failure in the short bowel syndrome. Gut. 1989;30:176–83.
55. MacGregor IL, Wiley ZD, Lavigne ME, Way LW. Total parenteral nutrition slows gastric emptying of solid food. Gastroenterology. 1978;74:1059.
56. Nylander G. Gastric evacuation and propulsive intestinal motility following resection of the small intestine in the rat. Acta Chir Scand. 1967;133:131–8.
57. Reynell PC, Spray GH. Small intestinal function in the rat after massive resections. Gastroenterology. 1956;31:361–8.
58. Dew MJ, Harries AD, Rhodes M, Rhodes J, Leach KG. Gastric emptying after intestinal resection in Crohn's disease. Br J Surg. 1983;70:92–3.
59. Nightingale JMD, Kamm MA, van der Sijp JRM, Walker ER, Ghatei MA, Bloom SR, Lennard-Jones JE. Gastrointestinal hormones in the short bowel syndrome. PYY may be the 'colonic brake' to gastric emptying. Gut. 1996;39:267–72.
60. Savage AP, Adrian TE, Carolan G, Chatterjee VK, Bloom SR. Effects of peptide YY (PYY) on mouth to caecum intestinal transit time and on the rate of gastric emptying in healthy volunteers. Gut. 1987;28:166–70.
61. Neal DE, Williams NS, Barker MJC, King RFGJ. The effect of resection of the distal ileum on gastric emptying, small bowel transit and absorption after proctocolectomy. Br J Surg. 1984;71:666–70.
62. Booth CC. The metabolic effects of intestinal resection in man. Postgrad Med J. 1961;37:725–39.
63. Remington M, Malagelada J-R, Zinsmeister A, Fleming CR. Abnormalities in gastrointestinal motor activity in patients with short bowels: effect of a synthetic opiate. Gastroenterology. 1983;85:629–36.
64. Schmidt T, Pfeiffer A, Hackelsberger N, Widmer R, Meisel C, Kaess H. Effect of intestinal resection on human small bowel motility. Gut. 1996;38:859–63.
65. Nightingale JMD. Physiological consequences of major small intestinal resection in man and their treatment. MD thesis, University of London; 1993. p. 190–95.
66. Stassoff B. Experimentelle Untersuchungen uber die Kompensatorischen Vorgange bei Darmresektionen. Beitr Klin Chir. 1914;89:527–86.
67. Sabsai BI. The effect of extensive resections of the proximal and distal portions of the small intestine on canine gastric secretion. Bull Exp Biol Med. 1963;55:387–90.
68. Landor JH, Baker WK. Gastric hypersecretion produced by massive small bowel resection in dogs. J Surg Res. 1964;4:518–22.
69. Westerheide RL, Elliot DW, Hardacre JM. The potential of the upper small bowel in regulating acid secretion. Surgery. 1965;58:73–81.
70. Frederick PL, Sizer JS, Osbourne MP. Relation of massive bowel resection to gastric secretion. N Engl J Med. 1965;272:509–14.

71. Reul GJ, Ellison EH. Effect of 75% distal small bowel resection on gastric secretion. Am J Surg. 1966;111:772–6.
72. Osbourne MP, Frederick PL, Sizer JS, Blair D, Cole P, Thum W. Mechanism of gastric hypersecretion following massive intestinal resection; clinical and experimental observations. Ann Surg. 1966;164:622–34.
73. Grundberg AB, Lopez AS, Dragstedt LR. Effect of intestinal reversal and massive resection on gastric secretion. Arch Surg. 1967;94:326–9.
74. Copeland EM, Miller LD, Smith GP. The complex nature of small bowel control of gastric secretion. Ann Surg. 1968;168:36–46.
75. Kerr G, Elliot DW, Endahl GL. Effect of antrectomy on gastric acid hypersecretion induced by isolation of the proximal small bowel. Am J Surg. 1968;115:157–64.
76. Santillana M, Wise L, Schuck M, Ballinger WF. Changes in gastric acid secretion following resection or exclusion of different segments of small intestine. Surgery. 1969;65:777–82.
77. Yakimets WW, Bondar GF. Hormonal stimulatory mechanism producing gastric hypersecretion following massive small intestinal resection. Can J Surg. 1969;12:241–4.
78. Windsor CWO, Fejfar J, Woodward DAK. Gastric secretion after massive small bowel resection. Gut. 1969;10:779–86.
79. Burrington JD, Hamilton JR. Steatorrhea after massive bowel resection: effects of surgical reduction of gastric acid secretion. Surg Forum. 1969;20:341–3.
80. Landor JH. Intestinal resection and gastric secretion in dogs with antrectomy. Arch Surg. 1969;98:645–6.
81. Wiens E, Bondar GF. Control of gastric hypersecretion following massive intestinal resection. Surg Forum. 1970;21:310–2.
82. Saik RP, Copeland EM, Miller LD, Smith GP. Effect of ileal exclusion on the Heidenhain pouch acid response to histamine in dogs. Ann Surg. 1971;173:67–77.
83. Landor JH, Alancia EY, Fulkerson CC. Effect of colectomy on gastric secretion in dogs. Am J Surg. 1967;113:32–6.
84. Landor JH, Behringer BR, Wild RA. Post enterectomy gastric hypersecretion in dogs: the relative importance of proximal versus distal resection. J Surg Res. 1971;11:238–42.
85. Fielding JF, Cooke WT. Peptic ulceration in Crohn's disease (regional enteritis). Gut. 1970;11:998–1000.
86. Fielding JF, Cooke WT, Williams JA. Gastric acid secretion in Crohn's disease in relation to disease activity and bowel resection. Lancet. 1971;1:1106–7.
87. Shelton EL, Blaine MH. Massive small bowel resection in postgastrectomy patients. Report of 2 cases. Texas J Med. 1954;50:96–101.
88. Craig TV, Stewart WRC. Massive bowel resection in a patient with 75% gastrectomy. Surgery. 1960;48:678–81.
89. Miura S, Shikata J, Hasebe M, Kobayashi K. Long-term outcome of massive small bowel resection. Am J Gastroenterol. 1991;86:454–9.
90. O'Keefe SJD, Haymond MW, Bennet WM, Oswald B, Nelson DK, Shorter RG. Long-acting somatostatin analogue therapy and protein metabolism in patients with jejunostomies. Gastroenterology. 1994;107:379–88.
91. Straus E, Gerson CD, Yalow RS. Hypersecretion of gastrin associated with the short bowel syndrome. Gastroenterology. 1974;66:175–80.
92. Williams NS, Evans P, King RFGJ. Gastric acid secretion and gastrin production in the short bowel syndrome. Gut. 1985;26:914–9.
93. Temperley JM, Stagg BH, Wyllie JH. Disappearance of gastrin and pentagastrin in the portal circulation. Gut. 1971;12:372–6.
94. Becker HD, Reeder DD, Thompson JC. Extraction of circulating endogenous gastrin by the small bowel. Gastroenterology. 1973;65:903–6.
95. Moossa AR, Hall AW, Skinner DB, Winans CS. Effect of 50% small bowel resection on gastric secretory function in Rhesus monkeys. Surgery. 1976;80:208–13.
96. Buxton B. Small bowel resection and gastric acid hypersecretion. Gut. 1974;15:229–38.
97. Fitzpatrick WJF, Zentler-Munro PL, Northfield TC. Ileal resection: effect of cimetidine and taurine on intrajejunal bile acid precipitation and lipid solubilisation. Gut. 1986;27:66–72.
98. Barbezat GO, Hansen JDL. The exocrine pancreas and protein-calorie malnutrition. Pediatrics. 1968;42:77–92.
99. Kotler DP, Levine GM. Reversible gastric and pancreatic hyposecretion after long-term total parenteral nutrition. N Engl J Med. 1979;300:241–2.
100. Remington M, Fleming CR, Malagelada J-R. Inhibition of postprandial pancreatic and biliary secretion by loperamide in patients with short bowel syndrome. Gut. 1982;23:98–101.
101. Socha J, Ryzko J, Bogoniowska Z, Cichy W, Creutzfeldt W. Exocrine and endocrine pancreatic functions in children with the short bowel syndrome. Mater Med Pol. 1987;3:169–73.
102. Hofmann AF, Poley JR. Role of bile acid malabsorption in the pathogenesis of diarrhoea and steatorrhoea in patients with ileal resection. I. Response to cholestyramine or replacement of dietary long chain triglyceride by medium chain triglycerides. Gastroenterology. 1972;62:918–34.
103. Kristensen M, Lenz K, Nielsen OV, Jarnum S. Short bowel syndrome following resection for Crohn's disease. Scand J Gastroenterol. 1974;9:559–65.
104. Greenberg GR, Wolman SL, Christofides ND, Bloom SR, Jeejeebhoy KN. Effect of total parenteral nutrition on gut hormone release in humans. Gastroenterology. 1981;80:988–93.
105. Andrews NJ, Irving MH. Human gut hormone profiles in patients with short bowel syndrome. Dig Dis Sci. 1992;37:729–32.
106. Lezoche E, Carlei F, Vagni V, Mora GV, Speranza V. Elevated plasma levels of vasoactive intestinal polypeptide in short bowel syndrome. Am J Surg. 1983;145:369–70.
107. Krsek M, Rosická M, Haluzík M, Svobodová J, Kotrlíková E, Justová V, Lacinová Z, Jarkovská Z. Plasma ghrelin levels in patients with short bowel syndrome. Endocr Res. 2002;28(1–2):27–33.
108. Jeppesen PB, Hartmann B, Hansen BS, Thulesen J, Holst JJ, Mortensen PB. Impaired stimulated glucagon-like peptide 2 response in ileal resected short bowel patients with intestinal failure. Gut. 1999;45:559–63.
109. Jeppesen PB, Hartmann B, Thulesen J, Hansen BS, Holst JJ, Poulsen SS, Mortensen PB. Elevated plasma glucagon-like peptide 1 and 2 concentrations in ileum-resected short bowel patients with a preserved colon. Gut. 2000;47:370–6.
110. Adrian TE, Savage AP, Fuessl HS, Wolfe K, Besterman HS, Bloom SR. Release of peptide YY (PYY) after resection of small bowel, colon or pancreas in man. Surgery. 1987;101:715–9.
111. Tappenden KA. Pathophysiology of short bowel syndrome: considerations of resected and residual anatomy. JPEN J Parenter Enteral Nutr. 2014;38(1 suppl):4S–22S.
112. Mayeur C, Gillard L, Le Beyec J, Bado A, Joly F, Thomas M. Extensive intestinal resection triggers behavioral adaptation, intestinal remodeling and microbiota transition in short bowel syndrome. Microorganisms. 2016;4(1):16.
113. Belenguer A, Holtrop G, Duncan SH, Anderson SE, Calder AG, Flint HJ, Lobley GE. Rates of production and utilization of lactate by microbial communities from the human colon. FEMS Microbiol Ecol. 2011;77(1):107–19.
114. Gillard L, Mayeur C, Robert V, Pingenot I, Le Beyec J, Bado A, Lepage P, Thomas M, Joly F. Microbiota is involved in post-resection adaptation in humans with short bowel syndrome. Front Physiol. 2017;8:224.

115. Bourriaud C, Robins RJ, Martin L, Kozlowski F, Tenailleau E, Cherbut C, Michel C. Lactate is mainly fermented to butyrate by human intestinal microfloras but inter-individual variation is evident. J Appl Microbiol. 2005;99(1):201–12.
116. Vaidyanathan S, von Unruh GE, Watson ID, Laube N, Willets S, Soni BL. Hyperoxaluria, hypocitraturia, hypomagnesiuria, and lack of intestinal colonization by Oxalobacter formigenes in a cervical spinal cord injury patient with suprapubic cystostomy, short bowel, and nephrolithiasis. Sci World J. 2006;6:2403–10.
117. Siener R, Bangen U, Sidhu H, Hönow R, von Unruh G, Hesse A. The role of Oxalobacter formigenes colonization in calcium oxalate stone disease. Kidney Int. 2013;83(6):1144–9.
118. Editorial. The colon, the rumen, and $_{D}$-lactic acidosis. Lancet. 1990;336:599–600.
119. McIntyre PB, Fitchew M, Lennard-Jones JE. Patients with a high jejunostomy do not need a special diet. Gastroenterology. 1986;91:25–33.
120. Woolf GM, Miller C, Kurian R, Jeejeebhoy KN. Nutritional absorption in short bowel syndrome. Evaluation of fluid, calorie and divalent cation requirements. Dig Dis Sci. 1987;32:8–15.
121. Whang R, Whang DD, Ryan MP. Refractory potassium repletion. A consequence of magnesium deficiency. Arch Intern Med. 1992;152:40–5.
122. Woolf GM, Miller C, Kurian R, Jeejeebhoy KN. Diet for patients with a short bowel: high fat or carbohydrate? Gastroenterology. 1983;84:823–8.
123. Vallee BL, Wacker WEC, Ulmer DD. The magnesium-deficiency tetany syndrome in man. N Engl J Med. 1960;262:155–61.
124. Hanna S, Harrison M, MacIntyre I, Fraser R. The syndrome of magnesium deficiency in man. Lancet. 1960;2:172–6.
125. Fletcher RF, Henly AA, Sammons HG, Squire JR. A case of magnesium deficiency following massive intestinal resection. Lancet. 1960;1:522–5.
126. Swenson SA, Lewis JW, Sebby KR. Magnesium metabolism in man with special reference to jejunoileal bypass for obesity. Am J Surg. 1974;127:250–5.
127. Hessov I, Hasselblad C, Fasth S, Hulten L. Magnesium deficiency after ileal resections for Crohn's disease. Scand J Gastroenterol. 1983;18:643–9.
128. Booth CC, Hanna S, Babouris N, MacIntyre I. Incidence of hypomagnesaemia in intestinal malabsorption. Br Med J. 1963;1:141–4.
129. Fleming CR, George L, Stoner GL, Tarrosa VB, Moyer TP. The importance of urinary magnesium values in patients with gut failure. Mayo Clin Proc. 1996;71:21–4.
130. Rude RK, Singer FR. Magnesium deficiency and excess. Ann Rev Med. 1981;32:245–59.
131. Fawcett SL, Cousins RJ. Magnesium poisoning following enema of Epsom salt solution. JAMA. 1943;123:1028–9.
132. Kayne LH, Lee DBN. Intestinal magnesium absorption. Miner Electrolyte Metab. 1993;19:210–7.
133. Hessov I, Andersson H, Isaksson B. Effects of a low-fat diet on mineral absorption in small-bowel disease. Scand J Gastroenterol. 1983;18:551–4.
134. Hanna S, MacIntyre I. The influence of aldosterone on magnesium metabolism. Lancet. 1960;2:348–50.
135. Horton R, Biglieri EG. Effect of aldosterone on the metabolism of magnesium. J Clin Endocrinol Metab. 1962;22:1187–92.
136. Fatemi S, Ryzen E, Flores J, Endres DB, Rude RK. Effect of experimental human magnesium depletion on parathyroid hormone secretion and 1,25 dihydroxy-vitamin D metabolism. J Clin Endocrinol Metab. 1991;73:1067–72.
137. Zofkova I, Kancheva RL. The relationship between magnesium and calciotropic hormones. Magnes Res. 1995;8:77–84.
138. Solomon R. The relationship between disorders of K^+ and Mg^+ homeostasis. Semin Nephrol. 1987;7:253–62.
139. Kaufman SS, Loseke CA, Anderson JB, Murray ND, Vanderhoof JA, Young RJ. Magnesium acetate vs magnesium gluconate supplementation in short bowel syndrome. J Pediatr Gastroenterol. 1993;16:104–5.
140. Schuette SA, Lashner BA, Janghorbani M. Bioavailability of magnesium diglycinate vs magnesium oxide in patients with ileal resection. J Parenter Enter Nutr. 1994;18:430–5.
141. Kass L, Rosanoff A, Tanner A, Sullivan K, McAuley W, Plesset M. Effect of transdermal magnesium cream on serum and urinary magnesium levels in humans: a pilot study. PLoS One. 2017;12(4):e0174817. https://doi.org/10.1371/journal.pone.0174817.
142. Selby PL, Peacock M, Bambach CP. Hypomagnesaemia after small bowel resection: treatment with 1 alpha-hydroxylated vitamin D metabolites. Br J Surg. 1984;71:334–7.
143. Fukumoto S, Matsumoto T, Tanaka Y, Harada S, Ogata E. Renal magnesium wasting in a patient with short bowel syndrome with magnesium deficiency: effect of 1 α-hydroxyvitamin D_3 treatment. J Clin Endocrinol Metab. 1987;65:1301–4.
144. Davis AT, Franz FP, Courtnay DA, Ullrey DE, Scholten DJ, Dean RE. Plasma and mineral status in home parenteral nutrition patients. J Parenter Enter Nutr. 1987;11:480–5.
145. Shenkin A, Fell GS, Halls DJ, Dunbar PM, Holbrook IB, Irving MH. Essential trace element provision to patients receiving home intravenous nutrition in the United Kingdom. Clin Nutr. 1986;5:91–7.
146. Rannem T, Ladefoged K, Hylander E, Hegnhoj J, Jarnum S. Selenium depletion in patients on home parenteral nutrition. The effect of selenium supplementation. Biol Trace Elem Res. 1993;39:81–90.
147. Rannem T, Hylander E, Ladefoged K, Staun M, Tjellesen L, Jarnum S. The metabolism of [^{75}Se] Selenite in patients with short bowel syndrome. J Parenter Enter Nutr. 1996;20:412–6.
148. Arthur JR, Beckett GJ. New metabolic roles for selenium. Proc Nutr Soc. 1994;53:615–24.
149. Press M, Hartop PJ, Prottey C. Correction of essential fatty-acid deficiency in man by cutaneous application of sunflower-seed oil. Lancet. 1974;2:597–9.
150. Wolman SL, Anderspon GH, Marliss EB, Jeejeebhoy KN. Zinc in total parenteral nutrition: requirements and metabolic effects. Gastroenterology. 1979;76:458–67.
151. Mock DM, DeLorimer AA, Liebman WM, Sweetman L, Baker H. Biotin deficiency: an unusual complication of parenteral alimentation. N Engl J Med. 1981;304:820–3.
152. Khalidi N, Wesley JR, Thoene JG, Whitehouse WM Jr, Baker WL. Biotin deficiency in a patient with short bowel syndrome during home parenteral nutrition. J Parenter Enter Nutr. 1984;8:311–4.
153. Matsusue S, Kashihara S, Takeda H, Koizumi S. Biotin deficiency during total parenteral nutrition: its clinical manifestation and plasma nonesterified fatty acid level. J Parenter Enter Nutr. 1985;9:760–3.
154. Yamada E, Wakabayashi Y, Saito A, Yoda K, Tanaka Y, Miyazaki M. Hyperammonaemia caused by essential aminoacid supplements in patient with short bowel. Lancet. 1993;341:1542–3.
155. Yokoyama K, Ogura Y, Kawabata M, et al. Hyper-ammonemia in a patient with short bowel syndrome and chronic renal failure. Nephron. 1996;72:693–5.
156. Brophy DF, Ford SL, Crouch MA. Warfarin resistance in a patient with short bowel syndrome. Pharmacotherapy. 1998;18:646–9.
157. Pullan JM. Massive intestinal resection. Proc R Soc Med. 1959;52:31–7.
158. Crenn P, Beloucif L, Morin MC, Thuillier F, Messing B. Adaptive hyperphagia and net digestive absorption in short bowel patients. Gastroenterology. 1997;112:A356.
159. Cosnes J, Carbonnel F, Beaugerie L, Ollivier J-M, Parc R, Gendre J-P, Le Quintrec Y. Functional adaptation after extensive

small bowel resection in humans. Eur J Gastroenterol Hepatol. 1994;6:197–202.
160. Weinstein LD, Shoemaker CP, Hersh T, Wright HK. Enhanced intestinal absorption after small bowel resection in man. Arch Surg. 1969;99:560–2.
161. Althausen TL, Doig RK, Uyeyama K, Weiden S. Digestion and absorption after massive resection of the small intestine. II. Recovery of the absorptive function as shown by intestinal absorption tests in two patients and a consideration of compensatory mechanisms. Gastroenterology. 1950;16:126–34.
162. Dowling RH, Booth CC. Functional compensation after small bowel resection in man: demonstration by direct measurement. Lancet. 1966;2:146–7.
163. Gouttebel MC, Saint Aubert B, Colette C, Astre C, Monnier LH, Joyeux H. Intestinal adaptation in patients with short bowel syndrome. Measurement by calcium absorption. Dig Dis Sci. 1989;34:709–15.
164. Adaba F, Rajendran A, Patel A, Cheung YK, Grant K, Vaizey CJ, Gabe SM, Warusavitarne J, Nightingale JM. Mesenteric infarction: clinical outcomes after restoration of bowel continuity. Ann Surg. 2015;262(6):1059–64.
165. Hill GL, Mair WSJ, Goligher JC. Impairment of 'ileostomy adaptation' in patients after ileal resection. Gut. 1974;15:982–7.
166. Heaton KW, Read AE. Gallstones in patients with disorders of the terminal ileum and disturbed bile salt metabolism. Br Med J. 1969;3:494–6.
167. Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. N Engl J Med. 1992;326:589–93.
168. Doty JE, Pitt HA, Porter-Fink V, Denbesten L. Cholecystokinin prophylaxis of parenteral nutrition-induced gallbladder disease. Ann Surg. 1985;201:76–80.
169. Thompson JS. The role of prophylactic cholecystectomy in the short bowel syndrome. Arch Surg. 1996;131:556–60.
170. Appleton ND, Lal S, Carlson GL, Shaw S, Stevens P, Peristerakis I, Soop M. Cholelithiasis and related morbidity in chronic intestinal failure: a longitudinal cohort study from a National Specialized Centre. J Gastrointest Surg. 2019;23(10):2002–6.
171. Oke S, Nightingale J, Jeppesen P, the BIFA committee. British Intestinal Failure Alliance (BIFA) position statement use of peptide growth factors for adult patients with intestinal failure. 2018. www.bapen.org.uk/pdfs/bifa/position-statements/use-of-peptide-growth-factors-for-adult-patients-with-intestinal-failure.pdf
172. Walker-Smith JA, Phillips AD, Walford N, Gregory H, Fitzgerald JD, MacCullagh K, Wright NA. Intravenous epidermal growth factor/urogastrone increases small-intestinal cell proliferation in congenital microvillous atrophy. Lancet. 1985;2:1239–40.
173. Sullivan PB, Brueton MJ, Tabara ZB, Goodlad RA, Lee CY, Wright NA. Epidermal growth factor in necrotising enteritis. Lancet. 1991;338:53–4.
174. Rokkas T, Vaja S, Murphy GM, Dowling RH. Aminoguanidine blocks intestinal diamine oxidase (DAO) activity and enhances the intestinal adaptive response to resection in the rat. Digestion. 1990;46(suppl 2):447–57.
175. Scolapio JS, Camilleri M, Fleming CR, Oenning LV, Burton DD, Sebo TJ, Batts KP, Kelly DG. Effect of growth hormone, glutamine, and diet on adaptation in short-bowel syndrome: a randomized, controlled study. Gastroenterology. 1997;113:1074–81.
176. Ellegård L, Bosaeus I, Nordgren S, Bengtsson BA. Low-dose recombinant human growth hormone increases body weight and lean body mass in patients with short bowel syndrome. Ann Surg. 1997;225(1):88–96.
177. Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomised, double blind, crossover, placebo controlled study. Gut. 2000;47:199–205.
178. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study. Gastroenterology. 2003;124(2):293–302.
179. Litvak DA, Iseki H, Evers M, et al. Characterization of two novel proabsorptive peptide YY analogs, BIM-43073D and BIM-43004C. Dig Dis Sci. 1999;44:643–8.
180. Gruy-Kapral C, Little KH, Fortran JS, Meziere TL, Hagey LR, Hofmann AF. Conjugated bile acid replacement therapy for short-bowel syndrome. Gastroenterology. 1999;116:15–21.
181. Heydorn S, Jeppesen PB, Mortensen PB. Bile acid replacement therapy with cholylsarcosine for short-bowel syndrome. Scand J Gastroenterol. 1999;34:818–23.
182. Campbell FC, Tait IS, Flint N, Evans GS. Transplantation of cultured small bowel enterocytes. Gut. 1993;34:1153–5.
183. Clevers H, Conder RK, Li VSW, Lutolf MP, Vallier L, Chan S, Grikscheit TC, Jensen KB, De Coppi P. Tissue-engineering the intestine: the trials before the trials. Cell Stem Cell. 2019;24(6):855–9.
184. Yamamoto T, Watanabe T. Strategies for the prevention of postoperative recurrence of Crohn's disease. Color Dis. 2013;15(12):1471–80.
185. Bala M, Kashuk J, Moore EE, Kluger Y, Biffl W, Gomes CA, Ben-Ishay O, Rubinstein C, Balogh ZJ, Civil I, Coccolini F, Leppaniemi A, Peitzman A, Ansaloni L, Sugrue M, Sartelli M, Di Saverio S, Fraga GP, Catena F. Acute mesenteric ischemia: guidelines of the World Society of Emergency Surgery. World J Emerg Surg. 2017;12:38.
186. Boley SJ, Sprayregan S, Siegelman SS, Veith FJ. Initial results from an aggressive roentgenological and surgical approach to acute mesenteric ischaemia. Surgery. 1977;82:848–55.
187. Anderson SHC, Dalton HR. Use of octreotide in the treatment of mesenteric angina. Am J Gastroenterol. 1997;92:1222–3.
188. Marston A. Acute intestinal ischaemia. Resection rather than revascularisation. Br Med J. 1990;301:1174–6.
189. Clavien PA. Diagnosis and management of mesenteric infarction. Br J Surg. 1990;77:601–3.
190. Levy PJ, Krausz MM, Manny J. Acute mesenteric ischaemia: improved results—a retrospective analysis of ninety-two patients. Surgery. 1990;107:372–80.
191. Messing B, Leman M, Landais P, et al. Prognosis of patients with nonmalignant chronic intestinal failure receiving long-term home parenteral nutrition. Gastroenterology. 1995;108:1005–10.
192. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology. 1999;117:1043–50.
193. Vantini I, Benini L, Bonfante F, et al. Survival rate and prognostic factors in patients with intestinal failure. Dig Liv Dis. 2004;36:46–55.
194. Dibb M, Soop M, Teubner A, Shaffer J, Abraham A, Carlson G, Lal S. Survival and nutritional dependence on home parenteral nutrition: three decades of experience from a single referral centre. Clin Nutr. 2017;36(2):570–6.
195. Joly F, Baxter J, Staun M, et al., ESPEN HAN CIF Group. Five-year survival and causes of death in patients on home parenteral nutrition for severe chronic and benign intestinal failure. Clin Nutr. 2018;37(4):1415–22.
196. Oke SM, Nightingale JM, Donnelly SC, Naghibi M, Willsmore J, Lloyd DAJ, Gabe SM. Outcome of adult patients receiving parenteral support at home: 36 years' experience at a tertiary referral centre. Clin Nutr. 2021;40(11):5639–47.

Chronic Small Bowel Dysfunction

Jeremy M.D. Nightingale and Peter Paine

Key Points

1. Patients with chronic small bowel dysmotility have predominantly a myopathy (usually dilated gut and classical chronic intestinal pseudo-obstruction (CIPO)), a neuropathy or idiopathic.
2. The patient's primary symptoms/problems are listed in order of importance to the physician and patient.
3. Contributing factors (e.g. drug therapy, psychosocial and quality of life issues) are evaluated.
4. Mechanical obstruction must be excluded (especially if dilated loops of bowel are noted) usually with a CT scan of the abdomen with oral contrast.
5. The patient's nutritional status is assessed and if poor, nutritional treatment is begun while taking into account/treating refeeding risks.
6. Tests to help establish a clinical diagnosis are performed when the patient is not taking any medications that affect gastrointestinal motility (e.g. opiods and cyslizine) and ideally when they have achieved a normal body mass index.
7. A definite diagnosis of dysmotility should not be given unless it is certain. Terms such as possible/probable or working diagnosis are preferred as a label of dysmotility is difficult to remove. As the clinical situation changes the diagnosis may be reconsidered.
8. A plan and treatment goals are agreed to help symptoms, nutritional status, psycho-social issues and quality of life. This should be with a multidisciplinary team (includes psychology and pain management specialists). All members of the team should give the same agreed information to the patient/family.
9. Surgical options may be considered. These include insertion of jejunal feeding tubes, venting stomas, a full thickness jejunal biopsy and selected bypasses/resections or rarely small bowel transplantation.
10. Opioids and intravenous cyclizine should be avoided.

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Introduction

Chronic small intestinal dysmotility occurs when, for more than 6 months, there is a failure of coordinated intestinal propulsion, giving rise to the symptoms and signs of intestinal obstruction (colicky abdominal pain, nausea, vomiting usually with abdominal distension, and often a dilated bowel) in the absence of a mechanical cause [1–3]. It may be defined as severe when there is objective evidence of malnutrition, dehydration or electrolyte disturbance (e.g. BMI of less than 18.5 kg/m^2 or more than 10% unintentional weight loss in last 3 months) and thus clinically assisted nutrition and hydration (CANH) therapy may be needed. A classical obstructive picture with distended bowel is not always the case, especially if there is a neurological aetiology.

Normal gastrointestinal motility is determined by intestinal smooth muscle function which in turn is influenced by neural and humoral factors. A disorder of one or more of these systems can result in intestinal pseudo-obstruction [2]. Dysmotility may occur not only in the small bowel but also in other areas of the gastro-intestinal tract (e.g. oesophagus, stomach and colon) and their involvement may complicate diagnostic tests and treatments. There are many causes of acute or reversible/temporary intestinal dysmotility which include abdominal surgery, trauma, sepsis, metabolic (e.g. hypokalaemia) or endocrine problems (e.g. hypothyroidism); and there are other medical causes of abdominal pain (e.g. functional dyspepsia, irritiable bowel syndrome, centrally mediated abdominal pain, familial mediterranean fever, ischaemia, angio-oedema, abdominal migraine and

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lead poisoning) which are not specifically discussed in this chapter but the clinician must be aware of them.

The diagnosis of these patients can be very difficult and may be empirical. Different diagnostic labels have been given to these patients based upon the diagnostic test used. Histology in an expert centre may be the most definitive but is often not available and indeed it may be inappropriate to obtain it due to associated risks and lack of specific therapy implications. Histology may show abnormalities but the extent they are due to malnutrition, previous surgery (including defunctioning bowel) or drug therapy is not clear. The clinical features, results of investigations (e.g. manometry) and histology may not all combine to indicate one specific diagnosis. Other factors that can give rise to the clinical picture or aggravate the condition are: unrecognised organic small bowel obstruction/the effects of previous abdominal surgery (including adhesions and neuropathic pain), drug usage (particularly opioids and drugs with anticholinergic effects), psychosocial problems including abnormal illness behaviour and malnutrition. In practice, all of these often play a part and contribute to the patient's presentation (Figs. 1 and 2). Untangling which of these factors gives rise to the dominant symptom can be challenging and needs the help of a multidisciplinary team that ideally consists of a gastroenterologist, gastrointestinal physiologist, gastrointestinal surgeon, pain team, psychiatrist/psychologist, rheumatologist (including a specialist in fatigue management), urologist, gynaecologist, neurologist, clinical biochemist, histopathologist, radiologist and nutritional support team.

If there is uncertainty about the diagnosis this should be clearly documented and only described as working (probable or possible) and the contributing factors to this should be stated on the patient's problem list (e.g. previous surgery, opioid or cyclizine use, psychosocial problems or undernutrition). A definitive diagnosis should only be given if there is a clear cause identified. It is very difficult to remove a diagnostic label once it has been given and a premature or erroneous organic diagnosis in those with predominantly psychosocial issues or abnormal illness behavior may make the management of contributing issues very difficult. A definite diagnosis although satisfying to have, rarely affects the patient's clinical management.

This document discusses the differential diagnoses, the medical and nutritional treatment of chronic small intestinal dysmotility, which result in malnutrition. In its most severe form patients with small bowel dysmotility may need long-term PN or even a small intestinal transplant, while in a milder form dietary adjustment may suffice.

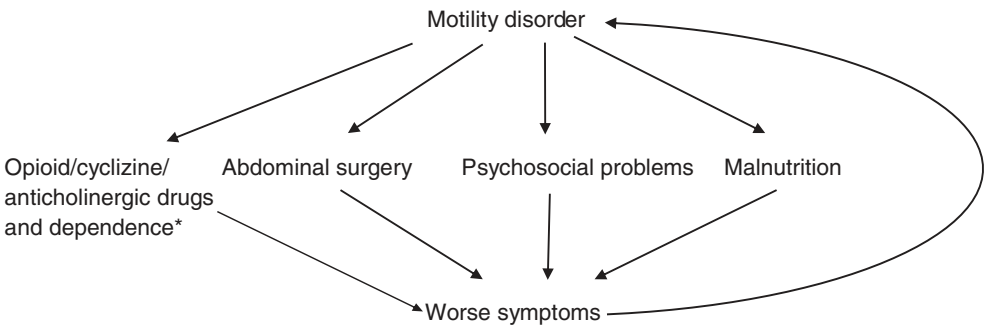

Fig. 1 Progression of dysmotility

*some other drugs can have similar problems (e.g. calcium channel blockers, antidepressants etc)

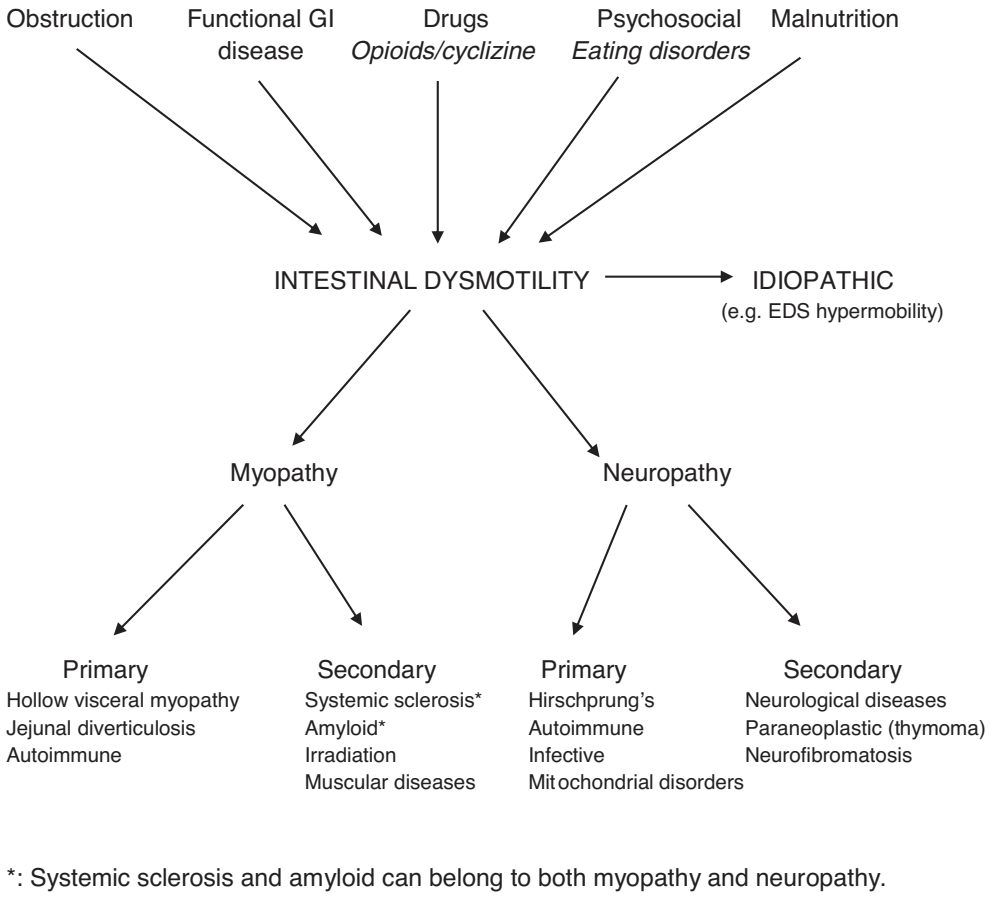

Fig. 2 Factors contributing/mimicking severe chronic intestinal dysmotility and its traditional classification

Conditions that Mimic or Can Contribute to the Presentation

A patient with suspected small bowel dysmotility will have had basal investigations to exclude other causes; these include inflammatory markers (CRP, albumin, platelets and faecal calprotectin) which, if normal, make active inflammatory bowel disease unlikely. These may be followed, as appropriate, with the use of endoscopies and cross-sectional imaging including with intravenous contrast to diagnose structural/mucosal diseases. Several other conditions may appear as severe chronic intestinal dysmotility but with no primary bowel pathology (Fig. 1). In one series the most frequent misdiagnoses for dysmotility were volvulus, megacolon and chronic constipation [4].

Organic Obstruction

A major problem, that is often not diagnosed, is a localised bowel obstruction as a result of adhesion formation. This may be suspected clinically when a patient has had a number of abdominal operations (with or without extensive adhesion division) [5]. A history of intermittent colicky abdominal pain with abdominal distention, loud bowel sounds, no bowel or stoma action and vomiting suggest this. A distal obstruction is suggested if the vomit is faeculent, while a more proximal one by green/yellow vomit. During an obstructive episode the bowel secretes more fluid and when the obstruction resolves diarrhoea follows (or a high stomal output). If a patient sticks to a low residue diet or even a liquid diet, the obstructive episodes may reduce or even be abolished. This approach, if successful, can be a useful supportive diagnostic test.

Radiologically the clue to an organic obstruction is the demonstration of a distinct transition point between dilated and normal sized bowel but this may not be apparent either because the obstruction has resolved or the bowel is fixed by adhesions and thus cannot dilate. It can be helpful to obtain an abdominal CT scan when the patient has an episode of severe pain. Contrast follow-through studies or MRI scans although useful when positive may not be tolerated in the acute setting and do not always demonstrate the obstruction. Unsuspected diagnoses may be revealed (e.g. small bowel volvulus from a band adhesion or an intussusception). Further clues to an organic obstruction are visible small bowel peristalsis, worse pain after prokinetic drugs or giant jejunal contractions on manometry [6, 7].

Multiple laparotomies themselves may result in secondary dysmotility, especially if the bowel becomes encased in fibrous tissue as can occur with sclerosing peritonitis. In addition upper gut surgery (e.g. a vagotomy, Whipple's resection, gastro-enterostomy, bariatric procedures or any bowel anastomosis) can result in secondary small bowel dysmotility [8].

Radiation damage can cause strictures and a localised obstruction and/or a generalised secondary dysmotility. Problems caused by radiation damage tend to be progressive over many years.

Opioid and Other Drug Effects on the Bowel

Opioid-induced bowel dysfunction (OBD) can result from both opioid withdrawal and chronic opioid usage and manifests with features of dysmotility (especially constipation) when pain is not the dominant issue. The narcotic bowel syndrome (NBS) may result from chronic usage and is defined as chronic, worsening or frequently occurring abdominal pain despite continued or escalating doses of narcotics in addition to dysmotility [9]. The opioid usage induces a hyperalgesic effect. It may be becoming more prevalent but it is often not recognised by clinicians [10, 11]. In addition to being acknowledged to occur in patients with gastrointestinal disease (functional or organic) it also occurs in patients with no pre-existing gastrointestinal problems who take high doses of the opioids for other painful conditions (e.g. joint problems or following surgery).

The components of therapy for NBS are recognition of the disorder, a trusting therapeutic relationship with the patient, replacement using neuropathic type pain drugs and controlled reduction in the opioid dose [12]. Specific drug treatments have been tried for OBD and NBS and include clonidine (to reduce withdrawal symptoms), and peripheral mu opioid antagonists (naldemidine, naloxone, methylnaltrexone, alvimopan) [13–15].

Opioids inhibit intestinal motility and so invalidate the tests of small bowel motility. They may also increase the risk of catheter-related blood stream infections (CRBSI) in patients on long term PN.

Survivors of cancer treatment may have bowel dysmotility which may be due to chemotherapy or opioid medication. Their management may require a wider MDT input.

Cyclizine is both an antihistamine and anti-cholinergic drug that acts as a centrally acting anti-emetic. There are many reports of it being taken for its euphoric effect which is most marked when taken intra-venously. In addition to causing addictive behaviour, it is of a low pH and so damages veins. It is not recommended for long-term use, especially in patients receiving PN [16].

Other drugs such as anti-cholinergics, anti-depressants, calcium channel blockers, chronic laxative abuse or some chemotherapeutic drugs (e.g. vincristine) may also cause reduced gut propulsion.

Functional Gastrointestinal Disorders

Many of the symptoms of small intestinal dysmotility are the same as for patients with other functional abdominal gastrointestinal disorders (e.g. irritable bowel syndrome, functional dyspepsia, cyclical vomiting, functional bloating/distension, functional constipation/diarrhea and centrally mediated disorders of gastrointestinal pain) [17].

The differentiation and overlap with these functional gastrointestinal disorders is difficult. They all may have genetic and psychosocial influences (early life trauma, life stresses, coping mechanisms, lack of social support etc.). In addition bacterial flora, inflammation, visceral sensation and motility may all contribute to the symptoms. In irritable bowel syndrome there may be an overlap with enteric neuropathy as increased lymphocytes have been observed in the jejunal myenteric plexus [18]. However, significant malnutrition is rarely a consequence of these disorders.

The treatment as for all dysmotility problems is to identify and treat the main symptoms. If weight loss has occurred nutritional support is given at the same time as therapies as for intestinal dysmotility. Significant caution should be exercised to avoid escalating to more invasive forms of nutrition support in patients with functional symptoms, especially in pain predominant presentations, in the absence of objective features (e.g. no biochemical disturbance or who having a normal body mass index). Escalation of invasive intervention in these patients risks causing iatrogenic problems, and in clinical practice does not appear to improve global function, quality of life or symptoms.

Psychological/Psychiatric Problems

Anorexia Nervosa

The American Psychiatric Association (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-5) stated in 2013 that to diagnose a person with Anorexia Nervosa they must display: (1) Persistent restriction of energy intake leading to significantly low body weight (in context of what is minimally expected for age, sex, developmental trajectory, and physical health). (2) Either an intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain (even though significantly low weight). (3) Disturbance in the way one's body weight or shape is experienced, undue influence of body shape and

weight on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight [19].

However the patients that present to gastroenterologists often do not have this typical presentation. Delayed gastric emptying, especially of solid, and delayed small and large bowel transit have been described in patients with anorexia nervosa [20–23]. There is a report of a patient having a mega-duodenum and no propagating migrating motor complexes (MMC) which both improved with an increased nutritional intake [24].

Avoidant/Restrictive Eating

Some patients who have had psychosocial problems in the past may have disordered gut motility partly due to a disordered eating pattern, undernutrition and the drug treatments which they received [25]. The Avoidant Restrictive Food Intake Disorder (DSM 5) is an increasingly recognized condition in patients with neurogastroenterology and malnutrition presentations and is best managed with a nutritional and psychological rehabilitation approach.

Psychiatric Disorders and Psychological Distress

Other major psychiatric disorders can be encountered, sometimes masquerading as or confounding a dysmotility diagnosis [26]. It is not uncommon for some of these patients to be referred to an Intestinal Failure (IF) unit. Psychological distress is common (Table 1) and so an MDT approach, including both clinical psychology and liaison psychiatry expertise is ideal.

Effect of Undernutrition on Gut Function

Malnutrition itself can impair gut function and cause malabsorption with mucosal atrophy, reduced gastric acid and pancreatic enzyme secretion and more bacterial colonization of the upper gut [27, 28]. The effects of undernutrition upon gut motility and histological appearance are uncertain.

There is a large literature on the superior mesenteric artery syndrome (Wilkie's syndrome) in which the third part of the duodenum is compressed between the superior mesenteric artery and the aorta (when the left renal vein is compressed it is referred to as 'nutcracker syndrome'). It is reported to be prevalent in patients who have suddenly lost weight and reported to improve when either the patient becomes better nourished or a duodeno-jejunostomy (bypass) is formed to avoid the obstruction. The symptoms attributed to this are post-prandial epigastric pain, nausea/vomiting and loss of weight [29–33]. Whether this is cause or consequence of malnutrition and whether it is a radiological rather than true clinical entity remains contentious and some clinicians dispute its existence and think it is over diagnosed. The risks of any surgery should be very carefully considered especially as the benefits of surgery are not always predictable or clear.

Table 1 Contributing psychological factors

• Delay in diagnosis
• Poor knowledge within the medical community
• No cure
• Pain and problems of analgesic drugs (including addiction)
• Anxiety, depression, somatisation, poor coping, sickness role
• Interaction with family, carers and job leading to low self-esteem/confidence/mood

Hypermobile Ehlers-Danlos Syndrome (EDS) (Joint Hypermobility Syndrome or Ehlers-Danlos Syndrome Hypermobility Type)

Hypermobile EDS with its gastrointestinal associations is difficult to classify as most patients with EDS do not have a dysmotility of the small bowel, but mainly visceral hypersensitivity. Its symptoms may mimic dysmotility (neuropathy) and the presence of EDS can contribute to dysmotility, usually if postural tachycardia syndrome (PoTS), or other associated factors such as opiates are present. According to the 2017 classification patients previously diagnosed with joint hypermobility syndrome and Ehlers-Danlos Syndrome-Hypermobility Type were reclassified as hypermobile Ehlers-Danlos Syndrome (hEDS) if they met the strict criteria or Hypermobile Spectrum Disorders (HSD) if they had many but not all of the characteristics of hEDS [34]. Patients with hEDS and HSD represent a third of patients referred to a tertiary neurogastroenterology clinic in the UK and these patients tended to be young, female with a poor quality of life [35]. hEDS/HSD is associated with a range of gut disorders (acid reflux, abdominal pain (especially typical is pain after eating or when any food arrives in the gut even from an enteral feed) and constipation) [36]. There is often autonomic dysregulation, particularly PoTS [37], chronic urinary retention due to a failure of the urethral sphincter to relax (Fowler's syndrome), and hypoglycaemia [35]. Mast cell activation disorder [37] is being increasingly reported (most commonly in those having PoTs) but is poorly defined and not often objectively confirmed. An increasing number of patients with joint hypermobility and gut dysmotility are being seen by nutrition support teams because of weight loss and malnutrition. This group seems especially sensitive to opioids and cyclizine both of which can exacerbate/mimic all of their symptoms [16]. It is currently unclear the degree to which the association of hypermobile EDS with gut symptoms encompasses specifically any greater degree of chronic small intestinal dysmotility, nor whether there are any different treatment approaches to patients without hypermobile EDS who have the same functional symptoms and it seems to be more prevalent in presenting to intestinal failure units

in the UK than the rest of Europe. The same cautions therefore should apply when considering escalating invasiveness of nutrition support in this group as to that of functional gastrointestinal disorders in general, especially if there is a pain predominant presentation. In Fig. 1 these patients have been inco-orporated into the idiopathic dysmotility group but may represent a mainly pain sensitivity problem rather than true dysmotility.

Pathophysiology

The propulsive failure of pseudo-obstruction is usually a consequence of either temporary dysfunction or irreversible damage to enteric neural networks (neuropathy), or less frequently, to disease of the effector system (myopathy). The pathophysiological basis of pseudo-obstruction is propulsive failure. In this context, the term 'motility' is confusing, because it refers to both transit and to the contractile activity of the gut. Clearly when there is reduced transit, there is, in one sense, 'reduced motility'. In the small bowel, however, the most common motor abnormality, in impaired propulsion, is an overall increase in the incidence of contractions; this can be regarded as 'increased motility'. The increased activity, probably due to a reduction in the inhibitory neural input, is obstructive rather than propulsive. This explains why 'prokinetic' drugs, which are designed to increase contractile activity, are usually ineffective in treating propulsive failure.

In the small bowel, the abnormal contractile activity results in distortion of the fasting migrating myoelectric complex (MMC) pattern. This is most easily seen during nocturnal sleep, when fasting activity is always present and consists largely, in health, of alternating sequences of quiescence and the 'migrating' contractions of phase III. In propulsive failure, the nocturnal motor quiescence is replaced by intermittent single or clustered contractions. Phase III episodes are prolonged in duration, and 'migrate' more slowly; phase III may even be altogether absent. In the colon, the high amplitude propagated contractions that usually occur 2–6 times daily are reduced in chronic constipation.

Classification of Chronic Small Intestinal Dysmotility

There are three major histopathological entities recognised—myopathies, neuropathies and mesenchymopathies depending respectively upon the predominant involvement of smooth muscle cells, enteric neurons or the interstitial cells of Cajal (ICC). Mesenchymopathies, which involve ICC, which are the gut pacemakers, are being recognised. The abnormalities described include a decreased ICC density, loss of processes and damaged intracellular cytoskeleton and organelles as revealed by immunohistochemical analysis and electron microscopy. It may be that abnormalities with the ICC are the primary event or may result from a neuropathy. In baby's, immaturity may result in delay in maturation of ICCs that can lead to the appearance of a reduction in these cells, so care needs to be taken with the histological diagnosis. (1) As conditions specifically falling into this category are few, this chapter will only discuss conditions traditionally classified as a myopathy of neuropathy. In general, a myopathy results in a dilated non propulsive gut and includes those termed chronic intestinal pseudo-obstruction (CIPO). A neuropathy more generally results in hypersensitivity and poorly co-ordinated bowel contactions (often increased) without bowel dilatation and is often referred to as enteric dysmotility (Fig. 2, Table 2).

It can be hard to determine if a condition is primarily a myopathy or neuropathy as some secondary conditions (e.g. systemic sclerosis, vasculitis or amyloid) may appear as

Table 2 Classification of intestinal dysmotility

Myopathies
Primary
Familial
Hereditary myopathy (e.g. Hollow visceral myopathy)
Acquired
Auto-immune
Jejunal diverticulosis
Secondary
Systemic sclerosis [and other connective tissue disorders (e.g. SLE)]
Amyloidosis
Chronic irradiation damage
Muscular diseases
Muscular dystrophies
Myofibrillar myopathies (e.g. *Desmin myopathy*)
Hereditary inclusion body myopathies
Metabolic storage disorder
Neuropathies[a]
Primary (*intrinsic*)
Familial/Congenital/Developmental
Hirschprung's disease
Neurofibromatosis
Mitochondrial disorders (MNGIE, DNA depletion, Alpes or Pearson's syndromes)
Neuronal dysplasia
Infant colic (Developmental)
Auto-immune
Anti-neuronal antibodies
Ganglionosis
Infective
Chaga's disease,
Herpes viruses (e.g. EBV, CMV, VZV) or
Polyoma viruses (JC virus)

(continued)

Table 2 (continued)

Secondary (*extrinsic*)
Generalised neurological disorders
Brain stem lesions
Spinal cord injury
Multiple sclerosis
Parkinson's disease
Neurological effects of diabetes mellitus
Autonomic system degeneration
Paraneoplastic syndromes [often with anti-neuronal antibodies (especially anti Hu)]
Small cell lung cancer
Carcinoid
Neuroblastoma
Thymoma
Drugs/toxins
Vincristine, adriamycin
Antidepressants, Ca channel blockers, anti-cholergic drugs
Opiates
Clonidine
Izoniazid
Other
MEN IIb
Porphyria (Acute intermittent)
Fabry's disease

Note: in most cases an empirical working diagnosis of idiopathic dysmotility will be applied

[a]Histology is generally inflammatory or degenerative

both. The end result of a neuropathy is often dysfunctional enteric muscle which occasionally can dilate, as in a myopathy. Overall a neuropathy (often a secondary one) is more common than a myopathy in causing small bowel dysmotility. The diagnosis can be difficult to define partly because the radiological, isotopic, manometric and histologic diagnoses may be different.

Myopathies

Primary myopathies most commonly occur in children and young adults and are often familial (genetic). Myopathies often have multivisceral involvement and thus a relatively high mortality. They may show reduced propulsive activity on manometry (Fig. 3b) and in the most severe form they are associated with massive gut dilatation (CIPO). Many predominantly affect the circular muscle (except hollow visceral myopathy). Primary myopathies are more common in children whereas secondary myopathies are more common in adults.

Primary Myopathies

Primary myopathies are due to abnormalities in enteric muscle (e.g. hollow visceral myopathy or autoimmune myopathy). There has been interest in reduced immunostaining of alpha-isoactin in jejunal circular muscle, observed in one [38] then 28 more patients (overall 24% of patients having full thickness jejunal biopsies) [39]. However it is not clear if this is the primary pathology or secondary to other factors (e.g. drugs, undernutrition or previous surgery) or a normal anatomical variant, and therefore not a specific finding [40]. Precise information as to the location of the biopsy—jejunum or ileum is essential for interpretation in this context.

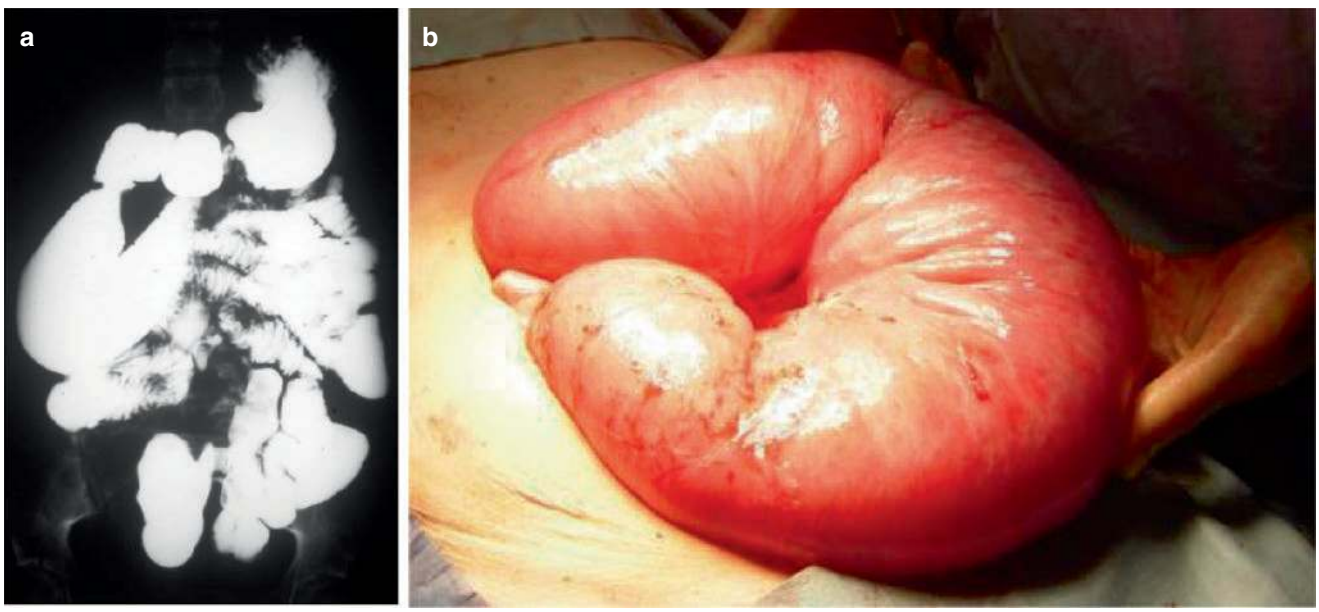

Fig. 3 (**a**) Plain abdominal radiograph of a patient with visceral myopathy. Note huge duodenal loop. Kindly supplied by M.A. Kamm. (**b**) Dilated small bowel in patient with visceral myopathy. Kindly supplied by N. Wyer

Familial

Hollow visceral myopathy is the best know example of a familial visceral myopathy. It is a rare congenital disorder that usually presents in the first or second decade of life and in addition to gross dilatation of the gastrointestinal tract (Fig. 3) (that often starts with a megaduodenum) there may also be associated dilatation of the urinary tract and associated frequent urinary tract infections [41–43]. The disease has been reported to follow an autosomal dominant mode of inheritance [44, 45]. In infants other features may include malrotation, pyloric stenosis and bladder atony. There is a loss of enteric smooth muscle with vacuolar degeneration and fibrosis [46]. The longitudinal muscle is predominantly affected. This may be due to the transformation of smooth muscle cells to collagen synthesizing myofibroblasts [47]. In one study of adult patients four of six patients had urinary tract involvement with dilatation of the ureters and/or incomplete bladder emptying [41].

Acquired-Autoimmune Myopathy

A few cases only of a lymphocytic enteric leiomyositis involving the smooth muscle cells have been reported [48–50]. Eosinophilic leiomyositis has also been reported, and in this context must prompt investigation for parasites, including dog hookworm.

Jejunal Diverticulosis

Diverticula in the jejunum usually result from congenital abnormalities or dysmotility (e.g. disordered high pressure bowel contractions) and may be associated with sub-clinical systemic sclerosis. Careful examination of any respected specimen should be carried out to examine the muscle and nerve layers of the bowel wall both in the region of the diverticula and adjacent bowel.

Secondary Myopathies

Secondary myopathies occur as part of a multi-system disease (e.g. systemic sclerosis, amyloid, chronic irradiation damage or muscular diseases) [51]. The problems of pseudo-obstruction are often only clinically apparent towards the end of the illness when nutritional support may be needed.

Systemic Sclerosis (Scleroderma) and Other Connective Tissue Disorders

Most patients with systemic sclerosis do get gastrointestinal involvement (Fig. 4) particularly of the oesophagus [52]. While the end result and main pathology is smooth muscle atrophy and gut wall fibrosis [53] it may start with microvasculature damage due to collagen deposits and inflammation which cause neural damage that progresses to muscle dysfunction and fibrosis. While systemic sclerosis patients with gross gastrointestinal involvement present in the terminal phase of the illness, this is not always the case and some present with the gastrointestinal involvement early in the disease without cutaneous involvement and the disease may not progress for many years. The clinical outcome in elderly scleroderma patients is the poorest of all adult onset dysmotility patients [54]. However, where indicated, long term PN can offer a safe and effective means of nutritional support in patients with severe small bowel involvement [55]. Other connective tissue and rheumatological disorders have been associated with dysmotility including SLE, RA and Stills disease [56, 57].

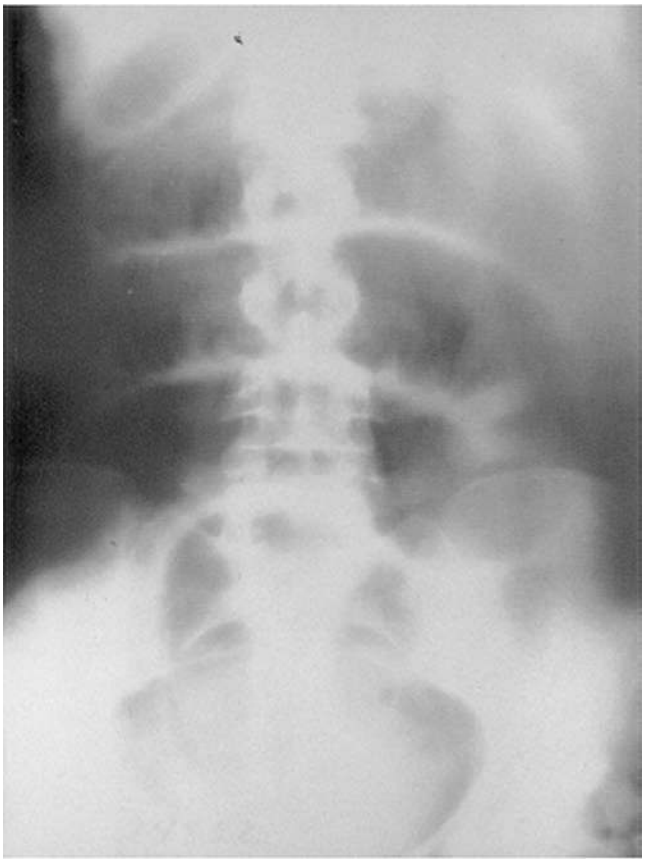

Fig. 4 Abdominal radiograph of a patient with progressive systemic sclerosis. Kindly supplied by E.A. Quigley

Amyloidosis

The primary type distribution may be associated with gut involvement. The most common underlying diagnosis is myeloma (often producing lambda chains). While classified as a myopathy it can also cause neurological damage and, like systemic sclerosis, may cause both a myopathy and a neuropathy. The rectum can be spared and so duodenal sampling should also be considered. Any full thickness biopsy

for motility investigation should also be examined for amyloidosis. Genetic testing is now readily available for the hereditary type of amyloidosis which may present more commonly in men and with peripheral neuropathy and cardiac as well as gut involvement.

Chronic Irradiation Damage

This usually occurs after pelvic irradiation for gynaecological cancers or genital-urinary cancers. The sigmoid and terminal ileal areas are often most involved. However, the whole small bowel can be involved giving rise to a pseudo-obstruction picture or as discrete areas of strictures. Surgery is very difficult and has a high risk of an enterocutaneous fistula(s) being created. Gut permeability, secretion, motility and blood supply can all be affected giving rise to any or all of the following: malabsorption, protein losing enteropathy, diarrhoea, perforation/fistulas, bleeding and obstruction. These problems can all occur months or years after more than 50 Gy irradiation has been given. The irradiation is more likely to give problems if a patient is already malnourished, has diabetes mellitus, hypertension or a vasculitis [58].

Muscular Diseases

Myopathies may occur associated with congenital muscular disorders (muscular dystrophies, myofibrillar myopathies (e.g. *Desmin myopathy*), hereditary inclusion body myopathies) but the muscle weakness (and often cardiac problems) dominates the clinical picture though gastrointestinal problems if sought are common. Metabolic storage disorders can have a myopathic process and occasionally can be treated with specific enzyme-replacement therapy [59].

Neuropathies

An enteric neuropathy may occur as a primary pathology (congenital, autoimmune or infective), secondary to a generalised neurological disorder, paraneoplastic process, metabolic disorder (e.g. diabetes) or drugs/toxins or as a developmental abnormality. Visceral neuropathy is less well reported in the literature than visceral myopathy. Visceral neuropathy is commonly acquired in adulthood or in old age and is associated with a high morbidity usually due to factors other than the neuropathy. Luminal dilatation is rarely seen except at the end stage of the disease.

Two forms of pathology are found either enteric neural *degeneration* (in the absence of inflammation) or *inflammatory* [60]. Degenerative neuropathies can result from mitochondrial dysfunction and the pathological findings include neuronal swelling, intranuclear inclusions, axonal degeneration and hypoganglionosis. The aetiology of many degenerative enteric neuropathies will remain idiopathic. Inflammatory neuropathies may include both plexitis and neuritis, and can be lymphocytic or less commonly eosinophilic, the former promoting autoimmune screening, the latter investigation for parasites.

Manometry may show intense but apparently uncoordinated motor activity with no propulsive contractions (Fig. 3c) and there may be no fasting MMC.

Primary Neuropathy

The enteric neuropathies can affect both the submucosal and myenteric plexuses, but the myenteric plexus is predominantly affected. The term visceral neuropathy is used for primary intrinsic enteric nervous damage.

Congenital/Familial/Developmental

Familial visceral neuropathies include Hirschprung's disease, mitochondrial cytopathies and Von Recklinghausen's disease. Hirschprung's disease can affect any part of the gut.

Mitochondrial disorders are relatively common if specifically sought. One study showed 19% of 80 adult patients labelled as CIPO to have this [61]. Mitochondrial cytopathies such as mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) (the most common) (also referred to as Thymidine Phosphorylase Deficiency) is an autosomal recessive disorder characterised by severe gastrointestinal dysmotility (including bacterial overgrowth and lactic acidosis); cachexia, and neurological problems including leukoencephalopathy (96%), polyneuropathy (96%), ophthalmoplegia (91%) (with ptosis) and hearing loss (55%) [62, 63]. The disease is caused by mutations in the thymidine phosphorylase (TP) gene. Gastrointestinal dysmotility is the most prominent manifestation, with recurrent diarrhoea and symptoms of obstruction. Patients with MNGIE present between the first and third decade (mean age 18 years) [64] and usually have a much reduced life expectancy and tend to die in early adulthood (mean 37.6 years; range, 26–58 years). It, like all mitochondrial defects, can be tested for by plasma and urine thymidine deoxyuridine, white cell thymine phosphorylase, the Tymp gene, MR brain scanning and muscle biopsy.

Autoimmune

Auto-antibodies directed at enteric neurons, usually neuronal ion channels (e.g. voltage-gated potassium channels) can occur as a paraneoplastic phenomenon, when the anti-neuronal nuclear antibody (ANNA-1 or anti-Hu) is most commonly found, and antineuronal antibodies can occur in non-paraneoplastic motility disorders [65–67]. Other auto-antibodies associated with dysmotility include acetyl cholinesterase receptor antibody (AchR) (ganglionic, nicotinic and M3 type), antibodies against the voltage gated potassium

channel-complex (VGKC-complex), voltage gated calcium channel antibodies (VGCC), smooth muscle and gonadotropin-releasing hormone (GnRH) [57]. The pathogenetic role of auto-antibodies is currently however unclear. Coeliac disease has also been implicated in some cases of dysmotility.

Infective

Both herpes (Epstein-Barr virus and cytomegalovirus) [68] and polyoma viruses [John Cunningham (JC) virus] [69, 70] have had their DNA isolated in the myenteric plexuses of some patients with visceral neuropathy. They may be causative agents rather than innocent bystanders, but this has yet to be proven. Chagas' disease (South American trypanosomiasis) typically causes a megaesophagus and megacolon. Chagas' enteropathy is common and gives rise to dyspepsia, intestinal pseudo-obstruction with bacterial overgrowth [71]. Lyme disease and botulism have also been reported as reversible causes of dysmotility.

Secondary Neuropathy

The neuropathic process may affect the nerves external (extrinsic neuropathy) to the gut and so indirectly affect gut motility or may be part of a generalised illness. Indeed, most cases of visceral neuropathy are part of a generalized neurological disorder rather than a primary neuronal disorder of the gastrointestinal tract.

Generalised Neurological Disorders

Disorders of the parasympathetic or sympathetic nerves that innervate the gut (including autonomic system degeneration and the neurological effects of diabetes mellitus (most common) and other endocrine or metabolic disorders) can indirectly cause gut dysmotility. Brainstem lesions, spinal cord injury, multiple sclerosis, Parkinson's disease (basal ganglia calcification) and leukoencephalopathy can all affect gut motility [72, 73]. A lymphocytic leiomyositis and myenteric ganglionitis have been described in the ileum of children with cystic fibrosis and distal ileal obstruction [74]. Myotonic dystrophy, multiple sclerosis, Parkinson's disease and porphyria may all be associated with an enteric neuropathy.

Paraneoplastic

Small cell lung cancer, carcinoid tumours, neuroblastoma and thymoma with anti-neuronal nuclear antibodies have all been described to cause an enteral neuropathy. There is often a dense inflammatory infiltrate of lymphocytes and plasma cells affecting both plexuses but mainly the myenteric (myenteric ganglionitis). Anti-Hu neuronal antibody is characteristic [75]. Removal of a thymoma may result in resolution of the dysmotility and the patient gaining weight. CRMP 5 (CV2) and AchR auto-antibodies have also been associated with paraneoplastic dysmotility and should prompt a careful search for occult malignancy [57].

Drugs/Toxins

Vincristine is directly neurotoxic and causes a visceral neuropathy. Anticholinergics (e.g. phenothiazines and tricyclic anti-depressants) have been associated with severe dysmotility. A case series of 102 life-threatening episodes of clozapine-induced gastrointestinal dysmotility episodes were collated with some evidence for dose dependence [76]. A number of other drugs have been associated with severe dysmotility, which, in most cases, improves with stopping the drug or reducing the dose; these include baclofen, buserelin, clonidine, fludaribine, phenytoin and verapamil. Lead poisoning can be a rare reversible cause [57].

Idiopathic

In the majority of patients and in most centres, the precise aetiology of chronic severe intestinal dysmotility is not characterised histopathologically and remains based on the clinical presentation, physiological testing and exclusion of obstructive and mucosal disease. This in part reflects a low uptake of full thickness biopsies outside of the context of stoma formation or other surgical intervention. In selected populations of PN dependent patients with dysmotility, high rates of full thickness biopsies were associated with high rates of neuromuscular abnormalities of which 2/3 were primary and 1/3 secondary causes, although not all biopsies yielded a diagnosis. The threshold and acceptability of full thickness biopsy testing, especially as most will not lead to a change in management, has not currently achieved consensus. There also remain some unresolved issues for gastrointestinal neuromuscular pathology standardisation and interpretation [57]. For the near future therefore it is likely that the aetiology in the majority of dysmotility patients will remain idiopathic.

Physiological Consequences of Severe Small Intestinal Dysmotility

Impairment of Coordinated Gut Contractions and the Migrating Myoelectric Complex

If the migrating myoelectric complex (MMC) is impaired, then the small bowel will not be cleared of debris predisposing to gut stasis and bacterial overgrowth. With enteric neuropathies gut co-ordination is disrupted and the presence of chyme in the small bowel can cause severe painful non-propulsive large contractions. This is one of the causes of abdominal pain shortly after eating.

Gut Stasis

The failure of forward propulsion may also cause constipation, and this is often the first symptom. Gut stasis results in abdominal distension and if much fluid accumulates (oral intake and normal gut secretions) it may produce a large volume vomit. The vomit may be faeculent and contain food debris from several days previously.

Bacterial Overgrowth and Malabsorption

The combination of a dilated gut with reduced propulsion and ineffective MMC allows anaerobic bacteria to proliferate in stagnant loops of bowel. This bacterial overgrowth results in bile salts being deconjugated, less effective secondary bile acids (e.g. lithocolic acid) being made and pancreatic enzyme degradation occurs so that steatorrhoea and malnutrition may occur. Associated with steatorrhoea is malabsorption of the fat-soluble vitamins A and E (less so D and rarely K) with deficiency symptoms (night blindness, poor colour vision, dry flaky skin and ataxia). Vitamin B_{12} may be malabsorbed but both folic acid and vitamin K can be manufactured by the bacteria and so may give rise to high serum levels.

Occasionally the bacteria can manufacture D-lactic acid (normally L-isomer) giving rise to D-lactic acidosis (high anion gap acidosis) and other bacteria can manufacture ammonia which may appear in high levels in the blood.

Small intestinal bacterial over growth (SIBO) is when excess micro-organisms are present in the small intestine and lead to a malabsorption syndrome with occasionally a protein losing enteropathy. Subtotal villous atrophy may be found on histology. There are several endogenous mechanisms for preventing bacterial overgrowth: gastric acid secretion, intestinal motility, intact ileo-caecal valve, intestinal immunoglobulin secretion and bacteriostatic properties of pancreatic and biliary secretions. The aetiology of SIBO is usually complex, associated with disorders of these mechanisms. In some patients more than one factor may be involved.

There is currently no gold standard for diagnosis of SIBO and the commonly available methodologies (the culture of jejunal aspirates and a variety of breath tests) are limited by large variations in their performance and interpretation [77].

Problems of Undernutrition

Patients who rapidly lose more than 10% of their body weight frequently have demonstrable physiological changes which include, skeletal and cardiac muscle weakness, poor concentration and mental function including memory, prolonged sleeping, reduced sexual function, a low body temperature and a propensity to develop infections which are potentially severe [78]. In the gut, malabsorption with mucosal atrophy, reduced gastric acid and pancreatic enzyme secretion and more bacterial colonization of the upper gut can occur though the experimental backing for this is inferred from studies in patients with anorexia nervosa [20–24].

Clinical Features of Chronic Small Intestinal Dysmotility and Management Plan

History, Examination and Blood Tests

The clinical history and examination should determine if there are associated systemic neuromuscular, connective tissue, or endocrine diseases (muscular diseases, neurological disease, storage diseases, systemic sclerosis, diabetes mellitus, irradiation etc.) and thus if the myopathy or neuropathy is a primary or secondary disorder. Exploring the family history will detect some congenital diseases as will asking about foreign travel (Chagas disease). Examination especially includes the neuromuscular system and testing for joint hypermobility. Autonomic neuropathy should be considered if orthostatic, pupillary or sudomotor (sweating) dysfunction accompanies dysmotility. Simple clinical bed-side assessment of orthostatic pulse rate change (lying to standing) may identify PoTs.

Symptoms need to be listed in order of importance to the patient, and a record made of all the drugs currently taken or that have been taken for long periods (especially opioids and cyclizine).

A basic nutritional assessment will include measuring the patient's height and weight and asking their usual weight in health and their weight change over the last 2 weeks, 3 and 6 months. From these their body mass index and percentage weight loss can be calculated. In addition, they are asked about recent changes in their food intake.

The ideal logical sequence in the diagnosis of these patients is:

- The confirmation that there is abnormally impaired transit of luminal content
- The identification of the region of the bowel that is affected
- The identification of the propulsive abnormality
- The identification of specific pathology.

A management plan is made, including tests to help make the diagnosis (Table 3). Blood tests will include routine blood count, renal (including potassium and magnesium), liver, bone chemistry, thyroid function, glucose, myeloma screen, anti-tissue transglutaminase (for Coeliac disease). Nutritional measures if undernourished or steatorrhoea include vitamin

Table 3 Management plan for small intestinal dysmotility

1. Determine and order the primary symptoms
2. Exclude mechanical obstruction (CT abdomen with oral contrast)
3. Evaluate other contributing factors: drug therapy (e.g. opioids, cyclizine and anti-cholinergics), psychosocial (may need formal psychological/psychiatric assessment) and quality of life issues
4. Nutritional assessment (BMI, percentage weight loss and other anthropometric tests)
5. Start nutritional treatment if necessary and consider/treat refeeding risks
6. Perform specific blood tests to help establish aetiology and consider tests of autonomic function
(a) Screen for hypothyroidism, coeliac disease and diabetes.
(b) Chest X-ray (or CT/PET CT) for *thymoma or other neoplastic conditions* (e.g. small cell carcinoma of lung)
(c) Antibodies for scleroderma (anti-centromere, anti Sc170, anti M3R) and other connective tissue disorders (ANA, ANCA, anti DNA, anti SMA)
(d) Antibodies that may be associated with paraneoplastic diseases (mainly small cell carcinoma and thymoma). These include type 1 anti-neuronal nuclear antibody (ANNA-1 "anti Hu"), anti-collapsin response mediator protein 5 (anti CRMP-5 also known as anti CV2), ganglionic acetyl cholinesterase receptor antibody (AChR antibody) especially if autonomic dysfunction [49], and anti-voltage gated potassium channel (VGKC)-complex antibodies
(e) Test for *mitochondrial disorders* with plasma and urine thymidine and deoxyuridine, WBC thymine phosphorylase. If there is a high suspicion then test for the TYMP gene and also screen for related diseases (e.g. "MELAS" (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes) with the m.3243A>G mutation). Muscle biopsy and sequencing of mitochondrial genome may be considered
7. Therapeutic plan/objectives of care to address patient's symptoms, nutritional status, psycho-social issues and quality of life
8. Try to establish a clinical diagnosis (or probable one). Perform physiologic assessment of the parts of the gastrointestinal (GI) tract that may be involved. These are done when nutritional status is near normal and the patient is off drugs likely to affect GI motility. Consider full thickness jejunal biopsy
9. Consider surgical options
10. Regular review and reconsider diagnosis as the clinical situation changes. Treat the predominant symptom/problem

A, E, D, INR, iron, ferritin. B_{12}, red blood cell folate, selenium, zinc and copper. Consideration is given to requesting auto-antibodies associated with connective tissue disorders and neoplasia (especially anti-neuronal antibodies) and tests for mitochondrial disorders.

In MNGIE (a mitochondrial disorder) direct evidence is provided by a plasma thymidine concentration greater than 3 μmol/L and a plasma deoxyuridine concentration greater than 5 μmol/L. Thymidine phosphorylase enzyme activity in leukocytes will be less than 10% of the control mean. Molecular genetic testing of TYMP, the gene encoding thymidine phosphorylase, detects mutations in affected individuals.

Rectal examination with an unprepared sigmoidoscopy will identify stool consistency and colour and permit biopsy for amyloid. Steatorrhoea will be detected, and constipation/diarrhoea confirmed. Basic tests of autonomic function include lying and standing systolic blood pressure and heart rate with electrocardiogram (ECG) confirmation.

Diagnosis made by radiology (contrast follow through, MRI and isotope studies), manometry and/or histology.

Myopathy

Symptoms include chronic abdominal pain, abdominal distension and bloating, early satiety, recurrent nausea and vomiting and alternating diarrhoea and constipation. Without treatment, weight loss and protein-energy malnutrition may ensue [78]. The symptoms in 28 patients with a probable enteric myopathy were abdominal pain (100%), distension (82%) nausea/vomiting (79%), constipation (61%) and diarrhoea (21%); weight loss occurred in 36%, 5 of whom were given parenteral support [39]. The vomiting may be faeculent and often of high-volume giving rise to a risk of pulmonary aspiration.

In hollow visceral myopathy (HVM) in addition to the features above patients have a very dilated small bowel. They may have urological complaints including bladder-emptying dysfunction [41–43]. Children with HVM may present at or before birth with hydronephrosis, megaureters and megacystis, or in the first year of life with constipation and episodes of intestinal pseudo-obstruction [41, 42]. The presence of digital arches on fingerprint, mitral valve prolapse, joint laxity and constipation before age 10 years all favour the diagnosis [72]. HVM may present at any age, but early adulthood is most common [44, 45].

Signs of autoimmune disease (arthropathy, Raynauds disease or proteinuria) may suggest a secondary myopathy, or the pseudo-obstructive syndrome associated with scleroderma may be declared by the cutaneous manifestations of this disease.

Neuropathy

Many of the features are the same as for a myopathy particularly with severe abdominal pain after food however abdominal distension is often absent and the plain abdominal radiograph may appear normal [79].

Radiological Tests

The diagnosis is usually first suspected after plain abdominal radiographs have shown a dilated small and large bowel. Once suspected, investigations aim to confirm that there is impaired transit of luminal contents, to identify the region of the bowel affected, ideally to identify the propulsive abnormality and to show a specific pathology [4]. Investigations help establish the presence of intestinal pseudo-obstruction and may delineate an underlying cause. In practice the diagnosis is often presumed after several laparotomies have excluded a physical obstruction, although computerised tomography/barium follow through/MR enterography

excluding a transition point in a diffusely distended small bowel suggests CIPO and may prevent unnecessary laparotomy. Computerised tomography (CT) may also help distinguish severe dysmotility from functional bloating due to abdomino-phrenic dysinergia [80]. Dynamic magnetic resonance imaging (MRI) of the small bowel is becoming increasingly helpful [81, 82] though is less established. MRI brain can be helpful in the diagnosis of MNGIE [55].

The measurement of whole gut time can be measured by serial X-rays of ingested radio-opaque markers (small lengths of barium-impregnated polyvinyl tubing).

Small bowel transit using a barium follow-through examination will usually give some indication of accelerated or delayed transit and a dilated duodenal loop (megaduodenum) may be one of the earliest signs of visceral myopathy [4]. In addition in HVM there may be oesophageal aperistalsis and variable dilatation of the small and large bowel.

Radioisotopic Investigations

Gastric emptying can be measured using gamma scintigraphy to obtain serial images of labelled solid (scrambled eggs, liver or pancake), semi-solid (thick soup) or liquid (orange juice) meals in the stomach. Gastric emptying measurements may be helpful in determining whether the stomach is involved in a generalised disorder of propulsion or a localised one (e.g. Chagas' disease). These isotopic meals can be extended to measuring the transit of the meal through the small bowel and if the isotope has a long half-life oro-caecal and colonic transit may be determined. Liquid meals may not clearly demonstrate an abnormality.

Endoscopic Tests

Jejunal aspirate for bacterial overgrowth is infrequently performed but usually by endoscopy (or fluoroscopy with jejunal intubation). A clinically significant overgrowth is when counts exceed 10^5/mL (usual is less than 10^4/mL). Common species include bacteroides, enterooccus and lactobacillus. But most of the bacteria likely to be relevant in causing symptoms cannot be cultured. Endoscopy also has a role in mucosal sampling and palliative venting. Capsule endoscopy examination can rarely give transit information but is seldom used due to the risk of the capsule being retained and some regard it as contraindicated.

Non-invasive Investigations of Gut Transit

Orocaecal transit can be measured using the rise in breath hydrogen due to the degradation of ingested polysaccharides (e.g. lactulose), in health this is caused by caecal bacteria fermenting the ingested agent but this is unhelpful if there is propulsive failure as small bowel bacterial overgrowth is common and is not a recommended test for this application [83, 84]. It is also unhelpful following a significant small bowel resection or if there is an enteric fistula.

Breath tests to diagnose bacterial overgrowth may be misleading and produce false negative results compared to culture of small bowel aspirate [77, 85]. This has in part been due to broad variations in how these tests are performed and interpreted. Recent work in the UK and US has taken place to develop evidence based consensus guidelines for breath testing in terms of dose of substrate (75 g glucose, 10 g of lactulose) and cut off values. In addition, whilst hydrogen only breath testing was previously used, modern testing protocols have incorporated the measurement of methane. Increased intestinal methane levels have been associated with delayed small bowel transit as measured by scintigraphy and therefore should be measured in patients with suspected small bowel dysmotility to improve the tests utility [85]. Other tests that may indicate bacterial overgrowth include raised urinary indicans, blood D-lactate or alcohol levels.

Manometry

Intraluminal pressure sensors incorporated into a catheter can detect the patterns of contractile events. For the diagnosis of pseudo-obstruction, the logical investigation is small bowel manometry. Small bowel motor activity was initially studied using multi-lumen perfused tube systems, with a pump and strain gauge transducers external to the patient [86]. This gave information on motor activity in the antrum and proximal duodenum, and detected abnormal motility [87] and some types of pseudo-obstruction [88, 89]. This technique required the patient to remain in a laboratory attached to a machine for more than 6 h and was not good at recording fasting, and postprandial activity (Fig. 5) [90].

An alternative is the wireless motility capsule (WMC) which is an ambulatory, minimally invasive diagnostic modality that allows continuous assessment of intraluminal pH, temperature, and pressure during its transit through the gastrointestinal tract. The technology allows for both measurement of transit times in multiple regions of the upper and lower gastrointestinal tract, as well as pressure profiles in the antro-duodenum. The standardised equipment and procedures in WMC allow the comparisons of data across multicenters. The role of the technology has been best established in the evaluation of a large number of healthy volunteers [91] and in patients with suspected gastroparesis and suspected chronic constipation. The worry with this is technique in these patients is that the capsule may remain in the bowel and not be passed. However, a paper in patients with Crohn's disease has shown that the same precautions used when considering patients for capsule endoscopy (i.e. clinical and radiological assessment and use of a patency capsule) can mitigate much of the risk in potential WMC patients [92].

Twenty-four hour ambulatory jejunal manometry [93] uses a catheter with built-in miniature strain gauge transducers [94] and records data to a solid-state digital recorder [95].

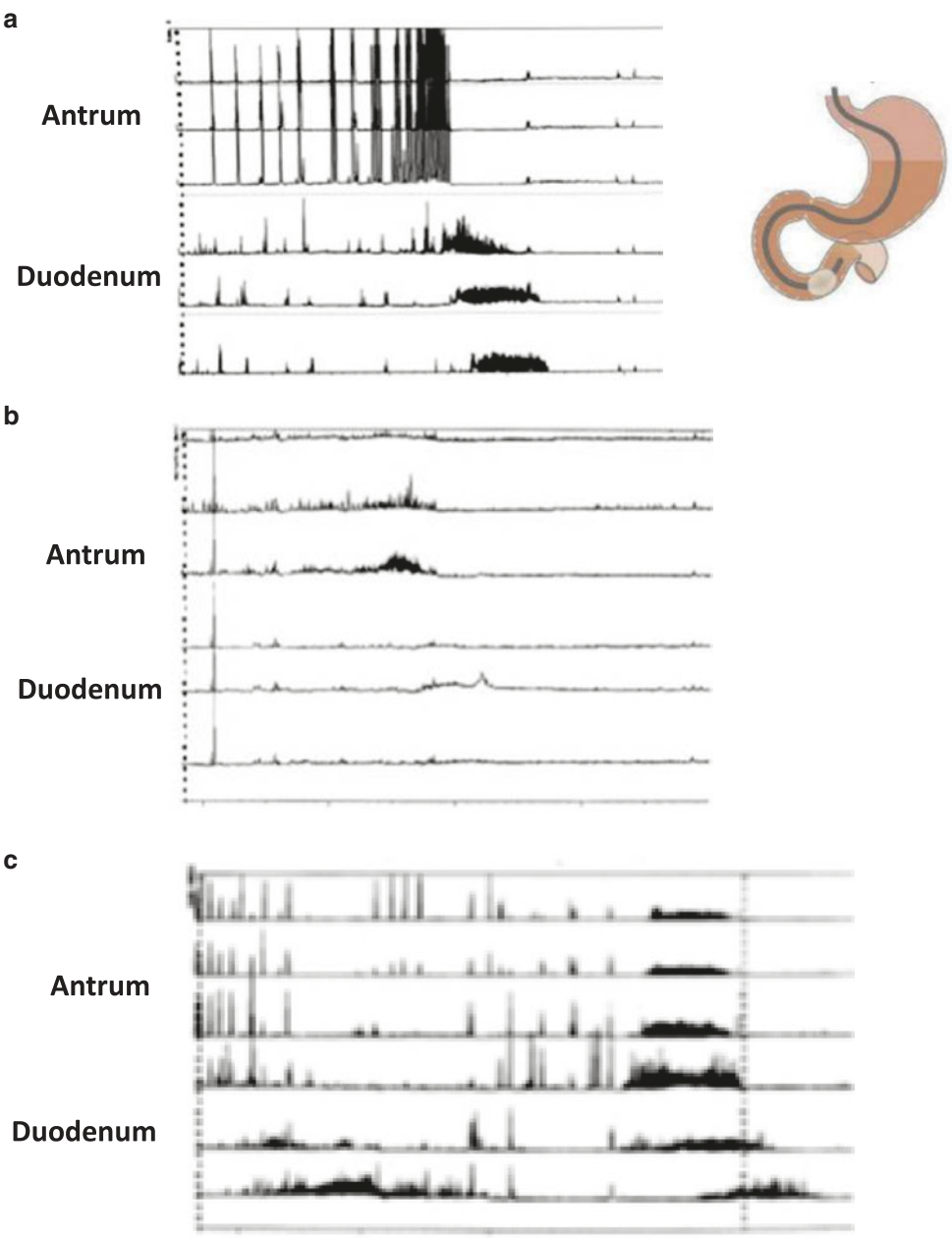

Fig. 5 (**a**) Fasting antro-duodenal motor activity from a control subject. Simultaneous recording of antral (top three channels) and duodenal (lower three channels) motor activity demonstrates the sequential phases of the Migrating Motor Complex (MMC). The sequence begins, on the left, with phase II, irregular activity, is followed by phase III a period of uninterrupted phasic activity which migrates along the intestine and finishes with phase I, motor quiescence. (**b**) Recording from a patient with a visceral myopathy, at a similar moment in an MMC cycle as in (**a**); in this instance, however, the amplitude of individual contractions in the antrum (top two channels) and the duodenum (bottom four channels) is markedly reduced through the organization of motor events is preserved. (**c**) Recording from a patient with a visceral neuropathy, again taken at a similar moment in the MMC cycle. The tracing features intense but apparently uncoordinated motor activity. In this example the phase III seen in the middle of the trace appears bi-directional in propagation and is not followed by the expected quiescence of phase I; the tracing also contains a phase III-like burst during what should be phase II and repeated bursts of intense contractile activity

The digital encoding of pressure data simplifies the analysis of continuous 24-h recordings by computer software [96, 97]. This technique has proved useful in several conditions [98, 99] including pseudo-obstruction. During nocturnal sleep normal stereotypic MMC activity is clearly evident [100] and in some patients with pseudo-obstruction the abnormal contractile activity of the small bowel results in distortion of the fasting MMC pattern. Manometry of patients with pseudo-obstruction can be difficult in the later stages of disease because the peristaltic activity required to propel a manometry catheter into position in the proximal jejunum is lacking, and endoscopic assistance may be needed. A patient with a neuropathy may have a normal diameter gut but it may be hyperactive with many uncoordinated and often strong contractions (bursts) [89].

The effect of any drugs the patient may be taking must be taken into account in interpreting any results (for example opioids, anticholinergics and cyclizine). Manometry does not always produce results that are clinically helpful [89].

Pathology and Histology

The biochemical testsrecommended are listed in Table 3. Adequate biopsy material is not often available and few laboratories have an experienced gastrointestinal neuropathologist. There also remain some additional pitfalls for collecting and analysing samples including sampling error, effects of

bowel handling, sparsity of normal data and specificity. Good histological samples are needed to make a firm diagnosis. Close liaison between surgeon and pathology laboratory is crucial so that a full thickness specimen of bowel is immediately processed. The samples should be divided; in an ideal situation some is snap-frozen in liquid nitrogen, and the main portion fixed for routine histology and electron microscopy, in practice the latter two may be the best option. The immediate processing of samples is important if a detailed examination of the nerves, ganglia and muscle tissue is to be carried out. Diagnosis of a neuropathy may be difficult in conventionally oriented and stained sections of gut, and whole mount plexus assessment is a research tool. The most important element is to ensure that enough sections and material is examined, in a centre with experience of dysmotility.

A full thickness jejunal biopsy is usually taken laparoscopically and is often helpful diagnostically but the procedure in centres without much experience can be unhelpful and have a significant risk. Published data from centres with expertise suggest a median operating time of 50 min, conversion rate to open operation 2% and length of stay 1 day with an 8% readmission rate for obstructive symptoms [101]. In myopathies the diagnosis may be established. A neuropathy in general shows either degenerative changes or inflammation.

All full thickness biopsies should be stained with Congo red stains to look for the presence of amyloid. As full thickness jejunal biopsies may not change the clinical management and are associated with risks, they are often performed when a laparotomy does not find an organic cause of obstruction or when the patient happens to be undergoing surgery for another reason (e.g. a jejunal tube placement) [102].

MNGIE can be diagnosed with a skeletal muscle biopsy in addition to the blood and genetic testing.

Treatments

The drug treatments for intestinal dysmotility are shown in Table 4. Most of the drugs are commonly used to treat milder forms of the symptoms. Treatment is occasionally directed at the underlying condition but more often is targeted at a specific symptom.

Underlying Condition

An underlying disease may need to be treated (e.g. connective tissue disorder, enteric myositis, neoplastic disease or myotonic dystrophy). Diabetic control should be very good and may necessitate an insulin pump. Electrolyte, mineral or endocrine abnormalities should be prevented and treated when detected.

Immunosuppressive treatment has a small evidence base restricted to case series or reports. Prednisolone and cyclosporin have been reported to be of particular benefit in autoimmune myopathy [103]. There is a case report of an improvement with initially prednisolone 1 mg/kg and azathioprine 2 mg/kg/day then subsequently the prednisolone was replaced with budesonide 9 mg/day [50].

Table 4 Drug therapies for intestinal dysmotility

Laxatives (after adequate fluid in diet)	
Osmotic	Macrogols (PEG), lactulose, magnesium salts
Stimulant	Anthraquinone group (senna and dantron), bisacodyl, sodium picosulfate, docusate sodium, phosphate enema, glycerol suppository parasympathomimetics—bethanechol, neostigmine, pyridostigmine $5HT_4$ receptor agonists—prucalopride
Bulk forming	Unprocessed wheat bran, methylcellulose, ispaghula, and sterculia
Faecal softeners/ lubricants	Liquid paraffin, arachis oil (ground-nut oil, peanut oil) enemas
Peripheral opioid-receptor antagonists	Methylnaltrexone, naldemidine
Secretagoges	Linaclotide, tenapanor[a]
Antispasmodics	
Antimuscarinics	Tertiary amine—dicycloverine hydrochloride
	Quaternary ammonium compounds—propantheline bromide, hyoscine butylbromide
Direct smooth muscle relaxant	Alverine, mebeverine, and peppermint oil
Prokinetics	
Dopamine receptor 2 antagonists	Metoclopramide, domperidone
Macrolides	Erythromycin
Antidiarrhoeal drugs	Loperamide, codeine phosphate, diphenoxylate
Anti-emetics	D_2 receptor antagonists (see above)
	Cyclizine, ondansetron, romosetron[a]
Analgesics	Tricyclic antidepressant (low dose)—amitriptyline
	Selective serotonin reuptake inhibitor
	SNRI (duloxetine)
	Gabapentin
	Pregabalin
	Antispasmodic drugs
	Opioids (low dose)
Antibiotics for bacterial overgrowth	Amoxycillin-claevulinic acid
	Ciprofloxacin
	Metronidazole, tinidazole
	Cephalosporin
	Tetracycline, doxycycline
	Non-absorbable antibiotics—rifaxamin, neomycin

[a]Not licensed in the UK

There must always be awareness that organic obstruction can be missed as a diagnosis and if a prokinetic drug [104] makes pain worse then an organic obstruction must be considered. Similarly, a successful trial of a low fibre or liquid diet suggests an organic obstruction.

Some metabolic storage disorders can be treated with specific enzyme-replacement therapy [59].

Specific Drug Treatments of Symptoms

No treatment is ideal and even though some help to correct physiological abnormalities, they may not affect the patient's symptoms. Drug therapy [105] can be difficult and often drugs with conflicting actions are used (prokinetic for constipation and anticholinergic for colicky pain). Essentially the drug therapy is targeted at the symptom perceived as most important by the patient (Table 4).

Prokinetic treatments are used to try and improve the dysmotility itself and can return some of the measured abnormalities towards normal. They may especially help with vomiting and constipation. Prokinetic drugs are generally not used after a bowel anastomosis. Some of the previously used prokinetic drugs have been withdrawn or can only be used with extreme caution. They include domperidone and metoclopramide (D_2 dopamine receptors antagonists) which stimulate gastric emptying and small intestinal transit, and enhance the strength of oesophageal sphincter contraction. Metoclopramide also increases the release of acetylcholine from some enteric nerves. Domperidone is a selective antagonist of peripheral D_2 dopamine receptors, which does not have the acetyl-choline like effect of metoclopramide. *National Patient Safety Agency* (NPSA) alerts have been issued for Domperidone that highlighted problems with prolonged QTc therefore long-term use should be subject to QTc monitoring. The extra-pyramidal side-effects of metoclopramide (especially in children) and the potentially irreversible tardive dyskinesia in the elderly, together with no evidence of consistent benefit in gastroparesis, caused the European Medicines Agency's Committee to recommend that metoclopramide is not used in the long-term [106]. Cisapride, a 5-HT_4 agonist, enhances acetylcholine release in the myenteric plexus without having anti-dopaminergic effects and may have been of particular benefit if MMCs were present on small intestinal manometry. In a 6 week double-blind, placebo-controlled trial in 26 patients, cisapride helped abdominal pain, improved solid gastric emptying and the MMC [104]. Unfortunately, due to an increased risk of fatal cardiac arrhythmias (probably relating to a prolonged QT interval) in patients taking other medications or suffering from underlying conditions known to increase the risk of cardiac arrhythmias, cisapride was withdrawn. Tegaserod, a 5-HT_4 receptor partial agonist, increased stool frequency in IBS [107, 108] and improved the symptoms in functional dyspepsia [109] but was withdrawn due to an increased risk of heart attacks or strokes.

Prucalopride, a high affinity selective $5HT_4$ receptor agonist has been used for constipation and appears not to have the cardiac risks of cisapride or tegaserod as it does not affect the QT interval. This is by having no significant action on the 5-$HT_{1B/D}$ and on the cardiac human ether-a-go-go K+ channels [110].

Erythromycin, a motilin agonist, is potentially useful [111] if there are absent or impaired antroduodenal migrating complexes but is subject to tachyphylaxis. Doses of 900 mg/day have been recommended [112]. Azithromycin may be more effective for small bowel dysmotility [113].

A somatostatin analogue (octreotide), is given by a relatively painful subcutaneous injection, may be dramatically beneficial, especially in systemic sclerosis when other treatments have failed [114–116]. It can improve vomiting and pain, partly because octreotide (in normal subjects) reduces the perception of volume distension due to inhibition of sensory afferent pathways [114]. Octreotide may cause low amplitude MMC's to return [116]. Octreotide may have a beneficial effect when erythromycin has been unsuccessful; its effect (50–100 μg once or twice a day) is apparent within 48 h and lasts for more than 2 years. It may be more effective when combined with erythromycin [117].

The parasympathomimetics bethanechol, distigmine, neostigmine, and pyridostigmine enhance parasympathetic activity in the gut and increase intestinal motility. They are rarely used because of both their gastro-intestinal and cardiovascular side effects (diarrhoea and severe bradycardia). Pyridostigmine has however been shown to help refractory constipation (including in diabetes) and was well tolerated using a stepped dosing regimen [118, 119].

Naloxone 1.6 mg given subcutaneously each day, or methylnaltrexone subcutaneously alternate days may be beneficial in blocking dysmotility effects of opioids or in improving motility through blocking endogenous opioids [120].

Constipation

Constipation may be a problem in early stages, but is rarely present when IF occurs. In the early stages of these diseases' constipation may be managed by diet ensuring that it includes an adequate intake of fibre and fluid. Bulk forming laxatives such as unprocessed wheat bran (or oat bran), taken with food or fruit juice are effective and methylcellulose (which is also a faecal softener), ispaghula, and sterculia are useful in patients who cannot tolerate bran.

Osmotic laxatives [macrogols (polyethylene glycol), lactulose, or magnesium salts] increase the amount of water in the large bowel, either by drawing fluid from the body into the bowel or by retaining the fluid that was adminis-

tered. Macrogols are inert polymers of ethylene glycol (PEG) which sequester fluid in the bowel. Lactulose is a semi-synthetic disaccharide, which is not absorbed from the gastro-intestinal tract. It produces osmotic diarrhoea of low pH and prevents the proliferation of ammonia-producing organisms. Magnesium salts are useful where rapid bowel evacuation is required. Sodium salts should be avoided as they may give rise to sodium and water retention.

If there is an inadequate response to an osmotic laxative, a *stimulant laxative* can be added. Stimulant laxatives increase intestinal motility and often cause abdominal cramp; they should be avoided in intestinal obstruction. Excessive use of stimulant laxatives can cause diarrhoea and hypokalaemia. The anthraquinone laxatives (senna, dantron, cascara) are converted in the intestine to active sennosides, which may function by stimulating the myenteric plexus in the colon and by inhibiting colonic water absorption. Their principal effect is in the descending and sigmoid colon. Their effect is largely local and depends upon sufficient intestinal motility to present them to the colon for bacterial degradation to their active form. Sennosides, with prolonged use, had been thought to damage the intestine muscle and or myenteric neurons but there is no clinical or animal evidence to support this [121, 122]. Poorly absorbed diphenylmethane derivatives (bisacodyl, phenolphthalein, sodium picosulfate) stimulate sensory nerves in the proximal colon and increase sodium and water movement into the colonic lumen. Castor oil can have a place with its principal effect on small bowel fluid secretion. Docusate sodium probably acts both as a stimulant and as a softening agent.

Dantron, cascara and castor oil are rarely used, dantron because of potential carcinogenicity.

$5HT_4$ receptor agonists (Prucalopride) are selective serotonin $5HT_4$ receptor agonists with prokinetic properties. Prucalopride is licensed for the treatment of chronic constipation, when other laxatives have failed to provide an adequate response. Headache and gastro-intestinal symptoms (including abdominal pain, nausea, and diarrhoea) are the most frequent but rare side-effects. The side-effects generally occur at the start of treatment and are usually transient. It has the potential to be a useful prokinetic drug now that cicapride and tegaserod have largely been withdrawn. Linaclotide (a 14-amino acid peptide) which acts in the intestinal lumen on guanylate cyclase-C (GC-C) so generating cyclic guanosine monophosphate (cGMP), which stimulates chloride secretion, resulting in increased luminal fluid secretion and an acceleration of intestinal transit. It also may have some visceral analgesic activity.

Methylnaltrexone is a peripherally acting mu-opioid-receptor antagonist that is licensed for the treatment of opioid-induced constipation in patients receiving palliative care, when response to other laxatives is inadequate; it should be used as an adjunct to existing laxative therapy. Methylnaltrexone does not alter the central analgesic effect of opioids. Naloxegol and naldemidine are oral agents and have the same properties.

Faecal softeners (Liquid paraffin), the traditional lubricant, has potential disadvantages of minimal efficacy (hence usually used in combination with other agents) and safety issues (aspiration of paraffin or, perianal burning). Bulk laxatives and non-ionic surfactant 'wetting' agents (docusate sodium) also have softening properties. Enemas containing arachis oil (ground-nut oil, peanut oil) lubricate and soften impacted faeces and promote a bowel movement. Dioctyl sulfosuccinate, an anionic detergent, can be used to break down hard stools.

Stimulant suppositories (glycerol) or enemas (phosphate) may also be effective though are often less acceptable to the patient. Glycerol suppositories act as a rectal stimulant by virtue of the mildly irritant action of glycerol. Constipation may need regular enemas initially using low volume phosphate preparations progressing to high volume saline washouts or trans-anal irrigation systems.

Treatment of faecal impaction may need a manual evacuation under anaesthetic if disimpaction does not occur after oral and rectal treatment, or if there is a megarectum. The outcome of colectomy +/− ileorectal anastomosis is poor for these patients and best avoided. Sometimes a defunctioning loop ileostomy, which is reversible, may be performed before considering a total colectomy.

Pain

Pain is often poorly correlated with motor events (chapter "Chronic Abdominal Pain"). A simple measure such as reducing fibre in the diet can reduce abdominal distension by reducing bacterial fermentation and the production of gases. Low FODMAP diets may also have a role but are restrictive in nature and should not be used in an already malnourished individual. Peppermint oil may also help.

Anti-muscarinics that are used for gastro-intestinal smooth muscle spasm include the tertiary amine dicycloverine hydrochloride and the quaternary ammonium compounds propantheline bromide and hyoscine butylbromide. The quaternary ammonium compounds are less lipid soluble than atropine and are less likely to cross the blood–brain barrier; they are also less well absorbed from the gastro-intestinal tract. Dicycloverine hydrochloride has a much less marked anti-muscarinic action than atropine and may also have some direct action on smooth muscle. Hyoscine butylbromide is advocated as a gastro-intestinal antispasmodic and is commonly tried, but it is poorly absorbed, therefore intramuscular preparations may be more effective and can be used in the long-term at home [123].

Direct relaxants of intestinal smooth muscle (alverine citrate, mebeverine, and peppermint oil) that may relieve

pain in irritable bowel syndrome are commonly tried and have no serious adverse effects.

Persistent abdominal pain may be a major problem and its mechanism may include central nervous system sensitisation making it very difficult to treat. Features of neuropathic pain should be sought and managed with neuropathic agents. Opioid induced hyperalgesia as part of the narcotic bowel syndrome can also develop and needs appropriate management by opioid reduction and withdrawal. If other analgesics prove ineffective opioids and their derivatives may be cautiously tried though they themselves have pro-absorptive/antisecretory effects and cause slowing of intestinal transit. Some opioids, such as tapentadol, may have a better dysmotility side effect profile. Targinact® (oxycodone and naloxone combined) is marketed as a way of giving analgesia without causing constipation. A small amount of naloxone crosses the blood brain barrier to block the dependence action of oxycodone though when first used may precipitate some withdrawal symptoms from the previous opioid like drug. Naloxegol is a PEGylated naloxone formulation not combined with opioid and therefore should not cross the blood-brain barrier, owing to the PEGylation, to minimise withdrawal side effects.

Oral liquid preparations may be used but sublingual or transdermal buprenorphine or fentanyl has the advantage of bypassing the abnormal gut function. It may be of value to give a patient a "pain holiday" in hospital during which sedation and continuous subcutaneous opiates, or even epidural anaesthesia, may reduce the pain threshold so allowing a reduction in maintenance analgesic dosage. Escalation beyond a low dose of opioid is likely to be ineffective in managing chronic pain and is associated with unacceptable risks, including catheter related blood stream infections, and should be de-escalated or discontinued if the chronic pain persists, even if no other effective pain medication is available [124].

There is a growing appreciation for the role in abdominal pain management of the gut-brain neuromodulators, frequently used in neuropathic pain management [125]. These include a tricyclic agent which can be used at sub-antidepressant doses for abdominal pain or discomfort in patients who have not responded to laxatives, loperamide, or antispasmodics. Low doses of a tricyclic antidepressant are used (e.g. amitriptyline, initially 5–10 mg each night, increased if necessary in steps of 10 mg at intervals of at least 2 weeks to max. 30–50 mg each night). A selective serotonin reuptake inhibitor (SSRI) may be considered in those who do not respond to a tricyclic antidepressant but they are considered to be less effective analgesics than the serotonin-norepinephrine reuptake inhibitors (SNRIs), of which duloxetine is the first choice [126]. The role of gabapentin and pregabalin is well established for chronic neuropathic pain, and there is emerging evidence that the use of combination gut-brain neuromodulators from more than one class is more effective than monotherapy although gabapentin and pregabalin are classed as controlled drugs in some countries including the UK [125, 127]. SNRI and SSRI classes however should not be combined due to risks of serotonin syndrome.

Vomiting

Now that domperidone and metoclopramide are no longer used in the long-term and as cyclizine can cause psychological dependence and addictive behaviour [16], the 5-HT_3 antagonists like ondansetron are most commonly used but can result in constipation.

If a naso-gastric draining tube helps symptoms, then a venting gastrostomy (ideally over 20 *French gauge* (FG)) usually inserted endoscopically (though may also be done radiologically or surgically) may reduce vomiting by decompressing the stomach. The difficulty is having a large enough gastrostomy tube to allow all debris from the stomach to drain. Sometimes a tube can be inserted into the small bowel if very dilated to decompress it. These venting ostomies are often successful but are associated with many complications such as leakage and infection (often with candida) and generally need to be changed more regularly than a feeding ostomy.

Diarrhoea: Bacterial Overgrowth and Bile Salt Malabsorption

Antidiarrhoeal drugs such as loperamide, diphenoxylate, or rarely codeine phosphate are very occasionally used for symptomatic benefit. Opioids with a central action, such as codeine, are not the first choice because of the risk of dependence and sedation.

Steatorrhea may be secondary to an overgrowth of anaerobic bacteria in the motionless dilated loops of bowel.

As the disease progresses bacterial overgrowth can result in diarrhoea. This can be reduced with oral amoxycillin-claevulinic acid combination, metronidazole/tinidazole, cephalosporin, tetracycline (doxycycline), ciprofloxacin, cotrimoxazole, or non-absorbable antibiotics such as rifaximin or neomycin. Rifaxamin is often the first choice if it is on the local drug formulary. These may be used as necessary or in repeated courses every 2–6 weeks often rotating (sometimes with a 1–2 week period of no antibiotic) to another antibiotic for a similar period of time before repeating. If metronidazole is used in the long-term, the patient must be warned to stop if they develop numbness or tingling in their feet as an early sign of reversible peripheral neuropathy and be used at the lowest dose possible. Ciprofloxacin use longer term can cause tendonitis and rupture and again low dose and vigilance are required. The risk of resistant organisms, including *Clostridioides difficile*, should also be considered. There is no data currently about the use of probiotics.

Bacterial overgrowth is virtually inevitable and can cause cachexia without necessarily causing diarrhoea, thus antibiotics, as suggested above, may be needed.

Bile salt malabsorption may occur and respond, if tolerated, to bile salt sequestrants (cholestyramine and colesevelam). It is most likely if terminal ileum has been resected or if there are large areas of fluid filled dilated bowel.

Octreotide occasionally used for its effects in reducing secretions and slowing gastrointestinal motility, has also been used in refractory SIBO.

Bloating/Distension

Bloating and distension are common symptoms and not easy to treat. Reducing gas forming microbes (e.g. those producing CO_2, methane and hydrogen sulphide) with a low fibre diet or an antibiotic (rifaxamin), giving simethicone or peppermint oil or reducing visceral hypersensitivity (antidepressants) or constipation may help along with increasing physical exercise [126].

Neuromodulation (Pacemakers)

There is some limited evidence for Gastric electrical stimulation (gastric pacing) to improve vomiting symptoms where gastroparesis is prominent and small bowel function relatively intact [128–130]. Patients with diabetic gastroparesis respond best and in general responders tend to have more severe vomiting. Patients with idiopathic gastroparesis have a potentially higher rate of poor response to gastric electrical stimulation [131]. Non-invasive vagal nerve stimulation has shown some promise both for improving gastro-duodenal motility and reducing pain sensitivity [132].

The dorsal column pathways are involved in the transmission of visceral pelvic pain. Spinal cord stimulation suppresses the visceral response to colon distension in an animal model and therefore may be an effective therapy for chronic pelvic pain of visceral origin. There has been success reported in one study of 35 patients in whom the catheter tip was situated at T5 position for a median of 9 days (range 4–14) [133], the Cochrane database concludes that more studies are needed [134].

Sacral nerve stimulation (SNS) uses electrical stimulation applied to the sacral nerves, eliciting a physiological effect on the lower bowel, anal sphincter and pelvic floor and has shown some success in treating faecal incontinence and constipation [135–137]. A Cochrane review concluded that from three studies there was "very limited evidence that sacral nerve stimulation can improve continence in selected people with faecal incontinence, and reduce symptoms in selected people with constipation" and larger "good quality randomised crossover trials are needed" [138]. There is no evidence that SNS helps any of the symptoms in patients with chronic intestinal pseudo-obstruction.

Small intestinal electrical stimulation is at an experimental stage.

Nutritional Support

Nutritional assessment and support is an important aspect of management. With appropriate therapy, many patients with chronic intestinal pseudo-obstruction manage to maintain their nutritional status through the oral/enteral route, without the need for parenteral support.

Dietary Adjustments/Fluid Management

Gastric motility may be far less deranged for liquids than for solids with the result that many patients tolerate liquid feeds better than solid meals. Sometimes frequent small meals with a low-fat, low-fibre and liquid nutritional supplements may be helpful.

If the patient has a stoma and a short bowel, fluid restriction, a sipped glucose saline solution, use of loperamide sometimes in high dose (occasionally with the addition of codeine phosphate) will reduce the risks of dehydration, sodium and magnesium depletion. If a high net secretory output occurs, a proton pump inhibitor (or occasionally octreotide) may be needed [139].

Post-feeding orthostatic symptoms in partial autonomic failure may respond to dietary adjustments and drugs such as fludrocortisone, midodrine and octreotide.

Vitamin/Mineral Deficiencies

Care is needed to ensure that micronutrient deficiencies particularly of iron, vitamin B_{12} and the fat-soluble vitamins, especially vitamin A, D and E, do not occur. Magnesium deficiency is common especially if a high output stoma. Magnesium oxide may cause less osmotic effects than other preparations but is expensive.

Bone mineral density is important to address and should be assessed with dual energy X-ray absorptiometry (DEXA) scanning in those with malnutrition. For patients who cannot take oral measures to improve bone density then parenteral bisphosphonates such as zoledronate should be considered.

Enteral Nutrition

Enteral nutrition is preferred if the gut is accessible and absorbing. In carefully selected patients, feeding jejunostomy with or without decompression (venting) gastrostomy may be tried. A percutaneous endoscopic or radiological gastro-jejunostomy is preferred to a direct jeunostomy where possible as direct jejunostomy tubes are more subject to leakage, retention, pain and skin problems and the gastro-

jejunostomies can achieve both post-pyloric feeding and venting with generally easier endoscopic placement whereas direct jejunal tubes will often need to placed surgically. Invasive enteral tube insertion should be preceded where possible by a trial of naso-enteral tube feeding to ensure absorption and tolerance prior to running the risks of mortality and morbidity associated with invasive tube placement.

If liquid enteral feeds are given, any excess can be aspirated by enteric tube or gastrostomy before the start of the next meal to ensure that excess volumes do not accumulate in the stomach. Gastrostomies can be used, therefore, to aspirate liquid gastric contents (decompression of venting gastrostomy) as well as a conduit for feeding, particularly when there is a need to bypass a malfunctioning oesophagus and or stomach. Pulmonary aspiration of large volume vomits is a very serious complication that may be difficult to prevent. A low antral site for gastro-jejunal tube placement is preferred to optimise drainage/venting and stability of the jejunal extension.

Parenteral Support

Long term parenteral support (PS) should be reserved for patients with significant malnutrition or electrolyte disturbance who cannot tolerate enteral nutrition. Complications associated with total PS include infections, sepsis, and cholestatic hepatic dysfunction.

If safe nutritional status cannot be maintained through the oral and enteral route, then home parenteral support (HPS) may be required. These patients, when receiving HPS, have more problems than do patients with a short bowel [102]. They particularly have a higher incidence of catheter-related blood stream infection (CRBSI), septicaemia and venous thrombosis. The reasons for this are not entirely clear. Procoagulation states sometimes exist, and it is possible that there is increased bacterial translocation from the gut. Opioid medication (which at high doses suppresses some aspects of immune function) and/or cyclizine increase the risk of CRBSI partly as the care taken by the patient in the management of their infusions at home [140], due to cognitive effects, is reduced. The use of feeding lines to administer any drug is to be strongly discouraged because of the risk of catheter infection. Such patients test the capabilities of the best-organized nutrition teams to the full and should be managed in centres with a large experience [141]. Vigilance for psychopathology and ongoing involvement of psychology and liaison psychiatry should be offered. There may be a benefit from the mutual support patients can give to each other in these situations, although patients with significant psychopathology can have a detrimental effect on others.

Howard et al. [142] have emphasized that clinical outcome on home parenteral feeding, like mortality risk, is to a large extent a reflection of the underlying condition. While about 70% of patients with Crohn's disease or ischaemic bowel conditions are fully rehabilitated after the first year on HPN, only a third of those with chronic intestinal dysmotility are similarly rehabilitated and it is most likely if the gut is not dilated [98]. Weaning from HPN is less likely when the diagnosis is idiopathic dysmotility [95, 102] and when the post-absorptive plasma citrulline is lower than 20 mmol/L [143] Impairment of strength and of wellbeing as a result of undernutrition and fluid and electrolyte imbalance will be corrected by HPN but if the patient continues to experience vomiting, diarrhoea or abdominal pain from the underlying condition quality of life will remain suboptimal. The annual risk of catheter-related sepsis among HPN patients is consistently around 0.5 per 1000 catheter days but tend to be higher among those with chronic pseudo-obstruction especially if they remain on opioid analgesia [102, 144]; by contrast, patients with systemic sclerosis who may tend to have lower opioid requirements, have lower catheter infection rates [145].

Over half those with pseudo-obstruction receiving HPN will be alive at 10 years [146].

Surgical Options

Surgery is to be avoided in this group of patients who are at high risk of iatrogenic injury; however judicious palliative surgical intervention [resection, bypass (Fig. 6) or stoma formation] can improve symptoms and quality of life [147, 148]. If constipation is difficult to manage and high-volume saline washouts are needed then colectomy with ileorectal anastomosis or ileostomy may be necessary but diarrhoea or continuing episodes of obstruction may remain a problem. Adhesiolysis in the absence of a clear focal obstruction carries a high risk of severe complications and morbidity with ultimately more adhesion recurrence and worsening pain. Often urology input is needed to help with neuromuscular disorders of the urinary tract (dilated ureters and bladder) and may need to insert stents and/or a supra-pubic catheter. Especially in women there may be fertility problems due to dilated non-functioning fallopian tubes. Often the pains experienced result in gynaecological referrals.

Bypass Surgery and Enteric Resections

There are several reports of surgery in adults to help patients with pseudo-obstruction though the clear separation into those with a myopathy and those with a neuropathy is not always made [89, 147]. After diagnostic laparotomy, bypass operations (gastroenterostomy, duodeno-jejunostomy and jejuno-enterostomy) can be performed in adults to reduce vomiting if there is dilated gut. If gastric surgery is being performed, a vagotomy must be avoided, as this will further retard gastrointestinal transit. Many have an ileostomy [54, 89] often to treat constipation and some develop a short

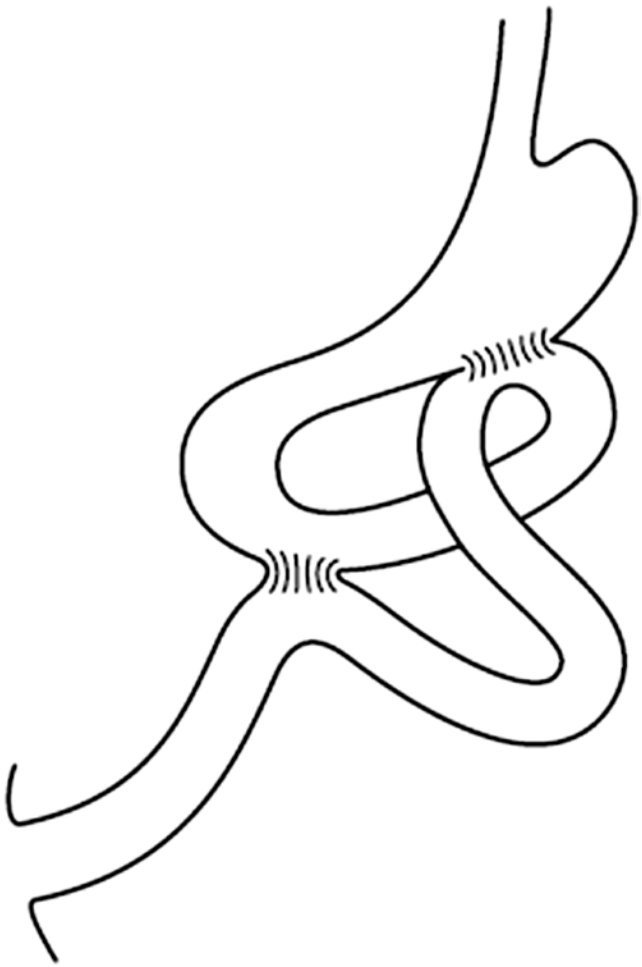

Fig. 6 Drainage procedures (gastro-jejunostomy, duodenojejunostomy, and ileostomy) occasionally performed in patients with visceral myopathy (after P. Hawley, St Mark's Hospital, London)

bowel from multiple resections. The reports of success are variable and any undertaking of surgery needs to be a multidisciplinary decision and based upon each individual patient. Outcome is poorer in patients with evidence of small bowel dysmotility who undergo colectomy.

Small Intestinal Transplantation

Dysmotility is a rare indication for intestinal transplant in adults with dysmotility needing HPN but since the outcomes of HPN are currently better, transplantation should be reserved for those who develop complications related to PN including IF associated liver disease, central vein thrombosis with reduced venous access, and recurrent catheter-related blood stream infections [139, 148, 149]. If other organs are damaged a multivisceral transplantation may be considered. The role of small bowel transplantation solely to improve quality of life by ceasing PN is somewhat contentious, but as worldwide experience of transplantation increases with corresponding improvements in survival rates, the indications for transplantation may broaden in the future. It is vital that all patients considered for transplantation are reviewed by an experienced multidisciplinary team with expertise in IF, and a transplant centre [150]. Pain is not an indication for a transplant.

Psychosocial Treatments

Psychological support from nurses, physicians, and psychologists is important. Vigilance needs to be maintained for the presence of psychopathology even in patients with a strong suspicion of gastrointestinal neuromuscular disorder. In one case series, six patients diagnosed initially with IF had significant psychopathology requiring specialised psychiatric unit treatment [23]. In addition to psychological distress including anxiety and depression; other psychological problems encountered can include somatisation disorder, personality disorders, substance misuse and disordered eating. Dysmotility disorders can also be associated with a risk of self-harm including suicide. Clinical psychology and liaison psychiatry provide overlapping but complimentary approaches and ideally a multi-disciplinary team involving both specialties should be available.

Outcomes

Outcome can vary from minor symptoms consistent with irritable bowel syndrome to problems resulting in home parenteral feeding, opioid analgesics and frequent hospital admissions. Causes of death in these patients include pulmonary aspiration, pulmonary embolism, cardiac failure and suicide. Cardiac failure may be the terminal event in hollow visceral myopathy. The relationship between "megaduodenum" and upper gastrointestinal tract cancer seems tenuous if it exists. Death will often be related to the underlying condition—obviously so in the case of pseudo-obstruction occurring as a paraneoplastic phenomenon, and also particularly in the degenerative neuropathies, collagen vascular disorders and infiltrative conditions such as amyloid. Amiot et al. reported 51 patients with CIPO who required HPN, representing 26-years of experience and found that surgery was required in 84% of patients and survival probability was 94%, 78%, 75% and 68% at 1, 5, 10 and 15 years respectively [54]. Higher mortality was associated with systemic sclerosis. 20-year experience of HPN from the Mayo clinic found that the survival for motility patients was second worse only to cancer, due to the progression of the underlying disease, which was similar in data from United Kingdom St Mark's hospital. Recently published data from the Salford IF Unit have demonstrated worse outcomes for patients with a CIPO than non-CIPO dysmotility phenotype [140]. However,

it would appear that there is room for improved outcomes in this challenging patient population by cost-effective investment in tertiary multi-disciplinary provision.

Conclusions

Most cases of intestinal dysmotility will be without a clear diagnosis and thus labelled as idiopathic. Addressing the patient's primary symptoms and treating malnutrition are the keys to management.

References

1. Nightingale JMD, Paine P, McLaughlin J, Emmanuel A, Martin J, Lal S. The management of adult patients with severe chronic small intestinal dysmotility. Gut. 2020;69:2074–92.
2. Powell-Tuck J, Martin J, Domizio P, Wingate D. Intestinal pseudo-obstruction. In: Nightingale JMD, editor. Intestinal failure. London: Greenwich Medical Media Limited; 2001. p. 123–39.
3. Kamm MA. Intestinal pseudo-obstruction. Gut. 2000;47(suppl IV):iv84.
4. Mann SD, Debinski HS, Kamm MA. Clinical characteristics of chronic idiopathic intestinal pseudo-obstruction in adults. Gut. 1997;41:675–81.
5. Parker MC, Wilson MS, van Goor H, Moran BJ, Jeekel J, Duron JJ, Menzies D, Wexner SD, Ellis H. Adhesions and colorectal surgery—call for action. Color Dis. 2007;9 Suppl 2:66–72.
6. Bassotti G, Sietchiping-Nzepa F, de Roberto G, Castellani D, Morelli A. Pseudo-pseudo-obstruction. Eur J Gastroenterol Hepatol. 2004;16:1039–41.
7. Silk DB. Pseudo-pseudo-obstruction: lessons in diagnosis and management. Eur J Gastroenterol Hepatol. 2004;16(10):959–60.
8. Holdstock DJ, Misiewicz JJ. Factors controlling colonic motility: colonic pressures and transit after meals in patients with total gastrectomy, pernicious anaemia or duodenal ulcer. Gut. 1970;11:100–10.
9. Rogers M, Cerda JJ. The Narcotic bowel syndrome. J Clin Gastroenterol. 1989;11:132–5.
10. Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. Neurogastroenterol Motil. 2010;22:424–30, e96. Epub 2010 Jan 21.
11. Choung RS, Locke GR 3rd, Zinsmeister AR, Schleck CD, Talley NJ. Opioid bowel dysfunction and narcotic bowel syndrome: a population-based study. Am J Gastroenterol. 2009;104(5):1199–204. Epub 2009 Apr 14.
12. Drossman DA, Morris CB, Edwards H, Wrennall CE, Weinland SR, Aderoju AO, Kulkarni-Kelapure RR, Hu YJ, Dalton C, Bouma MH, Zimmerman J, Rooker C, Leserman J, Bangdiwala SI. Diagnosis, characterization, and 3-month outcome after detoxification of 39 patients with narcotic bowel syndrome. Am J Gastroenterol. 2012;107:1426–40.
13. McNicol ED, Boyce D, Schumann R, Carr DB. Mu-opioid antagonists for opioid-induced bowel dysfunction. Cochrane Database Syst Rev. 2008;(2):CD006332.
14. Sandgren JE, McPhee MS, Greenberger NJ. Narcotic bowel syndrome treated with clonidine. Resolution of abdominal pain and intestinal pseudo-obstruction. Ann Intern Med. 1984;101(3):331–4.
15. Akhondzadeh S, Ahmadi-Abhari SA, Assadi SM, Shabestari OL, Kashani AR, Farzanehgan ZM. Double-blind randomized controlled trial of baclofen vs. clonidine in the treatment of opiates withdrawal. J Clin Pharm Ther. 2000;25(5):347–53.
16. Nightingale J, Meade U, Leahy G; The BIFA Committee. The use of cyclizine in patients receiving parenteral nutrition. 2018. www.bapen.org.uk/pdfs/bifa/position-statements/position-statement-on-use-of-cyclizine-in-patients-receiving-pn.pdf.
17. Drossman DA, Chang L, Chey W, Tack J, Whitehead W, editors. Rome IV: the functional gastrointestinal disorders. Rome Foundation: Raleigh, NC; 2016.
18. Tornblom H, Lindberg G, Nyberg G, Veress B. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. Gastroenterology. 2002;123:1972–9.
19. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013.
20. Robinson PH, Clarke M, Barrett J. Determinants of delayed gastric emptying in anorexia nervosa and bulimia nervosa. Gut. 1988;29(4):458–64.
21. Hutson WR, Wald A. Gastric emptying in patients with bulimia nervosa and anorexia nervosa. Am J Gastroenterol. 1990;85:41–6.
22. Hirakawa M, Okada T, Iida M, Tamai H, Kobayashi N, Nakagawa T, Fujishima M. Small bowel transit time measured by hydrogen breath test in patients with anorexia nervosa. Dig Dis Sci. 1990;35:733–6.
23. Kamal N, Chami T, Andersen A, Rosell FA, Schuster MM, Whitehead WE. Delayed gastrointestinal transit times in anorexia nervosa and bulimia nervosa. Gastroenterology. 1991;101:1320–4.
24. Buchman AL, Ament ME, Weiner M, Kodner A, Mayer EA. Reversal of megaduodenum and duodenal dysmotility associated with improvement in nutritional status in primary anorexia nervosa. Dig Dis Sci. 1994;39:433–40.
25. Paine P, McMahon M, Farrer K, et al. Jejunal feeding: when is it the right thing to do? Front Gastroenterol. 2019;11(5):397–403.
26. Bourke J, Soldan J, Silk DB, Aziz Q, Libby GW. 'Idiopathic' intestinal failure-the importance of identifying and treating primary psychopathology. Neurogastroenterol Motil. 2012;24:242–51.
27. Winter TA, Lemmer ER, O'Keefe SJ, Ogden JM. The effect of severe undernutrition, and subsequent refeeding on digestive function in human patients. Eur J Gastroenterol Hepatol. 2000;12(2):191–6.
28. Reynolds JV, O'Farrelly C, Feighery C, Murchan P, Leonard N, Fulton G, O'Morain C, Keane FB, Tanner WA. Impaired gut barrier function in malnourished patients. Br J Surg. 1996;83:1288–91.
29. Thieme ET, Postmus R. Superior mesenteric artery syndrome. Ann Surg. 1961;154(suppl):139–43.
30. Welsch T, Büchler MW, Kienle P. Recalling superior mesenteric artery syndrome. Dig Surg. 2007;24:149–56.
31. Merrett ND, Wilson RB, Cosman P, Biankin AV. Superior mesenteric artery syndrome: diagnosis and treatment strategies. J Gastrointest Surg. 2009;13:287–92.
32. Smith BG, Hakim-Zargar M, Thomson JD. Low body mass index: a risk factor for superior mesenteric artery syndrome in adolescents undergoing spinal fusion for scoliosis. J Spinal Disord Tech. 2009;22(2):144–8.
33. Wyten R, Kelty CJ, Falk GL. Laparoscopic duodenojejunostomy for the treatment of superior mesenteric artery (SMA) syndrome: case series. J Laparoendosc Adv Surg Tech A. 2010;20(2):173–6.
34. Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, Castori M, Cohen H, Colombi M, Demirdas S, De Backer J, De Paepe A, Fournel-Gigleux S, Frank M, Ghali N, Giunta C, Grahame R, Hakim A, Jeunemaitre X, Johnson D, Juul-Kristensen B, Kapferer-Seebacher I, Kazkaz H, Kosho T, Lavallee ME, Levy H,

Mendoza-Londono R, Pepin M, Pope FM, Reinstein E, Robert L, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheeldon N, Zschocke J, Tinkle B. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175:8–26.
35. Fikree A, Grahame R, Aktar R, Farmer AD, Hakim AJ, Morris JK, Knowles CH, Aziz Q. A prospective evaluation of undiagnosed joint hypermobility syndrome in patients with gastrointestinal symptoms. Clin Gastroenterol Hepatol. 2014;12:1680–8.
36. Beckers AB, Keszthelyi D, Fikree A, Vork L, Masclee A, Farmer AD, Aziz Q. Gastrointestinal disorders in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type: a review for the gastroenterologist. Neurogastroenterol Motil. 2017;29:e13013.
37. Valent P, Akin C. Doctor, i think i am suffering from MCAS: differential diagnosis and separating facts from fiction. J Allergy Clin Immunol Pract. 2019;7(4):1109–14.
38. Smith VV, Lake BD, Kamm MA. Intestinal pseudo-obstruction with deficient smooth muscle alpha-actin. Histopathology. 1992;21:535–42.
39. Knowles CH, Silk DBA, Darzi A, Veress B, Feakins R, Raimundo AH, Crompton T, Browning EC, Lindberg G, Martin JE. Deranged smooth muscle alpha actin: as a biomarker of intestinal pseudo-obstruction: a controlled multinational case series. Gut. 2004;53:1583–9.
40. Gamba E, Carr NJ, Bateman AC. Deficient alpha smooth muscle actin expression as a cause of intestinal pseudo-obstruction: fact or fiction? J Clin Pathol. 2004;57(11):1168–71.
41. Schuffler MD, Lowe MC, Bill AH. Studies of idiopathic intestinal pseudo-obstruction. 1. Hereditary hollow visceral myopathy: clinical and pathological studies. Gastroenterology. 1977;73:327–38.
42. Schuffler MD, Pagon RA, Schwartz R, Bill AH. Visceral myopathy of the gastrointestinal and genitourinary tracts in infants. Gastroenterology. 1988;94:892–8.
43. Higman D, Peters P, Stewart M. Familial hollow visceral myopathy with varying urological manifestations. Br J Urol. 1992;70:435–8.
44. Schuffler MD, Pope CE 2nd. Studies of idiopathic intestinal pseudoobstruction. II. Hereditary hollow visceral myopathy: family studies. Gastroenterology. 1977;73:339–44.
45. Rodrigues CA, Shepherd NA, Lennard-Jones JE, Hawley PR, Thompson HH. Familial visceral myopathy: a family with at least six involved members. Gut. 1989;30(9):1285–92.
46. Fitzgibbons PL, Chandrasoma PT. Familial visceral myopathy. Evidence of diffuse involvement of intestinal smooth muscle. Am J Surg Pathol. 1987;11:846–54.
47. Martin JE, Benson M, Swash M, Salih V, Gray A. Myofibroblasts in hollow visceral myopathy: the origin of gastrointestinal fibrosis? Gut. 1993;34(7):999–1001.
48. Smith VV, Milla PJ. Histological phenotypes of enteric smooth muscle disease causing functional intestinal obstruction in childhood. Histopathology. 1997;31(2):112–22.
49. Ruuska TH, Karikoski R, Smith VV, Milla PJ. Acquired myopathic intestinal pseudo-obstruction may be due to autoimmune enteric leiomyositis. Gastroenterology. 2002;122:1133–9.
50. Oton E, Moreira V, Redondo C, Lopez-San-Roman A, Foruny JR, Plaza G, de Vicente E, Quijano Y. Chronic intestinal pseudo-obstruction due to lymphocytic leiomyositis: is there a place for immunomodulatory therapy? Gut. 2005;54:1343–4.
51. Schuffler MD, Rohrmann CA, Chaffee RG, Brand DL, Delaney JH, Young JH. Chronic intestinal pseudo-obstruction. A report of 27 cases and review of the literature. Medicine. 1981;60:173–96.
52. Domsic R, Fasanella K, Bielefeldt K. Gastrointestinal manifestations of systemic sclerosis. Dig Dis Sci. 2008;53:1163–74.
53. Schuffler MD, Beegle RG. Progressive systemic sclerosis of the gastrointestinal tract and hereditary hollow visceral myopathy. Two distinguishable disorders of intestinal smooth muscle. Gastroenterology. 1979;77:664–71.
54. Amiot A, Joly F, Alves A, Panis Y, Bouhnik Y, Messing B. Long-term outcome of chronic intestinal pseudo-obstruction adult patients requiring home parental nutrition. Am J Gastroenterol. 2009;104:1262–70.
55. Harrison E, Herrick AL, Dibb M, McLaughlin JT, Lal S. Long-term outcome of patients with systemic sclerosis requiring home parenteral nutrition. Clin Nutr. 2015;34:991–6.
56. Perlemuter G, Chaussade S, Wechsler B, Cacoub P, Dapoigny M, Kahan A, Godeau P, Couturier D. Chronic intestinal pseudo-obstruction in systemic lupus erythematosus. Gut. 1998;43:117–22.
57. Paine P, McLaughlin J, Lal S. Review article: The assessment and management of chronic severe gastrointestinal dysmotility in adults. Aliment Pharmacol Ther. 2013;38:1209–29.
58. Forbes A. Radiation enteritis. In: Nightingale JMD, editor. Intestinal failure. London: Greenwich Medical Media Limited; 2001. p. 141–52.
59. Cousins AJ. Home enzyme replacement therapy for lysosomal storage disorders. Br J Home Healthc. 2008;4:7–9.
60. Veress B, Nyberg B, Tornblom H, Lindberg G. Intestinal lymphocytic epithelioganglionitis: a unique combination of inflammation in bowel dysmotility: a histopathological and immunohistochemical analysis of 28 cases. Histopathology. 2009;54:539–49.
61. Amiot A, Tchikviladzé M, Joly F, Slama A, Hatem DC, Jardel C, Messing B, Lombès A. Frequency of mitochondrial defects in patients with chronic intestinal pseudo-obstruction. Gastroenterology. 2009;137:101–9.
62. Nishino I, Spinazzola A, Papadimitriou A, Hammans S, Steiner I, Hahn CD, Connolly AM, Verloes A, Guimarães J, Maillard I, Hamano H, Donati MA, Semrad CE, Russell JA, Andreu AL, Hadjigeorgiou GM, Vu TH, Tadesse S, Nygaard TG, Nonaka I, Hirano I, Bonilla E, Rowland LP, DiMauro S, Hirano M. Mitochondrial neurogastrointestinal encephalomyopathy: an autosomal recessive disorder due to thymidine phosphorylase mutations. Ann Neurol. 2000;47:792–800.
63. Blondon H, Polivka M, Joly F, Flourie B, Mikol J, Messing B. Digestive smooth muscle mitochondrial myopathy in patients with mitochondrial-neuro-gastro-intestinal encephalomyopathy (MNGIE). Gastroenterol Clin Biol. 2005;29:773–8.
64. Rahman S. Gastrointestinal and hepatic manifestations of mitochondrial disorders. J Inherit Metab Dis. 2013;36:659–73.
65. Knowles CH, Lang B, Clover L, Scott SM, Gotti C, Vincent A, Martin JE. A role for autoantibodies in some cases of acquired non-paraneoplastic gut dysmotility. Scand J Gastroenterol. 2002;37:166–70.
66. Törnblom H, Lang B, Clover L, Knowles CH, Vincent A, Lindberg G. Autoantibodies in patients with gut motility disorders and enteric neuropathy. Scand J Gastroenterol. 2007;42:1289–93.
67. Kashyap P, Farrugia G. Enteric autoantibodies and gut motility disorders. Gastroenterol Clin N Am. 2008;37(2):397–410, vi-vii.
68. Debinski HS, Kamm MA, Talbot IC, et al. DNA viruses in the pathogenesis of sporadic chronic idiopathic intestinal pseudo-obstruction (CIIP). Gut. 1997;41:100–6.
69. Selgrad M, De Giorgio R, Fini L, Cogliandro RF, Williams S, Stanghellini V, Barbara G, Tonini M, Corinaldesi R, Genta RM, Domiati-Saad R, Meyer R, Goel A, Boland CR, Ricciardiello L. JC virus infects the enteric glia of patients with chronic idiopathic intestinal pseudo-obstruction. Gut. 2009;58(1):25–32. Epub 2008 Jul 1.
70. Lindberg G. Chronic intestinal pseudo-obstruction: how important is JC virus infection? Gut. 2009;58(1):2–3.
71. Meneghelli UG. Chagasic enteropathy. Rev Soc Bras Med Trop. 2004;37:252–60.

72. Pulliam TJ, Schuster MM. Congenital markers for chronic intestinal pseudoobstruction. Am J Gastroenterol. 1995;90:922–6.
73. Matulis SR, McJunkin B, Chang HH. Familial gastrointestinal neuropathy as part of a diffuse neuronal syndrome: four fatal cases in one sibship. Am J Gastroenterol. 1994;89:792–6.
74. Smith VV, Schäppi MG, Bisset WM, Kiparissi F, Jaffe A, Milla PJ, Lindley KJ. Lymphocytic leiomyositis and myenteric ganglionitis are intrinsic features of cystic fibrosis: studies in distal intestinal obstruction syndrome and meconium ileus. J Pediatr Gastroenterol Nutr. 2009;49(1):42–51.
75. Vianello M, Vitaliani R, Pezzani R, Nicolao P, Betterie C, Keir G, Thompson EJ, Tavolato B, Scaravilli F, Giometto B. The spectrum of anti-neuronal antibodies in a series on neurological patients. J Neurol Sci. 2004;220:29–36.
76. Palmer SE, McLean RM, Ellis PM, Harrison-Woolrych M. Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. J Clin Psychiatry. 2008;69(5):759–68.
77. Arasaradnam RP, Brown S, Forbes A, Fox MR, Hungin P, Kelman L, Major G, O'Connor M, Sanders DS, Sinha R, Smith SC, Thomas P, Walters JRF. Guidelines for the investigation of chronic diarrhoea in adults: British Society of Gastroenterology, 3rd edition. Gut. 2018;67:1380–99.
78. National Collaborating Centre for Acute Care. NICE guidelines. Nutritional support in adults: oral supplements, enteral and parenteral feeding. London: National Collaborating Centre for Acute Care; 2006.
79. Di Nardo G, Blandizzi C, Volta U, Colucci R, Stanghellinis V, Barbaras G, Del Tacca M, Tonini M, Corinaldesi R, De Giorgio R. Review article: Molecular, pathological and therapeutic features of human enteric neuropathies. Aliment Pharmacol Ther. 2008;28:25–42.
80. Accarino A, Perez F, Azpiroz F, Quiroga S, Malagelada JR. Abdominal distention results from caudo-ventral redistribution of contents. Gastroenterology. 2009;136(5):1544–51.
81. Menys A, Butt S, Emmanuel A, Plumb AA, Fikree A, Knowles C, Atkinson D, Zarate N, Halligan S, Taylor SA. Comparative quantitative assessment of global small bowel motility using magnetic resonance imaging in chronic intestinal pseudo-obstruction and healthy controls. Neurogastroenterol Motil. 2016;28(3):376–83.
82. de Jonge CS, Smout AJPM, Nederveen AJ, Stoker J. Evaluation of gastrointestinal motility with MRI: advances, challenges and opportunities. Neurogastroenterol Motil. 2018;30:e13257.
83. Rezaie A, Buresi M, Lembo A, Lin H, McCallum R, Rao S, Schmulson M, Valdovinos M, Zakko S, Pimentel M. Hydrogen and methane-based breath testing in gastrointestinal disorders: the North American Consensus. Am J Gastroenterol. 2017;112(5):775–84.
84. Valdovinos MA, Camilleri M, Thomforde GM, Frie C. Reduced accuracy of 14C-D-xylose breath test for detecting bacterial overgrowth in gastrointestinal motility disorders. Scand J Gastroenterol. 1993;28:963–8.
85. Suri J, Kataria R, Malik Z, Parkman HP, Schey R. Elevated methane levels in small intestinal bacterial overgrowth suggests delayed small bowel and colonic transit. Medicine (Baltimore). 2018;97(21):e10554 1-6.
86. Vantrappen G, Janssens J, Hellemans J, Ghoos Y. The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. J Clin Invest. 1977;59:1158–66.
87. Oliveira RB, Meneghelli UG, de Godoy RA, Dantas RO, Padovan W. Abnormalities of interdigestive motility of the small intestine in patients with Chagas' disease. Dig Dis Sci. 1983;28:294–9.
88. Stanghellini V, Camilleri M, Malagelada JR. Chronic idiopathic intestinal pseudo-obstruction: clinical and intestinal manometric findings. Gut. 1987;28:5–12.
89. Stanghellini V, Cogliandro RF, De Giorgio R, Barbara G, Morselli-Labate AM, Cogliandro L, Corinaldes R. Natural history of chronic intestinal pseudo-obstruction in adults: a single center study. Clin Gastroenterol Hepatol. 2005;3:449–58.
90. Quigley EM, Donovan JP, Lane MJ, Gallagher TF. Antroduodenal manometry. Usefulness and limitations as an outpatient study. Dig Dis Sci. 1992;37:20–8.
91. Wang YT, Mohammed SD, Farmer AD, Wang D, Zarate N, Hobson AR, Hellström PM, Semler JR, Kuo B, Rao SS, Hasler WL, Camilleri M, Scott SM. Regional gastrointestinal transit and pH studied in 215 healthy volunteers using the wireless motility capsule: influence of age, gender, study country and testing protocol. Aliment Pharmacol Ther. 2015;42(6):761–72. https://doi.org/10.1111/apt.13329. Epub 2015 Jul 29.
92. Yung D, Douglas S, Hobson AR, Giannakou A, Plevris JN, Koulaouzidis A. Morpho-functional evaluation of small bowel using wireless motility capsule and video capsule endoscopy in patients with known or suspected Crohn's disease: pilot study. Endosc Int Open. 2016;4(4):E480–6.
93. Quigley EM, Deprez PH, Hellstrom P, Husebye E, Soffer EE, Stanghellini V, Summers RW, Wilmer A, Wingate DL. Ambulatory intestinal manometry: a consensus report on its clinical role. Dig Dis Sci. 1997;42:2395–400.
94. Gill RC, Kellow JE, Browning C, Wingate DL. The use of intraluminal strain gauges for recording ambulant small bowel motility. Am J Phys. 1990;258(4 Pt 1):G610–5.
95. Lindberg G, Iwarzon M, Stal P, Seensalu R. Digital ambulatory monitoring of small-bowel motility. Scand J Gastroenterol. 1990;25:216–24.
96. Waldron B, Storey BE, Smith D, Cullen PT, Campbell FC. Computerised method for acquisition and display of gastrointestinal motility data. Med Biol Eng Comput. 1991;29:304–8.
97. Benson MJ, Castillo FD, Wingate DL, Demetrakopoulos J, Spyrou NM. The computer as referee in the analysis of human small bowel motility. Am J Physiol. 1993;264(4 Pt 1):G645–54.
98. Oliveira RB, Wingate DL, Castillo FD, et al. Prolonged small bowel manometry in Chagas' disease: a model for the diagnosis of enteric dysmotility. Gastroenterology. 1997;112:A800.
99. Hackelsberger N, Schmidt T, Renner R, Widmer R, Pfeiffer A, Kaess H. Ambulatory long-term jejunal manometry in diabetic patients with cardiac autonomic neuropathy. Neurogastroenterol Motil. 1997;9:77–83.
100. Kellow JE, Gill RC, Wingate DL. Prolonged ambulant recordings of small bowel motility demonstrate abnormalities in the irritable bowel syndrome. Gastroenterology. 1990;98:1208–18.
101. Knowles CH, Veress B, Tornblom H, Wallace S, Paraskeva P, Darzi A, Martin JE, Nyberg B, Lindberg G. Safety and diagnostic yield of laparoscopically assisted full-thickness bowel biospy. Neurogastroenterol Motil. 2008;20:774–9.
102. Vasant DH, Kalaiselvan R, Ablett J, Bond A, Abraham A, Teubner A, Green D, Paine PA, Lal S. The chronic intestinal pseudo-obstruction subtype has prognostic significance in patients with severe gastrointestinal dysmotility related intestinal failure. Clin Nutr. 2018;37:1967–75.
103. Ginies JL, Francois H, Joseph MG, Champion G, Coupris L, Limal JM. A curable cause of chronic idiopathic intestinal pseudo-obstruction in children: idiopathic myositis of the small intestine. J Pediatr Gastroenterol Nutr. 1996;23:426–9.
104. Camilleri M, Malagelada JR, Abell TL, Brown ML, Hench V, Zinsmeister AR. Effect of six weeks of treatment with cisapride in gastroparesis and intestinal pseudoobstruction. Gastroenterology. 1989;96:704–12.
105. British National Formulary. 59; March 2010. www.bnf.org.
106. European Medicines Agency. European Medicines Agency recommends changes to the use of metoclopramide. Changes aim mainly to reduce the risk of neurological side effects. Amsterdam: EMA. EMA/443003/2013. 26 July 2013.

107. Evans BW, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. Cochrane Database Syst Rev. 2007;(4):CD003960.
108. Bardhan KD, Forbes A, Marsden CL, Mason T, Short G. The effects of withdrawing tegaserod treatment in comparison with continuous treatment in irritable bowel syndrome patients with abdominal pain/discomfort, bloating and constipation: a clinical study. Aliment Pharmacol Ther. 2004;20(2):213–22.
109. Chey WD, Howden CW, Tack J, Ligozio G, Earnest DL. Long-term tegaserod treatment for dysmotility-like functional dyspepsia: results of two identical 1-year cohort studies. Dig Dis Sci. 2010;55(3):684–97. Epub 2009 Dec 3.
110. Emmanuel AV, Kamm MA, Roy AJ, Kerstens R, Vandeplassche L. Randomised clinical trial: the efficacy of prucalopride in patients with chronic intestinal pseudo-obstruction—a double-blind, placebo-controlled, cross-over, multiple n = 1 study. Aliment Pharmacol Ther. 2012;35(1):48–55.
111. Surrenti E, Camilleri M, Kammer PP, Prather CM, Schei AJ, RB. H. Antral axial forces postprandially and after erythromycin in organic and functional dysmotilities. Dig Dis Sci. 1996;41:697–704.
112. Minami T, Nishibayashi H, Shinomura Y, Matsuzawa Y. Effects of erythromycin in chronic idiopathic intestinal pseudo-obstruction. J Gastroenterol. 1996;31:855–9.
113. Chini P, Toskes PP, Waseem S, Hou W, McDonald R, Moshiree B. Effect of azithromycin on small bowel motility in patients with gastrointestinal dysmotility. Scand J Gastroenterol. 2012;47(4):422–7.
114. Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. N Engl J Med. 1991;325:1461–7.
115. Owyang C. Octreotide in gastrointestinal motility disorders. Gut. 1994;35(3 suppl):S11–4.
116. Perlemuter G, Cacoub P, Chaussade S, Wechsler B, Couturier D, Piette J-C. Octreotide treatment of chronic intestinal pseudoobstruction secondary to connective tissue diseases. Arthritis Rheum. 1999;42:1545–9.
117. Verne GN, Eaker EY, Hardy E, Sninsky CA. Effect of octreotide and erythromycin on idiopathic and scleroderma-associated intestinal pseudo-obstruction. Dig Dis Sci. 1995;40:1892–901.
118. Bharucha AE, Low PA, Camilleri M, Burton D, Gehrking TL, Zinsmeister AR. Pilot study of pyridostigmine in constipated patients with autonomic neuropathy. Clin Auton Res. 2008;18:194–202.
119. Bharucha AE, Low P, Camilleri M, Veil E, Burton D, Kudva Y, Shah P, Gehrking T, Zinsmeister AR. A randomised controlled study of the effect of cholinesterase inhibition on colon function in patients with diabetes mellitus and constipation. Gut. 2013;62:708–15.
120. Schang JC, Devroede G. Beneficial effects of naloxone in a patient with intestinal pseudo-obstruction. Am J Gastroenterol. 1985;80:407–11.
121. Dufour P, Gendre P. Long-term mucosal alterations by sennosides and related compounds. Pharmacology. 1988;36(Suppl 1):194–202.
122. Kiernan JA, Heinicke EA. Sennosides do not kill myenteric neurons in the colon of the rat or mouse. Neuroscience. 1989;30(3):837–42.
123. Pearson JS, Pollard C, Whorwell PJ. Avoiding analgesic escalation and excessive healthcare utilization in severe irritable bowel syndrome: a role for intramuscular anticholinergics? Ther Adv Gastroenterol. 2014;7:232–7.
124. Faculty of Pain Medicine of the Royal College of Anaethetists. Opioids aware. www.fpm.ac.uk/opioids-aware
125. Sobin WH, Heinrich TW, Drossman DA. Central neuromodulators for treating functional GI disorders: a primer. Am J Gastroenterol. 2017;112(5):693–702.
126. Mari A, Abu Backer F, Mahamid M, Amara H, Carter D, Boltin D, Dickman R. Bloating and abdominal distension: clinical approach and management. Adv Ther. 2019;36(5):1075–84.
127. Kilgallon E, Vasant DH, Green D, Shields PL, Hamdy S, Lal S, Paine P. Chronic continuous abdominal pain: evaluation of diagnostic features, iatrogenesis and drug treatments in a cohort of 103 patients. Aliment Pharmacol Ther. 2019;9(10):1282–92.
128. Abell T, McCallum R, Hocking M, Koch K, Abrahamsson H, Leblanc I, Lindberg G, Konturek J, Nowak T, Quigley EM, Tougas G, Starkebaum W. Gastric electrical stimulation for medically refractory gastroparesis. Gastroenterology. 2003;125:421–8.
129. Andersson S, Lönroth H, Simrén M, Ringström G, Elfvin A, Abrahamsson H. Gastric electrical stimulation for intractable vomiting in patients with chronic intestinal pseudoobstruction. Neurogastroenterol Motil. 2006;18(9):823–30.
130. Soffer E, Abell T, Lin Z, Lorincz A, McCallum R, Parkman H, Policker S, Ordog T. Review article: Gastric electrical stimulation for gastroparesis—physiological foundations, technical aspects and clinical implications. Aliment Pharmacol Ther. 2009;30:681–94.
131. Musunuru S, Beverstein G, Gould J. Preoperative predictors of significant symptomatic response after 1 year of gastric electrical stimulation for gastroparesis. World J Surg. 2010;34(8):1853–8.
132. Frøkjaer JB, Bergmann S, Brock C, Madzak A, Farmer AD, Ellrich J, Drewes AM. Modulation of vagal tone enhances gastroduodenal motility and reduces somatic pain sensitivity. Neurogastroenterol Motil. 2016;28:592–8.
133. Kapural L, Nagem H, Tlucek H, Sessler DI. Spinal cord stimulation for chronic visceral abdominal pain. Pain Med. 2010;11(3):347–55.
134. Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R. Spinal cord stimulation for chronic pain. Cochrane Database Syst Rev. 2004;(3):CD003783.
135. Jarrett ME, Varma JS, Duthie GS, Nicholls RJ, Kamm MA. Sacral nerve stimulation for faecal incontinence in the UK. Br J Surg. 2004;91(6):755–61.
136. Kenefick NJ. Sacral nerve neuromodulation for the treatment of lower bowel motility disorders. Ann R Coll Surg Engl. 2006;88(7):617–23.
137. Kamm MA, Dudding TC, Melenhorst J, Jarrett M, Wang Z, Buntzen S, Johansson C, Laurberg S, Rosen H, Vaizey CJ, Matzel K, Baeten C. Sacral nerve stimulation for intractable constipation. Gut. 2010;59(3):333–40.
138. Mowatt G, Glazener C, Jarrett M. Sacral nerve stimulation for faecal incontinence and constipation in adults. Cochrane Database Syst Rev. 2007;(3):CD004464.
139. Nightingale JMD, Woodward J, Small Bowel/Nutrition Committee of BSG. Guidelines for the management of patients with a short bowel. Gut. 2006;55(suppl IV).
140. Dibb M, , Soop M, Teubner A, Shaffer J, Abraham A, Carlson G, Lal S. Survival and nutritional dependence on home parenteral nutrition: three decades of experience from a single referral centre. Clin Nutr 2017; 36(2): 570–576.
141. Pironi L, Steiger E, Joly F, Wanten G, Chambrier C, Aimasso U, Sasdelli A, Szczepanek K, Jukes A, Theilla M, Kunecki M, Daniels J, Serlie M, Cooper S, Poullenot F, Rasmussen H, Compher C, Crivelli A, Hughes SJ, Santarpia L, Guglielmi F, Kozjek N, Ellegard L, Schneider S, Matras P, Forbes A, Wyer N, Zmarzly A, Taus M, O'Callaghan M, Osland M, Thibault R, Cuerda C, Jones L, Chapman B, Sahin P, Virgili N, Lee A, Orlandoni P, Matysiak K, Di Caro S, Doitchinova-Simeonova M, Masconale L, Spaggiari

C, Garde C, Serralde-Zúñiga A, Olveira G, Krznaric Z, Jáuregui E, Murillo A, Suárez-Llanos J, Nardi E, Van Gossum A, Lal S. The intravenous supplementation type and volume is associated with one-year outcome and major complications in patients with chronic intestinal failure. Gut. 2020;69:1787–95.

142. Howard L, Heaphy L, Fleming R, Lininger L, Steiger E. Four years of North American registry home parenteral nutrition outcome data and their implications for patient management. J Parenter Enter Nutr. 1991;15:384–93.
143. Pironi L, Goulet O, Buchman A, Messing B, Gabe S, Candusso M, Bond G, Gupte G, Pertkiewicz M, Steiger E, Forbes A, Van Gossum A, Pinna AD. Outcome on home parenteral nutrition for benign intestinal failure: a review of the literature and benchmarking with the European prospective survey of ESPEN. Clin Nutr. 2012;31:831–45.
144. Richards DM, Scott NA, Shaffer JL, Irving M. Opiate and sedative dependence predicts a poor outcome for patients receiving home parenteral nutrition. J Parenter Enter Nutr. 1997;21:336–8.
145. Harrison E, Herrick AL, McLaughlin J, Lal S. 22 years' experience managing patients with systemic sclerosis on home parenteral nutrition. Clin Nutr ESPEN. 2015;10(5):e178.
146. Lloyd DAJ, Vega R, Bassett P, Forbes A, Gabe SM. Survival and dependence on home parenteral nutrition: experience over a 25-year period in a UK referral centre. Aliment Pharmacol Ther. 2006;24:1231–40.
147. Mughal MM, Irving MH. Treatment of end stage chronic intestinal pseudo-obstruction by subtotal enterectomy and home parenteral nutrition. Gut. 1988;29:1613–7.
148. Murr MM, Sarr MG, Camilleri M. The surgeons role in the treatment of chronic intestinal pseudo-obstruction. Am J Gastroenterol. 1995;90:2147–51.
149. Kaufman SS, Avitzur Y, Beath SV, Ceulemans LJ, Gondolesi GE, Mazariegos GV, Pironi L. New insights into the indications for intestinal transplantation—consensus in the year 2019. Transplantation. 2020;104(5):937–46. https://doi.org/10.1097/TP.0000000000003065.
150. Lauro A, Pinna AD, Tossani E, Stanghellini V, Manno M, Caio G, Golfieri L, Zanfi C, Cautero N, Bagni A, Volta U, Di Simone M, Pironi L, Cogliandro RF, Serra M, Venturoli A, Grandi S, De Giorgio R. Multimodal surgical approach for adult patients with chronic intestinal pseudo-obstruction: clinical and psychosocial long-term outcomes. Transplant Proc. 2018;50(1):226–33.

Pelvic Radiation Disease and the Gastrointestinal Tract

Darren Fernandes and Jervoise Andreyev

Key Points

1. Radiotherapy to a pelvic tumour causes a spectrum of disorders within and outside the GI tract which should be considered a progressive condition with a defined pathology which has recently been termed pelvic radiation disease (PRD)
2. Simple "trigger" questions can be used to alert any clinician to the fact that significant PRD may be occurring and the patient needs specialist help
3. Large numbers of survivors of cancer suffer from PRD which is often not acknowledged or recognised by health care workers
4. Following published checklists and treatment algorithms are efficient and inexpensive at ameliorating the GI symptoms of PRD and much more effective than relying on "clinical intuition" or experience
5. The underlying ischaemia and fibrosis which develops in the tissues exposed to radiotherapy means that endoscopic and surgical approaches which work in inflammatory or malignant tissues are potentially hazardous in patients with PRD
6. The progressive ischaemic and fibrotic pathological changes which are the basis for PRD offer opportunities to halt or reverse the changes of radiotherapy and clinical trials to assess the effectiveness of many agents which might do this are a priority
7. Identifying an objective biomarker of progressive radiation change is a key step in radiation research

Why Patients Develop Symptoms

Most patients starting pelvic radiotherapy will have normal gastrointestinal function apart from possible local tumour effects. During radiotherapy, normal tissues that surround the tumour will be exposed to some radiation. The rectum and sigmoid are in close physical proximity to the area being treated and are at particular risk. The caecum is relatively immobile and may too receive a significant dose. The transverse colon and small bowel frequently loop down into the pelvis, putting them at risk, so too is the proximal small bowel and pancreas especially when para-aortic nodes are irradiated [1]. The presence of abdominal adhesions may increase the risk to normally mobile bowel loops. Other factors related to the risk of toxicity are outlined in Table 1.

Almost all data on development of radiation injury at a molecular level are derived from animal models. However, animal models represent poorly what happens in humans for many reasons limiting clinical relevance of the results. Indeed, adequate animal models for many aspects of late radiation enteropathy have not yet been developed.

It was once thought that the radiation dose was entirely responsible for the damage that may develop but increasingly, patient related factors are understood to be important. The gastrointestinal immune system, the enteric nervous system and the intestinal microvasculature play key roles in

Table 1 Factors significantly associated with the development of Radiation Pelvic Disease

Therapy-related factors
Radiation dose
Volume of bowel irradiated
Time-dose-fractionation parameters
Concomitant chemotherapy or biological therapy
Patient-related factors
Diabetes mellitus
Tobacco smoking
HIV disease
Inflammatory bowel disease
Collagen vascular disease
Previous pelvic or abdominal surgery
Pelvic inflammatory disease
Low BMI
Colonic microbiota
Genetic polymorphisms
Hypertension (protective)

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the development of radiation enteropathy [2]. Emerging data increasingly suggest that the 100 trillion bacteria in the gut lumen, tenfold the number of cells in the human body, are also crucial determinants of radiation enteropathy severity [3].

In the past, radiation injury was classified as "early" or "late" depending on the timing of its clinical expression that was founded on two different, but not mutually exclusive, mechanistic models of injury—the "target cell" and "vascular injury" models [4].

However, the recognition that delayed radiation injury might develop clinically in the wake of severe acute injury was recognised by Bourne et al. [5] and Peters et al. [6] who subsequently coined the term "consequential late effects". In 2001, in a very important paper, a new terminology for classifying healthy tissue radiation responses was described [4]. In this paper, Denham and Hauer-Jensen classified lesions producing radiation injury into three interacting categories: cytocidal effects, indirect effects and functional effects.

Cytocidal effects relate to the phenomena characterised by the "target cell" model, where rapidly proliferating cells give rise to early pathology and more slowly proliferating target cells show delayed effects [7]. Hence, the time between irradiation and manifestation of injury depends on target cell characteristics (radiation sensitivity, repair capacity, proliferation rate, etc.) and tissue organisation. In rapid renewal tissues, such as the gastrointestinal epithelium, injury manifests itself clinically within days of first radiation exposure, when cells in the "differentiated" cellular compartment are no longer replaced by cells from the progenitor compartments. These tissues have been dubbed "early-reacting tissues". Cellular turn over, however, is much slower in connective tissues and organs that are composed of cells capable of re-entering the cell cycle. Radiation injury may therefore be expressed months or even years after exposure if cell death occurs when cellular division is attempted, and these tissues are said to be "late reacting" [4].

"Indirect" effects are reactive phenomena that occur in response to radiation-induced injury in other cells or tissues, and include phenomena such as parenchymal cell depletion secondary to vascular damage, the "bystander" effect and tissue reactions to vasoactive, procoagulant, and inflammatory mediators, including cytokines, growth factors and chemokines [4].

"Functional" effects from non-lethal effects on different intra- and extracellular molecules and changes in gene expression in irradiated cells lead, for example, to direct inactivation of anticoagulant molecules, activation of latent growth factors and activation of proteases. They include phenomena such as the inhibition of cellular replicative ability and accelerated senescence that lead to decreased tissue vitality [4].

Tissue injury after radiation therapy can therefore occur either quickly or after a prolonged period of time and these processes can clinically present as [8]:

1. Damage to specific neurological, enzyme based and muscular functions (and probably also local hormonal and immunological regulation) of the gastrointestinal tract
2. Acute inflammatory processes and chronic cytokine activation
3. Development of chronic ischaemia within the gastrointestinal wall, surrounding stroma and mesenteries
4. Progressive fibrosis within the gastrointestinal wall, surrounding stroma and mesenteries
5. Changes in preexisting conditions or the development of new conditions unrelated to radiotherapy, which also cause symptoms indistinguishable from those arising as a result of radiotherapy.

Epidemiology of Radiation Damage to Gut

Over 17,000 men and women are treated with pelvic radiotherapy in the UK annually and an estimated one million worldwide. While oncologists frequently report that 10–15% develop moderate or severe GI toxicity, patient focused research suggests that up to 50% depending on the site treated develop permanent gastrointestinal symptoms interfering with daily activity [9, 10]. It can be difficult to define exactly when symptoms start to affect quality of life and why some people seek help for specific gastrointestinal symptoms when others do not. Prospective studies using comprehensive, validated methodology concentrating on bowel toxicity with adequate follow-up are very few. It is frequently claimed that modern techniques of radiotherapy for pelvic malignancy have substantially reduced acute toxicity but as yet there are few randomized controlled trial data to support this assertion and almost no long term high quality follow up data.

Examples of the weakness and variability in the reported data can be quickly exemplified by from a number of studies. In one prospective study in which about two-thirds of patients had prostate cancer and most of the rest had gynaecological cancer, 2-year follow-up was only available in 57%. Of these, only 12% reported bowel problems moderately affecting daily activity [11]**.** In the Swedish Rectal Cancer Trial which helped establish short course preoperative (5 × 5 Gy) radiotherapy as an important therapeutic modality, meaningful follow up data were obtained from 77% of the 92% of survivors followed for more than 5 years. This showed that 30% of the irradiated group had a significantly impaired social life because of bowel dysfunction, compared with 10% of the surgery-alone group [12]. In a third prospective

study, a small subset of surviving patients who had undergone adjuvant radiotherapy after surgery for rectal cancer were questioned and investigated in detail and compared with a small subgroup of patients randomised to surgery alone. Bowel frequency (80% vs 23%), loose or liquid stools (60% vs 23%), faecal incontinence (60% vs 8%) and the need to wear a pad more often (47% vs 0%) were all significantly more frequent in the radiotherapy patients [13]. A large recent study confirms the continuing adverse health related quality of life outcomes in patients with colorectal cancer, 16% of survivors without a stoma reported having no control of their bowels, with a further 17% reporting moderate problems. With regards to sexual matters, 15.9% of respondents reported experiencing severe difficulties with patients with rectal cancer reporting a higher percentage (25.1%) and 15.4% reported severe urinary problems [14].

What does seem clear from these and other patient-centred studies, of all the symptoms that can arise after pelvic radiotherapy, new bowel symptoms seem to have the greatest effect on quality of life [15]. Studies that have assessed 'symptoms causing moderate or severe distress' or whether their symptoms prevent them doing things on a regular basis in patients suggest that if radiotherapy was part of their treatment approximately half of all patients treated for rectal cancer, one-third of bladder and gynaecological patients and one in five of all patients treated for prostate cancer are left with significant gastrointestinal symptoms [16]. While the risk of bias in some of these studies from patients lost to follow up or because the studies are retrospective must be acknowledged, however, consistent data suggest that unrecognised toxicity causes a significant burden and is an important unmet need for large numbers of patients.

Is Bowel Morbidity Adequately Documented?

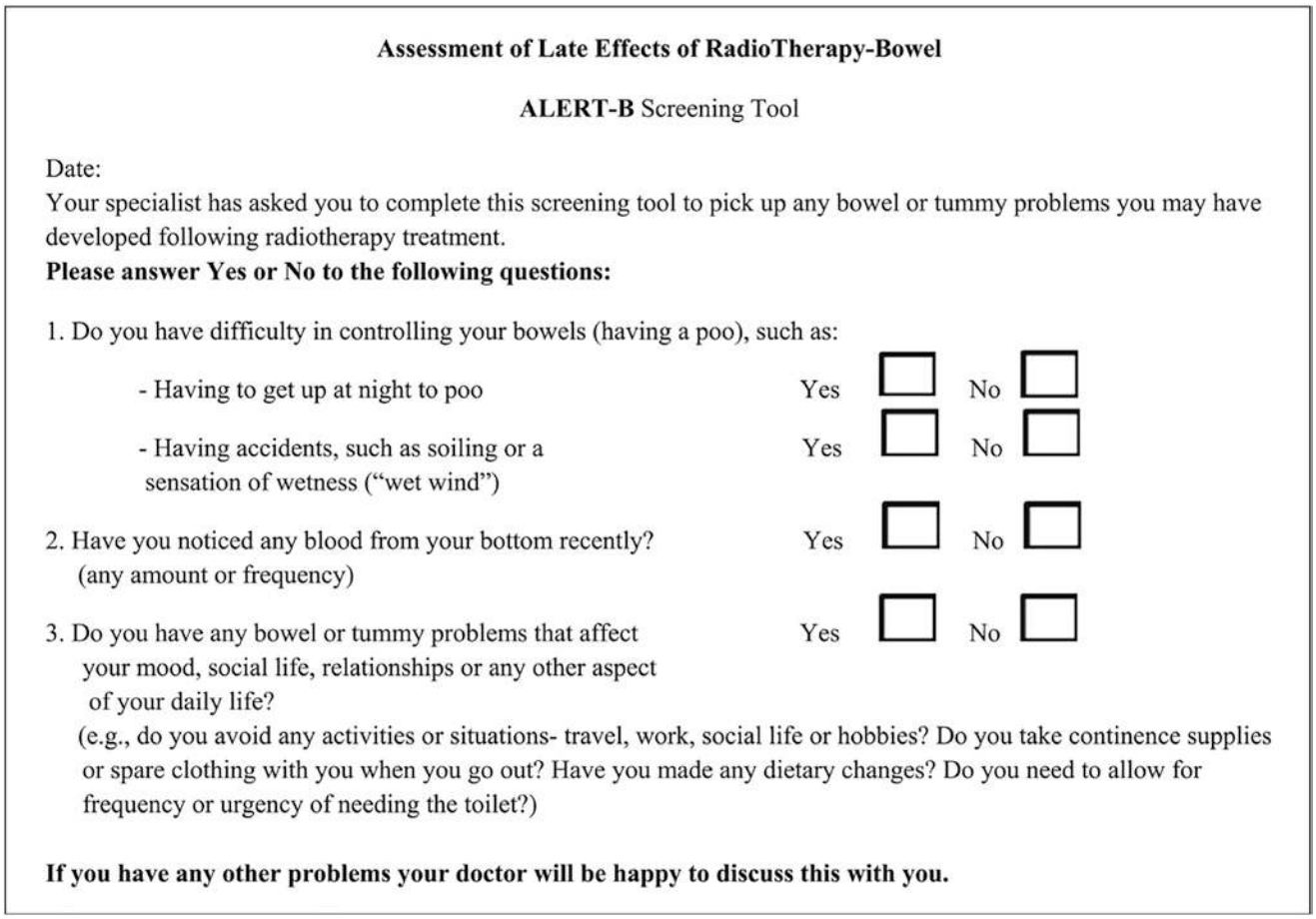
The frequent under-reporting of chronic bowel symptoms that occur after radiotherapy raises concerns as to the assessment and recognition of late effects in clinical practice and the potential value of "trigger" questions to identify those running into significant difficulty (see Fig. 1). Symptoms can occur months to years after radiotherapy and many clinicians from primary to tertiary care often fail to consider and are unfamiliar with the spectrum of late radiotherapy effects.

Simple "trigger" questions have been described in a paper endorsed by all GI professional bodies in the UK that any clinician could use to help identify patient in need of specialist help [17]. These have been validated in a subsequent study and the ALERT B can be a useful tool used in any patient waiting room (Fig. 1) [18]. However, a raised awareness of the potential problems that can be experienced by everyone who comes into contact with a patient previously treated for cancer is required if we are to make significant progress with helping patients with consequences of cancer therapy [19].

There are extensive data which tell us which symptoms impact patient's most [20]. Yet, when Chen et al. assessed rectal cancer specialists' understanding of which bowel dysfunction symptoms truly matter to patients after sphincter-preserving treatment, they found that there was considerable discrepancy between the specialist's perspective and patient experience. For example, specialists tended to overestimate the impact of incontinence for liquid stool and frequent bowel movements, while underestimating the impact of urgency and clustering [21].

The lack of incidence data may be as a consequence of lack of information how best to assess and define abnormal bowel problems and the somewhat subjective nature of chronic symptoms. A retrospective study by Tom et al. 2017 demonstrated this [22] when they examined and compared patient and clinician reports of acute gastrointestinal toxicity during chemoradiation therapy and found discrepancies in reported symptoms. Going forwards, there needs to be better measurement of toxicity not just within research but also in clinical practice during follow-up visits. Furthermore, which scoring systems and tools should be used to document and score the late effects of radiotherapy and how best to measure bowel effects objectively needs to be assessed.

The scoring systems that have been used include the Radiation Therapy Oncology Group (RTOG) score, Late Effects Normal Tissue-Subjective, Objective, Management (LENT-SOM) scales and Common Terminology Criteria for Adverse Events (CTCAE). However, these are not only insensitive measures of the patient experience and frequently underestimate the amount of toxicity suffered but also cannot explain clinical outcomes [23, 24]. We have routinely augmented our standard medical assessment with a modified Gastrointestinal Symptom Rating Scale that patients complete at each clinic visit, along with a Bristol Stool Chart [25]. This helps focus the consultation on all of the patient's GI issues. In addition, offering all new patients a holistic needs assessment questionnaire pays dividends. In addition to their GI problems, 80% of these patients report moderate or severe bother from fatigue, 45% from urinary problems, 36% from nutritional issues, 35% from sexual issues, 11% from emotional concerns and 2% from dermatological issues. So whilst the focus is on gastrointestinal and nutritional issues, these other areas cannot be ignored and require thoughtful management strategies [26] albeit often by a different specialist in a different service setting.



Assessment of Late Effects of RadioTherapy-Bowel

ALERT-B Screening Tool

Date:

Your specialist has asked you to complete this screening tool to pick up any bowel or tummy problems you may have developed following radiotherapy treatment.

Please answer Yes or No to the following questions:

1. Do you have difficulty in controlling your bowels (having a poo), such as:

- Having to get up at night to poo — Yes ☐ No ☐
- Having accidents, such as soiling or a sensation of wetness ("wet wind") — Yes ☐ No ☐

2. Have you noticed any blood from your bottom recently? (any amount or frequency) — Yes ☐ No ☐

3. Do you have any bowel or tummy problems that affect your mood, social life, relationships or any other aspect of your daily life? — Yes ☐ No ☐

(e.g., do you avoid any activities or situations- travel, work, social life or hobbies? Do you take continence supplies or spare clothing with you when you go out? Have you made any dietary changes? Do you need to allow for frequency or urgency of needing the toilet?)

If you have any other problems your doctor will be happy to discuss this with you.

Fig. 1 The ALERT-B questionnaire for screening for significant GI toxicity after previous pelvic irradiation [18]

Diagnosis and Management

Men presenting to a gastroenterology clinic after radiotherapy frequently have a median of 11 symptoms (range 1–16) while women have a median of 12 symptoms (range 4–16). Presenting with a cluster of "typical symptoms of radiation toxicity" has been shown to be highly unreliable at predicting the underlying cause. These clusters can be present before radiation and are aggravated by, or amplify, the inflammatory symptoms that occur during radiation as well as being related to the more permanent injuries that present after radiotherapy [27]. Furthermore, it is difficult even for experienced clinicians to predict how symptom clusters relate to bowel pathology. This was shown in a recent prospective study that assessed experienced clinicians' predictions of possible diagnoses for patients presenting with troublesome gastrointestinal symptoms compared to the actual diagnoses made following comprehensive investigation following a checklist. While 168 actual diagnoses were identified, only 92 were predicted and of those only 24% matched the diagnoses made. The majority of patients had multiple causes contributing to their symptoms and none of the participating clinicians predicted the correct combination of diagnoses [28] (Table 2).

Table 2 Clinicians prediction of commonly suspected causes of changes in gastrointestinal function following cancer based on clinical acumen have poor sensitivity and specificity [28]

Contributing GI pathology	Sensitivity (95% CI)	Specificity (95% CI)
Small intestinal bacterial overgrowth	67% (41–86%)	48% (29–67%)
Bile acid malabsorption	50% (21–79%)	86% (70–95%)
Pancreatic insufficiency	22% (3–60%)	87% (72–96%)

The lack of accuracy of empirical treatment without adequate investigation perhaps explains why so many of these patients continue to be highly symptomatic after gastroenterological intervention. An alternative approach, which has been shown in both randomised trials and in cohort studies to be highly effective, is to use a detailed checklist to investigate these patients and when the investigations are abnormal instigate treatment following a management algorithm sys-

tematically. Indeed, patients can be significantly helped and need only a median of six investigations and three clinic visits [8, 29–31] and this costs approximately £1563 [32]. The benefit of this approach has been confirmed by others [31]. The ORBIT trial also showed, in an era when there are huge numbers of affected patients, is that a nurse can be trained to manage the patients following checklists and algorithm and, with adequate gastroenterology support, can obtain outcomes similar to those obtained by a senior gastroenterologist in most cases. This algorithm is now freely available to clinicians [33].

Physiological Model of Symptoms

The real conceptual advance in the treatment of patients with complex GI symptoms however, comes from the understanding that the aetiology of GI symptoms depends not on pathological change, but rather depends on physiological change (Fig. 2).

It is this realisation that symptoms are caused not by pathological changes *per se*, but by 'changes in the normal physiology' of the GI tract, that has allowed the management of complex symptoms to be effective.

Initial Assessment

The first step towards diagnosing and formulating a management plan that will improve patients' symptoms is to take an accurate history. This needs to elicit:

- What was bowel function like before the cancer emerged?
- How have the symptoms changed over time?
- Are key features indicative of reversible underlying pathology present, for example:
  - Steatorrhoea
    - Is there an oily film in the lavatory water?
    - Is the stool ever pale/putty-like/foul smelling/difficult to flush/floating?
    - Has there been rapid weight loss?
  - Nocturnal waking to defaecate
  - Symptoms suggestive of recurrent cancer or a new primary?
- Is there a consistent impact of a specific component of diet on their symptoms, especially:
  - Fibre: how much are they eating—too much/too little?
  - Fat: does this promote type 6–7 stool/steatorrhoea?
  - Lactose-containing foods?
  - Gluten-containing foods?
  - Alcohol intake?
  - Caffeine intake
- Is there an association between the start of specific medication or increase in its dose and their symptoms—for example, metformin, proton pump inhibitor, α-blockers?
- What individual symptoms are present. We particularly favour the use of sensitive symptom questionnaires which patients can fill in before their clinic appointment and help everyone understand which issues are important [25]. Each symptom may have a different physiological cause and so understanding in detail which symptoms are present help us identify what tests need to be arranged.

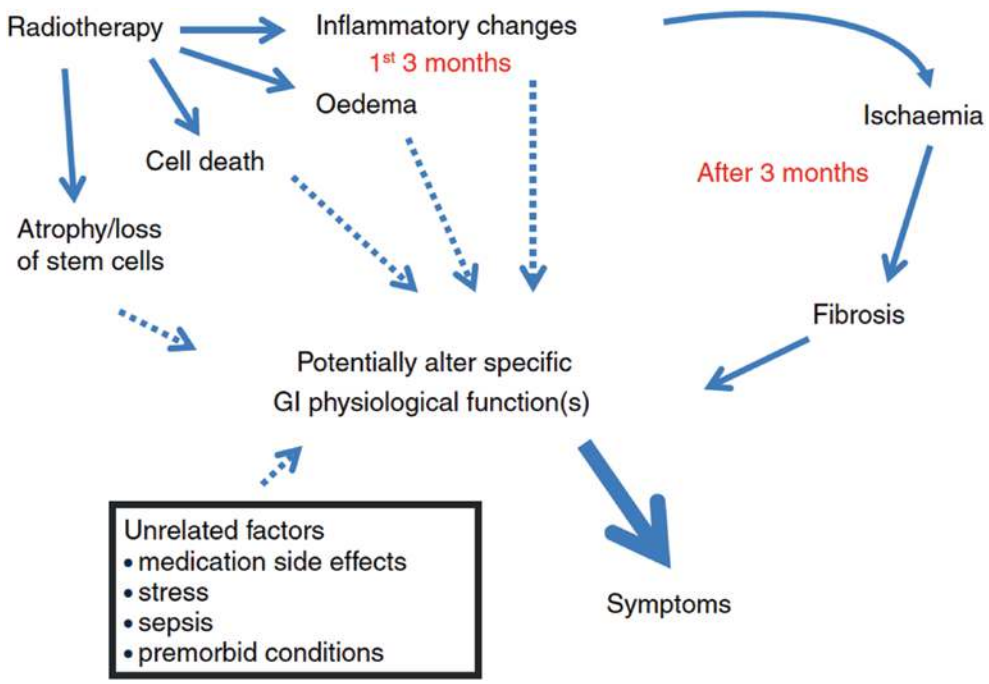


Fig. 2 Physiological model of symptom aetiology [34]

Loose Stool or Diarrhoea

This common symptom may be due to multiple causes. The frequency of these causes during and after radiotherapy as far as they have been reported is shown in Table 3 and then the more important causes are discussed in more detail below.

Small Bowel Bacterial Overgrowth

Radiotherapy has a direct effect on small bowel motility. This change in motility in turn predisposes to bacterial overgrowth and in some patients episodic pseudo-obstruction [16]**.** Small-bowel bacterial overgrowth occurs in 25% of patients [35] during the acute phase of radiotherapy. In the chronic setting, motility changes caused by radiotherapy are the main cause of such overgrowth [36]—particularly that of gram-negative bacilli, which in 4–45% patients may cause a wide variety of gastrointestinal symptoms [9, 36–38]. Three studies [9, 37, 38] suggest that in 8–15% of patients with diarrhoea, the diarrhoea is caused by bacterial overgrowth and improves after antibiotic treatment.

Reliable diagnosis of bacterial overgrowth is difficult and better diagnostic tests using modern molecular techniques are urgently required. Currently available diagnostic techniques include breath tests—breath tests which just look for expired hydrogen levels and do not measure methane will miss 25% of patients with bacterial overgrowth—direct culture of small-bowel contents which is particularly helpful for defining bacterial sensitivity to specific antibiotics, or determination of bile acid products in the blood. Some patients have low vitamin B12 levels or modestly raided CRP—<15—which normalise once bacteria are eradicated from the small bowel [39].

Optimal strategies for the management of bacterial overgrowth are not defined. Appropriate antibiotics to which the specific bacteria are sensitive, used for 1–2 weeks may abolish symptoms within a few days of starting treatment. However, symptoms can recur any time after antibiotics are stopped—from a few days to many years later—because the underlying cause of bacterial overgrowth has not gone away. If symptoms return, retreatment with antibiotics might help. In patients with recurrent symptoms, use of antibiotics for a few days every month, or continually at the lowest effective dose, might be effective [1].

Table 3 Causes for diarrhea during and after radiotherapy. It is not unusual especially after radiotherapy for several causes to coexist. Therefore, empirical treatment is rarely effective as it is difficult to guess the cause(s) accurately. This list does not include other common reasons such as excess fibre which is often poorly tolerated after radiotherapy, excess caffeine or alcohol. Clearly many of the causes in this list can be cured with simple interventions if they are diagnosed accurately

	During radiotherapy	After radiotherapy
Lactose intolerance	50%	5–7%
Other disaccharide malabsorption	Not known	Yes but frequency unknown
Bile acid malabsorption	50%	1–83%
Small bowel bacterial overgrowth	25%	8–45%
Large bowel strictures	–	3–15%
Pancreatic insufficiency	Not known	Yes but frequency unknown
Rapid transit	100%	Yes but frequency unknown
Viral infection	Not known	Not known
Clostridium difficile	Not known	Not known
Cancer relapse	–	4–10%
Drug related (non chemotherapy)	10%	5%
New GI neoplasia	–	10%
New onset IBD		2%
Other	Not known	5%

Bile Acid Malabsorption

Up to half of patients who develop diarrhoea acutely during radiotherapy will have bile acid malabsorption [40] because of a direct effect on the mechanisms of bile reabsorption; accelerated transit that reduces bile absorption [41, 42]; or colon damage that exacerbates symptoms [43]. After radiotherapy, a chronic reduction in bile acid absorption is common [44, 45] but does not cause symptoms in most patients [40, 46, 47]. Bile acid malabsorption can cause a variety of symptoms. Intermittent or constant loose stool is universal but patients may also develop abdominal cramps, frequency and/or urgency of defaecation, nocturnal defaecation or incontinence. The development of bile acid malabsorption should be considered in all patients who have episodes of loose (type 6) or liquid (type 7 stool as per the Bristol stool chart) and if these patients are subjected to a Selenium homocholic acid taurocholate (SeHCAT) scan, consistent data suggest that approximately 50% have developed the condition across a wide range of diseases (see Fig. 3) [48].

The gold standard for measurement of bile acid malabsorption is the SeHCAT (selenium 75 homo-cholic acid conjugated with taurine) scan. Bile acid is secreted in response to dietary intake of fat, so reducing dietary fat intake, can be a useful therapeutic approach in patients with mild malabsorption. Regular use of antidiarrhoeal drugs such as loperamide or codeine phosphate [49], especially if taken 30–60 min before eating, may improve symptoms. Most patients however require bile acid sequestrants which

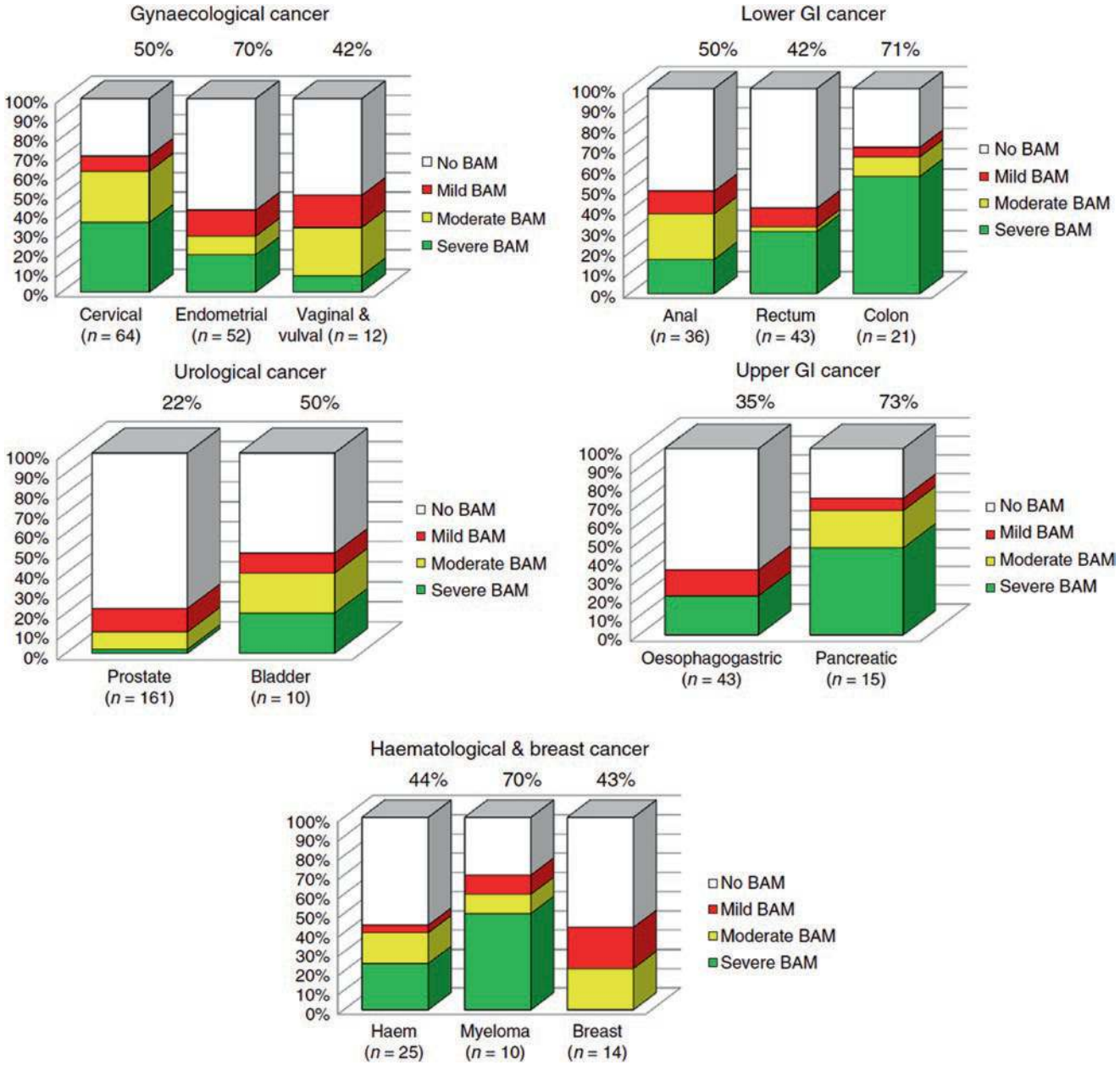


Fig. 3 Taken from Phillips et al [48] showing the frequency and severity of bile acid malabsorption (BAM) in 506 patients undergoing a SeHCAT scan. Not all had been treated with pelvic radiotherapy

have been shown to be beneficial in several series [37, 46, 49–52]. Most of these data are for use of colestyramine. However, many people cannot tolerate bile-binding resins. An effective and well-tolerated alternative is colesevelam [53]. As a last resort a diet where medium-chain triglycerides replace most of the fat can be tried [54] though this diet is unpalatable and is rarely required. A logical therapeutic approach which has been shown to be highly beneficial is described in Fig. 4.

Carbohydrate Malabsorption

De-novo lactose malabsorption occurs in 50% of patients by the fourth week of pelvic radiotherapy [53]. The severity of malabsorption correlates with the length of small bowel irradiated [55]. New-onset lactose malabsorption persists in about 5% of patients and frequently causes diarrhoea [44, 56]. If lactose malabsorption occurs, it is likely that malabsorption of other disaccharides also occurs. No studies have

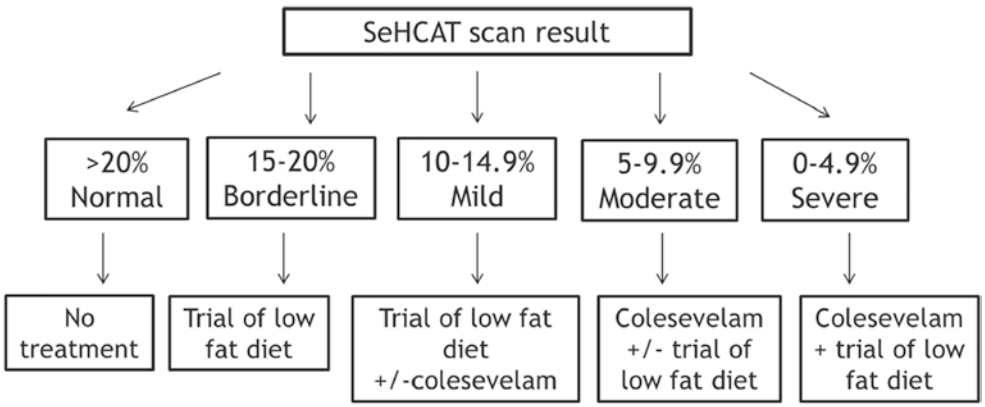


Fig. 4 Taken from Gupta A et al [30] suggesting a therapeutic approach to bile acid malabsorption based on the SeHCAT scan value

investigated this systematically although clinical experience suggests that malabsorption of other sugars does sometimes occurs. Clinical experience suggests that many patients who believe they have lactose intolerance, in fact have developed bile acid malabsorption and their symptoms arise from the fat found in milk containing products rather than from the lactose.

Investigation for carbohydrate malabsorption can include stool chromatography, oral-tolerance tests that measure blood or breath responses, use of isotope-labelled carbohydrate, direct biopsy proof of enzyme deficiency or empirical trials of diet. Dietary advice to avoid the unabsorbed sugars, which could include one or more of lactose, fructose, sucrose and starches is needed and should be given by a qualified dietician because diets can be complex and lactose avoidance changes calcium intake, which might affect bone health a potential problem in people who have had radiotherapy and are known to suffer from an increased risk of bone fracture [1].

Risk of Second Cancers

Endoscopic surveillance should probably be discussed with all patients 5 years after radiotherapy and probably should be continued long term. Large studies have concluded that after radiotherapy there is a significant risk of secondary colon cancer and rectal cancer [57]; rectal (but not colon) cancer [58–60]; or either rectal cancer or colon cancer but only in parts of the gastrointestinal tract that were included in the radiation field [61] and that risk increases over time.

Steatorrhoea

Steatorrhoea is loose stool caused by the presence of excessive undigested fat (i.e., >0.3 g per kg a day). It causes unpleasant symptoms of frequency of defaecation, urgency, faecal incontinence, perianal irritation, and severe, socially debilitating flatulence. Patients with substantial fat malabsorption especially when it occurs together with small bowel bacterial overgrowth can develop severe abdominal cramps and vomiting, which can sometimes be mistaken for acute obstruction.

In a patient who has had pelvic radiotherapy, steatorrhoea is commonly caused by bile acid malabsorption or bacterial overgrowth. More rarely, it is caused by chronic pancreatic insufficiency or by the little-recognised disorder of free fatty-acid malabsorption. Very rarely it may be due to Addison's disease, thyrotoxicosis, the development of a hormone secreting neuroendocrine tumour, intestinal lymphangiectasia or very extensive new onset small bowel inflammatory disease.

Steatorrhoea needs to be diagnosed by direct questioning—is the stool pale, extremely offensive, with a tendency to float and difficult to flush away? Of most usefulness, patients sometimes describe a frequent oily film on the surface of the lavatory water.

It is now almost impossible to obtain laboratory quantification of stool fat levels [1] so these should not be requested.

Radiation-Induced Pancreatic Insufficiency

The pancreas is thought to be fairly radio-resistant. However, chronic pancreatic insufficiency can develop after pancreatic irradiation [9, 62–68]. The pancreas frequently appears completely normal on magnetic resonance cholangiopancreatography, even in the presence of severe radiotherapy-induced pancreatic insufficiency. Invasive tests of pancreatic function are rarely justified. Faecal elastase levels may be artificially lowered in patients with undiagnosed coeliac disease or small intestinal bacterial overgrowth (SIBO) but SIBO is often present in patients with pancreatic insufficiency and is not an uncommon reason why patients do not tolerate pancreatic supplements. If SIBO is eradicated then pancreatic supplements, if tried again, will usually be tolerated.

Free-Fatty-Acid Malabsorption

Malabsorption of free fatty acids occasionally occurs after small-bowel irradiation [69] and may be related to the development of lymphangectasia [70] (which rarely, is the only cause of steatorrhoea). A low-fat diet (i.e., 20–30 g a day), or occasionally a diet rich in medium-chain triglycerides, is needed in addition to optimum treatment of other causes of steatorrhoea.

Faecal Incontinence, Urgency, Tenesmus, Mucus Discharge, and Frequency of Defaecation

Of all gastrointestinal symptoms that can occur after radiotherapy, urgency of defaceation and faecal incontinence causes the greatest distress [71–73]; however, it is the most difficult symptom for patients to discuss.

Changes in stool consistency, reduced rectal volume, psychological issues, inflammation, or neoplasia in the lower gastrointestinal tract might increase the frequency of defaecation. In all patients with these symptoms, rectal examination with assessment of anal tone and flexible sigmoidoscopy is the minimum investigation needed. In patients with frequency of defaecation or changes in stool consistency, a full blood screen is appropriate. Local rectal or sigmoid pathology, such as a mucus-secreting tubulovillous adenoma or carcinoma, might cause faecal incontinence, and flexible sigmoidoscopy will exclude new onset inflammation of the lower GI tract unrelated to pelvic radiotherapy (which occurs in about 2% of patients in one series) [9]. Endoanal ultrasonography might define sphincter defects (e.g., after childbirth or those caused by radiotherapy).

A retrospective study [74] that evaluated the management of patients with faecal incontinence after pelvic radiotherapy found that the use of phenylephrine gel benefited three quarters of all patients with incontinence that had not responded to other treatments.

As these symptoms are commonly characterised by muscle spasm, several treatments exist that might help, including use of correct positioning on the lavatory, pelvic floor exercises, biofeedback, correct use of anti-diarrhoeal drugs, non-fermented stool- bulking agents (e.g., sterculia), and low doses of antidepressants. Surgery to divert the faecal flow and stoma formation might have a role in the few patients who have substantial loss of rectal volume and who have not responded to other interventions [1]. There have been suggestions that sacral nerve stimulators may be of use for faecal incontinence but this very expensive device should be implanted only with great caution into tissues made ischaemic after radiotherapy because of the high risk of complications and definitely only after all the other causes for faecal incontinence after radiotherapy—especially when there is diarrhea or steatorrhoea - have been excluded.

Rectal Bleeding

The natural history of radiation-induced bleeding after conformal radiotherapy is that it starts to be clinically apparent 6–12 months after radiotherapy, may get worse over the next 5 years or so and then slowly improve over the next 5–10 years. Some newer radiotherapy techniques may lead to a more prolonged time to recovery and cessation of all bleeding. The likelihood of bleeding is closely related to the dose of radiotherapy delivered to the anterior rectal wall. Up to half of all patients have some rectal bleeding after pelvic radiotherapy [75–77], for many it will be trivial but it is reported to impair quality of life in up to 6% of patients [78]. Incidence of transfusion-dependent bleeding is 1–5% of patients [78, 79].

The mucosal lesion that typically is associated with radiation-induced bleeding is angiectasia, which are a response to radiation-induced ischaemia. All patients, within weeks to months after treatment, develop endothelial dysfunction, with subsequent vascular sclerosis and wall fibrosis [80]. This can lead to narrowing or thrombosis of small arteries and arterioles, progressive ischaemia to the supplied tissues, and consequent neo-angiogenesis [81, 82]. Intermittent bleeding can frequently follow from these fragile new vessels which it on the surface of the mucosa.

All patients with any rectal bleeding should be offered assessment with at least flexible sigmoidoscopy; proctoscopy and rigid sigmoidoscopy are inadequate. Colonoscopy can be reserved for those with symptoms or signs that suggest pathological changes to the proximal colon [83]. There is no role for routine biopsy of typical radiation change and in patients who have undergone brachytherapy there is a significant risk of fistula formation after endoscopically guided biopsy of the anterior rectal wall. Lower GI endoscopy can be more difficult after previous radiotherapy and we recommend that only experienced endoscopists should assess these patients and that clinicians should consider routinely using either a paediatric colonoscope in this population or even a gastroscope rather than a normal colonoscope to reduce the risk of perforation around fixed loops in the sigmoid.

Several series have suggested that the nature of bleeding does not discriminate between the different causes and that radiotherapy is not the cause of rectal bleeding in 25–60% of patients [1]. For patients with severe bleeding, anticoagulants or antiplatelet therapies should be discontinued or reduced, if possible. Patients should be advised to maintain regular bowel habits and we often prescribe non fermentable stool bulking agents (we favour the use of sterculia above all other preparations) when needed to avoid addi-

tional trauma to the rectal mucosa from hard stool. For patients with trivial bleeding not causing anaemia or interfering with daily activities, once serious underlying pathology has been ruled out, should be reassured that they need no treatment [84].

Endoscopy

Endoscopy is frequently the first treatment option considered for patients with rectal bleeding. However, there have been only a very few controlled studies to evaluate its safety and efficacy in these patients and these rarely report symptom severity adequately so it is difficult to assess whether the intervention was required. Overall, based on retrospective and uncontrolled prospective studies, endoscopic treatment seems to be effective for about 80% of cases; the specific treatment given usually depends on the endoscopist's preference and expertise [85, 86]. However, when we worked in a specialist centre we were referred a steady flow of patients with serious complications of the endoscopic intervention; either perforation or non-healing ulceration. This is unsurprising as there is significant risk of non-healing after the use of a thermal therapy such as argon plasma in ischaemic tissue. While argon plasma and formalin therapy in small randomized controlled studies [87, 88] seem equally effective in reducing rectal bleeding our preference is to avoid argon plasma if at all possible and, if there is no ulceration present, use the technique of intra-rectal formalin instillation described by Cullen et al. [89].

Thermal Coagulation

If thermal coagulation therapy is used, it should only be performed by experienced endoscopists because of the frequency of serious procedure-related side effects [90–93]. Thermal coagulation therapy destroys bleeding vessels but also potentially the mucosa and submucosa. It therefore can lead to ulceration, which sometimes is associated with increased bleeding, chronic pain and slow healing (or no healing at all), and subsequent rectal stricture and loss of function. Prospective studies showed that as many as 50% of patients develop rectal ulcers after treatment [94]. Therefore, it is reasonable to propose reducing argon flow rates (≤2 L/min) and wattage (≤40 watt), with precise application, to try to reduce the number of complications [91].

Recently, the technique of Radiofrequency Ablation has been proposed as an effective solution for bleeding radiation proctopathy. It cannot be recommended until there are published data showing it is safe.

Formalin

Formalin solutions of 4–10% are applied directly to the mucosa, where they cauterize tissue and seal fragile neovasculature to prevent further bleeding. However, studies published on the effects of this approach are of poor quality, and important outcomes, including the risk of serious complications, are not well defined [95].

Endoscopic cryoablation and radiofrequency ablation have been proposed as alternative treatments and have shown initial promising results. However, results from only a few pilot, uncontrolled studies have been published [96, 97]. Additional well-performed studies are needed before the effects of endoscopic cryoablation can be recommended.

Nonendoscopic Therapies

Medicine

Patients with radiation-induced injuries have minimal amounts of inflammation, although pelvic radiation disease is frequently called *radiation proctitis*. This misleading term results in inappropriate treatment, such as with anti-inflammatory agents (steroids and 5-aminosalicylic acids), being frequently proposed as first-line treatment for pelvic radiation disease [98]. A systematic review of randomised and nonrandomised, prospective, comparative trials clearly show that these agents have no beneficial effects for patients with radiation toxicity [99]. At the moment, only 2 treatments have been shown (in small, non–placebo controlled, randomized trials) to be effective therapies for chronic radiation-induced telangiectasias: a 4-week course of oral metronidazole [100] and sucralfate enemas [101].

Antibiotics

Antibiotics have been used to treat patients with radiation-induced bleeding. Metronidazole kills anaerobic and microaerophilic bacteria, which contribute to hypoxia; it also can act as an immunomodulator. However, it is not clear how this antibiotic might reduce bleeding. Cavcic et al. [99] performed a study of 60 patients with radiation-induced rectal bleeding and diarrhea who were given either the combination of metronidazole (3 × 400 mg/day orally), mesalazine and betamethasone, or the combination of mesalazine and betamethasone. After 12 months of follow-up evaluation, they observed significant reductions in the incidence of rectal bleeding, ulceration, and diarrhoea in the metronidazole group. We belive that these findings indicate that improved

bowel function may have been seen as a result of effective treatment of small-bowel bacterial overgrowth and as a result of this improved bowel function, this is why bleeding was reduced.

Sucralfate Enema

A Cochrane review [101] has summarised the evidence for treatment of rectal bleeding from radiotherapy. Sucralfate enemas (2 g sucralfate suspension made-up with 30–50 mL water in a bladder syringe injected twice a day via a lubricated foley catheter passed through the anus into the rectum) are often effective but need often to be continued long term. It should be noted that systematic review suggests that corticosteroid or mesalazine enemas are ineffective for treating bleeding from radiation proctopathy.

Hyperbaric Oxygen

Hyperbaric oxygen therapy provides the best evidence that radiotherapy morbidity can be modified. This therapy seems to stimulate angiogenesis, fibroplasia, and tissue restructuring through an increase in oxygen gradients in ischaemic tissues. A systematic review [102] has summarised the efficacy of hyperbaric oxygen in the management of radiation-induced bleeding and other symptoms. These data (none of which are randomised and much of which are retrospective) are encouraging, but they lack consistency in scoring of symptoms and response criteria. Two randomized controlled trials have been published—one showed benefit [103]. Our own trial did not although in patients with bleeding possibly there was a trend to improvement [104]. Our own view is that there is a definite role for hyperbaric oxygen in patients with severe rectal ulceration but further studies are needed especially as hyperbaric oxygen is expensive and has a low risk of side-effects, including the theoretical risk of promoting the growth of occult metastases [1].

Surgery

A final treatment option is surgery to defunction or resect the bleeding area. However, these procedures have high morbidity. In view of the potential of all interventions to cause substantial harm to patients who may already have major problems, there is an urgent need for carefully designed multicentre randomised trials to assess the management of post-radiotherapy bleeding [1].

A clinical algorithm [17] for treating problematic radiation bleeding is shown in Table 4.

Table 4 Suggested steps for managing GI bleeding after pelvic radiotherapy

Step 1: Investigate with flexible endoscopy to determine the cause of the bleeding
Step 2: Optimise bowel function and stool consistency which may reduce the amount of bleeding
Step 3: If bleeding is not affecting quality of life (eg, staining clothes, causing anaemia, interfering with daily activities), reassure and do nothing further
Step 4: If bleeding affects quality of life, stop/reduce anticoagulants if possible and, if very severe, start sucralfate enemas
Step 5: Discuss definitive treatment to ablate the telangiectasia with the patient; options include:
(a) Hyperbaric oxygen therapy
(b) Argon plasma coagulation
(c) Formalin therapy

Preventing Radiation Injury: Future Perspectives

As yet, no objective biomarkers of radiation-induced toxicity exist; their discovery should be a very high research priority. The need for these markers has intensified due to the growing number of cancer survivors at risk for developing toxicity from cancer therapies and would allow us to select patients for trials of therapies to reduce that risk of toxicity [105].

A second priority is to develop treatments that are safe, easily administered and effective at reducing or eliminating adverse health effects to individuals from radiation exposure.

A number of radiation countermeasures are currently under investigation; however, these must undergo further trials before being approved for use on humans. Importantly, protective or mitigating agents can only be considered for clinical use if they do not hamper the anti-tumour effect of the radiotherapy treatment [102]. With regard to efficacy, it is crucial that both the effects on acute and late intestinal radiation injury are assessed as both agents that reduce acute and late injury are needed in order to improve the quality of life of patients [106].

Somatostatin Analogues

Radiation exposure causes breakdown of the intestinal epithelial barrier due to a decrease in intestinal crypt/stem cell proliferation and inadequate cell supplies to compensate for continuous enterocyte loss. As a result, sub epithelial tissues may be exposed to intraluminal pancreatic enzymes that subsequently aggravate the injury by initiating auto-digestion of the intestine and the induction of inflammatory processes [107, 108]. Strategies to reduce exogenous pancreatic

secretion, like pharmacological inhibition with somatostatin analogues, have been shown effective in reducing intestinal radiation toxicity in animals [109, 110]. Human studies investigating the effect of octreotide on post-irradiation diarrhoea in patients being treated for rectal or anal cancer have had mixed results [111, 112]. This might, in part, be because of the limited volume of small intestine in the radiation field, the site at which somatostatin analogues are expected to exert their effect.

The recently developed somatostatin analogue SOM230 (Pasireotide) may be more effective in reducing radiation injury than octreotide. It has a more favourable pharmacokinetic profile and broader receptor affinity. It was also found to reduce radiation toxicity when started up to 48 h after exposure [113]. Studies are now needed to determine the safety and potential efficacy of SOM230 in abdominal and pelvic radiotherapy.

Growth Factors and Growth Factor-Like Agents

The use of growth factors and growth factor-like agents to improve post-irradiation intestinal epithelial recovery has been researched over the past several years. Glucagon-like peptide 2 as well as keratinocyte and fibroblast growth factors has been shown to ameliorate post-irradiation intestinal injury in various animal models [114–119]. Moreover, recombinant human epidermal growth factor as well as R-spondin 1, an intestinal stem cell growth factor, has been shown to reduce apoptosis and improve recovery of the intestinal villi [120, 121]. Growth factor-like agents have also been be used to reduce radiation injury. For example, the growth factor-like lipid mediator lysophosphatidic acid (LPA) was shown to reduce post-irradiation intestinal apoptosis through the LPA receptor 2 subtype [122].

Going forwards, it is important that these agents do not affect radiation-induced tumour cell kill, tumour growth or other malignant tumour properties. In the animal studies performed, this did not appear to be the case. However, further research is needed to confirm these results and if they are shown to be effective, serious discussions are required to make them an affordable option.

Agents Acting on the Toll-Like Receptor 5 Pathway

Toll-like receptors (TLR) are an important component of the intestinal innate immunity. Activation of TLRs by commensal microflora is essential for the protection against intestinal injury and in the regulation of epithelial repair [123, 124]. Activation of TLRs reduces the sensitivity of enterocytes to radiation-induced apoptosis. The bacterial protein flagellin is a natural agonist of toll-like receptor 5 (TLR5). Both flagellin and the less toxic synthetic flagellin derivate CBLB502 have been shown to be potent radioprotectors in mice and non-human primates [125, 126].

Pretreatment with Toll-like receptor 5 agonist prevents radiation-induced apoptosis of intestinal epithelial cells and subsequent injury [126, 127]. A concern regarding the use of TLR5 receptor agonist is the possible induction of systemic inflammation [128]. Further research is thus needed to determine the safety and efficacy of the above mentioned agents before they can be used clinically to prevent intestinal radiation injury.

Endothelial Protectants

It is thought that post-irradiation, endothelial apoptosis contributes to intestinal stem cell dysfunction and mucosal injury [129]. Treatments that reduce radiation-induced microvascular endothelial cell apoptosis may therefore be able to prevent intestinal radiation injury [129]. The sphingolipid, ceramide, has been shown to play a crucial role in radiation-induced endothelial apoptosis. Radiation exposure can cause hydrolysis of cell membrane sphingomyelin by acid sphingomyelase which results in the formation of ceramide. Ceramide then initiates the apoptotic process via the mitochondrial system [130]. Bonnaud et al. showed that inhibition of post-irradiation ceramide production promotes post-irradiation endothelial survival and ameliorates intestinal injury in mice [131]. In addition, as well as reducing endothelial apoptosis, endothelial function may be improved post-irradiation with agents like 3-hydroxy-3-methylglutaryl-CoA (MHG-CoA) reductase inhibitors that have been shown to reduce intestinal radiation injury in animal models [132, 133].

γ-Tocotrienol

Another group of promising new agents targeted at reducing intestinal radiation injury are Vitamin E analogues or so called tocols that are powerful antioxidants with favourable toxicity profiles. Hence, they have strong potential to be developed as radioprotectants. γ-Tocotrienol may be so effective in reducing intestinal radiation injury because tocotrienols accumulate in the small intestine and colon to a higher level than tocopherols supplemented in the same concentration [134]. Other properties that may contribute to the powerful radioprotective effects of γ-tocotrienol are its ability to concentrate in endothelial cells to levels that are 30–50 fold greater compared to α-tocopherol and to inhibit the enzyme MHG-CoA reductase [135, 136].

At present, little is known about the effects of γ-tocotrienol on tumour cells during radiotherapy. γ-Tocotrienol may sensitise tumour cells to radiation exposure and chemotherapeutic agents [137, 138], however, further studies are needed to confirm that it does not protect tumour cells against radiation. With regard to the safety of γ-tocotrienol in human beings, studies from other fields have shown that γ-tocotrienol supplementation is well tolerated in human subjects [139, 140]. We have just completed a randomised double blind trial of tocotrienol combined with pentoxifylline and its utility in treating established radiation injury not responsive to other modalities. The results should be available soon.

Pentoxifylline +/− Vitamin E

Pentoxifylline is a methylxanthine derivative originally developed for the treatment of regional microcirculation disorders and shown to have anti-inflammatory and immunomodulatory properties. Consistent with animal data, the majority of studies published from the use of pentoxifylline in humans to treat radiation-induced fibrosis including some randomised trials have reported improvement. The total number of enrolled patients in these studies is 336 and looking through these studies gives an impression that pentoxifylline is more effective when used in combination with vitamin E but that any benefits achieved may take many months to become apparent. There is a pressing need for appropriately powered randomised studies, which should be double-blind placebo-controlled in view of the subjective nature of most clinical endpoints to confirm these encouraging findings.

Interleukin-11 (IL-11, Oprelvekin)

IL-11 is a multifunctional cytokine of the interleukin-6 (IL-6) family. It stimulates maturation of megakaryocytes and has anti-inflammatory properties as well as cytoprotective effects on gastrointestinal crypt cells [102]. Administration of IL-11 improves crypt survival and reduces GI mucosal injury after total-body irradiation in mice [141]. It also protects the clonogenic stem cells in murine small-intestinal crypts from impairment of their reproductive capacity by radiation [142]. Although IL-11 is well-tolerated in animals, significant adverse effects including fluid retention, multisystem organ failure and pleural effusion have limited its clinical use in humans.

OrbeShield®/Beclomethasone 17,21-Dipropionate (BDP)

BDP is a potent, topically-active corticosteroid currently under development as an orally-administered radiation countermeasure for GI-acute radiation syndrome (GI-ARS) [143]. It offers potent anti-inflammatory effects with minimal toxicity compared with other systemic corticosteroids. BDP showed significant survival benefit in a canine model of GI sub-syndrome [143]. In this model, canines received total body irradiation (TBI), followed by autologous BM administration and supportive care. This was coupled to experimental treatments with either the test agent or placebo. The study suggested that BDP can reduce inflammation of tissues of the GI mucosa after irradiation and can improve survival, even when treatment is initiated as late as 24 h post-irradiation [144].

Myeloid Progenitor Cells (MPC)

MPC can improve the survival of mice after exposure to high doses of radiation. It has been evaluated for use as a bridging therapy for radiation injuries and to mitigate the effects of lethal doses of ^{60}Co γ-irradiation and X-rays in different strains of mice [145]. Results from studies have demonstrated that cryopreserved allogeneic MPC significantly improved survival in strains of mice irradiated with lethal doses of ^{60}Co γ-radiation (CD2F1, 9.2 Gy) and X-ray exposures (BALB/c, 9 Gy) that are known to cause ARS in hematopoietic tissues [135]. The survival benefit was MPC-dose-dependent and significant even when MPC administration was delayed up to 7 day's post-irradiation. Additionally, MPC administration decreased deaths from ARS at radiation doses up to 15 Gy (^{60}Co γ-radiation, CD2F1 mice). Exposure levels of such magnitude can cause mice to succumb to multi-organ failure. Even at doses of up to 14 Gy ^{60}Co γ-radiation, MPC administration could be delayed up to 5 days in CD2F1 mice and still provide significant benefit to 30-day survival.

In addition, MPC also improves the structural integrity of GI tissue after irradiaton. This has been observed in a study that looked into the structural integrity of the GI tract of mice who had received MPC treatment after doses of radiation capable of causing GI injury and found that it improves the structural integrity of GI tissue and inhibits bacterial translocation from the GI tract [146]. These results give support to the administration of MPC as a bridging therapy for GI tissue. However, as promising as these studies are, further work

with extended observational periods are needed in order to investigate whether any potentially late-arising pathologies stem from graft versus host disease.

Enterade®/Amino Acid-Based Oral Rehydration Solution

Enterade® is an amino acid-based oral rehydration solution recently developed by researchers at the University of Florida. Studies in irradiated mice have shown that specific combinations of amino acids increase Na^+ absorption via amino acids-coupled Na + absorption while there is no stimulation of Cl^- secretion and, therefore, fluid secretion [147]. In addition, Enterade® led to tightening of the mucosal barrier, increased crypt count and villus length in intestinal tissue. The animal data are highly suggestive that Enterade® is an effective radiation mucosal protectant [147]. Publications subsequently suggest that it is palatable and safe and so the results of ongoing interventional human studies are eagerly awaited.

Human Microbiome

Recent research has shown how the gut microbiota interacts with the host to promote homoeostasis. These mechanisms could be important in our understanding of the gastrointestinal symptoms that are seen after pelvic radiotherapy. A study of 231 patients showed that 12% of microbial metabolic pathways were changed in patients with inflammatory bowel disease compared with only a 2% change in the microbial genera profile [148], with a shift towards a phenotype that allows the microbiota to cope with oxidative stress. Thus, dysbiosis associated with intestinal inflammation promotes a selection of bacteria capable of withstanding a highly oxidative environment, also present after radiotherapy [3].

Additionally, anaerobic bacteria convert primary bile acids into secondary bile acids. Secondary bile acids are anti-inflammatory and inhibit TNFα, interleukin 1α, interleukin 1β, and interleukin 6 through the bile acid specific receptor, TGR5. In inflammatory bowel disease, dysbiosis modifies this balance as it decreases the production of secondary bile acids, creating a proinflammatory environment [149]. Similar imbalances in the microbiota produced after intestinal radiation have been observed [150], suggesting that this mechanism could also be of importance in pelvic radiation disease.

Propionate, butyrate, and acetate are short-chain fatty acids with anti-inflammatory properties, suppressing proinflammatory cytokines such as NFκB, TNFα, interleukin 1a, or interleukin 6 [151, 152]. Butyrate also has a role in maintaining the stability of the intestinal epithelial barrier [153]. The microbiota plays a role in determining the availability and production of these molecules. Fibrolytic bacteria degrade large polysaccharides into smaller carbohydrates, which are then fermented into short-chain fatty acids [154, 155]. The *Roseburia* genus is an acetate consumer and butyrate producer, whereas *Phascolarctobacterium* is a propionate producer; they are both reduced in inflammatory bowel disease. *Faecalibacterium prausnitzii* is a major butyrate producer and is reduced in Crohn's disease [155]. These effects are clinically relevant in inflammatory bowel disease [155] and in acute radiation proctitis [156], and could also be relevant in pelvic radiation disease.

Thus, being able to characterise the gut microbiota and research its role further may allow the development of genomic and metabolomic profiles for risk assessment of patients and enable manipulation of the intestinal flora for prevention and treatment of pelvic radiation disease [3].

The development of next-generation sequencing technologies and metabolic phenotyping could make stratification of patients at risk of radiotherapy-induced gastrointestinal toxicity a realistic possibility. This is further supported by studies of common bacterial traits in patients with radiation-induced gastrointestinal symptoms [157]. A recent pilot study used an electronic nose and field asymmetrical ion mobility spectrometry to detect selected metabolites in the stool of 23 patients before and 4 weeks after pelvic radiotherapy, with promising results in risk prediction [158]. It is attractive to attribute this difference to changes in the microbiota. Nevertheless, these results should be carefully interpreted because at present faecal metabolomes do not stratify populations according to their gut bacteria [159].

Finally faecal microbiota transplantation has recently been reintroduced as a treatment for *Clostridium difficile*-induced colitis and evidence of its benefit is steadily growing [160]. It has not been tried in the context of radiation intestinal toxicity; however, its clinical potential seems exciting because it could be an inexpensive, potentially effective radiation-response modifier, possibly allowing for increases in the therapeutic index of pelvic radiotherapy [3].

Overall, the potential of the microbiota as a risk assessment and treatment instrument for radiation-induced gut toxicity seems promising. If confirmed, this could be an important step forward in oncology, allowing for inexpensive, patient-tailored treatment to modulate toxicity.

References

1. Andreyev HJN. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. Lancet Oncol. 2007;8:1007–17.
2. Wang J, Hauer-Jensen M. Neuroimmune interactions: potential target for mitigating or treating intestinal radiation injury. Br J Radiol. 2007;80(Spec. 1):S41–8.

3. Ferreira MR, Muls A, Dearnaley DP, Andreyev HJN. Microbiota and radiation-induced bowel toxicity - lessons from inflammatory bowel disease for the radiation oncologist. Lancet Oncol. 2014;15(3):e139–47.
4. Denham JW, Hauer-Jensen M, Peters LJ. Is it time for a new formalism to categorize normal tissue radiation injury? Int J Radiat Oncol Biol Phys. 2001;50(5):1105–6.
5. Bourne RG, Kearsley JH, Grove WD, Roberts SJ. The relationship between early and late gastrointestinal complications of radiation therapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys. 1983;9:1445–50.
6. Peters LJ, Ang KK, Thames HD Jr. Accelerated fractionation in the radiation treatment of head and neck cancer. A critical comparison of different strategies. Acta Oncol. 1988;27:185–94.
7. Hauer-Jensen M, Denham JW, Andreyev HJN. Radiation enteropathy—pathogenesis, treatment and prevention. Nat Rev Gastroenterol Hepatol. 2014;11(8):470–9. https://doi.org/10.1038/nrgastro.2014.
8. Andreyev HJN, Wotherspoon A, Denham JW, Hauer-Jensen M. "Pelvic radiation disease": new understanding and new solutions for a new disease in the era of cancer survivorship. Scand J Gastroenterol. 2011;46:389–97.
9. Andreyev HJ, Vlavianos P, Blake P, et al. Gastrointestinal symptoms after pelvic radiotherapy: role for the gastroenterologist? Int J Radiat Oncol Biol Phys. 2005;62:1464–71.
10. Andreyev HJN. Gastrointestinal complications of pelvic radiotherapy: are they of importance? Gut. 2005;54:1051–4.
11. Kozelsky T, Meyers G, Sloan J, et al. Phase III double-blind study of glutamine versus placebo for the prevention of acute diarrhea in patients receiving pelvic radiation therapy. J Clin Oncol. 2003;21:1669–74.
12. Dahlberg M, Glimelius B, Graf W, Pahlman L. Preoperative irradiation affects functional results after surgery for rectal cancer. Dis Colon Rectum. 1998;41(5):543–51.
13. Lundby L, Krogh K, Jensen V, et al. Long-term anorectal dysfunction after postoperative radiotherapy for rectal cancer. Dis Colon Rectum. 2005;48:1343–52.
14. Downing A, Morris EJA, Richards M, Corner J, Wright P, Sebag-Montefiore D, Finan P, Kind P, Wood C, Lawton S, Feltbower R, Wagland R, Vernon S, Thomas J, Glaser AW. Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of Individuals12 to 36 months after diagnosis. J Clin Oncol. 2015;33:616–24.
15. Bacon C, Giovannucci E, Testa M, Glass T, Kawachi I. The association of treatment-related symptoms with quality-of-life outcomes for localized prostate carcinoma patients. Cancer. 2002;94:862–71.
16. Andreyev HJN. Gastrointestinal problems after pelvic radiotherapy: the past, the present and the future. Clin Oncol. 2007;19:790–9.
17. Andreyev HJ, Davidson SE, Gillespie C, Allum WH, Swarbrick E. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut. 2012;61(2):179–92.
18. Taylor S, Byrne A, Adams R, Turner J, Hanna L, Staffurth J, Farnell D, Sivell S, Nelson A, Green J. Clin Oncol (R Coll Radiol). 2016;28(10):e139–47.
19. Davidson SE, Faithfull S. Late radiotherapy effects: is bowel morbidity adequately documented or patients' needs managed appropriately? Clin Oncol. 2006;18:419–20.
20. Gillespie C, Goode C, Hackett C, Andreyev HJ. Aliment Pharmacol Ther. 2007;26(4):555–63.
21. Chen TYT, Emmertsen KJ, Laurberg S. Bowel dysfunction after rectal cancer treatment: a study comparing the specialist's versus patient's perspective. BMJ Open. 2013;4:e003374.
22. Tom A, Bennett AV, Rothenstein D, Law E, Goodman KA. Prevalence of patient-reported gastrointestinal symptoms and agreement with clinician toxicity assessments in radiation therapy for anal cancer. Qual Life Res. 2018;27(1):97–103.
23. Olopade FO, Norman AR, Blake P, Dearnaley DP, Harrington KJ, Khoo V, et al. The inflammatory bowel disease questionnaire and the Vaizey incontinence questionnaire are useful to identify gastrointestinal toxicity after pelvic radiotherapy. Br J Cancer. 2005;92:1663–70.
24. Andreyev J, Ross P, Donnellan C, Lennan E, Leonard P, Waters C, et al. Guidance on the management of diarrhoea during cancer chemotherapy. Lancet Oncol. 2014;15:e447–60.
25. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32:920–4.
26. Andreyev HJN. GI consequences of cancer treatment: a clinical perspective. Radiat Res. 2016;185:341–8.
27. Capp A, Inostroza-Ponta M, Bill D, Moscato P, Lai C, Christie D, Lamb D, Turner S, Joseph D, Matthews J, Atkinson C, North J, Poulsen M, Spry NA, Tai KH, Wynne C, Duchesne G, Steigler A, Denham JW. Is there more than one proctitis syndrome? A revisitation using data from the TROG 96.01 trial. J Radiother Oncol. 2009;90:400–7.
28. Muls M, Klimova K, Andreyev HJN. Clinical decision-making in managing changes in gastrointestinal function following cancer therapies: is experience enough? Eur J Cancer Care. 2018;27:e12766.
29. Andreyev HJ, Benton BE, Lalji A, Norton C, Mohammed K, Gage H, Lindsay JO. Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial. Lancet. 2013;382(9910):2084–92.
30. Gupta A, Muls AC, Lalji A, Thomas K, Watson L, Shaw C, Andreyev HJ. Outcomes from treating bile acid malabsorp- tion using a multidisciplinary approach. Support Care Cancer. 2015;23(10):2881–90. https://doi.org/10.1007/s00520-015-2653-5.
31. Henson CC, Davidson SE, Ang Y, Babbs C, Crampton J, Kelly M, et al. Structured gastroenterological intervention and improved outcome for patients with chronic gastrointestinal symptoms following pelvic radiotherapy. Support Care Cancer. 2013;21(8):2255–65.
32. Muls AC, Lalji A, Marshall C, Butler L, Shaw C, Vyoral S, et al. The holistic management of consequences of cancer treatment by a gastrointestinal and nutrition team: A financially viable ap- proach to an enormous problem? Clin Med (Lond). 2016;16(3):240–6.
33. Andreyev HJN, Muls AC, Norton C, et al. Guidance: the practical management of the gastrointestinal symptoms of pelvic radiation disease. Frontline Gastroenterol. 2014;6:53–72. https://doi.org/10.1136/flgastro-2014-100468.
34. Andreyev HJ. Pelvic radiation disease. Color Dis. 2015;17(1):2–6.
35. Wedlake L, Thomas K, McGough C, Andreyev HJN. Small bowel bacterial overgrowth and lactose intolerance during radical pelvic radiotherapy: an observational study. Eur J Cancer. 2008;44(15):2212–7.
36. Ludgate S, Merrick M. The pathogenesis of post-irradiation chronic diarrhoea: measurement of SeHCAT and B12 absorption for differential diagnosis determines treatment. Clin Radiol. 1985;36:275–8.
37. Danielsson A, Nyhlin H, Persson H, et al. Chronic diarrhoea after radiotherapy for gynaecological cancer: occurrence and aetiology. Gut. 1991;32:1180–7.
38. Stryker J, Hepner G, Mortel R. The effect of pelvic irradiation on ileal function. Radiology. 1977;124:213–6.
39. Grace E, Shaw C, Whelan K, Andreyev HJN. Review article: small intestinal bacterial overgrowth - prevalence, clinical fea-

tures, current and developing diagnostic tests, and treatment. Aliment Pharmacol Ther. 2013;38(7):674–88.
40. Yeoh E, Lui D, Lee N. The mechanism of diarrhoea resulting from pelvic and abdominal radiotherapy; a prospective study using selenium-75 labelled conjugated bile acid and cobalt-58 labelled cyanocobalamin. Br J Radiol. 1984;57:1131–6.
41. Miholic J, Vogelsang H, Schlappack O, et al. Small bowel function after surgery for chronic radiation enteritis. Digestion. 1989;42:30–8.
42. Heusinkveld R, Manning M, Aristizabal S. Control of radiation-induced diarrhea with cholestyramine. Int J Radiat Oncol Biol Phys. 1978;4:687–90.
43. Yeoh E, Horowitz M, Russo A, et al. Effect of pelvic irradiation on gastrointestinal function. Am J Med. 1993;95:397–406.
44. Newman A, Katsaris J, Blendis L, et al. Small-intestinal injury in women who have had pelvic radiotherapy. Lancet. 1973;2:1471–3.
45. Scarpello J, Sladen G. Malabsorption in relation to abdominal irradiation and quadruple chemotherapy for lymphosarcoma. Postgrad Med J. 1977;53:218–21.
46. Schuster J, Stryker J, Demers L, Mortel R. Absence of bile acid malabsorption as a late effect of pelvic irradiation. Int J Radiat Oncol Biol Phys. 1986;12:1605–10.
47. Bosaeus I, Andersson H, Nystrom C. Effect of a low-fat diet on bile salt excretion and diarrhoea in the gastrointestinal radiation syndrome. Acta Radiol Oncol Radiat Phys Biol. 1979;18:460–4.
48. Phillips F, Muls AC, Lalji A, Andreyev HJ. Are bile acid malabsorption and bile acid diarrhoea important causes of loose stool complicating cancer therapy? Color Dis. 2015;17(8):730–4.
49. Arlow F, Dekovich A, Priest R, Beher W. Bile acids in radiation-induced diarrhea. South Med J. 1987;80:1259–61.
50. Hofmann A, Poley J. Role of bile acid malabsorption in pathogenesis of diarrhea and steatorrhea in patients with ileal resection. I. Response to cholestyramine or replacement of dietary long chain triglyceride by medium chain triglyceride. Gastroenterology. 1972;62:918–34.
51. Ford GA, Preece JD, Davies IH, Wilkinson SP. Use of SeHCAT test in the investigation of diarrhoea. Postgrad Med J. 1992;68:272–6.
52. Puleston J, Morgan H, Andreyev HJN. New treatment for bile salt malabsorption. Gut. 2005;54:441–2.
53. Weiss R, Stryker J. 14C-lactose breath tests during pelvic radiotherapy: the effect of the amount of small bowel irradiated. Radiology. 1982;142:507–10.
54. Olmos R, den Hartog JF, Hoefnagel C, Taal B. Imaging and retention measurements of selenium 75 homocholic acid conjugated with taurine, and the carbon 14 glycochol breath test to document ileal dysfunction due to late radiation damage. Eur J Nucl Med. 1991;18:124–8.
55. Beer W, Fan A, Halsted C. Clinical and nutritional implications of radiation enteritis. Am J Clin Nutr. 1985;41:85–91.
56. Pickles T, Phillips N. The risk of second malignancy in men with prostate cancer treated with or without radiation in British Columbia, 1984–2000. Radiother Oncol. 2002;65:145–51.
57. Boice JDJ, Engholm G, Kleinerman RA, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat Res. 1988;116:3–55.
58. Kleinerman R, Boice JJ, Storm H, et al. Second primary cancer after treatment for cervical cancer. An international cancer registries study. Cancer. 1995;76:442–52.
59. Brenner D, Curtis R, Hall E, Ron E. Second malignancies in prostate carcinoma patients after pelvic radiotherapy compared with surgery. Cancer. 2000;88:398–406.
60. Baxter NN, Tepper JE, Durham SB, et al. Increased risk of rectal cancer after prostate radiation: a population-based study. Gastroenterology. 2005;128:819–24.
61. Mitchell C, Simpson F, Davison A, Losowsky M. Radiation pancreatitis: a clinical entity? Digestion. 1979;19:134–6.
62. Kingham J, Barrett A. Pancreatic insufficiency following abdominal irradiation. Postgrad Med J. 1980;56:804–5.
63. Nguyen T, Bugat R, Combes P. Postoperative irradiation of carcinoma of the head of the pancreas area: short-time tolerance and results to precision high-dose technique in 18 patients. Cancer. 1982;50:53–6.
64. Sindelar WF, Hoekstra H, Restrepo C, Kinsella TJ. Pathological tissue changes following intraoperative radiotherapy. Am J Clin Oncol. 1986;9:504–9.
65. Levy P, Menzelxhiu A, Paillot B, et al. Abdominal radiotherapy is a cause for chronic pancreatitis. Gastroenterology. 1993;105:905–9.
66. Dookeran K, Thompson M, Allum W. Pancreatic insufficiency secondary to abdominal radiotherapy. Eur J Surg Oncol. 1993;19:95–6.
67. Santhiswaroop V, Dhir V, Mohandas KM. Abdominal radiotherapy and chronic pancreatitis. Gastroenterology. 1994;107:632.
68. Ratzkowski E, Hochman A. Gastro-intestinal function after abdominal cobalt irradiation. Acta Radiol Ther Phys Biol. 1968;7:417–32.
69. Rao SS, Dundas S, Holdsworth CD. Intestinal lymphangiectasia secondary to radiotherapy and chemotherapy. Dig Dis Sci. 1987;32:939–42.
70. al-Abany M, Helgason A, Cronqvist A, et al. Long-term symptoms after external beam radiation therapy for prostate cancer with three or four fields. Acta Oncol. 2002;41:532–42.
71. Henningsohn L, Wijkstrom H, Dickman P, et al. Distressful symptoms after radical radiotherapy for urinary bladder cancer. Radiother Oncol. 2002;62:215–25.
72. Bergmark K, Avall-Lundqvist E, Dickman P, et al. Patient-rating of distressful symptoms after treatment for early cervical cancer. Acta Obstet Gynecol Scand. 2002;81:443–50.
73. Badvie S, Andreyev HJN. Topical phenylephrine in the treatment of radiation-induced faecal incontinence. Clin Oncol. 2005;17:122–6.
74. Widmark A, Fransson P, Tavelin B. Self-assessment questionnaire for evaluating urinary and intestinal late side effects after pelvic radiotherapy in patients with prostate cancer compared with an age-matched control population. Cancer. 1994;74:2520–32.
75. Crook J, Esche B, Futter N. Effect of pelvic radiotherapy for prostate cancer on bowel, bladder, and sexual function: the patient's perspective. Urology. 1996;47:387–94.
76. Dearnaley D, Khoo V, Norman A, et al. Comparison of radiation side effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet. 1999;353:267–72.
77. Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. Aliment Pharmacol Ther. 2003;18:987–94.
78. Boersma L, van den Brink M, Bruce A, et al. Estimation of the incidence of late bladder and rectum complications after high-dose (70–78 Gy) conformal radiotherapy for prostate cancer, using dose- volume histograms. Int J Radiat Oncol Biol Phys. 1998;41:83–92.
79. Chun M, Kang S, Kil H-J, et al. Rectal bleeding and its management after irradiation for uterine cervical cancer. Int J Radiat Oncol Biol Phys. 2004;58:98–105.
80. Fuccio L, Guido A, Andreyev HJN. Management of intestinal complications in patients with pelvic radiation disease. Clin Gastroenterol Hepatol. 2012;10:1326–34.
81. Denham JW, Hauer-Jensen M. The radiotherapeutic injury–a com- plex "wound". Radiother Oncol. 2002;63:129–45.

82. Brenn T, Fletcher CD. Postradiation vascular proliferations: an increasing problem. Histopathology. 2006;48:106–14.
83. Williams HR, Vlavianos P, Blake P, et al. The significance of rectal bleeding after pelvic radiotherapy. Aliment Pharmacol Ther. 2005;21:1085–90.
84. Goldner G, Pötter R, Kranz A, et al. Healing of late endoscopic changes in the rectum between 12 and 65 months after external beam radiotherapy. Strahlenther Onkol. 2011;187:202–5.
85. Postgate A, Saunders B, Tjandra J, et al. Argon plasma coagulation in chronic radiation proctitis. Endoscopy. 2007;39:361–5.
86. Musunuri AS, Prabhakar B, Rao PK, et al. Topical formalin vs argon plasma coagulation for radiation proctitis–experience of a tertiary referral hospital in South India. Gastrointest Endosc. 2006;63(5):PAB205.
87. Tam WCE, Moore J, Conroy-Hiller TA, et al. Prospective randomised treatment trial of argon plasma coagulation and topical formalin for radiation proctitis. Gastrointest Endosc. 2001;53: AB1–240:AB184.
88. Taïeb S, Rolachon A, Cenni JC, et al. Effective use of argon plasma coagulation in the treatment of severe radiation proctitis. Dis Colon Rectum. 2001;44:1766–71.
89. Cullen SN, Frenz M, Mee A. Treatment of haemorrhagic radiation-induced proctopathy using small volume topical formalin instillation. Aliment Pharmacol Ther. 2006;23:1575–9.
90. Villavicencio RT, Rex DK, Rahmani E. Efficacy and complications of argon plasma coagulation for hematochezia related to radiation proctopathy. Gastrointest Endosc. 2002;55:70–4.
91. de Parades V, Etienney I, Bauer P, et al. Formalin application in the treatment of chronic radiation-induced hemorrhagic proctitis–an effective but not risk-free procedure: a prospective study of 33 patients. Dis Colon Rectum. 2005;48:1535–41.
92. Saclarides TJ, King DG, Franklin JL, et al. Formalin instillation for refractory radiation-induced hemorrhagic proctitis. Report of 16 patients. Dis Colon Rectum. 1996;39:196–9.
93. Ravizza D, Fiori G, Trovato C, et al. Frequency and outcomes of rectal ulcers during argon plasma coagulation for chronic radia- tion-induced proctopathy. Gastrointest Endosc. 2003;57:519–25.
94. Denton AS, Bentzen SM, Maher EJ. How useful are observational reports in the evaluation of interventions for radiation morbidity? An analysis of formalin therapy for late radiation proctitis. Radiother Oncol. 2002;64:291–5.
95. Hou JK, Abudayyeh S, Shaib Y. Treatment of chronic radiation proctitis with cryoablation. Gastrointest Endosc. 2011;73:383–9.
96. Zhou C, Adler DC, Becker L, et al. Effective treatment of chronic radiation proctitis using radiofrequency ablation. Therap Adv Gastroenterol. 2009;2:149–56.
97. Henson CC, Andreyev HJ, Symonds RP, et al. Late-onset bowel dysfunction after pelvic radiotherapy: a national survey of current practice and opinions of clinical oncologists. Clin Oncol (R Coll Radiol). 2011;23:552–7.
98. Denton AS, Andreyev HJ, Forbes A, et al. Systematic review for non-surgical interventions for the management of late radiation proctitis. Br J Cancer. 2002;87:134–43.
99. Cavcić J, Turcić J, Martinac P, et al. Metronidazole in the treatment of chronic radiation proctitis: clinical trial. Croat Med J. 2000;41:314–8.
100. Kochhar R, Patel F, Dhar A, et al. Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate. Dig Dis Sci. 1991;36:103–7.
101. Denton A, Forbes A, Andreyev HJN, Maher EJ. Non-surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis. Cochrane Database Syst Rev. 2002;1:CD003455.
102. Feldmeier J, Hampson N. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. Undersea Hyperb Med. 2002;29:4–30.
103. Clarke RE, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. Int J Radiat Oncol Biol Phys. 2008;72(1):134–43.
104. Glover M, et al. Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (HOT2): a randomised, double-blind, sham-controlled phase 3 trial. Lancet Oncol. 2016;17(2):224–33.
105. Okunieff P, Chen Y, Maguire DJ, Huser AK. Molecular markers of radiation-related Normal tissue toxicity. Cancer Metastasis Rev. 2008;27(3):363–74.
106. Singh VK, Garcia M, Seed TM. A review of radiation countermeasures focusing on injury-specific medicinals and regulatory approval status: part II. Countermeasures for limited indications, internalized radionuclides, emesis, late effects, and agents demonstrating efficacy in large animals with or without FDA IND status. Int J Radiat Biol. 2017;93(9):870–84.
107. Berbée M, Hauer-Jensen M. Novel drugs to ameliorate gastrointestinal normal tissue radiation toxicity in clinical practice: what is emerging from the laboratory. Curr Opin Support Palliat Care. 2012;6(1):54–9.
108. Morgenstern L, Hiatt N. Injurious effect of pancreatic secretions on post-radiation enteropathy. Gastroenterology. 1967;53(6):923–9.
109. Wang J, Zheng H, Sung CC, Hauer-Jensen M. The synthetic somatostatin analogue, octreotide, ameliorates acute and delayed intestinal radiation injury. Int J Radiat Oncol Biol Phys. 1999;45(5):1289–96.
110. Abbasoglu SD, Erbil Y, Eren T, et al. The effect of heme oxygenase-1 induction by octreotide on radiation enteritis. Peptides. 2006;27(6):1570–6.
111. Yavuz MN, Yavuz AA, Aydin F, et al. The efficacy of octreotide in the therapy of acute radiation-induced diarrhea: a randomized controlled study. Int J Radiat Oncol Biol Phys. 2002;54(1):195–202.
112. Zachariah B, Gwede CK, James J, et al. Octreotide acetate in prevention of chemoradiation-induced diarrhea in anorectal cancer: randomized RTOG trial 0315. J Natl Cancer Inst. 2010;102(8):547–56.
113. Fu Q, Berbee M, Wang W, et al. Preclinical evaluation of SOM230 as a radiation mitigator in a mouse model: postexposure time window and mechanisms of action. Radiat Res. 2011;175(6):728–35; This study shows that the somatostatin analogue SOM230 inhibits pancreatic secretion and reduces radiation-induced mortality even when administration is started as late as 48 hours after radiation exposure.
114. Farrell CL, Bready JV, Rex KL, et al. Keratinocyte growth factor protects mice from chemotherapy and radiation-induced gastrointestinal injury and mortality. Cancer Res. 1998;58(5):933–9.
115. Matsuu-Matsuyama M, Nakashima M, Shichijo K, et al. Basic fibroblast growth factor suppresses radiation-induced apoptosis and TP53 pathway in rat small intestine. Radiat Res. 2010;174:52–61.
116. Nakayama F, Hagiwara A, Umeda S, et al. Post treatment with an FGF chimeric growth factor enhances epithelial cell proliferation to improve recovery from radiation-induced intestinal damage. Int J Radiat Oncol Biol Phys. 2010;78(3):860–7.
117. Farrell CL, Rex KL, Chen JN, et al. The effects of keratinocyte growth factor in preclinical models of mucositis. Cell Prolif. 2002;35(Suppl 1):78–85.

118. Torres S, Thim L, Milliat F, et al. Glucagon-like peptide-2 improves both acute and late experimental radiation enteritis in the rat. Int J Radiat Oncol Biol Phys. 2007;69(5):1563–71.
119. Booth C, Booth D, Williamson S, et al. Teduglutide ([Gly2]GLP-2) protects small intestinal stem cells from radiation damage. Cell Prolif. 2004;37(6):385–400.
120. Oh H, Seong J, Kim W, et al. Recombinant human epidermal growth factor (rhEGF) protects radiation-induced intestine injury in murine system. J Radiat Res. 2010;51(5):535–41.
121. Bhanja P, Saha S, Kabarriti R, et al. Protective role of R-spondin1, an intestinal stem cell growth factor, against radiation-induced gastrointestinal syndrome in mice. PLoS One. 2009;4(11):e8014.
122. Deng W, Shuyu E, Tsukahara R, et al. The lysophosphatidic acid type 2 receptor is required for protection against radiation-induced intestinal injury. Gastroenterology. 2007;132(5):1834–51.
123. Fukata M, Chen A, Klepper A, et al. Cox-2 is regulated by toll-like receptor-4 (TLR4) signaling: role in proliferation and apoptosis in the intestine. Gastroenterology. 2006;131(3):862–77.
124. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, et al. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. Cell. 2004;118(2):229–41.
125. Vijay-Kumar M, Aitken JD, Sanders CJ, et al. Flagellin treatment protects against chemicals, bacteria, viruses, and radiation. J Immunol. 2008;180(12):8280–5.
126. Burdelya LG, Krivokrysenko VI, Tallant TC, et al. An agonist of toll-like receptor 5 has radioprotective activity in mouse and primate models. Science. 2008;320(5873):226–30.
127. Jones RM, Sloane VM, Wu H, et al. Flagellin administration protects gut mucosal tissue from irradiation-induced apoptosis via MKP-7 activity. Gut. 2011;60(5):648–57.
128. Abreu MT. Harnessing the power of bacteria to protect the gut. N Engl J Med. 2008;359(7):756–9.
129. Paris F, Fuks Z, Kang A, et al. Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice. Science. 2001;293(5528):293–7.
130. Kolesnick R, Fuks Z. Radiation and ceramide-induced apoptosis. Oncogene. 2003;22(37):5897–906.
131. Bonnaud S, Niaudet C, Legoux F, et al. Sphingosine-1-phosphate activates the AKT pathway to protect small intestines from radiation-induced endothelial apoptosis. Cancer Res. 2010;70(23):9905–15.
132. Haydont V, Bourgier C, Pocard M, et al. Pravastatin inhibits the Rho/CCN2/extracellular matrix cascade in human fibrosis explants and improves radiation-induced intestinal fibrosis in rats. Clin Cancer Res. 2007;13(18 Pt 1):5331–40.
133. Wang J, Boerma M, Fu Q, et al. Simvastatin ameliorates radiation enteropathy development after localized, fractionated irradiation by a protein C-independent mechanism. Int J Radiat Oncol Biol Phys. 2007;68(5):1483–90.
134. Yang Z, Lee MJ, Zhao Y, Yang CS. Metabolism of tocotrienols in animals and synergistic inhibitory actions of tocotrienols with atorvastatin in cancer cells. Genes Nutr. 2012;7(1):11–8.
135. Naito Y, Shimozawa M, Kuroda M, et al. Tocotrienols reduce 25-hydroxycholesterol-induced monocyte-endothelial cell interaction by inhibiting the surface expression of adhesion molecules. Atherosclerosis. 2005;180(1):19–25.
136. Pearce BC, Parker RA, Deason ME, et al. Hypocholesterolemic activity of synthetic and natural tocotrienols. J Med Chem. 1992;35(20):3595–606.
137. Kumar KS, Raghavan M, Hieber K, et al. Preferential radiation sensitization of prostate cancer in nude mice by nutraceutical antioxidant gamma-tocotrienol. Life Sci. 2006;78(18):2099–104.
138. Kunnumakkara AB, Sung B, Ravindran J, et al. Gamma-tocotrienol inhibits pancreatic tumours and sensitizes them to gemcitabine treatment by modulating the inflammatory microenvironment. Cancer Res. 2010;70(21):8695–705.
139. Mahalingam D, Radhakrishnan AK, Amom Z, et al. Effects of supplementation with tocotrienol-rich fraction on immune response to tetanus toxoid immunization in normal healthy volunteers. Eur J Clin Nutr. 2011;65(1):63–9.
140. Rasool AH, Yuen KH, Yusoff K, et al. Dose dependent elevation of plasma tocotrienol levels and its effect on arterial compliance, plasma total antioxidant status, and lipid profile in healthy humans supplemented with tocotrienol rich vitamin E. J Nutr Sci Vitaminol (Tokyo). 2006;52(6):473–8.
141. Potten CS. Interleukin-11 protects the clonogenic stem cells in murine small-intestinal crypts from impairment of their reproductive capacity by radiation. Int J Cancer. 1995;62:356–61.
142. Potten CS. Protection of the small intestinal clonogenic stem cells from radiation-induced damage by pretreatment with interleukin 11 also increases murine survival time. Stem Cells. 1996;14:452–9.
143. Soligenix Inc. OrbeShield™ for gastrointestinal acute radiation syndrome (GI ARS). Princeton, NJ: Soligenix, Inc.;2016. http://www.soligenix.com/pipeline/vaccinesbiodefense/orbeshield-for-gastrointestinal-acute-radiation-syndrome-gi-ars/. Accessed 24 Sept 2018.
144. Georges GE, Kuver RP, Jordan R, Aragon A, Yang Y, Lesnikova M, Lesnikov V, Sale GE, McDonald GB. Post-exposure oral 17,21-beclomethasone dipropionate (BDP) improves survival in a canine gastrointestinal acute radiation syndrome (GI-ARS) model. Poster presented at: 58th annual meeting of the Radiation Research Society, San Juan (PR); 2012.
145. Singh VK, Christensen J, Fatanmi OO, Gille D, Ducey EJ, Wise SY, Karsunky H, Sedello AK. Myeloid progenitors: a radiation countermeasure that is effective when initiated days after irradiation. Radiat Res. 2012;177:781–91.
146. Cellerant Therapeutics. CLT-008 myeloid progenitor cells [online]. Cellerant therapeutics. 2013. http://www.cellerant.com/. Accessed 24 Sept 2018.
147. Yin L, Gupta R, Vaught L, Grosche A, Okunieff P, Vidyasagar S. An amino acid-based oral rehydration solution (AA-ORS) enhanced intestinal epithelial proliferation in mice exposed to radiation. Sci Rep. 2016;6:37220.
148. Morgan XC, Tickle TL, Sokol H, et al. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biol. 2012;13:R79–97.
149. Duboc H, Rajca S, Rainteau D, et al. Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases. Gut. 2013;62:531–9.
150. Bowen R, Miller P, Shanahan MT, Packey CD, Sartor RB. Radiation exposure induces dysbioses throughout the small intestinal and colonic lumen and mucosa that resemble those seen in human inflammatory bowel diseases. Inflamm Bowel Dis. 2011;17(suppl 2):S86.
151. Tedelind S, Westberg F, Kjerrulf M, Vidal A. Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease. World J Gastroenterol. 2007;13:2826–32.
152. Segain JP, de la Blétière DR, Bourreille A, et al. Butyrate inhibits inflammatory responses through NFkappaB inhibition: implications for Crohn's disease. Gut. 2000;47:397–403.
153. Plöger S, Stumpff F, Penner GB, et al. Microbial butyrate and its role for barrier function in the gastrointestinal tract. Ann N Y Acad Sci. 2012;1258:52–9.
154. Hsiao WW, Metz C, Singh DP, Roth J. The microbes of the intestine: an introduction to their metabolic and signaling capabilities. Endocrinol Metab Clin N Am. 2008;37:857–71.

155. Craven M, Egan CE, Dowd SE, et al. Inflammation drives dysbiosis and bacterial invasion in murine models of ileal Crohn's disease. PLoS One. 2012;7:e41594.
156. Hille A, Herrmann MK, Kertesz T, et al. Sodium butyrate enemas in the treatment of acute radiation-induced proctitis in patients with prostate cancer and the impact on late proctitis. A prospective evaluation. Strahlenther Onkol. 2008;184:686–92.
157. Manichanh C, Varela E, Martinez C, et al. The gut microbiota predispose to the pathophysiology of acute postradiotherapy diarrhea. Am J Gastroenterol. 2008;103:1754–61.
158. Covington JA, Wedlake L, Andreyev J, et al. The detection of patients at risk of gastrointestinal toxicity during pelvic radiotherapy by electronic nose and FAIMS: a pilot study. Sensors (Basel). 2012;12:13002–18.
159. Holmes E, Li JV, Marchesi JR, Nicholson JK. Gut microbiota composition and activity in relation to host metabolic phenotype and disease risk. Cell Metab. 2012;16:559–64.
160. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med. 2013;368:407–15.

Problems After Gastric Surgery

Alastair Forbes and Alistair McIntyre

Key Points

1. Gastric surgery is most commonly a result of surgery for cancer (usually gastric) or as a result of complications of peptic ulceration (bleeding or perforation).
2. The anatomy and thus physiology must be understood following gastric surgery (e.g. how much of which part of the stomach was removed, how do pancreatico-biliary secretions enter the system etc.).
3. Malnutrition results from reduced intake (partly due to early satiety), poor gastric secretion/mixing and sieving functions, reduced pancreatic secretions (maldigestion) and dysmotility (fast gut transit due to neural disruption) all of which contribute to malabsorption. Most patients are chronically underweight.
4. General malnutrition and/or specific deficiencies (e.g. iron, B_{12}, folate, fat soluble vitamins (especially vit D), thiamine, pyridoxine and copper) may result.
5. Early and late dumping syndrome, small bowel bacterial overgrowth, post vagotomy diarrhoea, bile salt malabsorption and osteoporosis may occur. In addition there is an increased risk of gastric cancer.
6. These patients need long-term follow up for general/specific nutritional monitoring/giving appropriate supplements, treating fast transit (high dose loperamide or octreotide), small intestinal bacterial overgrowth (SIBO) (rotating antibiotics), bile salt malabsorption (cholestyramine) and monitoring for osteopenia/osteoporosis and gastric cancer.

Introduction and Background

Gastric surgery is very rarely a cause of intestinal failure. Only when there have been substantial operative complications or when gastric surgery is combined with some other insult to gastrointestinal integrity is intestinal failure at all likely to occur. However, although surgery for gastric pathology is now less often performed than in earlier decades, these combinations of multiple morbidity are seen and form a small but important part of intestinal failure practice. Additionally, the inclusion of gastric interventions in most bariatric procedures (chapter "Surgery for Obesity and Its Consequences") reinforces the value of an understanding of the consequences of disturbing the functions of this organ.

Operations have been performed on the stomach to treat cancer and peptic ulcer disease since Billroth's first partial gastrectomy in 1881. These operations initially disrupted normal gastrointestinal physiology to a very marked degree. As surgical techniques developed, mobility and mortality were reduced but some patients nonetheless developed major post-operative problems which were considered part of a post-gastrectomy syndrome. These problems can be attributed to alterations in gastric, intestinal and pancreatic physiology, and may result directly or indirectly in malabsorption and other nutritional deficiencies.

Elective surgery for peptic ulcer disease has become much less common because of a reduced incidence of ulcers and improved medical therapy with acid suppression and eradication of *Helicobacter pylori*. Emergency surgery for complications such as bleeding and perforation is still required but rarely necessitates gastrectomy; consequently there are few lasting effects on gastrointestinal physiology. By contrast there is a continued and increasing need for gastric resection for malignancy, particularly in the west, with the increasing recognition of early and potentially curable cancers.

Alistair McIntyre has died before the publication of this book.

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Undernutrition Following Gastric Surgery

Post-gastrectomy syndromes comprise a wide spectrum of conditions, many of which are associated with adverse nutritional consequences. Reduced intake and malabsorption both contribute to weight loss and are often seen together in affected patients.

Inadequate nutritional intake can result from early satiety due to a small volume gastric remnant and/or its lack of compliance. Operations which alter gastric motor function without an adequate drainage procedure being performed lead to delayed gastric emptying, which also leads to post-prandial fullness and early satiety. Alterations in gastric motility resulting in inadequate mixing, combined with surgically induced reduction of acid, pepsin and intrinsic factor secretion, contribute to a varying degree to subsequent malabsorption of the food that has been consumed.

It is common for gastric surgery to be followed by suboptimal pancreatic function given that pancreatic exocrine function is determined in part by an intact enteroendocrine system, and because procedures that create an afferent loop separate pancreatic secretions from the immediate outflow from the remaining stomach (or the oesophagus when a total gastrectomy has been performed) (see below), thus reducing their ability to contribute to digestion.

The gut hormone responses to food clearly differ substantially from those in normal individuals, the secretion profiles for insulin, glucagon-like peptide 1 and cholecystokinin all being significantly different after a liquid challenge in gastrectomised patients [1].

The function of the proximal small bowel may be compromised by rapid transit, limiting the time available for absorption of nutrients, and further if bacterial overgrowth occurs (see below). Nonetheless mucosal absorptive capacity appears to remain within normal limits in most cases.

Patients may dramatically reduce their intake of food in attempts to avoid post-prandial symptoms and especially so if they are affected by the dumping syndrome or diarrhoea (see below). Other patients may select an inappropriate diet, with large and insufficiently masticated particles of food, nutrients with especially high osmolality or simply excessive volumes. As well as contributing to unpleasant sensations of excess satiety these may also contribute to intestinal digestive malfunction.

There is no doubt that impaired quality of life is strongly associated with malnutrition and weight loss [2, 3], but it is more difficult to determine whether this is a causal relationship and if so in which direction the cause operates!

Direct Effects of Gastric Surgery

The disruption to physiological processes depends on the operation performed and also on the individual's response to that surgery. Many different procedures are or have been performed on the stomach (Figs. 1 and 2) and their pathological consequences are determined by the anatomical and physiological changes caused.

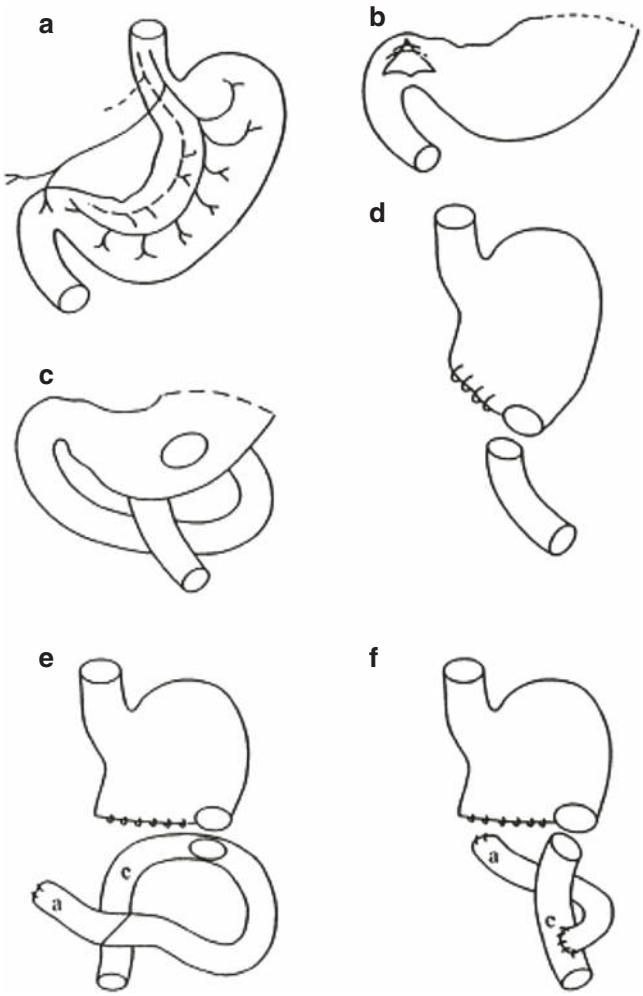

Fig. 1 Types of gastric surgery done for peptic ulceration. (**a**) The vagus nerve which supplies the stomach may be divided proximally (a truncal vagotomy), or more distally (selective or highly selective vagotomy). (**b**) Pyloroplasty (frequently used with truncal vagotomy to prevent delay in gastric emptying). (**c**) Gastroenterostomy (which enhances emptying by bypassing the pylorus). (**d**) Billroth I partial gastrectomy. (**e**) Billroth II (or Polya) gastrectomy with afferent (a) and efferent (e) small intestinal limbs. (**f**) Roux-en-Y reconstruction with afferent (a) and efferent (e) small intestinal limbs

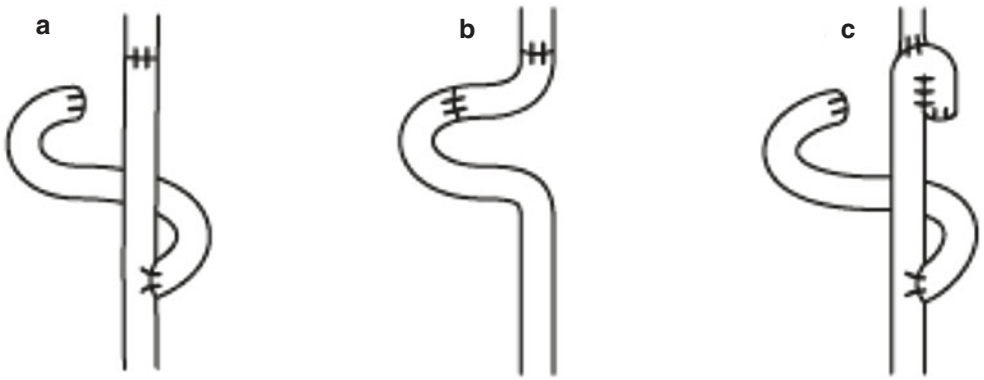

Fig. 2 Types of total gastrectomy. (**a**) Roux-en-Y oesophago-jejunostomy. (**b**) Interposition of jejunal, ileal or colonic loop. (**c**) Small bowel pouch and Roux-en-Y oesophago-jejunostomy

In broad terms the greater the magnitude of resection the greater the nutritional consequences, and (for example) near-total gastrectomy gives some protection compared to total gastrectomy, with less severe and less persistent objective markers of malabsorption than in the patients receiving the more radical surgery and without oncological hazard [4].

Vagotomy reduces acid secretion by interrupting the vagal simulation of the gastric parietal cells. When this is a highly selective procedure there is essentially no other effect, but a truncal vagotomy not only cuts acid secretion but also profoundly impairs gastric motor function and compliance, delays gastric emptying (but see below), and compromises pancreatic function.

Partial gastrectomy reduces the physical size of the stomach, and, depending on the site removed, will reduce acid secretion to a greater or lesser degree. The normal mixing and sieving functions will be impaired.

Drainage procedures such as pyloroplasty and forms of gastroenterostomy were introduced to overcome delayed gastric emptying caused by vagotomy or partial gastrectomy, but paradoxically can also be the main cause of precipitate gastric emptying, dumping syndrome and rapid intestinal transit (see below).

Reconstructional surgery to permit continuity of the gut for biliary and pancreatic secretions such as the Roux-en-Y procedure yields an afferent loop which can itself be responsible for additional physiological disturbance.

Gastric surgery may also be responsible for uncontrolled gastro-oesophageal reflux (which will often be alkaline) and places the patient at increased risk of malignancy in the gastric remnant as well as at risk of the full gamut of post-operative complications common to all abdominal surgery.

Weight Loss and Dietary Restriction

Loss of weight after gastric resection is so common as to be considered an expectation; even with optimal nutritional support the weight lost may be substantial. The magnitude to be expected with best practice remains difficult to predict as the various studies performed have had heterogeneous criteria for entry, type of surgery and nutritional intervention. This position is often aggravated by omission of baseline weight (many studies start using pre-operative weight which, from the nature of the diseases concerned, is generally lower than the patient's weight in health), and by a lack of appropriate control populations. As an example, one study claimed to show avoidance of weight loss but did not take account of the normal gradual increase in weight during middle-age nor the fact that the "baseline" weight was that immediately before the surgery [5]. Overall more than 50% of patients are and remain underweight indefinitely after gastric surgery [6, 7].

In general, patients with no symptoms after eating eat normally, while those with symptoms almost universally respond to this by eating less roughly in proportion to the severity of those symptoms. Weight loss indeed correlates strongly with reduced food intake [7–9] and also with the speed of orocaecal transit [10, 11].

Patients who are underweight after partial gastrectomy typically eat less than half the macronutrient intake of normal controls or those who have managed to maintain their weight after surgery [12]. In those who can be encouraged, and are able, to consume normal amounts of food, some weight gain can be expected. A major study of patients after various forms of cancer surgery accordingly confirmed that even as early as 3 months after operation differences in nutritional intake can be overcome, but showed that those with more invasive procedures did indeed have more persisting weight loss [13].

Other factors contributing to weight loss are however almost certainly important, including dysfunctionally exaggerated satiety (Table 1). The normal response to relative starvation (eating more) appears blunted in patients who have undergone partial gastrectomy.

The routine use of oral nutritional supplements has its advocates, and there is good evidence in support of this and other forms of artificial nutrition at the time of surgery for gastric cancer (e.g. [14, 15]) but evidence in favour of longer-term support is lacking, problems with compliance perhaps

Table 1 Nutritional effects of gastric resection

Reduced food intake
Maldigestion
Impaired gastric sieving
Impaired gastric secretion (acid and enzymes)
Malabsorption
Impaired gastric secretion
Impaired pancreatic secretion
Impaired intestinal secretion
Blind loops and bacterial overgrowth
Specific deficiencies (e.g. thiamine, vitamin B12)
Early and late dumping syndromes
Motility disorders affecting gastric emptying and intestinal transit

confounding possible benefit [16]. An educational approach taken in this regard may pay dividends [17].

Gastric Emptying

Disturbance of the stomach's normal role in processing food, so as to be suitable for transfer to the duodenum and optimal digestion thereafter, contributes to post-operative malabsorption. In health the stomach regulates the entry of nutrients into the duodenum in quantity, particle size, and nutritional content, titrating efflux against osmolality and energy load in such a way that proximal small intestinal function is facilitated and absorption maximised [18].

Gastric emptying is thus not a single simple process, and although (for example) vagotomy is generally considered to delay emptying it is also a potential cause of rapid emptying with precipitate "dumping" of nutrients into the small intestine [19]. Indeed liquids empty abnormally rapidly following vagotomy, with or without pyloroplasty, as well after all forms of gastric resection and reconstruction [20]. The emptying of solid food following gastric surgery is much more variable—the initial phase often results in rapid emptying of some solids, but after 30–60 min emptying of solids may become very slow or continue at rapid rates depending on the individual as well as on the procedure that has been performed. Following truncal vagotomy, even with pyloroplasty, emptying of solids is delayed [21] whilst emptying is abnormally rapid after essentially all forms of gastrectomy [20].

Many patients describe particular problems with fatty foods and most dramatically so when oils (liquid fats) are ingested. This is probably because their rapid gastric efflux overwhelms the digestive abilities of the pancreas, which is attuned to relatively slow exposure to fats after meals, given the usual sequence of solids leaving the stomach in which fats follow carbohydrate and protein. The absorptive capacity of the proximal small intestine can be exceeded for other nutrients also, and if the more distal intestine is insufficient in length or function to accommodate this then significant malabsorption may arise.

The study of gastric emptying using a two-phase (liquid and solid) double radio-isotopic method can provide objective evidence of the nature and rate of gastric emptying, but its clinical usefulness is limited given the variable response to interventions even when these are based on information specific to the patient concerned.

Gastric Sieving

The normal stomach yields duodenal access to liquids and—through the process known as gastric sieving—of particles only less than 1 mm in size [21]. This process is self-evidently greatly compromised by the more major gastric resections and those with a substantial enterotomy, but vagotomy with antrectomy or pyloroplasty can also disrupt the process and allow entry of larger particles into the small bowel following meals [22, 23]; only following proximal/selective vagotomy alone does normal gastric sieving appear to be preserved post-operatively [23].

In one small study (n = 9) vagotomy and antrectomy permitted the emptying of abnormally large meat particles into the small intestine, to the extent that 37% of the meat left the stomach while still more than 1 mm in size [22]. The effect on gastric emptying was however quite variable since two of the nine patients had normal sieving (<2% of the particles reaching the small intestine >1 mm) whilst in the worst affected patients 75% of particles were >2 mm in size. In a similar small study of patients after vagotomy and pyloroplasty two of seven patients had abnormal sieving [23].

Larger particles have a lower surface to mass ratio, and when these are presented to the small intestine their hydrolysis, overall digestion and absorption are slower than is normal [24, 25]. In a controlled experiment on dogs with Billroth I gastrectomies absorption of ^{14}C triolein from margarine in the liquid phase was—as in controls—almost complete by the mid-gut. However when the ^{14}C triolein was incorporated in steak and liver more than double the amount (50% vs 20%) was recovered unabsorbed in the mid small intestine in the gastrectomised animals. This was attributed to a failure of gastric sieving and to a shielding of fat from the digestive processes given the observation of many meat particles exceeding 0.5 mm in diameter, whereas fewer than 2% of particles were larger than 0.5 mm in the controls [24, 25]. There are no directly comparable studies in man, but investigation of iron absorption strongly suggests a similar phenomenon.

Under normal circumstances the absorption of radiolabelled iron from solid phase dietary muscle myoglobin is only minimally less than its absorption from an aqueous solution. However after Billroth I or Billroth II gastrectomy there is a markedly reduced absorption of iron from the solid phase [26]. It is thought that this reflects the failure of mixing

and sieving by the stomach, and the premature delivery of oversized iron-containing particles to the small bowel.

The Small Intestine After Gastric Surgery

Although there is some involvement of the small bowel in many gastric procedures—from the simple gastrojejunostomy to more complex multi-loop reconstructions—the general observation is that the small intestine remains normal macroscopically and histologically. At a cellular level the absorption of salt, water, soluble iron, glucose and fatty acids can all be shown to be normal [27].

Nonetheless intestinal factors contribute to post-gastrectomy malabsorption, mainly as a result of excessively rapid transit and a reduced time available for intraluminal digestion and absorption. When the intestine itself is normal this rarely presents a major nutritional challenge given generally high levels of reserve capacity [28], but if there is intestinal disease or if there has been small bowel resection then problems may be profound.

Pancreatic Function

The roles of the pancreas are closely aligned with those of the stomach, so it is to be expected that gastric surgery compromises its normal function to some extent. Selective proximal vagotomy appears to have no impact, but all gastric resections and drainage procedures reduce pancreatic exocrine function, typically by 30–50% from normal [22, 23], and a reduction of up to 70% has been reported after truncal vagotomy and pyloroplasty.

Direct study of pancreatic secretion is now rarely done and reference data are relatively aged, but robust evidence nonetheless exists for reduction in output of trypsin, chymotrypsin and amylase in response to secretin-cerulein stimulation. There is parallel perturbation of pancreatic endocrine function. Baseline and post-prandial levels of pancreatic polypeptide and gastrin are low, whilst meal-stimulated cholecystokinin is significantly increased [29], and abnormal glucose tolerance tests are common.

These reductions in pancreatic function are compounded by the loss of synchronous delivery of pancreatic secretions (and bile) as food enters the upper small intestine. The combined effect is of slower digestion of all macronutrients and especially of fat. The normal negative feedback loop that inhibits gastric emptying is also disrupted following many gastric surgical procedures adding to the problems, especially in the earlier phases of digestion.

Following all of the procedures in which the normal flow of nutrients across the outflow from the pancreas is disrupted (e.g. Billroth II gastrectomy and the Roux-en-Y reconstructions) pancreatic secretions are to some degree sequestered in the afferent loop of the small intestine and mix with the oesophagogastric effluent relatively late [10, 20].

The mechanisms that lead to pancreatic enzymes leaving the afferent loop are not fully elucidated, but are thought to depend on a combination of passive filling and overflow with some degree of active post-prandial motor function. It is probable that in most patients the reduction in pancreatic enzyme secretion is less important than the loss of synchronous timing of peak enzyme contact with food, as overt fat malabsorption can still be demonstrated in patients with more conservative procedures (such as Billroth I gastrectomy) where the total integral post-cibal pancreatic enzyme secretion is less affected. Maldigestion is most marked in the early phases after eating when there would normally be the most pronounced peak of enzyme secretion [20].

These observations have led to a range of suggested interventions to improve maldigestion and malabsorption of pancreatic origin after gastric surgery. Patients are usually advised to reduce the ingestion of oils and to take pancreatic enzyme supplements with meals. While these measures can be expected to ameliorate the pancreatic dysfunction [10, 30], the former restriction may add to the overall nutritional deficit. A small controlled trial of pancreatic enzymes after surgery for gastric cancer showed modest improvements in quality of life and a range of nutritional measures when compared with standard dietary advice alone [31]. When pancreatic enzymes are given it is important to prescribe preparations which do not depend on an acidic pH in order to release their contents.

More imaginatively (although as yet without convincing data) it is suggested that asynchrony is overcome by recommending that gastrectomised patients with an afferent pancreatobiliary loop should ingest a small quantity of fat or oil 60 min before ingestion of a meal [32]. This is intended to stimulate pancreatic secretion and to fill the afferent loop thus "priming" the system for the meal that is about to be ingested.

Overall Effects of Gastric Surgery on Absorption of Nutrients

Protein

Western diets generally yield protein intakes well in excess of requirements. Although some malabsorption of protein is demonstrable, along with azotorrhoea (protein in the stool), in patients who have undergone total or subtotal gastrectomy, it is not generally a clinical problem after gastric surgery.

Carbohydrates

Carbohydrate malabsorption is more of a problem. It is difficult to quantify accurately but it contributes to postoperative malnutrition, and also to a series of symptoms increasingly familiar to those exploring FODMAP intolerance in patients with irritable bowel syndrome and other functional disorders. The FODMAPs are Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols, and comprise a group of poorly absorbed short-chain carbohydrates. These are the most likely to be malabsorbed after gastric surgery, but to their number will be added lactose and longer chain molecules including starch [33]. Absorption of the FODMAPs and other carbohydrates by the small intestine is compromised here predominantly through the effects of excessively rapid intestinal transit.

Malabsorption of sugars can be precipitated in completely healthy subjects if the ingested dose exceeds a threshold dictated by the speed of intestinal transit [34], so the gastrectomised patient can be seen always to be vulnerable. Flatulence, bloating, cramps and diarrhoea can all result and subclinical lactose intolerance may be unmasked [35]. Rarely, even glucose may be malabsorbed [36].

Fats

Clinical fat malabsorption with steatorrhoea does not occur following vagotomy alone [37] and is seldom present in patients following vagotomy and pyloroplasty or Billroth I gastrectomies [30]. Under normal circumstances less than 6% of ingested fat is lost in the faeces, but following Billroth II gastrectomy or vagotomy with gastroenterostomy, levels in the region of 8% are found. Following total gastrectomy 15–20% of dietary fat is typically malassimilated [10, 30]. This correlates quite tightly with deficiency of the fat soluble vitamins and especially of vitamin D (see below).

Micronutrients

Vitamin D in bone disease and deficiencies of haematinics in contributing to the anaemia seen after gastric surgery are considered below, but there is also evidence for specific deficiency of thiamine in more than 25% of patients even after relatively conservative surgery such as the gastric sleeve [38]. These patients also show frequent deficiencies in copper and pyridoxine [39] and while the bariatric population may be at particular risk there is no reason to be confident that these could not occur after surgery for other indications.

In Combination

Although nitrogen balance is not especially compromised after gastric resection it is clear that the many deleterious effects on digestion and absorption of carbohydrates and fats contribute to a global tendency to malnutrition. However neither weight loss, nutritional status nor changes in body composition correlate well with any individual component of the malfunctioning physiology [9].

Bacterial Overgrowth

Gastric acid normally makes an important contribution to the relative sterility of the proximal small intestine so it is to be expected that procedures which diminish or eliminate acid secretion will sometimes be complicated by small bowel bacterial overgrowth (SBBO). Bacterial counts of $>10^4$ colony forming units/ml are generally considered abnormal and counts of above 10^6 to be diagnostic. Diagnostic levels are found in patients after all types of gastrectomy [40, 41]. When there is a partially defunctioned/blind loop more than 50% of patients will be affected, and only with selective vagotomy do rates remain below 10% (British Society of Gastroenterology (BSG) Guidelines, accessible via https://www.bsg.org.uk/resource/guidelines-for-the-investigation-of-chronic-diarrhoea-in-adults%2D%2Dbritish-society-of-gastroenterology%2D%2D3rd-edition.html). The presence of bacteria (which are usually of the types considered colonic/faecal) does not correlate closely with clinical manifestations however and in at least one study colonisation was equally common in those with and without symptoms [41].

Clinical features attributed to SBBO include bloating and diarrhoea and/or steatorrhoea together with evidence of malabsorption particularly of vitamin B12. Investigation is troublesome as, apart from direct culture of small bowel aspirates, the available tests have very considerable false positive and false negative rates, not least because of the underlying rapid intestinal transit (BSG Guidelines: https://www.bsg.org.uk/resource/guidelines-for-the-investigation-of-chronic-diarrhoea-in-adults%2D%2Dbritish-society-of-gastroenterology%2D%2D3rd-edition.html). SBBO is therefore often a clinical impression and one which may be subjected to a diagnostic trial of antibiotic therapy, although this too can result in some misinterpretation through the possibility of a placebo effect in one direction or the choice of an antibiotic to which there is already resistance in the other.

Dumping Syndrome

Dumping syndrome has come to be considered the archetypal symptomatic complication of gastric surgery. First reported by Hertz in 1913 [42] and given its name by Mix in 1922 [43], early dumping is characterised by weakness, faintness or syncope, palpitations, pallor, sweating, nausea and vomiting, colicky abdominal pain and diarrhoea, one or more of which occurs typically 20–30 min after eating. In some patients features may arise sooner but it is rare for these symptoms to begin much later. Dumping is a direct consequence of excessively rapid gastric emptying (particularly of the liquid phase) with resultant delivery of hypertonic fluid into the duodenum. The ensuing reduction in vascular volume combined with stimulation and dilatation of the duodenum cause a marked neurohumoral response, not necessarily with hypoglycaemia. Vasoactive intestinal peptide, serotonin, neurotensin, enteroglucagon, peptide YY and kinins are all implicated [44, 45]. Their vasomotor effects are responsible for most of the distressing symptoms.

The so-called late dumping syndrome occurs at least an hour after eating. Also responsible for faintness, palpitations, perspiration and confusion, this is a consequence of the rapid transit of food causing excessive release of gastric inhibitory peptide and insulin which results in reactive hypoglycaemia [46, 47].

The dumping syndromes can be a major contributing cause to malnutrition if their effects are sufficient to deter the patient from eating. Relatively small, frequent meals should be encouraged with an emphasis on foods of low glycaemic index. Monosaccharide-based drinks in particular should be avoided. Measures to slow gastric emptying with pectin, glucomannan, acarbose or loperamide can be helpful in some patients [47].

Somatostatin acts as a natural counterweight to the gastrointestinal neurohumoral response, and its longer-acting analogues octreotide and lanreotide can slow gastric emptying of liquids and solids, slow orocaecal transit, and reduce the plasma levels of several of the implicated hormones. In patients where simpler (and cheaper) measures have failed, octreotide (50–100 μg) given subcutaneously about 30 min before meals is often effective in control of dumping symptoms [47]; monthly injections of lanreotide may have a similar effect.

Post-vagotomy Diarrhoea

Diarrhoea is common after truncal vagotomy. Depending on the definition it occurs in 2% [48] to 53% of patients [49]. In a study of 102 patients studied a mean of 13 years after vagotomy and pyloroplasty, 53% had diarrhoea compared to 7% of a control group. In 11% the diarrhoea was continual, and a further 22% of patients had at least one episode of diarrhoea each week [49]. In 8% of patients the diarrhoea had been a serious problem because of sudden and unpredictable onset, sufficient at times to lead to incontinence.

The diarrhoea in this syndrome appears to be related to the truncal vagotomy and not to whether patients have had a pyloroplasty or a gastroenterostomy. The pathogenesis rests on rapid gastric emptying and rapid upper gastrointestinal transit which results in reduced digestion and absorption in the small intestine and delivery of an osmotic load to the colon (confirmed by intubation studies [50]). Transit can be so fast that it even overwhelms the gut's ability to absorb glucose [36, 50]. On glucose/hydrogen breath testing there is a rapid rise in breath hydrogen coinciding with delivery to the caecum at a mean transit time of 25 min. There may also be may a contribution from the cathartic action of bile acids reaching the colon. A controlled study demonstrated higher total bile acids in the faeces (in particular chenodeoxycholic acid), in patients with post-vagotomy diarrhoea than in controls [51]. Results from patients who had undergone a vagotomy but did not have diarrhoea lay between those from these two groups. Nonetheless, in affected patients, avoidance of food to reduce symptoms is more commonly the reason for weight loss than malabsorption. Vagotomised patients fortunate enough to avoid post-vagotomy diarrhoea are thought to have particularly efficient colonic salvage [28].

Treatment of post-vagotomy diarrhoea is predominantly with the use of antimotility agents. In one study codeine phosphate (60 mg) and loperamide (12–24 mg) delayed transit by 58 min and 63 min respectively, and improved symptoms dramatically in most patients [36]. It is key to give such drugs in sufficient dose and at least 30 min before a meal, since ingestion immediately prior to or with food may even aggravate dumping.

Treatment with Lomotil (diphenoxylate hydrochloride and atropine sulphate) reduced stool frequency to a significant degree, but did not prove useful in the prophylaxis of the more severe attacks of diarrhoea [52]. In an attempt to reduce the rapid efflux of food from the stomach to the small bowel, McKelvey *et al* reduced the liquid content of meals. Low fluid meals gave complete control of diarrhoea in two patients, and improved the diarrhoea in 12 patients, (less frequency: $n = 12$; less urgency: $n = 9$), only 4 failing to respond [19]. In patients with more resistant diarrhoea, however, such manipulation of meal content is less successful. Some patients will also respond to bile salt binding agents such as colestyramine [51, 53, 54] and there is a good case for SeHCAT scanning in gastrectomised patients with diarrhoea (BSG Guidelines: https://www.bsg.org.uk/resource/guidelines-for-the-investigation-of-chronic-diarrhoea-in-adults%2D%2Dbritish-society-of-gastroenterology%2D%2D3rd-edition.html).

Anaemia Following Gastric Surgery

Anaemia is common after gastric surgery. Although the reported incidence after resection ranges from 3% to 77%, in most series the frequency is around 30% [55–57]. Anaemia is more common following operations for gastric ulcer (e.g. 30%) than duodenal ulcer (e.g. 9%) [58, 59], and patients with Billroth II anastomoses are affected more commonly than those with a Billroth I anastomosis [55, 58, 60]. After uncomplicated gastroenterostomy anaemia (generally iron-deficient) is more unusual, and vagotomy and pyloroplasty alone are rarely followed by anaemia [18, 19].

Deficiencies of iron and B_{12} make approximately equal contributions to the incidence of anaemia following partial gastrectomy, with folate deficiency being less common [60]. The relative contributions are typified by Shafer et al.'s study of 142 male patients an average of 8.3 years after surgery, 33 of whom had Billroth I and 109 Billroth II gastrectomies [61]. Anaemia was present in 69 of the 142 patients, 32% of whom were found to have predominant iron deficiency, 42% vitamin B_{12} deficiency, and 25% folate deficiency. In 23% of the anaemic patients there was isolated iron deficiency, in 20% isolated B_{12} deficiency and in 9% isolated folate deficiency; mixed deficiencies were present in the remaining 48%.

Following total gastrectomy a similar frequency and spectrum of anaemia is found. Anaemia is present in about half of cases, with evidence of iron deficiency in half of these, the precise figures tending to increase the longer patients survive following surgery [62].

Iron Deficiency

Iron deficiency thus occurs in 30–50% of patients following partial gastrectomy and is the main cause of about 50% of post-operative anaemia [60]. The causes of iron deficiency are multifactorial. Dietary deficiency may contribute but is not found uniformly [59]. Chronic faecal blood loss, as measured by chromium-labelled red cell studies, is typically 3.2–6.5 ml/day and surely contributes to the anaemia [63]. It has been suggested that there is an inability to up-regulate absorption in the iron-deficient state [64]. Reduced acid secretion from the operated stomach reduces the absorption of inorganic iron, and there may be a contribution from high mucosal cell turnover. Rapid intestinal transit through the upper gut and/or bypass of the duodenum, which is the preferential site for iron absorption, almost certainly also contributes [65]. Replacement with oral iron is usually sufficient treatment when iron deficiency is found, provided other causes have been adequately excluded (see below).

Vitamin B_{12} Deficiency

The incidence of overt vitamin B_{12} deficiency following gastric resection is typically in excess of 15% [55, 59]. In one series of 351 patients with Billroth II anastomoses, 36% of patients had low (20%) or borderline low (16%) B_{12} levels [66], though other authors using more subtle measures such as red cell B_{12} and the presence of hypersegmented neutrophils suggest that minor deficiency may be present in 68–l00% of patients [60]. The prevalence of B_{12} deficiency increases with time from surgery. These figures are of course despite the well-recognised risks of B_{12} malabsorption and reflect a failure to use prophylactic treatment.

Lack of intrinsic factor contributes to the deficiency in about half of affected patients [59, 66], though elective assessment of B_{12} absorption shortly after surgery suggests it is usually normal at that stage [67]. The explanation may lie in that, although pure B_{12} absorption is normal when measured by conventional absorption tests, such as the Schilling test [68], the abnormal emptying of food particles from the stomach and their subsequent impaired digestion may reduce B_{12} availability from a normal diet [69].

It is unclear how much bacterial overgrowth in the small intestine contributes to B_{12} deficiency, but some bacteria certainly have the ability to compete for dietary B_{12}. In some patients with a Billroth II anastomosis, treatment with a broad-spectrum antibiotic has been shown to correct B_{12} deficiency. Similarly pancreatic insufficiency is a compounding factor in patients with Billroth II anastomoses and may too reduce the absorption of B_{12}. The relative contributions of these causes remain uncertain, but regular treatment with parenteral B_{12}—usually 1 mg im every 3 months—is safe and highly reliable and should be the preferred method when B_{12} deficiency is identified or strongly predicted.

Folate Deficiency

Although dietary inadequacy is common and serum folate levels are often a little low after gastric resection [59], resultant anaemia is relatively rare, being the main cause in no more than about 5% of patients [58]. It should nonetheless be sought in any patient who is anaemic. Oral replacement should be given orally when levels are low and also for short-term prophylactic cover in patients receiving iron or vitamin B_{12} for deficiencies of these haematinics to prevent the unmasking of borderline folate deficiency during the rapid haemopoiesis induced with treatment.

Metabolic Bone Disease

Metabolic bone disease—both osteoporosis and osteomalacia—are commonly reported after gastric surgery with an incidence of up to 25% [30]. When specifically sought, bone pain and tenderness are reported by 6 times as many patients as age-matched controls [70]. Serum calcium levels are also lower in patients (though usually within the normal range), associated with demonstrable reduction in calcium absorption [71]. Similarly, inorganic phosphate levels are low in 5% of patients and serum alkaline phosphatase tends to be elevated. Radiological evidence of osteopenia can be found in 24% (controls 4%).

It has been suggested that vitamin D and calcium loss may be proportional to loss of faecal fat, which would be consistent with the general observation that bone disease affects patients following total gastrectomy and Billroth II rather than Billroth I partial gastrectomy [70]. Dietary deficiency of vitamin D may contribute. In the bariatric population where there is a pre-operative tendency to secondary hyperparathyroidism the prevalence of this condition doubles post-operatively—again with a frequency related to the magnitude of the operative procedure [72].

It is reasonable to advise a higher than normal intake of vitamin D and calcium prophylactically after gastric resection. Regular (e.g. alternate year) monitoring of bone density should be considered. Those with overt bone disease should be managed actively with higher dose oral vitamin D and a low threshold for its parenteral administration if the serum level of hydroxy-vitamin D does not respond. In osteoporosis consideration of bisphosphonates will also often necessitate parenteral dosing given the poor absorption and frequent oesophageal toxicity of these drugs when given by mouth. Nonetheless, despite the frequency of metabolic bone disease after gastric surgery there is surprisingly little evidence of increases in fracture rates.

Other Complications of Gastric Surgery

Patients who have undergone gastric surgery remain at risk of the usual hazards of previous abdominal surgery such as incisional hernia and adhesions, which may occasionally lead to additional complications and thus a route to intestinal failure through the need for further surgery and the risk of short bowel syndrome.

Systemic infection is also more common in the post-gastrectomy patient indicating a general level of depressed immunity which is probably distinct from malnutrition and independent of underlying malignancy [73]. There are also more specific late complications of gastric surgery which warrant attention and in many cases formal endoscopic surveillance.

Anastomotic ulcers are most often seen in patients whose surgery was for peptic ulcer, and with modern medical management of ulcer disease these patients are becoming rare, but these can be responsible for significant overt upper gastrointestinal bleeding as well as for more subtle presentations with iron deficiency anaemia. Endoscopic detection (and sometimes therapy) in combination with proton pump inhibitors and eradication of residual *H. pylori* is usually sufficient, but revisional surgery with its attendant risks is occasionally required.

Neoplasia in the Residual Stomach

There is a definite increase in the risk of gastric carcinoma in the partially resected stomach, a risk which will normally be sufficient to justify long-term endoscopic surveillance. New symptoms, including late deterioration from a nutritional point of view, between procedures should also prompt consideration of this possibility.

Failure to Regain Weight Lost in the Absence of any Overt Explanation

The great majority of patients loses weight after gastric resection, and although some younger patients can make good this loss over a year or so, most patients will never regain their premorbid weight. There does not seem to be a single or reversible explanation for this and it is now becoming conventional to think of it as a form of sarcopenia. Progress in the management of sarcopenia in general may yield specific new interventions, but it is probable that a combination of optimized nutrition with a physical exercise programme offers the current best chance of success.

Summary

Subtotal and total gastrectomy frequently lead to symptoms resulting in a change in eating habit and more rarely result in malnutrition which reflects maldigestion, malabsorption and motility problems. The resultant malnutrition may be global, affecting all nutrient groups, or limited to specific nutritional deficiencies such as of lipid soluble elements or individual vitamins. Established intestinal failure is most unusual unless there have also been major post-operative complications. Less invasive gastric surgery is also associated with nutritional problems, but at lower levels of frequency and severity.

The causes of malnutrition are often multifactorial and a knowledge of the likely problems and an understanding of the pathophysiological mechanisms help to organize the approach for the individual patient. A combination of dietary changes, drug therapy to slow transit or bind bile salts, or supplementation with enzymes and addition of dietary supplements, usually leads to successful control of the problem. Nonetheless, most patients remain underweight in the long-term.

References

1. Santarpia L, Pagano MC, Cioffi I, Alfonsi L, Cuomo R, Labruna G, et al. Impaired enterohormone response following a liquid test meal in gastrectomized patients. Ann Nutr Metab. 2017;71(3–4):211–6.
2. Lee SS, Yu W, Chung HY, Kwon OK, Lee WK. Using quality of life scales with nutritional relevance after gastrectomy: a challenge for providing personalized treatment. J Gastric Cancer. 2017;17(4):342–53.
3. Park KB, Park JY, Lee SS, Kwon OK, Chung HY, Yu W. Impact of body mass index on the quality of life after Total gastrectomy for gastric cancer. Cancer Res Treat. 2018;50(3):852–60.
4. Seo HS, Jung YJ, Kim JH, Park CH, Kim IH, Lee HH. Long-term nutritional outcomes of near-total gastrectomy in gastric cancer treatment: a comparison with total gastrectomy using propensity score matching analysis. J Gastric Cancer. 2018;18(2):189–99.
5. Glober GA, Rhoads GC, Liu F, Kagan A. Long-term results of gastrectomy with respect to blood lipids, blood pressure, weight and living habits. Ann Surg. 1979;179:896–901.
6. Fischer AB. Twenty-five years after Billroth II gastrectomy for duodenal ulcer. World J Surg. 1984;8:293–302.
7. Wastell C. Long-term clinical and metabolic effects of vagotomy with either gastrojejunostomy or pyloroplasty. Ann R Coll Surg Eng. 1969;45:193–211.
8. Johnston IDA, Welboum R, Acheson K. Gastrectomy and loss of weight. Lancet. 1958;1:1242–5.
9. Robins RE, Robertson R, McIntosh HW. Fecal fat and nitrogen studies in postgastrectomy patients: the relationship of fat and nitrogen assimilation to weight loss and a comparison between Billroth I and Billroth II subtotal gastrectomies. Surgery. 1957;41:248–53.
10. Bradley EL, Isaacs JT, Hersh T, Chey WY. Pathophysiology and significance of malabsorption after Roux-en-Y reconstruction. Surgery. 1977;81:684–91.
11. Armbrecht U, Lundell L, Lindstedt G, Stockbruegger RW. Causes of malabsorption after total gastrectomy with Roux-en-Y reconstruction. Acta Chir Scand. 1988;154:37–41.
12. Tovey F. A comparison of Polya gastrectomy, total and selective vagotomy and of pyloroplasty and gastrojejunostomy. Br J Surg. 1969;56:281–6.
13. Eom BW, Kim J, Kim DH, Kim YI, Yoon HM, Cho SJ, et al. Recovery of food intake after gastrectomy for gastric cancer: based on a large-scale gastric cancer cohort. Dig Surg. 2018;35(3):220–9.
14. Imamura H, Nishikawa K, Kishi K, Inoue K, Matsuyama J, Akamaru Y, et al. Effects of an oral elemental nutritional supplement on post-gastrectomy body weight loss in gastric cancer patients: a randomized controlled clinical trial. Ann Surg Oncol. 2016;23(9):2928–35.
15. Ohkura Y, Haruta S, Tanaka T, Ueno M, Udagawa H. Effectiveness of postoperative elemental diet (Elental®) in elderly patients after gastrectomy. World J Surg Oncol. 2016;14(1):268.
16. Ben-Porat T, Elazary R, Goldenshluger A, Sherf Dagan S, Mintz Y, Weiss R. Nutritional deficiencies four years after laparoscopic sleeve gastrectomy-are supplements required for a lifetime? Surg Obes Relat Dis. 2017;13(7):1138–44.
17. Lee HO, Han SR, Choi SI, Lee JJ, Kim SH, Ahn HS, Lim H. Effects of intensive nutrition education on nutritional status and quality of life among postgastrectomy patients. Ann Surg Treat Res. 2016;90(2):79–88.
18. McIntyre AS. Studies on the adrenergic control of upper gastrointestinal function in man. MD Thesis, University of London, 1990.
19. McKelvey STD. Gastric incontinence and post-vagotomy diarrhoea. Br J Surg. 1970;57:741–7.
20. MacGregor IL, Parent J, Meyer JH. Gastric emptying of liquid meals and pancreatic and biliary secretion after subtotal gastrectomy or truncal vagotomy and pyloroplasty in man. Gastroenterology. 1977;72:195–205.
21. Kumar D. Gastric motor physiology and pathophysiology. In: Gustavsson S, Kumar D, Graham DY, editors. The stomach. Edinburgh: Churchill Livingstone; 1992. p. 129–42.
22. Mayer EA, Thomson JB, Jehn D, Reedy T, Elashoff J, Meyer JH. Gastric emptying and sieving of solid food and pancreatic and biliary secretion after solid meals in patients with truncal vagotomy and antrectomy. Gastroenterology. 1982;83:184–92.
23. Mayer EA, Thomson JB, Jehn D, Reedy T, Elashoff J, Deveny C, Meyer JH. Gastric emptying and sieving of solid food and pancreatic and biliary secretion after solid meals in patients with nonresective ulcer surgery. Gastroenterology. 1984;87:1264–71.
24. Doty JE, Meyer JH. Vagotomy and antrectomy impairs intracellular but not extracellular fat absorption in the dog. Gastroenterology. 1988;94:50–6.
25. Doty JE, Gu YG, Meyer JH. Vagotomy and antrectomy with gastrojejunostomy impairs fat absorption from liquid and solid food. Gastroenterology. 1989;96:A128.
26. Meyer JH, Porter-Fink V, Crott R, Figeuroa W. Absorption of heme iron after truncal vagotomy with antrectomy. Gastroenterology. 1987;92:1534.
27. Johnson JH, Horswell RR, Tyor MP, Owen EE, Ruffin JM. Effect of intestinal hormones on 131-I-triolein absorption in subtotal gastrectomy patients and intubated normal persons. Gastroenterology. 1961;41:215–9.
28. Read NW. Diarrhoea the failure of colonic salvage. Lancet. 1982;I:481–3.
29. Freiss H, Bohm J, Muller MW, Glasbrenner B, Riepl RL, Malferdieiner P, Buchler MW. Maldigestion after total gastrectomy is associated with pancreatic insufficiency. Am J Gastroenterol. 1996;91:341–7.
30. Meyer JH. Nutritional outcomes of gastric operations. Gastroenterol Clin N Am. 1994;23(2):227–60.
31. Catarci M, Berlanda M, Grassi GB, Masedu F, Guadagni S. Pancreatic enzyme supplementation after gastrectomy for gastric cancer: a randomized controlled trial. Gastric Cancer. 2018;21(3):542–51.
32. Tyor MP, Ruffin JM. The effect of prefeeding of fat on 131-I-triolein absorption in subtotal gastrectomy patients. Proc Soc Exp Biol Med. 1958;99:61–4.
33. Bond JH, Levitt MD. Use of pulmonary hydrogen measurements to quantitate carbohydrate absorption: study of partially gastrectomized patients. J Clin Invest. 1972;51:1219–25.
34. McIntyre AS, Thompson DG, Burnham WR, Walker ER. The effect of beta-adrenoreceptor agonists and antagonists on fructose absorption in man. Aliment Pharmacol Ther. 1993;7:267–74.
35. Condon JE, Westerholm P, Tanner NC. Lactose malabsorption and postgastrectomy milk intolerance. Gut. 1964;10:311–4.
36. O'Brien JD, Thompson DG, McIntyre A, Burnham VJR, Walker E. Effect of codeine and loperamide on upper intestinal transit and

absorption in normal subjects and patients with postvagotomy diarrhoea. Gut. 1988;29:312–8.
37. Edwards JP, Lyndon PJ, Smith RB, Johnston D. Faecal fat excretion after truncal, selective, and highly selective vagotomy. Gut. 1974;15:521–5.
38. Tang L, Alsulaim HA, Canner JK, Prokopowicz GP, Steele KE. Prevalence and predictors of postoperative thiamine deficiency after vertical sleeve gastrectomy. Surg Obes Relat Dis. 2018;14(7):943–50. https://doi.org/10.1016/j.soard.2018.03.024.
39. Pellitero S, Martínez E, Puig R, Leis A, Zavala R, Granada ML, et al. Evaluation of vitamin and trace element requirements after sleeve gastrectomy at long term. Obes Surg. 2017;27(7):1674–82.
40. Greenlee HB, Vivit R, Paez J, Dietz A. Bacterial flora of the jejunum following peptic ulcer surgery. Arch Surg. 1971;102:260–5.
41. Browning GG, Buchan KA, MacKay C. Clinical and laboratory study of postvagotomy diarrhoea. Gut. 1974;15:644–53.
42. Hertz AF. The cause and treatment of certain unfavourable aftereffects of gastroenterostomy. Ann Surg. 1913;58:466–72.
43. Mix CL. 'Dumping stomach' following gastrojejunostomy. Surg Clin N Am. 1922;2:617–22.
44. Woodward ER. The early postprandial dumping syndrome: clinical manifestations and pathogenesis. In: Bushkin FL, Woodward ER, editors. Postgastrectomy syndromes. Philadelphia: WB Saunders; 1976.
45. Ralphs DNL, Thomson JP, Haynes S, Lawson-Smith C, Hobsley M, Le Quesne LP. The relationship between the rate of gastric emptying and the dumping syndrome. Br J Surg. 1978;65:637–41.
46. Woodward ER, Neustein CL. The late postprandial dumping syndrome. In: Bushkin FL, Woodward ER, editors. Postgastrectomy syndromes. Philadelphia: WB Saunders; 1976.
47. Nightingale JMD. Octreotide to treat dumping and short bowel syndrome. Curr Med Lit Gastroenterol. 1993;12:75–82.
48. Stempien SJ, Dragadi AE, Lee ER, Simonton JH. Status of duodenal ulcer patients ten years or more after vagotomy-pyloroplasty (V-P). Am J Gastroenterol. 1971;56:99–108.
49. Raimes SA, Smimiotis V, Wheldon EJ, Venables CW, Johnston IDA. Postvagotomy diarrhoea put into perspective. Lancet. 1986;2:851–3.
50. Ladas SD, Isaacs PET, Quereshi Y, Sladen G. Role of the small intestine in postvagotomy diarrhea. Gastroenterology. 1983;85:1088–93.
51. Allan JG, Gerskowitch VP, Russell RI. The role of bile acids in the pathogenesis of postvagotomy diarrhoea. Br J Surg. 1974;61:516–8.
52. Collins CD. Lomotil in treatment of post-vagotomy diarrhoea. Br Med J. 1966;2:560–1.
53. Ayulo JA. Cholestyramine in postvagotomy diarrhoea. Am J Gastroenterol. 1972;57:207–25.
54. Duncombe VM, Bolin TD, Davis AE. Double-blind trial of cholestyramine in post-vagotomy diarrhoea. Gut. 1977;18:531–5.
55. Deller DJ, Wits LJ. Changes in the blood after partial gastrectomy with special reference to vitamin B_{12}. Q J Med. 1962;31:71–88.
56. Bjomeboc E, Farber H, Mikkelsen O, Toleiassen F. Surgical treatment of gastric and duodenal ulcer. Acta Med Scand. 1951;141:16–26.
57. Wallensten S. Results of surgical treatment of peptic ulcers by partial gastrectomy according to Billroth I and Billroth II methods. Acta Chir Scand. 1954;191(suppl):1–161.
58. Pryor JP, O'Shea JM, Brooks PL, Datar GK. The long-term metabolic consequences of partial gastrectomy. Am J Med. 1971;51:5–10.
59. Hines ID, Hoffbrand AV, Mollin DL. The haematologic complications following partial gastrectomy. Am J Med. 1967;43:555–69.
60. Mahmud K, Ripley D, Swaim WR, Doscherhohnen A. Haematologic complications of partial gastrectomy. Ann Surg. 1973;177:432–5.
61. Shafer RB, Ripley D, Swain WR, Mahmud K, Doscherholmen A. Hematologic alterations following partial gastrectomy. Am J Med Sci. 1973;266:240–8.
62. Bragelmann R, Armbrecht U, Rosemeyer D, Schneider B, Zilly W, Stockbrugger RW. Nutrient malassimulation following total gastrectomy. Scand J Gastroenterol. 1996;31(suppl 218):26–33.
63. Kimber C, Patterson JF, Weintraub AR. The pathogenesis of iron deficiency anaemia following partial gastrectomy. A study of iron balance. JAMA. 1967;202:935–8.
64. Baird IM, Wilson GM. The pathogenesis of anaemia after partial gastrectomy. II. Iron absorption after partial gastrectomy. Q J Med. 1959;28:35–40.
65. Wheby MS, Jones LG, Crosby WH. Studies on iron absorption. Intestinal regulatory mechanisms. J Clin Invest. 1964;43:1433–42.
66. Rygold O. Hypovitaminosis B_{12} following partial gastrectomy by the Billroth II method. Scand J Gastroenterol. 1974;29(suppl):57–64.
67. Loewenstein F. Absorption of Cobalt ^{60}-labeled vitamin B_{12} after subtotal gastrectomy. Blood. 1958;13:339–47.
68. Mahmud K, Ripley D, Dosherholmen A. Vitamin B_{12} absorption tests, their unreliability in post-gastrectomy states. JAMA. 1971;216:1167–71.
69. Dosherholmen A, Swaim WR. Impaired assimulation of egg Co^{57} vitamin B_{12} in patients with hypochlorhydria and achlorhydria and after gastric resection. Gastroenterology. 1973;64:913–9.
70. Eddy RL. Metabolic bone disease after gastrectomy. Am J Med. 1971;50:442–8.
71. Carrasco F, Basfi-Fer K, Rojas P, Csendes A, Papapietro K, Codoceo J, et al. Calcium absorption may be affected after either sleeve gastrectomy or Roux-en-Y gastric bypass in premenopausal women: a 2-y prospective study. Am J Clin Nutr. 2018;108(1):24–32.
72. Wei JH, Lee WJ, Chong K, Lee YC, Chen SC, Huang PH, Lin SJ. High incidence of secondary hyperparathyroidism in bariatric patients: comparing different procedures. Obes Surg. 2018;28(3):798–804.
73. Cheng KC, Liao KF, Lin CL, Lai SW. Gastrectomy correlates with increased risk of pulmonary tuberculosis: a population-based cohort study in Taiwan. Medicine (Baltimore). 2018;97(27):e11388. https://doi.org/10.1097/MD.0000000000011388.

Surgery for Obesity and Its Consequences

Cynthia-Michelle Borg and Jean Deguara

Key Points

1. Bariatric surgery is performed in patients suffering from obesity when non-surgical techniques have been unsuccessful and the BMI is greater than 40 kg/m^2 (or 35–40 kg/m^2 if obesity complications).
2. Laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass are the most commonly performed bariatric operations.
3. Patients with abdominal pain and vomiting at any time after a Roux-en-Y gastric bypass may have an internal (mesenteric) hernia and should be urgently investigated and treated (to prevent bowel resections due to ischaemia).
4. Patients should have lifelong annual follow up with regular blood tests depending on the operation and local guidelines.
5. Cholelithiasis is common and if suspected confirmed by ultrasound.
6. Some of these patients may present to IF/HPN centres due to weight loss (especially if small bowel has been resected due to ischaemia) or if an enterocutaneous fistula(s).

Introduction

Obesity is a chronic, progressive and complex disease. It is defined as an excessive accumulation of body fat that can impact the health or the wellbeing of an individual. A body mass index (BMI) of 30 kg/m^2 or more is often used to define obesity.

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In 2016, the World Health Organization (WHO) estimated that 13% of adults (18 years and over) worldwide suffered from obesity [1]. The Health Survey for England in 2018 reported that 26% of men and 29% of women were obese, with 2% of men and 4% of women suffering from morbid obesity (BMI of 40 or more) [2].

Obesity is associated with numerous medical complications, worse quality of life and a shorter life expectancy [3]. In particular, excess body weight is associated with metabolic problems including type 2 diabetes (T2D), non-alcoholic steatohepatitis (NASH) as well as cardiovascular disease and some types of cancers. Central weight distribution with a waist circumference of more than 80 cm in women and 94 cm in men puts the individual at higher risk of development of cardio-metabolic complications [4].

Mechanical problems like obstructive sleep apnoea and musculoskeletal issues are also common in patients suffering from obesity. They may also experience higher levels of depression, anxiety and low self-esteem.

Weight loss has been shown to improve cardio-metabolic problems associated with obesity as well as increase the life expectancy. A 10 kg weight loss has been found to be associated with a 10 mmHg fall in systolic blood pressure, a 20 mmHg fall in diastolic blood pressure, 10% lowering of the total cholesterol and improvement in the lipid profile. A fall of 30–50% in fasting blood glucose and improvement in HbA_{1c} are also observed with weight loss [5].

The regulation of food intake and body weight is complex with signals from body fat, the gut and the pancreas to the hypothalamus and the brainstem together with signals from the higher reward centres.

The ideal weight loss management should improve the health, wellbeing and life expectancy of the individual, prevent obesity related complications, be safe and lead to sustained weight loss. Although, lifestyle measures that involve dietary restrictions may initially be associated with good weight loss, long-term weight regain is common [6].

Bariatric surgery leads to significant, sustained weight loss with improved medical issues and survival [7]. This is

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because surgery not only induces a decrease in food intake but is also associated with changes in signals from the GI tract leading to increased satiety and fullness, decreased hunger sensation and changes in taste and smell [8].

Adequate patient preparation, proper choice of the primary procedure and long-term follow-up are very important. The criteria and indications for the use of bariatric surgery have been extensively debated in the surgical literature and in conferences. Most bariatric multidisciplinary teams use the guidelines published by the National Institute for Health in the USA [9] or by the National Institute of Clinical Excellence in the UK [10].

In its 2014 guidelines, NICE advises that patients undergoing bariatric surgery should have tried all appropriate, available non-surgical measures for weight reduction but failed to achieve or maintain clinically beneficial weight loss. They should have a BMI of 40 kg/m^2 or more, or between 35–40 kg/m^2 with obesity related co-morbidities. Patients with a BMI of 30–34.9 kg/m^2 who have recent-onset T2D should also be offered an assessment for bariatric/metabolic surgery. A slightly lower BMI may also be considered in patients with T2D of Asian family origin. Patients require multidisciplinary team management and should be fit for general anaesthesia and surgery. Pre-operatively, medical or psychological contraindications need to be excluded and patients are required to understand the need for long-term post-operative follow-up [10].

The number of bariatric surgery operations being performed has increased over time. The International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) Global registry collates data from around the world. In its latest publication, the most commonly performed primary operation was the sleeve gastrectomy (46.0%) followed by the Roux-en-Y gastric bypass (38.2%), the one anastomosis gastric bypass (7.6%) and gastric banding (5.0%) [11]. Bariatric surgery has evolved over the years.

Bariatric and Metabolic Procedures

Historic Operations: Jejuno-Ileal and Jejuno-Colic Bypass

The concept of surgery for severe obesity was introduced in the 1950s. The first reported case in the literature was an end-to-end jejuno-ileal bypass (JIB) in 1954 [12]. It aimed to induce weight loss by malabsorption. Jejuno-colic bypass (JCB) was also performed with the proximal 15 cm of the jejunum being joined to the mid-transverse colon [13]. In 1969, Payne et al. reported the results of 11 patients who had JCB. These patients had developed uncontrollable diarrhoea with associated dehydration and electrolyte imbalance. The authors thus advised against such procedures recommending JIB as an alternative [14]. Several variations, in terms of limb lengths and the faith of the bypassed small bowel, were described. JIB, though associated with excellent weight loss and improvement of hyperlipidaemia, was itself found to be associated with a multitude of serious complications. These included hypoalbuminaemia and deficiency of calcium, fat-soluble vitamins and vitamin B12 resulting in osteoporosis, osteomalacia, night blindness, anaemia and peripheral neuropathy [14]. Diarrhoea and electrolyte imbalance were also common. Migratory polyarthralgias, cholelithiasis, liver cirrhosis and liver failure developed in some patients [15]. Other long-term complications included renal disease secondary to hyperoxaluria with the development of oxalate stones and interstitial oxalate deposition potentially leading to renal failure [16]. The bypassed small bowel segment was also prone to various problems including intussusception and small intestinal bacterial overgrowth (SIBO). As a result of these serious complications, JIB was abandoned by the 1970s and most patients had their procedure reversed, with or without another metabolic/bariatric operation being performed concurrently. There are still, however, some patients living well with this operation. Most bariatric surgeons will advise close, lifelong follow-up in this patient group to detect complications early and most would offer reversal of the surgery should these arise.

Operations Involving the Stomach Only

Gastroplasty

Gastroplasty involved the partitioning of the stomach creating a small proximal pouch, which communicated with the distal and larger portion of the stomach via a restrictive channel. The most popular variety, developed by Mason [17], used a vertical segment of stomach along the lesser curve for the pouch (Fig. 1) and was thus called a vertical banded gastroplasty (VBG). The volume of the pouch was standardized to 14 mL at the time of surgery and a polypropylene band was placed around the lower end of the pouch to prevent dilatation. The band's circumference was standardized and fixed at 5 cm. Different variations of this procedure exist [17]. VBG was sometimes complicated with stomal stenosis and gastro-oesophageal reflux (GORD) symptoms. It had inferior long term weight loss when compared to RYGB often due to the formation of gastro-gastric fistulas between the two partitioned parts of the stomach thereby negating the restrictive effect. Since the development of adjustable gastric banding, VBG is obsolete although again, there are some patients still living with this operation.

Gastric Banding

Adjustable gastric banding involves the laparoscopic positioning of a silicone band around the upper part of the stom-

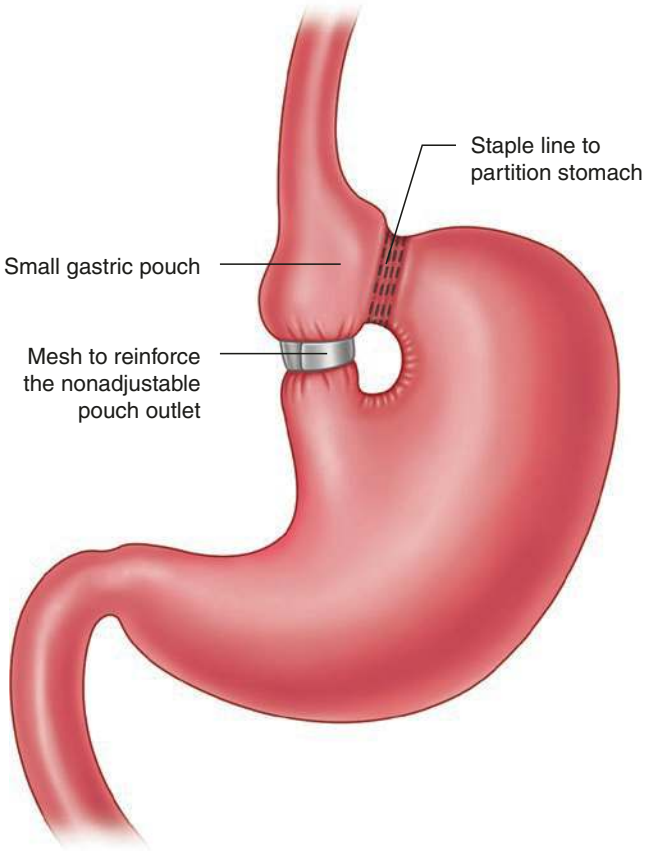


Fig. 1 Vertical banded gastroplasty VBG

ach (Fig. 2) creating a small proximal gastric pouch that is usually calibrated to have a capacity of 15–20 mL. The undersurface of the band has an inflatable inner cuff, which is connected by a tube to a subcutaneous port. The size of the pouch outlet can be adjusted by varying the volume of fluid in the band through the port using a non-coring needle. The amount of fluid is adjusted until the patient is in the 'green zone'—when weight loss is achieved by inducing an early feeling of satiety after eating smaller amounts of food than before the surgery.

While band insertion is safe and can often be performed as a daycase procedure, long-term complications like band erosion, slippage and pouch and oesophageal dilatation can occur. Between 30–40% of patients who undergo banding will require revision surgery by 7 years post-op [18]. Weight loss with GB is usually slower and lower than after RYGB and the SG. Results may vary from centre to centre depending on patient selection and the intensity of follow-up.

Sleeve Gastrectomy

Sleeve gastrectomy SG (Fig. 3) involves the excision of most of the greater curve of the stomach and the fundus using surgical staplers, with the remaining stomach having a tube like appearance with a reduced volume (usually less than 100 mL). The diameter of this tube is standardized by using an orogastric bougie which may vary in size from centre to centre [19]. Besides being a restrictive operation, sleeve gastrectomy has also been found to be associated with acceleration in gastric motility [20] and changes in gut hormones [8, 21]. Although initially intended as the first step before RYGB or duodenal switch (DS) operation in patients with very severe central obesity [22], sleeve gastrectomy is increasing being offered as a single stage bariatric procedure. It is currently the commonest primary bariatric procedure performed worldwide [11].

Most surgeons would regard the presence of Barrett's oesophagus as a contraindication for SG. Post-operative complications may include staple line bleeding, leaks, twists and strictures. Long-term issues with post-operative GORD may require lifelong medication or revision surgery.

Gastric Plication

Laparoscopic gastric plication is the infolding of the greater curvature to reduce stomach volume using running sutures. While cheaper than LSG, the long-term results and the durability of the operation are uncertain and most surgeons would regard it as investigational [23].

Operations Involving the Stomach and Small Bowel

Roux-en-Y Gastric Bypass (RYGB)

The RYGB has, for many years, been regarded as the gold standard bariatric operation (Fig. 4). It was first described in 1967 by Mason et al. [24], with the first laparoscopic procedure performed in 1994 [25]. It involves the creation of a small stomach pouch (based on the lesser curvature). A cut Roux loop of jejunum (the alimentary limb) is joined to the pouch to allow food to bypass the larger, distal part of the stomach, the duodenum and the first part of the small bowel (the biliopancreatic limb). The alimentary and biliopancreatic limb are anastomosed to allow intestinal continuation and mixing of food and digestive enzymes digestion occurs in the common channel. The standard length of the alimentary limb is usually around 100–150 cm with the biliary limb being 60–100 cm although some surgeons may use longer limbs especially in patients with a BMI of 50 kg/m^2 or more [26]. The small gastric pouch restricts the amount of food that can be eaten while bypassing of the duodenum induces changes in gut and pancreatic hormone secretion leading to metabolic and hormonal changes that are associated reduced appetite and an increased feeling of satiety and fullness.

Fig. 2 Gastric banding

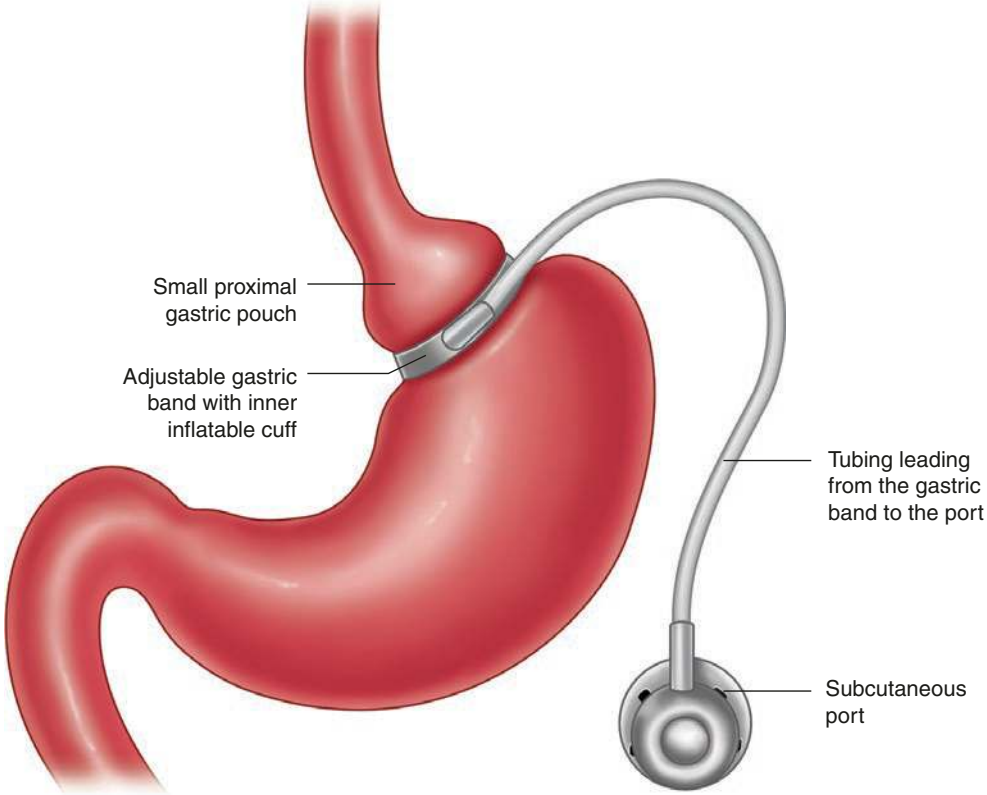
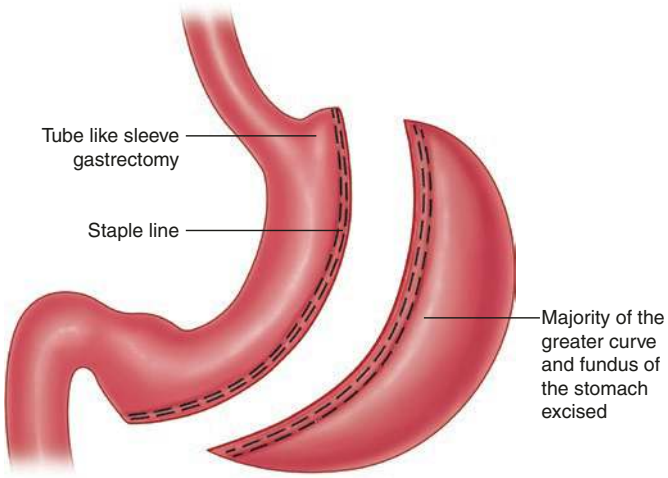


Fig. 3 Sleeve gastrectomy SG



There are also changes in gut microbiota, bile acid levels and composition and intestinal motility [8].

Contra-indications for RYGB include small bowel disease such as adhesions or Crohn's disease as well as conditions that require access to the stomach (eg in areas or families with high incidence of gastric cancers), the duodenum and biliary tree. Complications of RYGB may include bleeding, anastomotic leak, anastomotic ulceration and strictures, dumping syndrome, internal herniation and mineral and vitamin deficiency.

One Anastomosis Gastric Bypass (OAGB)

The OAGB was first described by Rutledge in 2001 [27]. It is also known as the single anastomosis or the mini-gastric bypass. A long tube-like proximal pouch of stomach is created from the lesser curvature side. Intestinal continuity is re-established by connecting the gastric pouch to a loop of jejunum bypassing up to 100–250 cm of the proximal jejunum (biliopancreatic limb). As it has one less anastomosis, OAGB has a shorter operating time when compared to RYGB.

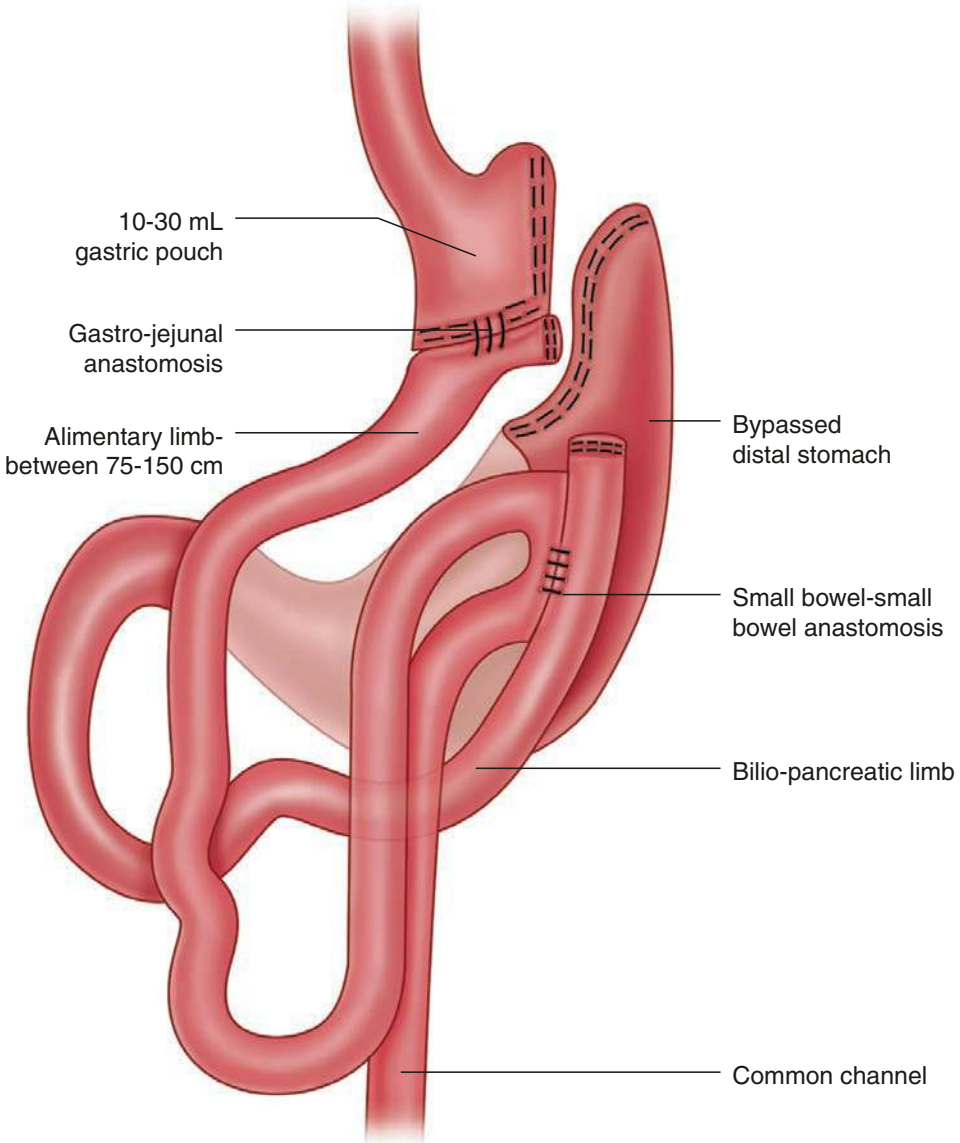


Fig. 4 Roux-en-Y gastric bypass RYGB

Long-term data shows that the OAGB using biliopancreatic limbs of over 150 cm may result in a slightly better weight loss and better resolution of diabetes than the RYGB [28]. Some surgeons believe that long-term, OAGB has a lower risk for internal herniation than the RYGB. The recent YOMEGA trial has been however showed that OAGB with a 200 cm small bowel biliopancreatic limb has more malabsorptive complications when compared to RYGB [29]. Bile reflux into the stomach with gastritis and oesophagitis is common and may adversely affect the patients' quality of life [30]. The long-term effects of this are uncertain.

Other Operations

The bilio-pancreatic diversion (BPD) (Fig. 5) was described by Scopinaro [31] and involved the creation of a 200–500 mL gastric pouch and a distal two-thirds gastrectomy. Intestinal continuity was achieved by the formation of a gastro-ileostomy 250 cm proximal to the ileocaecal valve. The biliopancreatic limb was then anastomosed to the alimentary limb creating a common channel, which originally was described as around 50 cm. Most surgeons increased the length of the common channel to at least 100 cm in an attempt to limit the malabsorptive symptoms. BPD is more technically demanding than other bariatric procedures and carries the morbidity of a partial gastrectomy. It has been reported to have the best results in terms of weight loss and resolution of T2DM [32]. It can result in significant malabsorptive complications and patients undergoing this procedure require strict compliance, close follow-up and long-term nutritional supplementation [33].

Variations of BPD include the duodenal switch (DS) as described by Hess [34]. This involves a sleeve gastrectomy with preservation of the pylorus (Fig. 6). Like the BPD, DS is technically challenging and may lead to protein, mineral

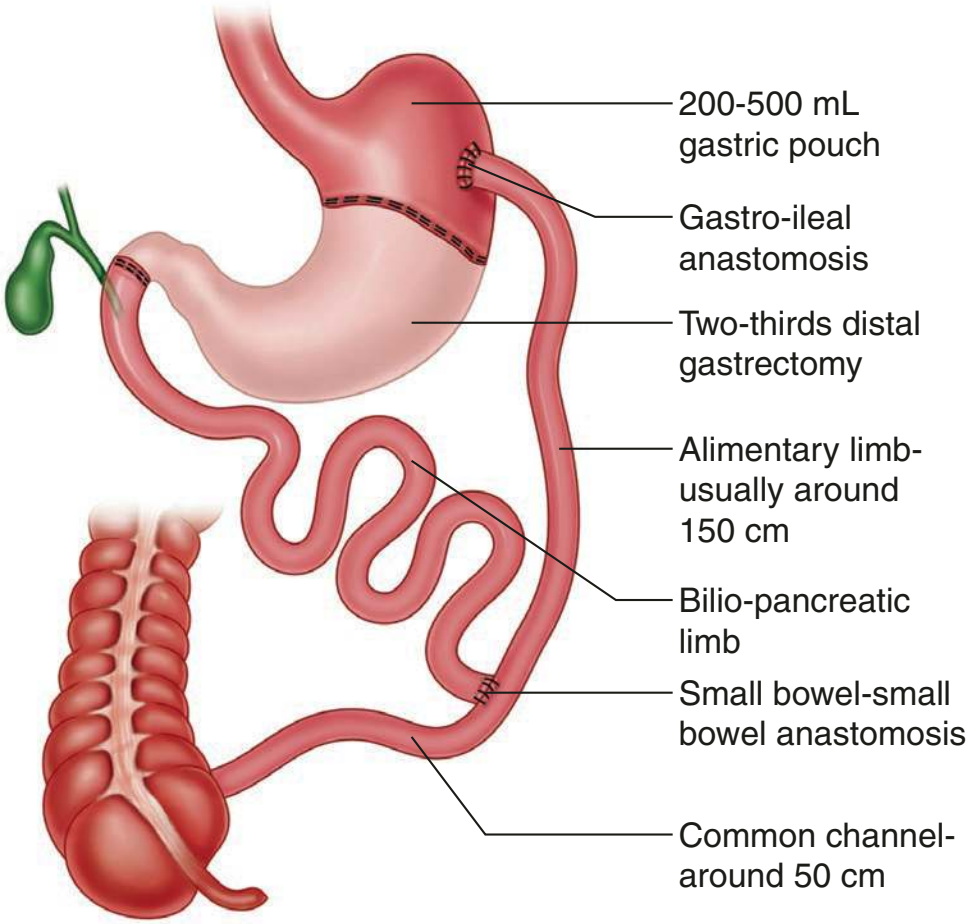


Fig. 5 Biliopancreatic diversion BPD

and vitamin deficiency. A further recent modification of DS, the single anastomosis duodenal-ileal bypass with sleeve gastrectomy SADI-S (also known as the one anastomosis duodenal switch), utilizes a single anastomosis. It was first described Sanchez-Pernaute et al. and anastomoses the duodenum directly to an omega loop of ileum 200–300 cm proximal to the ileo-caecal valve, eliminating the need for the Roux-en-Y jejunal-ileal anastomosis [35]. Such an operation may play a role in the management of patients who have a BMI of over 60 or for those with weight regain or poor weight loss after SG in the future. Both IFSO [36] and American Society for Metabolic and Bariatric Surgery (ASMBS) [37] have highlighted the lack of long-term data about SADI-S at this stage.

Endoscopic Bariatric and Metabolic Therapies

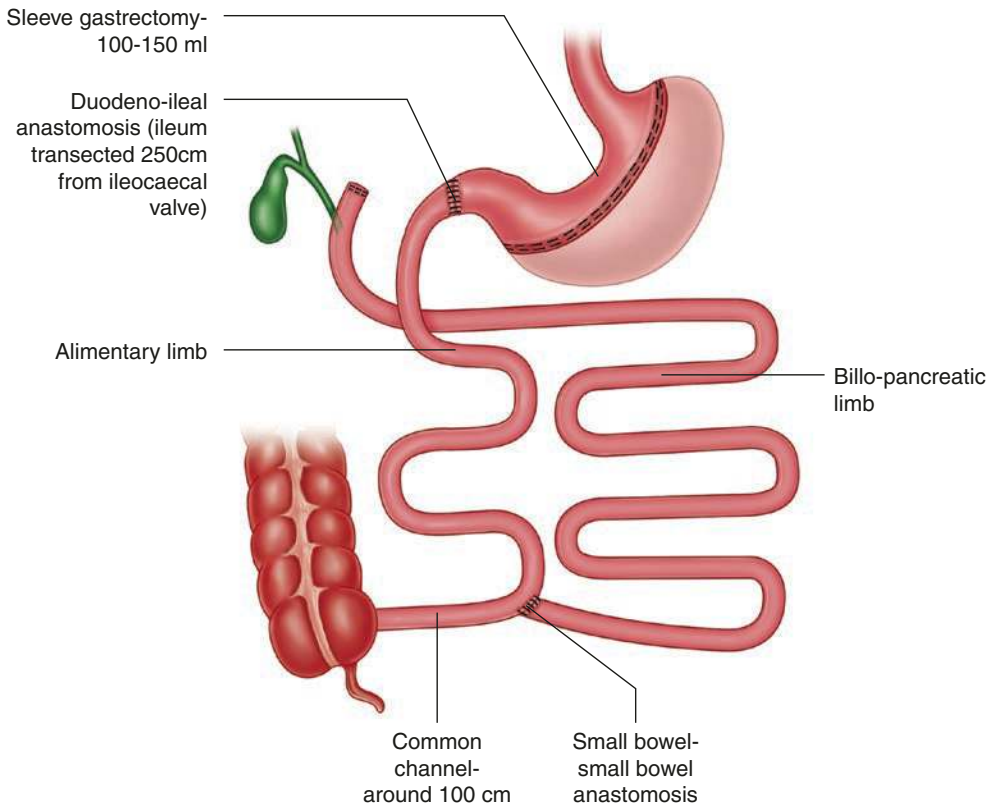
Endoscopic bariatric and metabolic therapies (EBMT) are a relatively new modality in the management of obesity. They are important, alternative treatment options for patients suffering with obesity but who have relatively low BMIs and those who are not keen to undergo surgery. They may also be used as a bridge to surgery in patients with severe obesity. They are generally divided into gastric and small bowel procedures.

The gastric therapies include intragastric balloons, the gastric aspiration system and endoscopic sleeve gastroplasty (ESG).

The intragastric balloon (IGB) is a space-occupying device. Several different types of IGBs are licensed for use including ones that are liquid or air filled, some that require endoscopic insertion and removal (usually made of soft silicone), others that do not need endoscopic removal as they disintegrate after 16 weeks and others that are swallowable. Most of the soft silicone balloons require endoscopic removal after 12 months. While they can be replaced by a new IGB, they are not a durable, long-term solution for severe obesity [38]. They however do result in modest weight loss and improvement in quality of life whilst in situ.

Contraindications to IGB placement include a history of gastrointestinal surgery and large hiatal hernia. Nausea is a common side-effect especially early on after IGB insertion. Although most patients will improve with time and antiemetics, some IGBs need to be removed early due to intolerance. The Brazilian Intragastric Balloon Consensus

Fig. 6 Duodenal switch DS



Statement reported on their experience of over 40,000 IGB implantations in 2018 and showed that that implantation is safe and effective [39]. The most common complications in this large series were hyperinflation, deflation, migration and ulceration [39]. Gastric perforation and small bowel obstruction secondary to migrated IGB are rare.

Gastric aspiration therapy involves the insertion of a gastrostomy tube (A-tube). Together with a siphon assembly, it allows the patient to aspirate gastric contents 20 min after eating. Aspiration usually takes about 10 min and reportedly removes approximately 30% of ingested calories. It is licensed for used in patients with a BMI of between 35–55 kg/m^2 in the setting of a multidisciplinary program to adjust eating behavior. In motivated and compliant patients, it has safe and durable weight loss [40]. Skin irritation around the stoma site is common. Persistent gastric fistula requiring surgical closure may occur once the A-tube is removed.

Endoscopic sleeve gastroplasty (ESG) attempts to reduce the volume of the stomach, recreating the gastric plication using a transoral endoscopic suturing platform. It is mostly used in patients with BMI 35.0–39.9 but it may be play a role in patients who are unfit for laparoscopic surgery. The technique results in short and medium term weight loss but long-term data regarding durability is lacking [38].

The duodenum and proximal jejunum have been recognized as a key metabolic signaling center. The EndoBarrier duodenal-jejunal bypass liner (DJBL) was developed to avoid contact of food with the mucosal lining of the duodenum and proximal jejunum. The device consists of a ring that anchors on the duodenal bulb connected to a 60 cm Teflon liner that covers the mucosal surface of the duodenum and proximal jejunum. It has a modest weight loss effect but has been shown to ameliorate T2D control whilst the device is in place [41]. It is not currently in clinical use due to a high incidence of adverse effects especially liver abscesses reported during a US pivotal trial.

Duodenal mucosal resurfacing involves circumferential mucosal lifting followed by hydrothermal ablation of duodenal mucosa. It has been showed to improve glycaemic control in patients with suboptimally controlled T2D [42]. The mechanism of how and why this happen is uncertain. Whether the effect will be sustained in the medium and long term is also unknown. Adverse effects are common, most are mild but duodenal stenosis may occur.

Consequences of Bariatric Surgery

Early Post-operative Complications

Laparoscopic bariatric surgery is safe and effective. In the UK, the in-hospital mortality rate is around 0.061% with the 30-day mortality being reported at 0.13% by Hospital Episode Statistics (HES) [43]. Although early complications often represent to the bariatric centres where the surgery was performed, awareness of such presentations by other clinicians is important especially due to the rise in bariatric tourism. Early complications may include leakage or bleeding from anastomosis and staple lines, venous thromboembolism and chest, wound and urinary infections.

Patients suffering from morbid obesity may not present with typical signs of sepsis and peritonism and a high index of suspicion is required. Tachycardia and tachypnoea may be the only features in this patient group.

Bleeding occurs in less than 1% of cases [44] and may be intra-luminal, presenting with meleana and haematemesis, or intra-peritoneal. Most patients settle with close monitoring and conservative management with or without blood products. Some however may need endoscopy or re-laparoscopy if unstable or having increased transfusion requirements.

Leaks may occur from anastomosis sites, from staple lines or from iatrogenic bowel injuries. With improvement in staple line technology and operative techniques, the risk of leaks continues to decrease and the incidence is currently quoted as less than 0.5% [44]. Leaks usually present between day 5–10 post-operatively. Abdominal pain may not be a feature with patients presenting with fever, shoulder tip pain and non-specific symptoms instead. A high index of suspicion and early investigation with contrast imaging or a re-laparoscopy is essential to avoid deterioration and long-term consequences.

Venous thromboembolism (VTE) was found to have a significant effect on readmission and mortality post-bariatric surgery [44]. Longer operations, past history of VTE and blood transfusion have been found to increase the risk of VTE [45]. Most surgeons encourage the peri-operative use of thromboembolic deterrent stockings, intermittent pneumatic compression intra-op, early mobilization, prophylactic anticoagulation and patient education for early recognition.

Portomesenteric and splenic vein thrombosis (PVT) is a rare yet occasionally catastrophic complication of bariatric surgery. PVT is a well-recognized complication of upper GI surgery including fundoplication and gastric resection. It may also occur within the first month after bariatric surgery especially after SG. Risk factors include recent oral contraceptive use, smoking, a history of malignancy, T2D and a history of pro-thrombotic genetic tendencies including Protein C and S deficiency and Prothrombin 20210 mutation [46, 47]. The use of high intraperitoneal pressure during laparoscopy may also play a role. Patients often present with non-specific abdominal pain. CT scan with intravenous contrast is often diagnostic. Most patients can be treated non-operatively with anticoagulation but some may require surgery if they develop bowel necrosis. Such patients may end up with massive small bowel resection and subsequent short-bowel syndrome. In the literature a mortality rate of about 4% is described with PVT.

Medium/Late Gastrointestinal Complications

Vomiting

Nausea and vomiting are common in the first few months after surgery and often settle as patients get used to their new eating habits. Patients may be unable to progress to a solid diet and persist on a liquid or soft diet. Common pitfalls include eating too fast, not chewing the food thoroughly and mixed food and water. If these symptoms persist, investigation of the post-operative anatomy with upper GI endoscopy and/or contrast studies is important to exclude strictures especially at the site of gastro-jejunal anastomosis or any other intra-operative mishap eg Roux-en-O reconstruction [48].

Sometimes with SG a functional twist can arise in the body of the sleeve. Although there is no anatomical obstruction on endoscopy, this may often be demonstrated with a contrast study. Other causes on nausea and vomiting including pregnancy need to also be excluded. Acute presentations with vomiting will require exclusion of acute band slippage in patients with gastric bands and internal hernias in patients with operations who involved small bowel anastomosis. Expeditious investigation and treatment are important to avoid ischaemia.

Empirical intra-venous thiamine replacement is important in patients with persistent vomiting to avoid precipitation of Wernicke's encephalopathy [49].

Gastro-oesophageal Reflux

Several studies have shown a higher incidence of GORD in patients who are overweight compared to the general population [50]. The Bristol Helicobacter project reported that patients who suffer from obesity are up to three times more likely to suffer from heartburn or regurgitation [51]. These patients are also at higher risk of developing GORD complications including erosive oesophagitis [52], Barrett's oesophagus and oesophageal and junctional adenocarcinoma than their lean counterparts [53]. Central obesity rather than BMI itself is closely associated with these complications. The pathophysiology of this may include increased intra-abdominal and intra-gastric pressure, reduced oesophageal

clearance, increased transient relaxations of lower oesophageal sphincter (LOS) and abnormal gastro-oesophageal junction anatomy with shorter, hypotensive LOS and increased incidence of hiatal hernia [54]. Increased mucosal sensitivity, larger gastric capacity, dietary habits and higher levels of leptin, interleukin 6 and TNF and lower levels of adiponectin may also be involved [55]. Non-surgical weight loss has been associated with a decrease in GORD symptoms in several studies [50, 56].

Pre-operative upper GI endoscopy is recommended prior to bariatric surgery [57] but not universally performed. A recent systematic review noted that only 7.6% of OGDs performed prior to bariatric surgery [58] lead to a change in the operative management. However over a third of patients undergoing bariatric surgery have abnormal OGD findings [57] and endoscopy often helps to establish appropriate operation planning, consent and follow-up. Most surgeons would consider repairing the hiatus if there is a significant hiatus hernia or opt for a RYGB, which has long been hailed as the best operation for patients with obesity and GORD [59]. De novo GORD may occur after surgery especially after gastric banding, SG [60] and OAGB [61] while the same operations can improve GORD in patients with pre-operative symptoms [55, 60, 62]. Studies are often difficult to interpret and compare due to different operative techniques including management of the hiatus, length of follow-up, medication use and how GORD was defined (symptoms, questionnaires, endoscopy, biopsies, pH studies). The topic of reflux and its potential consequences are hotly debated in bariatric surgical conferences and in the literature [63] and are not the remit of this chapter.

If patients with a history of bariatric surgery develop dysphagia or worsening reflux, 2-week wait or expedited endoscopy should be arranged. Some surgeons offer routine OGD every 2–3 years after SG and OAGB [57], as poor correlation between GORD symptoms, degree of oesophagitis and the development of Barrett's oesophagus has been shown, but this is no means the norm. Most patients who develop GORD can usually be managed with lifestyle modification and proton pump inhibitors (PPIs) although a small proportion may require revision surgery.

Anastomotic Complications: Ulceration, Stenosis, Perforation

Operations involving anastomosis of the stomach and small bowel like the RYGB and the OAGB may be complicated by ulceration, stenosis or perforation at or near the joint (marginal ulceration). Reduced blood flow and tension at the anastomosis site may play a role. Other risk factors include smoking, chronic NSAID use, a large proximal gastric pouch, the presence of a gastro-gastric fistula and Helicobacter pylori. Bile reflux may play a role in marginal and gastric ulceration after OAGB.

Patients with ulcers may be asymptomatic or may present with nausea, vomiting, epigastric pain and rapid weight loss. They may also present with anaemia due to chronic bleeding. Diagnosis is usually made with an upper GI endoscopy. Ulcers may be complicated by stricture formation. While these often respond to endoscopic dilatation, iatrogenic perforation and recurrence are not uncommon. Ulcer perforation may occur spontaneously and often require laparoscopy, washout and an omental patch repair.

Marginal ulceration may occur in 0.6–16% of patients with RYGB [64]. Most surgeons recommend PPIs for the first 3 months post-op to try and prevent this complication. PPIs, together with sucralfate, form the mainstay of treatment together with management of other risk factors including smoking cessation therapy. Up to a third of patients with recurrent or refractory ulceration after RYGB may need revision surgery.

Ulceration in OAGB may occur in up to 10% of patients and may be particularly difficult to treat as it is often the consequence of bile reflux. In these cases, conversion to traditional RYGB configuration is usually beneficial [65].

Dumping

Dumping syndrome has been reported with several bariatric operations but especially with the RYGB and SG [66]. It is often thought to be secondary to rapid post-prandial gastric emptying and is characterised by gastrointestinal and vasomotor symptoms. The clinical presentation is variable and symptoms are divided into early and late. Early dumping symptoms usually occur within 1 h after a meal and include abdominal pain, loose stools, nausea, vomiting and bloating. Patients can also present with vasomotor symptoms such as fatigue, tachycardia and facial flushing. The mechanisms underlying early dumping may involve the osmotic effects of food in the jejunum, gut hormone release and autonomic neural responses [67].

Late dumping symptoms (1–3 h postprandial) relate to hypoglycaemia and include perspiration, palpitations, hunger, fatigue, tremor and confusion [67]. In one study of 450 patients who had undergone RYGB or SG, over a third reported symptoms suggestive of postprandial hypoglycaemia [68]. Spontaneous plasma levels of glucose <2.8 mmol/L (50 mg/dL) are indicative of late dumping syndrome. Late dumping and the associated hypoglycaemia is thought to be secondary to an exaggerated GLP-1 response.

Most patients with symptoms of dumping are reviewed by a multidisciplinary team including the bariatric surgeon, physician and dietician. Dietary changes are usually successful in most patients. Rapidly absorbable carbohydrates should be eliminated from the diet to prevent symptoms of late dumping syndrome. They should be advised to eat a diet consisting of foods high in fibre and rich in protein, eaten slowly and chewed well. Some patients therefore find symp-

toms of dumping, a timely reminder that they may be eating 'the wrong types of food'.

In patients whose symptoms persist despite dietary manipulation, Acarbose and somatostatin analogues may be used. If conservative management fails, further endoscopic or surgical techniques may be offered to attempt to slow down the passage of food from the stomach into the small bowel [69].

Cholelithiasis

Gallstone disease can be found in 10–20% of general population. Out of these about 20% will develop symptoms including biliary colic, acute cholecystitis and gallstone pancreatitis. A eightfold rise in incidence has been documented in patients with BMI equal of more than 40 kg/m^2 [70]. Rapid weight loss induces gallbladder stasis and changes in bile composition with supersaturation of bile with cholesterol and raised concentrations of mucin [71]. These changes may result in the formation of biliary sludge and gallstones. Bariatric surgery is associated with a predisposition for further development of cholelithiasis in over 35% of patients [72]. Cholelithiasis is more common in the patients who have lost most weight [73].

Ursodeoxycholic acid (UDCA) is a secondary bile acid—a by-product of intestinal bacteria, which helps reduce the rate of cholesterol absorption in intestines, resulting in decreased cholesterol saturation of bile and gallstone incidence. UDCA has some side-effects such as diarrhoea, loose and pale stools, and pruritis which may decrease patient compliance to treatment. Prophylactic use of urseodeoxycolic acid for at least the first 6 months post-operatively has been shown to decrease the incidence of gallstone formation [73] and lower the risk of requiring an urgent cholecystectomy [74].

In the laparoscopic era, most surgeons would not advocate concomitant prophylactic cholecystectomy for normal gallbladders or for patients with asymptomatic gallstones.

Mineral, Vitamin and Protein Deficiency

Patients with severe and complex obesity often have nutritional deficiencies. The most common ones include low levels of vitamin D, iron, folate and B12 [75]. The dietician plays a crucial role in the care of patients prior to bariatric surgery as they would undertake a detailed nutritional and dietary assessment and help in patient education. Patients are also routinely screened for mineral and vitamin levels and for anaemia as part of their pre-operative preparation. It is important that such deficiencies are corrected prior to bariatric surgery as this will limit the intake and absorption of such supplements.

With patient education, protein malnutrition is uncommon post-operatively after gastric bands and SG. It is also unusual with the gastric bypass unless technical issues like strictures are present. Protein malnutrition is more common with OAGB, BPD, DS and SADI. These patients require between 60–120 g of protein per day to maintain their lean body mass. If malnutrition is suspected, patients should be admitted to hospital for investigation, mineral and vitamin supplementation and feeding (enteral/parenteral). Patients with protein malnutrition should be assumed to have accompanying mineral and vitamin deficiency until proven otherwise.

Most bariatric centers recommend that their patients should stay on lifelong mineral and vitamin supplementation due to a reduction in oral intake with food and reduced intestinal absorption. The dosage of these may vary depending on the operation, the patient's dietary habits (eg vegetarians) and in women with heavy periods. Routine blood tests to check levels are also very important. These usually include a full blood count, ferritin, folate, Vitamin B12, Vitamin D and calcium at 3, 6, 12 months post-operatively and then at least annually after that. Vitamin A, E and K1 should also be monitored after BPD and DS and may also be required after OAGB. Zinc, copper and selenium levels may be required if oral intake is poor, patients are loosing wait rapidly or have unexplained anaemia, neuropathy, cardiomyopathy, or diarrhea. The recent BOMSS updated guidelines should be consulted for more information about monitoring and nutrient replacement after bariatric surgery [76].

References

1. WHO. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 19 Sept 2020.
2. http://healthsurvey.hscic.gov.uk/support-guidance/public-health/health-survey-for-england-2018/overweight-and-obesity-in-adults-and-children.aspx. Accessed 19 Sept 2020.
3. Bhaskaran K, dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK. Lancet Diabetes Endocrinol. 2018;6(12):944–53.
4. Han TS, Van Leer EM, Seidell JC, Lean ME. Waist circumference as a screening tool for cardiovascular risk factors: evaluation of receiver operating characteristics (ROC). Obes Res. 1996;4(6):533–47.
5. Jung RT. Obesity as a disease. Br Med Bull. 1997;53(2):307–21.
6. Mann T, Tomiyama AJ, Westling E, Lew AM, Samuels B, Chatman J. Medicare's search for effective obesity treatments: diets are not the answer. Am Psychol. 2007;62(3):220.
7. Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. J Intern Med. 2013;273(3):219–34.
8. Pucci A, Batterham RL. Mechanisms underlying the weight loss effects of RYGB and SG: similar, yet different. J Endocrinol Investig. 2019;42(2):117–28.
9. Gastrointestinal Surgery for Severe Obesity. NIH consensus development conference. Consensus statement. Electronic. 1991;9(1):1–20.
10. National Institute for Health and Care Excellence. Obesity: identification, assessment and management. Clinical guideline CG189.

London: National Institute for Health and Care Excellence. 2014. https://www.nice.org.uk/guidance/cg189.
11. Welbourn R, Hollyman M, Kinsman R, Dixon J, Liem R, Ottosson J, Ramos A, Våge V, Al-Sabah S, Brown W, Cohen R. Bariatric surgery worldwide: baseline demographic description and one-year outcomes from the fourth IFSO global registry report 2018. Obes Surg. 2019;29(3):782–95.
12. Kremen AJ, Linner JH, Nelson CH. An experimental evaluation of the nutritional importance of proximal and distal small intestine. Ann Surg. 1954;140:439–48.
13. Lewis LA, Turnbull RB Jr, Page IH. Effects of jejunocolic shunt on obesity, serum lipoproteins, lipids, and electrolytes. Arch Intern Med. 1966;117:4–16.
14. Payne JH, DeWind LT. Surgical treatment of obesity. Am J Surg. 1969;118:141–7.
15. Requarth JA, Burchard KW, Colacchio TA, Stukel TA, Mott LA, Greenberg ER, Weismann RE. Long-term morbidity following jejunoileal bypass: the continuing potential need for surgical reversal. Arch Surg. 1995;130(3):318–25.
16. Mole DR, Tomson CR, Mortensen N, Winearls CG. Renal complications of jejunoileal bypass for obesity. QJM. 2001;94(2):69–77.
17. Mason EE. Development and future of gastroplasties for morbid obesity. Arch Surg. 2003;138(4):361–6.
18. Suter M, Calmes JM, Paroz A, Giusti V. A 10-year experience with laparoscopic gastric banding for morbid obesity: high long-term complication and failure rates. Obes Surg. 2006;16(7):829–35.
19. Dhar VK, Hanseman DJ, Watkins BM, Paquette IM, Shah SA, Thompson JR. What matters after sleeve gastrectomy: patient characteristics or surgical technique? Surgery. 2018;163(3):571–7.
20. Melissas J, Daskalakis M, Koukouraki S, Askoxylakis I, Metaxari M, Dimitriadis E, Stathaki M, Papadakis JA. Sleeve gastrectomy—a "food limiting" operation. Obes Surg. 2008;18(10):1251–6.
21. Papamargaritis D, le Roux CW, Sioka E, Koukoulis G, Tzovaras G, Zacharoulis D. Changes in gut hormone profile and glucose homeostasis after laparoscopic sleeve gastrectomy. Surg Obes Relat Dis. 2013;9(2):192–201.
22. Regan JP, Inabnet WB, Gagner M, Pomp A. Early experience with two-stage laparoscopic Roux-en-Y gastric bypass as an alternative in the super-super obese patient. Obes Surg. 2003;13(6):861–4.
23. Ji Y, Wang Y, Zhu J, Shen D. A systematic review of gastric plication for the treatment of obesity. Surg Obes Relat Dis. 2014;10(6):1226–32.
24. Mason EE, Ito C. Gastric bypass in obesity. Surg Clin N Am. 1967;47:1345–52.
25. Wittgrove AC, Clark GW, Tremblay LJ. Laparoscopic gastric bypass, Roux-en-Y: preliminary report of five cases. Obes Surg. 1994;4:353–7.
26. Mahawar KK, Kumar P, Parmar C, Graham Y, Carr WR, Jennings N, Schroeder N, Balupuri S, Small PK. Small bowel limb lengths and Roux-en-Y gastric bypass: a systematic review. Obes Surg. 2016;26(3):660–71.
27. Rutledge R. The mini-gastric bypass: experience with the first 1,274 cases. Obes Surg. 2001;11(3):276–80.
28. Jia D, Tan H, Faramand A, Fang F. One anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity: a systematic review and meta-analysis of randomized clinical trials. Obes Surg. 2020;30(4):1211–8.
29. Robert M, Espalieu P, Pelascini E, Caiazzo R, Sterkers A, Khamphommala L, Poghosyan T, Chevallier JM, Malherbe V, Chouillard E, Reche F. Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity (YOMEGA): a multicentre, randomised, open-label, non-inferiority trial. Lancet. 2019;393(10178):1299–309.
30. Saarinen T, Pietiläinen KH, Loimaala A, Ihalainen T, Sammalkorpi H, Penttilä A, Juuti A. Bile reflux is a common finding in the gastric pouch after one anastomosis gastric bypass. Obes Surg. 2020;30(3):875–81.
31. Scopinaro N, Gianetta E, Civalleri D, Bonalumi U, Bachi V. Biliopancreatic bypass for obesity: II. Initial experience in man. Br J Surg. 1979;66(9):618–20.
32. Scopinaro N, Marinari GM, Camerini GB, Papadia FS, Adami GF. Specific effects of biliopancreatic diversion on the major components of metabolic syndrome: a long-term follow-up study. Diabetes Care. 2005;28(10):2406–11.
33. Ballesteros-Pomar MD, De Francisco TG, Urioste-Fondo A, González-Herraez L, Calleja-Fernández A, Vidal-Casariego A, Simó-Fernández V, Cano-Rodríguez I. Biliopancreatic diversion for severe obesity: long-term effectiveness and nutritional complications. Obes Surg. 2016;26(1):38–44.
34. Hess DS, Hess DW. Biliopancreatic diversion with a duodenal switch. Obes Surg. 1998;8(3):267–82.
35. Sánchez-Pernaute A, Herrera MA, Pérez-Aguirre E, Pérez JC, Cabrerizo L, Valladares LD, Fernández C, Talavera P, Torres A. Proximal duodenal–ileal end-to-side bypass with sleeve gastrectomy: proposed technique. Obes Surg. 2007;17(12):1614–8.
36. Brown WA, Ooi G, Higa K, Himpens J, Torres A. Single anastomosis duodenal-ileal bypass with sleeve gastrectomy/one anastomosis duodenal switch (SADI-S/OADS) IFSO position statement. Obes Surg. 2018;28(5):1207–16.
37. Kallies K, Rogers AM. American Society for Metabolic and Bariatric Surgery updated statement on single-anastomosis duodenal switch. Surg Obes Relat Dis. 2020;16(7):825–30.
38. Singh S, de Moura DT, Khan A, Bilal M, Chowdhry M, Ryan MB, Bazarbashi AN, Thompson CC. Intragastric balloon versus endoscopic sleeve gastroplasty for the treatment of obesity: a systematic review and meta-analysis. Obes Surg. 2020;30:1–20.
39. Neto MG, Silva LB, Grecco E, de Quadros LG, Teixeira A, Souza T, Scarparo J, Parada AA, Dib R, Moon R, Campos J. Brazilian Intragastric Balloon Consensus Statement (BIBC): practical guidelines based on experience of over 40,000 cases. Surg Obes Relat Dis. 2018;14(2):151–9.
40. Thompson CC, Dayyeh BK, Kushnir V, Kushner RF, Jirapinyo P, Schorr AB, Aronne LJ, Amaro A, Jaffe DL, Schulman AR, Early D. Aspiration therapy for the treatment of obesity: 4-year results of a multicenter randomized controlled trial. Surg Obes Relat Dis. 2019;15(8):1348–54.
41. Betzel B, Cooiman MI, Aarts EO, Janssen IM, Wahab PJ, Groenen MJ, Drenth JP, Berends FJ. Clinical follow-up on weight loss, glycemic control, and safety aspects of 24 months of duodenal-jejunal bypass liner implantation. Surg Endosc. 2020;34(1):209–15.
42. van Baar AC, Holleman F, Crenier L, Haidry R, Magee C, Hopkins D, Grunert LR, Neto MG, Vignolo P, Hayee BH, Mertens A. Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes mellitus: one year results from the first international, open-label, prospective, multicentre study. Gut. 2020;69(2):295–303.
43. NBSR. Clinical outcomes 2019–2020. https://www.bomss.org.uk/clinical-outcomes-2019-2020/. Accessed 19 Sept 2020.
44. Daigle CR, Brethauer SA, Tu C, Petrick AT, Morton JM, Schauer PR, Aminian A. Which postoperative complications matter most after bariatric surgery? Prioritizing quality improvement efforts to improve national outcomes. Surg Obes Relat Dis. 2018;14(5):652–7.
45. Gambhir S, Inaba CS, Alizadeh RF, Nahmias J, Hinojosa M, Smith BR, Nguyen NT, Daly S. Venous thromboembolism risk for the contemporary bariatric surgeon. Surg Endosc. 2020;34(8):3521–6.
46. Shoar S, Saber AA, Rubenstein R, Safari S, Brethauer SA, Al-Thani H, Asarian AP, Aminian A. Portomesentric and splenic vein thrombosis (PMSVT) after bariatric surgery: a systematic review of 110 patients. Surg Obes Relat Dis. 2018;14(1):47–59.
47. Moon RC, Ghanem M, Teixeira AF, De La Cruz-Munoz N, Young MK, Domkowski P, Radecke J, Boyce SG, Rosenthal R, Menzo

EL, Blanco DG. Assessing risk factors, presentation, and management of portomesenteric vein thrombosis after sleeve gastrectomy: a multicenter case-control study. Surg Obes Relat Dis. 2018;14(4):478–83.
48. Rebiai R, Destinval C, Benchabane M. Roux-en-O gastric bypass: about one case report and literature review. Surg Obes Relat Dis. 2017;13(10):1796–800.
49. Oudman E, Wijnia JW, van Dam M, Biter LU, Postma A. Preventing Wernicke encephalopathy after bariatric surgery. Obes Surg. 2018;28(7):2060–8.
50. Singh M, Lee J, Gupta N, Gaddam S, Smith BK, Wani SB, Sullivan DK, Rastogi A, Bansal A, Donnelly JE, Sharma P. Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: a prospective intervention trial. Obesity. 2013;21(2):284–90.
51. Murray L, Johnston B, Lane A, Harvey I, Donovan J, Nair P, Harvey R. Relationship between body mass and gastro-oesophageal reflux symptoms: the Bristol Helicobacter project. Int J Epidemiol. 2003;32(4):645–50.
52. Lee HL, Eun CS, Lee OY, Jeon YC, Sohn JH, Han DS, Yoon BC, Choi HS, Hahm JS, Lee MH, Lee DH. Association between GERD-related erosive esophagitis and obesity. J Clin Gastroenterol. 2008;42(6):672–5.
53. Hoyo C, Cook MB, Kamangar F, Freedman ND, Whiteman DC, Bernstein L, Brown LM, Risch HA, Ye W, Sharp L, Wu AH. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol. 2012;41(6):1706–18.
54. Tolone S, Limongelli P, del Genio G, Brusciano L, Rossetti G, Amoroso V, Schettino P, Avellino M, Gili S, Docimo L. Gastroesophageal reflux disease and obesity: do we need to perform reflux testing in all candidates to bariatric surgery? Int J Surg. 2014;12:S173–7.
55. Chang P, Friedenberg F. Obesity and GERD. Gastroenterol Clin. 2014;43(1):161–73.
56. Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Weight loss and reduction in gastroesophageal reflux. A prospective population-based cohort study: the HUNT study. Am J Gastroenterol. 2013;108(3):376–82.
57. Brown WA, Shah YJ, Balalis G, Bashir A, Ramos A, Kow L, Herrera M, Shikora S, Campos GM, Himpens J, Higa K. IFSO position statement on the role of esophago-gastro-duodenal endoscopy prior to and after bariatric and metabolic surgery procedures. Obes Surg. 2020;30(8):3135.
58. Parikh M, Liu J, Vieira D, Tzimas D, Horwitz D, Antony A, Saunders JK, Ude-Welcome A, Goodman A. Preoperative endoscopy prior to bariatric surgery: a systematic review and meta-analysis of the literature. Obes Surg. 2016;26(12):2961–6.
59. Bevilacqua LA, Obeid NR, Yang J, Zhu C, Altieri MS, Spaniolas K, Pryor AD. Incidence of GERD, esophagitis, Barrett's esophagus, and esophageal adenocarcinoma after bariatric surgery. Surg Obes Relat Dis. 2020;16(11):1828–36.
60. Peng BQ, Zhang GX, Chen G, Cheng Z, Hu JK, Du X. Gastroesophageal reflux disease complicating laparoscopic sleeve gastrectomy: current knowledge and surgical therapies. Surg Obes Relat Dis. 2020;16(8):1145–55.
61. Doulami G, Triantafyllou S, Albanopoulos K, Natoudi M, Zografos G, Theodorou D. Acid and nonacid gastroesophageal reflux after single anastomosis gastric bypass. An objective assessment using 24-hour multichannel intraluminal impedance-pH metry. Surg Obes Relat Dis. 2018;14(4):484–8.
62. Kindel TL, Oleynikov D. The improvement of gastroesophageal reflux disease and Barrett's after bariatric surgery. Obes Surg. 2016;26(4):718–20.
63. Daher HB, Sharara AI. Gastroesophageal reflux disease, obesity and laparoscopic sleeve gastrectomy: the burning questions. World J Gastroenterol. 2019;25(33):4805.
64. Steinemann DC, Bueter M, Schiesser M, Amygdalos I, Clavien PA, Nocito A. Management of anastomotic ulcers after Roux-en-Y gastric bypass: results of an international survey. Obes Surg. 2014;24(5):741–6.
65. Mahawar KK, Reed AN, Graham YNH. Marginal ulcers after one anastomosis (mini) gastric bypass: a survey of surgeons. Clin Obes. 2017;7(3):151–6.
66. Ahmad A, Kornrich DB, Krasner H, Eckardt S, Ahmad Z, Braslow A, Broggelwirth B. Prevalence of dumping syndrome after laparoscopic sleeve gastrectomy and comparison with laparoscopic Roux-en-Y gastric bypass. Obes Surg. 2019;29(5):1506–13.
67. Scarpellini E, Arts J, Karamanolis G, Laurenius A, Siquini W, Suzuki H, Ukleja A, Van Beek A, Vanuytsel T, Bor S, Ceppa E. International consensus on the diagnosis and management of dumping syndrome. Nat Rev Endocrinol. 2020;16:1–9.
68. Lee CJ, Clark JM, Schweitzer M, Magnuson T, Steele K, Koerner O, Brown TT. Prevalence of and risk factors for hypoglycemic symptoms after gastric bypass and sleeve gastrectomy. Obesity. 2015;23(5):1079–84.
69. Tsai C, Steffen R, Kessler U, Merki H, Zehetner J. Short-term outcomes of endoscopic gastro-jejunal revisions for treatment of dumping syndrome after Roux-En-Y gastric bypass. Surg Endosc. 2020;34(8):3626–32.
70. Iglezias Brandao de Oliveira C, Adami Chaim E, da Silva BB. Impact of rapid weight reduction on risk of cholelithiasis after bariatric surgery. Obes Surg. 2003;13(4):625–8.
71. Fuller W, Rasmussen JJ, Ghosh J, Ali MR. Is routine cholecystectomy indicated for asymptomatic cholelithiasis in patients undergoing gastric bypass? Obes Surg. 2007;17(6):747–51.
72. Wudel LJ Jr, Wright JK, Debelak JP, Allos TM, Shyr Y, Chapman WC. Prevention of gallstone formation in morbidly obese patients undergoing rapid weight loss: results of a randomized controlled pilot study. J Surg Res. 2002;102(1):50–6.
73. Talha A, Abdelbaki T, Farouk A, Hasouna E, Azzam E, Shehata G. Cholelithiasis after bariatric surgery, incidence, and prophylaxis: randomized controlled trial. Surg Endosc. 2020;34:1–7.
74. Magouliotis DE, Tasiopoulou VS, Svokos AA, Svokos KA, Chatedaki C, Sioka E, Zacharoulis D. Ursodeoxycholic acid in the prevention of gallstone formation after bariatric surgery: an updated systematic review and meta-analysis. Obes Surg. 2017;27(11):3021–30.
75. Frame-Peterson LA, Megill RD, Carobrese S, Schweitzer M. Nutrient deficiencies are common prior to bariatric surgery. Nutr Clin Pract. 2017;32(4):463–9.
76. O'Kane M, Parretti HM, Pinkney J, Welbourn R, Hughes CA, Mok J, Walker N, Thomas D, Devin J, Coulman KD, Pinnock G. British Obesity and Metabolic Surgery Society Guidelines on perioperative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery—2020 update. Obes Rev. 2020;21(11):e13087.

Intestinal Failure in Childhood

Olivier Goulet and Cécile Lambe

Key Points

1. Pediatric IF is commonly due to congenital or neonatal intestinal diseases or malformations.
2. Three groups of patients are identified: those with a reduced intestinal length (short bowel syndrome), abnormal intestinal mucosal development, or severe intestinal dysmotility.
3. At birth, term-neonates have a SB length of approximately 250 cm and their intestines lengthen substantially during the first year of life.
4. IF associated liver disease (IFALD) (mainly cholestatic picture in children) develops frequently at an early age, especially in premature infants in whom liver immaturity, frequent sepsis and necrotizing enterocolitis (NEC) increase liver inflammation and severe damage. In older children it is associated with a dilated bowel with bacterial overgrowth.
5. Phytosterols contained in soybean oil are associated with IFALD progression and their exclusion from lipid bags may be beneficial in children receiving PN.
6. The major indications for HPN are SBS secondary to necrotizing enterocolitis, midgut volvulus, gastroschisis, long segment Hirschsprung Disease and intestinal atresia. Other conditions are congenital enteropathies, chronic intestinal pseudo-obstruction.

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Introduction

Intestinal failure (IF) is defined as a critical reduction of the gut mass or its function below the minimum needed to absorb nutrients and fluids required for adequate growth in children and weight maintenance in adults [1]. As a matter of fact, severe IF, results in the need for parenteral nutrition (PN). IF may be reversible or irreversible, depending on a number of factors such as the underlying disease and also on the treatment used to develop or restore intestinal capacity. Severe and even irreversible IF in children is very challenging. IF conditions being rare, there is not enough data to provide the scientific foundation needed to form treatment guidelines or for the creation of gold-standards for the care of such very specific patients. However, guidelines for PN may provide basic knowledge for the management of those complex patients [2, 3]. In clinical practice intestinal sufficiency may be indirectly measured by the level of PN required for normal or catch up growth [4]. Others indicators such as residual bowel length measured at last surgery and serum citrulline, though helpful, have not proven to be always reliable prognostic factors in children with short bowel syndrome (SBS) [5–7]. Therefore, PN requirements or PN dependency index (PNDI) remain the best measure of the degree of intestinal sufficiency in this setting [8].

Due to technical refinements and steady advances in the development of highly sophisticated nutrient solutions consisting of optimal combinations of macronutrients and micronutrients, PN plays an important role in patient management [2, 3]. PN has become a safe and efficient feeding technique. However, IF that requires long-term PN may be associated with various complications including catheter related blood stream infections (CRBSIs), growth failure, metabolic disorders, and bone disease [9]. Cholestatic liver disease (CLD) was rapidly identified as one of the limitations of long term IF management while CLD related factors are mostly related to IF rather PN supporting the wording "Intestinal Failure Associated Liver Disease" (IFALD) [10–13]. Severe liver disease may lead to the so-called "nutri-

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tional failure" which is considered as a major indication for intestinal transplantation or combined liver-intestinal transplantation [9].

Causes of Intestinal Failure

In industrialized countries pediatric IF is most commonly due to congenital or neonatal intestinal diseases or malformations that can be divided into three groups (Table 1): (a) IF with a reduced intestinal length and consequently reduced absorptive surface, such as in SBS or extensive aganglionosis (Long segment Hirschsprung disease); (b) IF related to an abnormal development of the intestinal mucosa such as congenital diseases of enterocyte development (CDED); (c) IF with intact length but with extensive motility dysfunction such as pediatric intestinal pseudo-obstruction syndromes (PIPOS).

Table 1 Causes of intestinal failure

Short bowel syndrome
• **Prenatal disease**
– Intestinal atresia
– Apple peel syndrome
– Gastroschisis
• **Post-natal disease**
– Necrotizing enterocolitis
– Mid gut volvulus
– Vascular thrombosis
– Tumor
– Traumatism
Congenital enteropathy
• Microvillous inclusion disease/microvillous atrophy
• Intestinal epithelial dysplasia/tufting enteropathy
• Syndromic diarrhea/trico-hepato-enteric syndrome
Neuromuscular intestinal disease
• Chronic intestinal pseudoobstruction syndrome
– Neuropathy
– Myopathy
– Mesenchymopathy
• **Long segment Hirschsprung disease/total or subtotal aganglionosis**

The Short Bowel Syndrome

Definition and Etiology

SBS is characterized by a compromised bowel absorptive capacity due to a severely reduced mucosal surface resulting in malabsorption with subsequent diarrhea, water-electrolytes imbalance, and malnutrition. SBS is the leading cause of pediatric IF, usually following extensive surgical resection leaving the SB length below a critical value for adequate nutritional supply [9]. Exact measurement of the remnant intestine remains difficult even with the help of radiographic assessment [14]. At birth, term-neonates have a SB length of approximately 250 cm and their intestines lengthen substantially during the first year of life [15]. Preterm infants have a greater potential for bowel growth since their intestines lengthen substantially during the last trimester of gestation [16].

The cut-off length for SBS is related to a number of factors. In general, SBS occurs after a massive resection leaving less than 40 cm of viable small bowel. A residual bowel length of only 15–40 cm has been associated with bowel adaptation, intestinal autonomy and PN weaning, but, most of the time, unfortunately with littleinformation regarding the long-term growth and the final stature [17–26]. Numerous factors determine SBS prognosis: the underlying diagnosis, the type of segments preserved, the presence of the ileo-caecal valve (ICV) and the colon, a long-term stoma *versus* a primary anastomosis, the number of surgical procedures, as well as the age of the patient at the time of surgery [17–26]. Classification of SBS in three type is helpful for the understanding of different outcomes (Fig. 1). Other factors are relevant to the development of SBS such as the functionality of the residual bowel, especially the motility disorders [24].

In children the conditions most commonly leading to extensive small bowel resections are necrotizing enterocolitis (NEC), midgut volvulus, gastroschisis, intestinal atresia and extensive aganglionosis (eg: long segment Hirschsprung disease, the last one leading to SBS without a functioning colon (SBS type 1) (Table 1 and Fig. 1).

Management of SBS

Bowel adaptation after small intestinal resection is a physiological process resulting in bowel lengthening and villous hyperplasia (Fig. 2) [27]. The management of SBS patients aims at promoting this physiological process by using as much as possible the GI tract especially by oral feeding (OF) which is more physiological than enteral tube feeding (ETF) [27]. ETF early in life, has been shown to promote oral feeding disorders [28].

PN itself aims in promoting normal somatic growth during the time bridge for achieving full intestinal autonomy. PN should not be stopped until adequate intake and growth can be achieved with only OF and/or ETF.

The optimal strategy for enteral feeding, OF *versus* ETF and continuous *versus* bolus, remains debated [27]. OF allows the maintenance of sucking and swallowing functions along with the psychological interest and enjoyment associated with eating, thus helping to prevent eating disorders. It is important to point that OF promotes the release of epidermal growth factor (EGF) from salivary glands and increases GI secretion of trophic factors [29]. Sialoadenectomy in animals significantly attenuates ileal villus height, total protein and DNA content after small

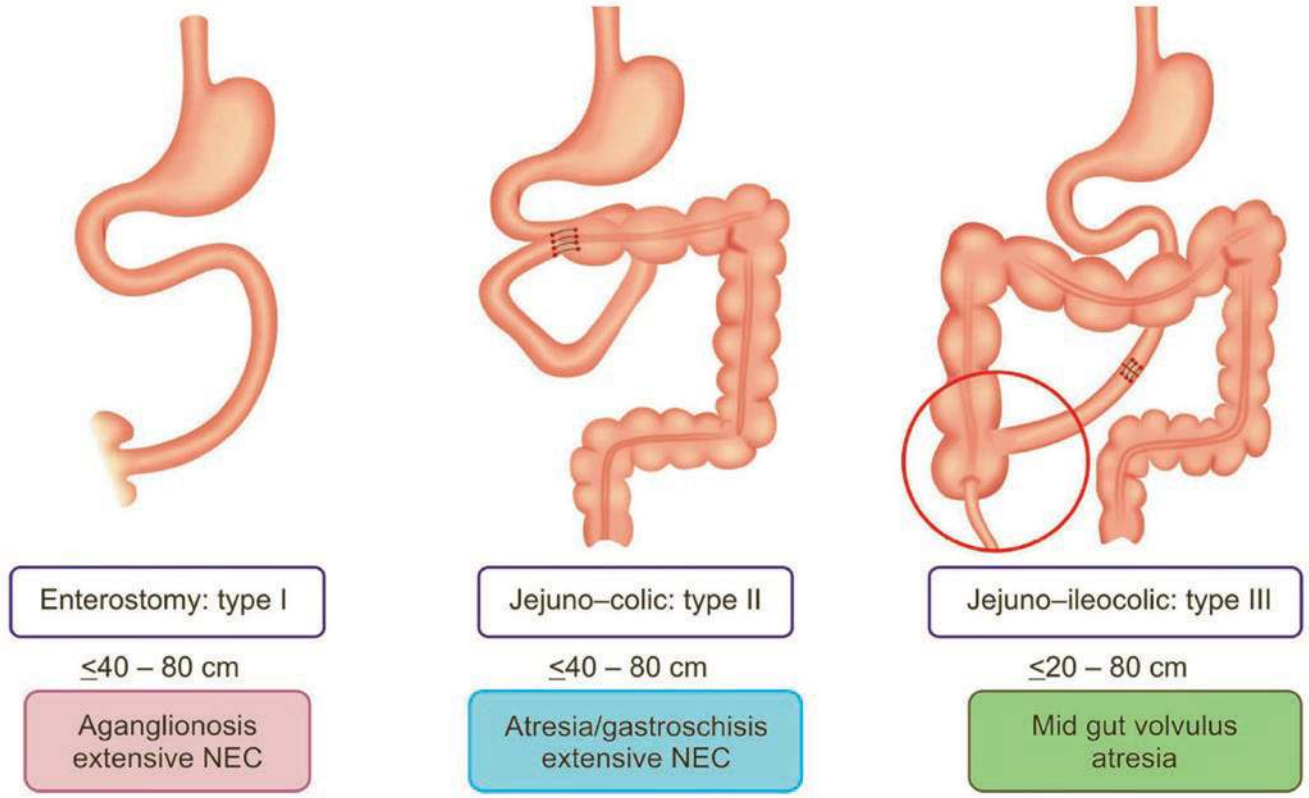

Fig. 1 Classification of short bowel syndrome (SBS) according to anatomy of the remnant intestine and different causes of intestinal resection

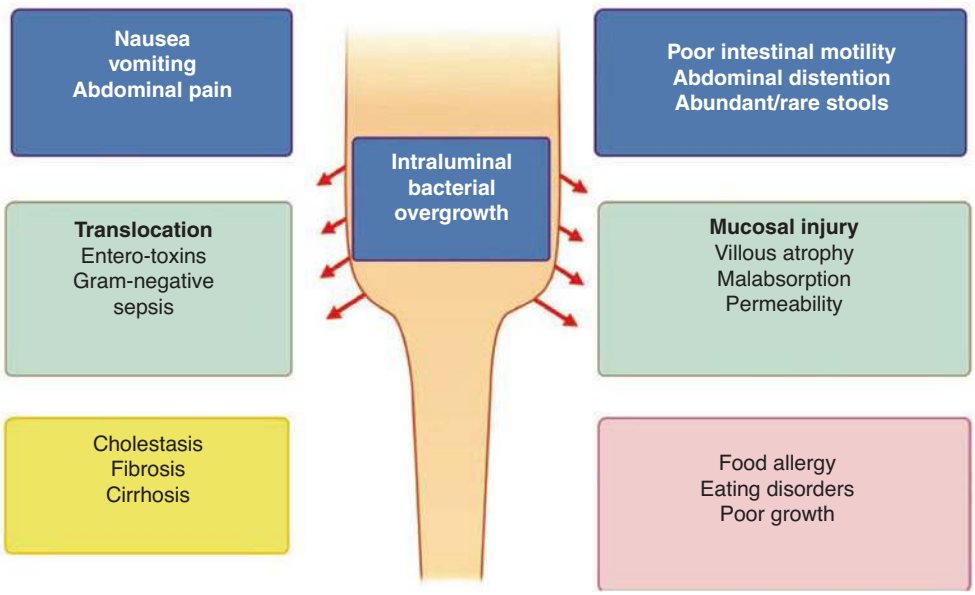

Fig. 2 Consequences of over-feeding a dilated and poorly motile intestine leading to intestinal stasis, small intestinal bacterial overgrowth (SIBO), mucosal injury, bacterial translocation, portal inflammation, cholestasis and fibrosis

bowel resection that is reversed by the administration of both systemic and oral EGF [30]. Moreover, the stimulation of hormones released by the GI tract promotes adaptation whereas alternating fasting and feeding periods along with cyclical PN avoid permanent release of insulin and excessive fat synthesis and deposition (steatosis, fat body mass).

Enteral - preferentially oral - feeding must be started as soon as possible after surgery. Breast feeding should be encouraged [31]. Human milk (HM) contains a number of factors supporting the developing neonate's intestinal microbiota and immune system including human milk oligosaccharides (HMOs), nucleotides, immunoglobulin A, and leucocytes [32–34]. HM also contains glutamine and growth

factors, such as EGF, which promote bowel adaptation [32]. Interestingly, polymeric diets containing whole protein, lactose, and long chain triglycerides (LCT), are not usually used while extensively hydrolyzed formulae (EHF) are preferred. The latter have the advantages of containing short peptides, better absorbed than free amino acids, as well as medium-chain triglycerides (MCT) [27]. Amino acid based formulas (AABF) are generally used in the treatment of food allergies or in case of milk protein hydrolyzate intolerance [35]. True food allergies have been rarely documented in children with SBS [36]. Andorsky reported less intestinal allergy by using AABF, without clearly defining the criteria for the diagnosis of allergy [18]. Two retrospective studies reported that the use of an AABF was associated with earlier weaning off PN and also a reduced rate of allergies [37, 38]. However, the very small sample sizes and the lack of control groups in these studies do not support the recommendation of using AABF in SBS patients. Moreover, commercially available AABF contain lower levels of MCT than EHF.

Feeds should be increased gradually as tolerated. Tolerance is evaluated by measuring stool number and volume and by the observation of vomiting, irritability and abdominal as well as intestinal distension. Many factors can affect stool volume in SBS, including the length of the residual intestinal segment and the type of segment (the more proximal the resection the larger the fluid and sodium losses), the mucosal and endoluminal variables (residual enzymatic activity and absorptive capacity, bacterial overgrowth). Forced continuous ETF may worsen fluid, minerals and nutrients malabsorption and may result in severe perianal skin lesions. Bile salts malabsorption may be suspected in children without ICV and/or colon, presenting with high stool volume and perianal injury that can be improved by using cholestyramine. Fluid losses in these patients are often accompanied by sodium and zinc losses with subsequent risks of severe depletion; supplements should therefore be provided.

The Many Faces of Intestinal Microbiota in Short Bowel Syndrome

Colonic Bacterial Metabolism

The Trophic Role of the Colon

When preserved, the colon, by hosting the largest part of intestinal microbiota plays a predominant role in the physiological adaptation of the intestine after large small intestinal resection. Colon is capable of reducing loss of energy and producing trophic factors [39, 40]. In animal models, supplementation of an elemental diet with pectin, which is fermented to short chain fatty acids (SCFAs) in the colon, improved adaptation of the small intestine and colon in SBS [41]. In piglets, the supplementation of PN with SCFAs or their intra-caecal infusion reduced mucosal atrophy and intestinal immune dysfunction following massive small bowel resection [42].

In addition to their local effects, systemic SCFAs, in animal studies, can affect the motility of both the stomach and the ileum through neuroendocrine mechanisms, probably through the expression of enteroglucagon family peptides and peptide YY [43]. Furthermore, both systemic and enteral SCFAs exert a trophic effect on the jejunum by increasing mucosal mass, DNA and villus height [44]. Since SCFAs are the preferred energy source for colonocytes, in patients with SBS the colon becomes an important organ for calories salvage. Unabsorbed carbohydrates are metabolized by the intestinal microbiota to SCFAs [40]. In turn, SCFAs may be considered as trophic factors directly by developing colon mucosa trophicity [45] or by promoting the release of GLP-2 [42].

Restoration of intestinal continuity, such as an anastomosis of the small intestine to the colon, should be done whenever possible. With improved colonic water and electrolyte absorption, PN can then be discontinued or at least decreased. In addition, anastomosis enables colonic fermentation of unabsorbed carbohydrates from the small intestine to occur, being an important source of energy assimilation. In spite of small intestine malabsorption in patients with SBS, both hyperphagia and adaptation of the remaining colon improve patient outcomes. A study evaluated morphology, proliferation status and transporters' expression level in the epithelium of the remaining colon of SBS adult patients compared to controls [45]. It seems that in hyperphagic SBS patients with severe malabsorption, adaptive colonic changes include an increased absorptive surface with an unchanged proliferative/apoptotic ratio and well-preserved absorption NHE2, NHE3 and PepT1 transporters mRNA levels [46]. As mentioned before, the preservation of the colon and its associated microbiota is essential for energy salvage, in reducing the need for PN and in improving the outcome of SBS patients. Bacteriological analysis based on culture-dependent methods has found that the microbiota of SBS patients is mainly composed of Lactobacilli, but neither qualitative nor quantitative information is available regarding the other main bacterial groups [47]. Few data have been reported in pediatric SBS but have mostly shown low intestinal microbiota diversity and dysbiosis [48, 49].

Colonic Hypermetabolism and D-Lactic Acidosis

Clinical manifestations such as abdominal distension, bloating and nausea - due to colonic microbiological hypermetabolism - may impair daily life and should be monitored. They are the consequences of the intestinal malabsorption

leading to huge load of undigested CHO reaching the colon. This condition may be worsened by hyperphagia or aggressive tube-feeding. One rare complication of colonic hypermetabolism, which is clearly different from small intestinal bacterial overgrowth (SIBO), is D-lactic acidosis.

D-lactic acidosis, also referred to as D-lactate encephalopathy, is a rare neurologic syndrome that occurs in individuals with SBS or following jejuno-ileal bypass surgery [50, 51]. Fortunately, this complication is very rare. Symptoms typically present after the ingestion of high-carbohydrate feedings. Neurologic symptoms include altered mental status, slurred speech and ataxia, with patients often appearing drunk. Onset of neurologic symptoms is accompanied by metabolic acidosis and elevation of D-lactate plasma concentration. L-lactate concentration, which is reflected by serum lactate concentration is normal. Thiamine deficiency should be excluded [52].

When present, *Lactobacilli* and other bacteria, including *Clostridium perfringens* and *Streptococcus bovis*, ferment unabsorbed carbohydrate to D-lactic acid, which cannot be metabolized by D-lactate dehydrogenase so it accumulates in the blood and may cause neurological symptoms. These organisms may proliferate in an acidic environment that may be promoted by the metabolism of unabsorbed carbohydrates to SCFAs. The mechanism for the symptoms with the high anion gap acidosis is unknown. They have been attributed to D-lactate, but it is unclear if this is the cause or whether other factors are responsible [45]. Treatments described in case reports have included nothing (with spontaneous resolution after reducing enteral feeding), oral metronidazole, neomycin, vancomycin, (for 10–14 days) and avoidance of "refined" carbohydrates [53, 54]. Probiotics, prebiotics and synbiotics have been used but without clear efficacy [55, 56].

Finally, one should consider the intestinal microbiota as a major factor for achieving intestinal adaptation and should be always respected and not be destroyed by unnecessary and/or inappropriate use of oral antibiotics worsening the so called SBS related intestinal dysbiosis [48, 49].

Small Intestinal Bacterial Overgrowth

Cholestatic liver disease (CLD) has been shown to be more frequent in the SBS patients than in any other IF conditions [57]. Out of 175 neonates with abdominal pathology requiring surgery, the patients with SBS (n = 40) suffered significantly more morbidity than the group without SBS in all categories of investigation (surgical complications, septic events, CRS, PN weaning delay, liver disease, and duration of hospitalization). The case fatality rate was 37.5% in patients with SBS versus 13.3% in patients without SBS (P = 0.001). Most of the deaths were caused by liver failure or sepsis and occurred within 1 year from the date of surgery. More recently, the US IF consortium reported a large cohort involving 272 infants [58]. Overall, they have a gestational age of 34 weeks and birth weight of 2.1 kg (range: 1.2–2.7 kg) and were followed up for 25.7 months (range: 11.2–40.9 months). Residual small bowel length in 144 patients was 41 cm (range: 25.0–65.5 cm). Diagnoses were NEC (26%), gastroschisis (16%), atresia (10%), volvulus (9%), combinations of these diagnoses (17%), long segment Hirschsprung disease (LSHD) (4%), and other single or multiple diagnoses (18%). Prescribed medications included oral antibiotics (76%), H2 blockers (69%), and proton pump inhibitors (57%). Enteral feeding approaches varied among centers; 19% of the cohort received human milk. The cohort experienced 8.9 new catheter-related blood stream infections per 1000 catheter days. The cumulative incidences for enteral autonomy, death, and intestinal transplantation were 47%, 27%, and 26%, respectively. Enteral autonomy continued into the fifth year after study entry. Interestingly, Finnish pediatric surgeons reported a link between bowel dilatation, sepsis and cholestatic liver disease [59].

It is generally accepted that continuous ETF offers the advantages of optimal digestion and absorption rate [31]. However, continuous infusion changes the intestinal motility pattern by missing fasting period [60]. Significant dysmotility - impairing intestinal bacterial clearance - leads to small intestinal bacterial overgrowth (SIBO) with subsequent Gram-negative sepsis. SIBO and cholestasis are common especially in patients without ICV and those having abnormal motility (eg: intestinal atresia, gastroschisis, NEC). Aggressive continuous ETF is often attempted for mimicking "hyperphagia" with the aim of weaning the child off PN that is thought to be the cause of liver injury. These patients present with dilated loops of bowel containing residual non-absorbed nutrients. This strategy results in increasing SIBO that can cause mucosal inflammation and increased permeability leading to sensitization and allergy as well as bacterial translocation, sepsis and cholestasis [9, 58, 61, 62] (Fig. 2). In addition, aggressive ETF may also result in such a overloaded gut syndrome with abdominal discomfort, intestinal distension and loss of self-regulation of intake leading to eating disorders.

Factors that link infection to cholestasis are either cytokines (mainly TNFα, IL-1β, IL-6) or microbial TLR2 or TLR4 agonists [63]. Liver targets primarily include hepatocytes, but also extend to Küpfer cells, cholangiocytes, endothelial cells, and stellate cells. There are no direct studies of bile flow in humans given endotoxin, but there is sufficient indirect evidence to link endotoxin and endotoxin-induced cytokines, to cholestasis. During severe sepsis, including septic shock, hyperbilirubinemia is usually a central clinical finding, often out of proportion to typically

mild elevations in serum transaminase. Interestingly, TNFα administered in humans has shown significant hyperbilirubinemia, further supporting a link between cytokines and cholestasis [64].

Peri-Anastomotic Ulcerations

Peri-anastomotic ulcerations (PAU) is a rare but severe complication after intestinal resection and anastomosis. It is described mostly in children [65, 66]. The main symptom is bleeding, leading to iron-deficiency anemia, which is life threatening. A series of 11 patients (7 boys) with PAU after an intestinal resection and anastomosis in infancy was reported [65]. The study focuses on predictive factors, medical and surgical treatment options, and long-term outcomes [65]. The diagnosis of PAU was often delayed for several years. No predictive factor (including the primary disease, the length of the remnant bowel, and the loss of the ileocaecal valve) could be identified. Numerous treatment options, including antibiotics, probiotics (*Saccharomyces boulardii*) and anti-inflammatory drugs, proved to be ineffective to induce prolonged remission. Even after surgical resection, relapses were observed in 5/7 children. The mechanism leading to PAU remains unknown. Another series reported 14 cases revealed by severe anemia, diarrhea, abdominal pain and growth failure in average 11.5 years after surgery [66]. Ulcerations were most often multiple (n = 11), located on the upper part of ileocolonic anastomoses (n = 12) and difficult to treat. No granulomas were seen but lymphoid follicules were frequent. In addition, either ASCA or ANCA were positive in 4/9 tested patients and 8/11 genotyped patients exhibited a NOD2 mutation ($P < 0.0002$ when compared to French healthy controls). A recent multicenter study involved 51 patients (29 boys) identified from 19 centers in 8 countries [67] Most patients were followed after necrotizing enterocolitis (n = 20) or Hirschsprung disease (n = 11). The anastomosis was performed at a median age (interquartile range) of 6 [1–23] months, and first symptoms occurred 39 [22–106] months after surgery. Anemia was the most prevalent symptom followed by diarrhea, abdominal pain, bloating, and failure to thrive. Hypoalbuminemia, elevated CRP, and fecal calprotectin were observed. Deep ulcerations were found in 59% of patients usually proximally to the anastomosis (68%). During a median follow-up of 40 [19–67] months, treatments reported to be the most effective included exclusive enteral nutrition (31/35, 88%), redo anastomosis (18/22, 82%), and alternate antibiotic treatment (37/64, 58%). Unfortunately, persistence of symptoms, failure to thrive, and abnormal laboratory tests at last follow-up in most of patients show the burden of PAU lacking optimal therapy and incomplete understanding of the pathophysiology.

Non-transplant Strategies for Enhancing Intestinal Capacity

Autologous Bowel Reconstruction

Surgical approaches aimed at maximising gastrointestinal digestive and absorptive function are crucial to the management of SBS. These include stoma closure and restoration of bowel continuity together with resection of strictures and closure of fistula. There are situations where surgical interventions aimed at reducing stasis in very dilated bowel, possibly decreasing SIBO (with its negative effects on digestion, absorption and a factor of IFALD) in the process and increasing contact time between luminal nutrients and mucosa might improve overall absorption. Indeed, these procedures aim not only to enhance the intestinal length and reduce the diameter of the distended intestinal loop with subsequent reduction of SIBO. The most common procedures are Longitudinal Intestinal Lengthening and Tapering (LILT) developed by Bianchi in Manchester, UK [68] and Serial Transverse Enteroplasty (STEP) developed by Kim et al. and mostly used in North America [69] (Fig. 3a, b).

The precise indications and the potential benefits of these procedures remain a matter of debate [70, 71]. Classical conditions and indications for bowel-lengthening surgery include the presence of a large intestinal diameter (>3–4 cm) for at least 20 cm of small bowel and a minimum total bowel length of 40 cm.

LILT involves longitudinal splitting of the small bowel remnant along its mesenteric and anti-mesenteric border, ending up with two tubes of bowel of identical length each with their own blood supply which are then joined together [68]. The advantages of the LILT procedure (Fig. 3a) include the conservation of the normal orientation of the muscular fibers allowing more physiological peristaltic contraction, and the possibility to further perform a STEP procedure on the operated segments. The disadvantages are the risk of vascular complications during surgery making LILT more technically demanding as compared to the STEP procedure [68, 69]. However, results after STEP and re-STEP procedure are not as performant as expected [72–75].

The STEP procedure involves the use of a surgical stapler applied sequentially from alternating and opposite directions to the dilated loop, in a transverse, partially overlapping fashion creating a zigzag–like channel of approximately 2–2.5 cm in diameter (Fig. 3b). This operation has the great advantage of being simple and reproducible. STEP is a more recent and less complex technique [69]; unlike LILT, no anastomosis is needed, and the mesenteric blood supply is not put at risk. If the bowel re-dilates, a further STEP procedure can be undertaken. Unfortunately, there are no surgical techniques that can reliably increase small bowel surface area, and by so doing rapidly achieve more than the background process of gut adaptation.

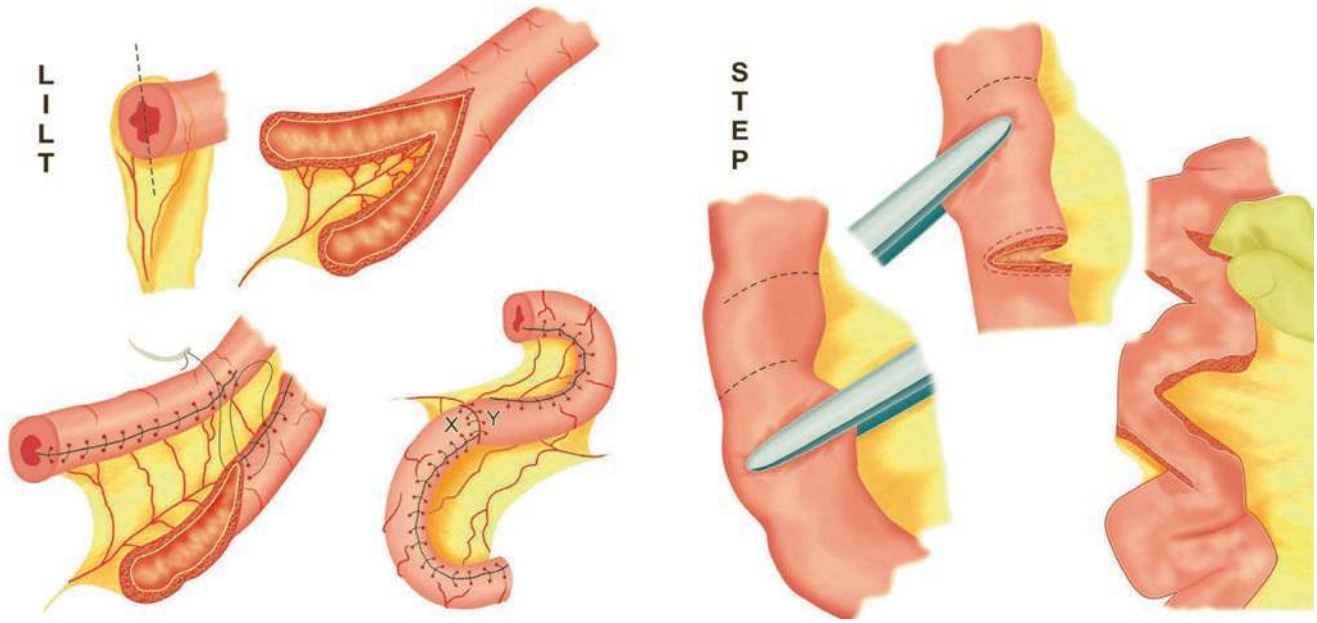

Fig. 3 The longitudinal intestinal lengthening and tailoring (LILT) procedure and the serial transverse enteroplasty (STEP) procedure

Plasma citrulline is a marker of small bowel enterocyte mass [5–7]. A 5-year follow-up cohort study after STEP confirms the efficiency of this procedure. Interestingly, both D-xylose - a marker of carbohydrate absorption and mucosal integrity - and plasma citrulline - a marker of small bowel enterocyte mass -increased significantly postoperatively [76]. This suggests that STEP procedure by reducing SIBO, restores small intestinal mucosa integrity and improves villous size within the first weeks following the procedure. However recent data showed no adaptive mucosal hyperplasia or muscular alterations occurred between first and repeat STEP [75]. This suggest that persistent inflammation and lacking mucosal growth may contribute to continuing bowel dysfunction in SBS children, who require repeat STEP procedure, especially after removal of the ileocecal valve.

A more recent described procedure is the spiral intestinal lengthening and tailoring, which consists of a spiral incision of the intestinal wall and in the elongation longitudinally of the intestine by sliding one flap over the other [77]. The final intestinal lengthening is strictly dependent on a series of parameters, some of which are defined by the surgeon.

The gut overload syndrome may be defined as the association of dilated intestinal loops, abdominal discomfort, SIBO, cholestasis and failure to thrive in a SBS patient who is partially or totally enterally fed. Surgical bowel-tapering with or without lengthening should be considered in such setting whatever the patient is PN-dependent or not.

Hormonal Therapy and Other Adaptive Treatments

Hormonal therapy is promising in the management of infants with SBS. The role of recombinant human growth hormone (rhGH) alone or in combination with glutamine has been investigated. Inconsistent results have been reported in adults receiving rhGH, with reported side effects [78]. A few studies of rhGH alone or in combination with glutamine have been carried out in PN dependent children with SBS [79–81]. Despite some decrease in PN requirements during treatment these trials showed little benefit on body composition and mucosal absorption in the long-term [79–81].

Glucagon-like peptide 2 (GLP-2) is produced by the L-cells of the terminal ileum in response to luminal nutrients and has a trophic effect on the intestine, promoting absorption and adaptation [81]. GLP-2 has been shown to increase the surface area of the gut mucosa, up-regulate nutrient absorption, improve gut-barrier function, increase intestinal blood flow and decrease bone resorption [81]. Patients with low levels of GLP-2 following the resection of the terminal ileum and/or the ileo-caecal valve improved intestinal absorption and nutritional status after treatment with GLP-2 [82]. A 12-week, open-label study, enrolled SBS PN dependent patients aged 1–17 years [83]. It has been concluded that Teduglutide (GLP-2 analogue) was well tolerated at 0.025 or 0.05 mg/kg/day and was associated with trends toward reductions in PN requirements and advancements in enteral feeding. The above pilot study validated the recommended dose of Teduglutide to be used as 0.05 mg/kg per

day. However, study limitations included its short-term, open-label design, small sample size and heterogeneity of both patients and management because of the multicenter study. An other 24-week, open-label study, has been reported [84]. A 24-week, phase III trial included 59 patients with 2 randomized, double-blind teduglutide dose groups and a non-blinded standard of care (SOC) arm was used; patients received 0.025 mg/kg or 0.05 mg/kg teduglutide once daily: (0.025 mg/kg, n = 24; 0.05 mg/kg, n = 26; SOC, n = 9) [84]. Safety end points included treatment-emergent adverse events (TEAEs) and growth parameters. The primary efficacy/pharmacodynamic end point was the number of patients who achieved a ≥ 20% reduction in parenteral support (PS) from baseline at week 24. TEAEs were reported by 98% and 100% of patients in the teduglutide and SOC groups, respectively. The most common TEAEs in the teduglutide-treated groups were pyrexia and vomiting. The primary end point was achieved by 13 (54.2%), 18 (69.2%), and 1 (11.1%) patients who received 0.025 mg/kg teduglutide, 0.05 mg/kg teduglutide, and SOC, respectively ($P < 0.05$ vs SOC). Both 0.025-mg/kg and 0.05-mg/kg teduglutide groups showed clinically significant reductions in PS volume ($P < 0.05$ vs SOC), PS calories, days per week and hours per day of PS infusions, and increases in enteral nutrition and plasma citrulline at week 24 compared with baseline. Two (8.3%, 0.025 mg/kg teduglutide) and 3 patients (11.5%, 0.05 mg/kg teduglutide) achieved enteral autonomy. In a monocenter open trial of 48 weeks treatment with teduglutide (0.05 mg/kg/day) currently under submission, we report a PN weaning rate in 8 patients (32%) a significant increased of citrulline plasma levels ($p < 0.001$) ($p < 0.001$) and a significant decrease of the PN dependency index ($p < 0.0001$).

Monocenter trials are required for addressing recommendations and extend the use of GLP-2 analog (eg: Teduglutide Revestive®) at a dose of 0.05 mg/kg/d. Oral insulin has been shown to be beneficial in animal models and might be assessed very soon in infants and children [85]. Other relevant treatments associated with a trophic effect on the bowel mucosa such as short chain fatty acids may be beneficial in children with SBS [82]. Finally, there is also interest in the use of other trophic factors such as epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF-1) in children with IF and SBS [83].

Outcome of SBS and Long-Term Growth

Mortality decreased during the last decade especially following the implementation of the so called "intestinal rehabilitation centres" (IRC) [86–90]. Multidisciplinary management, improved prevention of sepsis by performing autologous bowel reconstruction [68], by preventing catheter related blood stream infections (CRBSIs) with taurolidine or ethanol lock procedures [91, 92], by using the last generation of lipid emulsions [11] [see below]. In the mean time, the rate of intestinal transplantation decreased with these measures [93].

Some studies have been reported, involving the long-term growth and nutrition status of children with neonatal SBS after weaning off PN [22, 94–96]. Improved care of patients with SBS significantly achieved more optimal weight gain for age compared with decade 1980 [94]. However, the final genetic target size is not always achieved while some deficiencies may be evidenced [95, 96]. Indeed, children with SBS are still at risk for different nutrient malabsorption even after weaning off PN for a long time. They may develop such an "overloaded gut syndrome" with failure to thrive requiring, for some, PN to be restarted. Therefore, they need long-term, regular monitoring and intensive nutritional care to prevent various nutrient deficiencies. Too early PN weaning may be responsible for both "overloaded gut syndrome" and failure to thrive.

Neuro-Muscular Intestinal Diseases

Intestinal motility is under the control of the enteric nervous system that is functionally independent from the central nervous system and is therefore efficient even in completely disconnected bowel loops, such as intestinal transplants. Normal motility is achieved through the transmission of the signals from the enteric nervous system to the enteric smooth muscle generating healthy peristaltic waves. Therefore, neuromuscular intestinal disease (NMID) may derive from either enteric nerve or muscle dysfunction. Severe gastrointestinal conditions classified among the NMID lead to intestinal failure: extensive Hirschsprung Disease and chronic intestinal pseudo-obstruction syndrome (CIPOs).

Hirschsprung Disease

Total or subtotal intestinal aganglionosis (TIA) leaving the child with less than 50 cm normally innervated small intestine below the ligament of Treitz (LOT) is a rare condition. It may be considered as a SBS type 1. Appropriate management strategies are not well established. Surgery is performed as a simple jejunostomy below the LOT with or without or short-segment longitudinal myomectomy [97–99].

Nutritional management includes cyclic PN (home-PN) associated with oral feeding for reducing the risk of liver disease and promoting oral skills [8]. Continuous attention is needed in the daily long-term management of these unstable infants and children with a permanent risk of dehydration and subsequent complications such as hypercalcemia, renal

failure. ITx is undertaken according to the occurrence of complications (water-electrolytes disorders, CRC, and IFALD) and/or the wish of parents for another quality of life. In 12 patients with TIA, it was reported an outcome rate of 62.5% in the LITx group and 75% in the ITx group, both with half colon grafting [100]. All the surviving patients were fully weaned from total PN, after a median of 57 days. Pull through of the colon allograft was carried out in all patients. Fecal continence is normal in all but one of the surviving children. When graft is tolerated on the long-term, growth is normal and quality of life is improved [101, 102]. A monocenter survey included 25 patients born between 2000 and 2015 were followed for a median of 10.9 years [103]. Fifteen patients had less than 80 cm of ganglionic small bowel (SB) with a median of 20 cm. Ten patients had more than 80 cm of ganglionic SB with a median of 115 cm. The median PN duration was significantly shorter for patients with more than 80 cm: 0.9 *versus* 7.5 years in those with less than 80 cm ($P < 0.001$). No patient with less than 80 cm was weaned off PN, except 1 who underwent ITx. Ten patients with less than 80 cm develop enterocolitis on the excluded segment, leading to emergency entero-colectomy in 5. Liver disease was more frequent in patients with less than 80 cm (11 vs 0). Three patients required combined liver-ITx; 2 underwent an isolated ITx. The more severe complication was enterocolitis. Liver disease compromised long-term survival without transplantation. Both complications should be prevented by early diversion and enterectomy of the whole aganglionic segment. Follow-up in or together with a multidisciplinary IRC is mandatory.

Chronic Intestinal Pseudobstruction

Chronic intestinal pseudo-obstruction syndrome (CIPOS) is a condition considered as the most severe disorders of gut motility. CIPOS continue to be very challenging despite recent progress in the understanding of its pathophysiology, resulting in a high levels of morbidity and mortality. Major contributors to the disappointing lack of progress in paediatric CIPOS include a dearth of clarity and uniformity across all aspects of clinical care from definition and diagnosis to management.

CIPOS is a descriptive term pooling together several disorders of the enteric muscles or nerves [104]. Thus it may have heterogeneous features but has a similar phenotype characterized by recurrent bouts of intestinal obstruction without demonstrable mechanical occlusion. CIPOs are the cause of approximately 15% of all pediatric cases of IF [9]. Repeated surgical procedures can negatively affect the course of the disease [105].

CIPOs may be due to several diseases that can be either congenital or acquired. The most severe forms are usually congenital and present shortly after birth with episodes of intestinal obstruction. CIPOs have been conventionally divided into two groups, according to the pathogenesis of dysmotility: neuropathies and myopathies. The former is due to the involvement of the enteric nervous system and the latter is due to the dysfunction of intestinal muscles. CIPOs due to muscle dysfunction are rare but seem to be more severe. Urinary tract disorders such as megacystis and megaureter can be associated both with neuro and myopathies causing CIPOs. These should be managed by experienced urologists although, surprisingly, they may be better tolerated than other more common obstructive urinary tract disorders [106].

Diagnosis

The diagnosis of CIPOs is based on clinical and radiological analysis. Tools helpful to assess a severe motility disorder include radiological and histological evaluations and, if feasible, gastrointestinal manometry [104]. However, intestinal manometry is not highly contributive for either the diagnosis of CIPO or its treatment. CIPOs management is mainly based on clinical and radiological features. In CIPOs a plain abdominal x-ray typically shows air-fluid levels and dilatation of the bowel loops. Contrast studies, such as the barium small bowel follow-through study, are helpful to rule out mechanical obstruction, but may not reveal motility abnormalities. The presence of a systemic autoimmune disease as well as severe infections and endocrinopathies suggests an acquired form of CIPOs that sometimes can be managed by treating the underlying illness. Congenital forms of CIPOs can be misdiagnosed as Hirschsprung Disease, even resulting in surgery. However, surgical biopsies reveal normal enteric ganglia. In these cases, bowel resections should be avoided [105]. When CIPO is strongly suspected laparoscopic full-thickness biopsies may support the diagnosis with a minimally invasive procedure. Nevertheless, histological hallmarks are scant and the sample should be evaluated in referral centers by expert pathologists who have experience in similar cases and access to specific immunohistochemistry and electron microscopy allowing the recognition of immune-mediated conditions, congenital neuromuscular disorders and mitochondrial cytopathies [107].

Genetics of CIPOS is complex and partially known [104, 108]. Most patients do not show familial recurrence (sporadic cases) but syndromic autosomal-dominant, autosomal-recessive and X-linked forms have been described. In particular, an X-linked locus has been mapped to the Xq28 region. Although both familial and sporadic CIPOs have been widely reported, so far only a few genes have been identified as responsible for syndromic CIPO: the thymidine phosphorylase gene (*TP*, also known as endothelial cell growth factor-1, *ECGF1*), the DNA polymerase-γ gene (*POLG*) and *SOX10*.

Management

Management is based on a multidisciplinary intervention by medical, surgical and allied professionals. Children with CIPOs almost invariably require some surgical intervention. The major barriers to food progression in patients with inefficient propulsive strength are the natural GI tract bottlenecks: the pylorus and the ileo-cecal valve. These can cause a functional occlusion of the gastric outlet or small bowel clogging, which can be easily resolved by the formation of a gastrostomy (or jejunostomy) and an ileostomy respectively. The formation of a stoma can improve the quality of life and reduce symptoms in up to 50% of children with CIPOs [105]. It is sometimes possible to localize the segments of the bowel the most responsible for the dysmotility symptoms: in such cases a loop resection can improve the intestinal transit and allow enteral feeding and a return to a more normal life. Near total small bowel resection has been proposed as treatment of CIPOs in some cases [109].

Due to the heterogeneity of the syndrome, a key issue is to adapt the treatment/management to each individual patient according to age at onset, severity, and the outcome of surgical procedures such as a primary ileostomy. These children need to maintain the ability and the pleasure to eat normal food and this can be permitted by taking small and frequent meals with liquids or, in more severe cases, by using the gastrostomy as a venting device; the known benefits of delivering enteral feeding in children with IF make it mandatory to attempt intermittent gastrostomy closure and gastric or gastro-duodenal low-fiber feeding [110].

Only a few medications have been shown to improve gastrointestinal motility in patients with an intact enteric nervous system. Erythromycin at low or full antibiotic doses may improve gastric emptying in children with CIPOs and gastroparesis [111]. Several other drugs with a demonstrated effect on gastric motility, such as the serotoninergic agents cisapride and tegaserod, have been withdrawn from the market because of the occurrence of rare but severe cardiac adverse events including arrhythmias, heart attacks and strokes. Colonic acute pseudo-obstruction can be managed successfully by the infusion of the anticholinergic drug neostigmine, but this drug has not been tested on a long-term regimen.

Children with CIPOs may experience small bowel bacterial overgrowth and can thus occasionally benefit from a course of antibiotics such as metronidazole, aminoglycosides or cotrimoxazole. These drugs should be prescribed only in case of clinical symptoms rather than regularly, in order to avoid the emergence of bacterial resistance.

A French multicenter study including 105 children, 18 with prenatal diagnosis and 80 younger than 12 months of age at onset, showed that early age at presentation, PN dependency and the number of surgical procedures were associated with a poor prognosis [112]. In the most severe forms of CIPOs children end up with an ileostomy, a gastrostomy with almost permanent aspiration due to gastroparesis, frequent bowel obstructions, and total PN dependency. Patients with such a poor quality of life may benefit from transplantation that should include the stomach (i.e. modified multivisceral transplantation) [113].

Congenital Enteropathies

Congenital diseases of enterocyte development (CDED) are a group of rare disorders causing IF in early infancy. Children with these disorders have usually neonatal onset of severe diarrhea that requires PN support [114].

The etiology includes defects in nutrient-electrolyte absorption and disorders of enterocyte differentiation and polarization [115, 116]. Clinically it is important to differentiate protracted from intractable diarrhea of infancy (IDI) - the latter being irreversible. Figure 4 proposes a simple algorithm to approach newborns and infants with severe diarrhea.

Microvillous Inclusion Disease

The most common causes of IDI are microvillus inclusion disease (MVID, also known as microvillus atrophy), congenital tufting enteropathy (CTE, also known as intestinal epithelial dysplasia), syndromic or phenotypic diarrhea, and autoimmune enteropathy. The latter is not considered to be intractable unless all available treatments fail. Several genes responsible for these disorders have been identified by studies based on genome-wide analysis of polymorphisms, adding new tools for the diagnosis of intractable diarrhea of infancy [116].

The first described form of MVID was related to MYO5B mutation [117, 118]. Severe watery diarrhea develops in the first few days after birth and can rapidly reach a total fecal output of 200–300 ml/kg of body weight per day. Diarrhea does not stop during fasting and causes life-threatening electrolyte and acid-base imbalances, rapid and severe dehydration and hypovolemic shock. Children with MVID are usually dependent on continuous PN infusion not allowing for cyclic PN. Some patients have associated disorders involving biliary acids metabolism and some develop liver disease leading liver failure within the first few years of life [117, 118]. Currently, the survival rate for these children is around 70%, including those patients (up to half) who received intestinal or liver-intestinal graft [119, 120].

The second gene in which MVID causing mutations were identified is STX3 [121, 122]. Patients were reported with

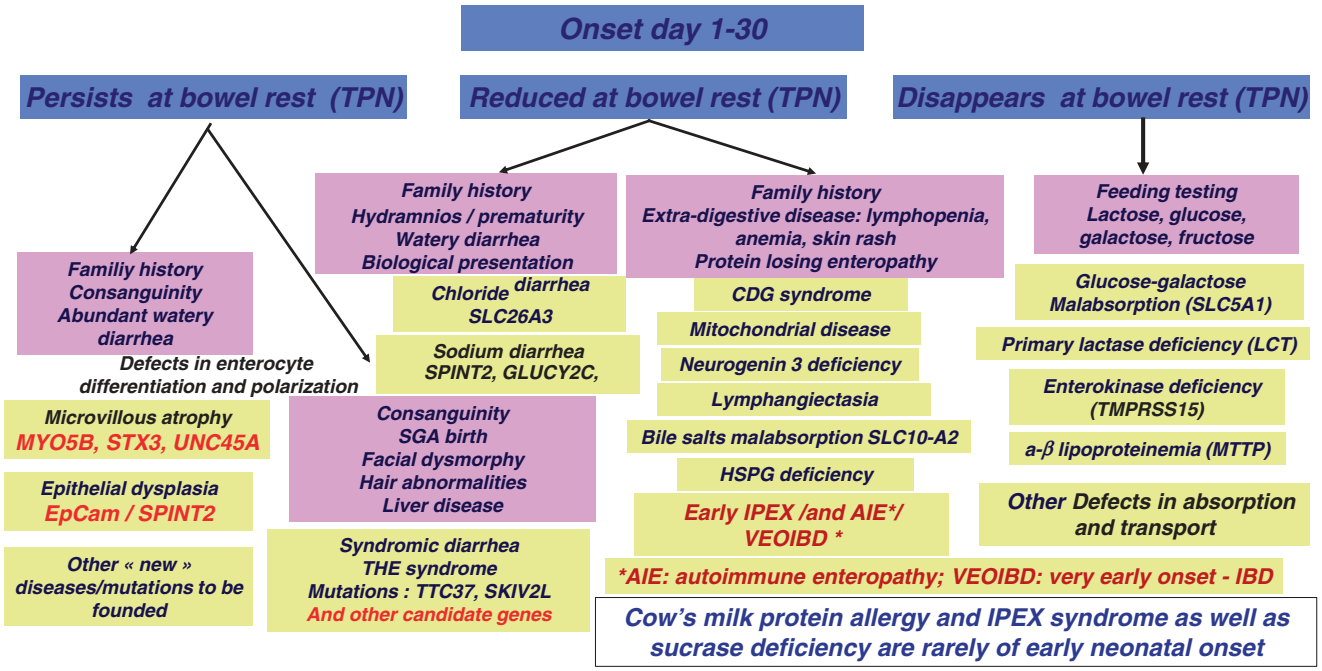

Fig. 4 Clinical approach of early onset severe diarrhoea

nonsense mutations resulting in truncations of the apically targeted N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein syntaxin3. No genotype-phenotype correlation with respect to *MYO5B* and *STX3*-related MVID has been reported so far, due to the small number of patients with *STX3* mutations. Genetic counseling can be performed for this autosomal recessive disorder when mutations in *MYO5B*, *STX3* are identified. An international registry has been set up [122].

UNC45A belongs to the UCS protein family (UNC-45/CRO1/She4p). *C. elegans* unc-45 was first described after a screening for mutations causing motility disorders (UNC stands for uncoordinated) [76]. The UNC-45 protein has three recognizable domains: an N-terminal tetratricopeptide repeat (TRP) domain (115 amino acids), a central domain of 400 amino acids, and a C-terminal UCS domain (400 amino acids). The TPR domain participates in protein-protein interactions, especially with Hsp70 and Hsp90 HSP90AA1. The role of the central domain remains unclear, while the C-terminal UCS domain is critical for myosin binding [77]. Whether or not variants located within specific domains of UNC45A lead to different functional outcomes is still unknown. UNC45A appears to be ubiquitously expressed and has been postulated to be involved in cytoskeletal functions, such as cell division or exocytosis [78]. Data are consistent with the multi-organ defects observed in children, as well as the structural pathology in the gut in a zebrafish mutants [79]. However, other features of the protein are not reflected in the phenotype seen in humans.

Congenital Tufting Enteropathy

Neonates with congenital tufting enteropathy (CTE) develop a severe neonatal diarrhea persisting at bowel rest [123]. Often there is a family history of consanguinity and neonatal deaths related to severe diarrhea and dehydration. Indeed CTE has been found to be associated with mutations in the genes encoding for epithelial cell adhesion molecule (EpCAM and Spint2) [124]. There are reported clusters of cases in the Arabic Gulf area [125]. Infants with CTE typically experience a worsening of diarrhea during continuous ETF even when given extensively hydrolyzed or amino acid-based formula, resulting in failure to thrive and protein-energy malnutrition. Diarrhea is usually less severe than in children with MVID; some patients may be weaned from PN. Nevertheless, most remain PN dependent and sometimes require ITx [123]. Expert histological review of duodenal biopsies is the key to making the diagnosis of this severe cause of IF. The so-called Congenital Sodium Diarrhea (CSD) has been reported as related to SPINT2 mutations [126]. Clinical presentation associated extra-intestinal disorders and histological features suggest a link between CTE and CSD [127]. Thirteen patients presenting with IF, and TE histology were retrospectively reviewed for up to 30 years [128]. It was concluded that IED cases have >92% chance of long-term survival and >50% chance of enteral autonomy by/in early adult life and 75% by 25 years. Patients with IED managed on PN at home by an IF rehabilitation service should avoid intestinal transplant [128].

THE Syndromic Diarrhea/Trichohepatoenteric Syndrome (SD/THE)

It is a rare and multi-system genetic disorder [129, 130]. This disorder is characterized by life-threatening diarrhea starting within the first 6 months of life, wooly and poorly-pigmented hair, facial dysmorphism including prominent forehead and cheeks and hypertelorism, hypopigmentation, cardiac defects, immunodeficiency, and liver disease. It includes extensive hepatic fibrosis and cirrhosis, affecting about half of patients. SD/THE is caused by mutation in *SKIV2L* or in *TTC37*, two genes encoding subunits of the putative human SKI complex involved in RNA degradation [130]. There are currently no specific biochemical profiles in these patients although a functional T-cell immune deficiency with defective antibody production has been reported [131]. Microscopic analysis of the hair shows twisted hair (pili torti), aniso- and poikilotrichosis, and trichorrhexis nodosa. Histopathological analysis of small intestine biopsies shows non-specific villous atrophy with low or no mononuclear cell infiltration of the lamina propria and no specific histological abnormalities involving the epithelium. Early management consists of total PN. Some infants have a milder phenotype requiring partial PN or only enteral feeding. Prognosis of this syndrome is poor but most patients now survive and some patients may be weaned off PN at adolescence. Even treated patients have a short stature and often a mental retardation [130]. Other severe persistent diarrhea causing chronic IF, with or without extra-digestive manifestations, have been described with genetic molecular biology based diagnosis [132, 133].

Deletion of the Percc1 Gene

Eight patients from seven families (2 consanguineous) of common ethno-geographic origin with IDI were recently reported [133]. They presented an early onset severe diarrhea (7–21 days) with mild villous atrophy and variable PN dependency. Deletions of a sequence termed intestine-critical region (ICR) on chromosome 16 were identified. Transgenic mouse reporter assays showed that the ICR contains a regulatory sequence that activates transcription during development of the gastrointestinal system. Targeted deletion of the ICR in mice caused symptoms recapitulating the human condition. Transcriptome analysis uncovered an unannotated open reading frame (Percc1) flanking the regulatory sequence whose expression was lost in the developing gut of ICR knockout animals. Targeted deletion of the Percc1 gene in mice causes phenotypes similar to those observed upon ICR deletion in mice and patients, whereas an ICR-driven Percc1 transgene was sufficient to rescue the phenotypes found in ICR knockout mice. The molecular, cellular, and physiological phenotypes observed in human patients and engineered mice indicate that PERCC1 is required for normal development of EECs and normal entero-endocrine hormone secretion.

Intestinal Failure Associated Liver Disease

Many peoples continue to talk about PN-related liver disease suggesting that PN is the cause of liver disease. Nowadays IF should be considered as the main cause of cholestatic liver disease. The most appropriate wording should be intestinal failure associated (or related) liver disease (IFALD) [10]. It is probably the most important complication affecting children with IF on long-term PN. The prevalence of the disorder is unknown because there is no established definition of liver disease in this setting and it is unclear as to whether IFALD should be diagnosed on the basis of clinical, biological or histological criteria. Indeed, there are insufficient data on the degree and type of liver involvement in patients with long term PN.

Causes and Mechanisms of IFALD

The main factors contributing to liver injury in these patients are recurrent catheter related sepsis, *p*rematurity and low birth weight, lack of enteral feeding, disruption of enterohepatic biliary acid cycle *(proximal stoma, ileal resection),* intestinal stasis and SIBO *(obstruction, dysmotility, lack of ileo-caecal valve, over-tube feeding…).* Table 2 reports the IF and PN related factors causing liver injury.

It should be stressed that the most important factors leading to IFALD are those related to individual patient characteristics and, importantly, the episodes of catheter related blood stream infections (CRBSIs) or SIBO [134–136] An important role in this process is played by liver inflammation caused by extra-hepatic infections in which microbial products brought to the liver through the blood stream, either directly or through production of cytokines, lead to alterations of bile flow. The inflammation associated with these changes may cause rapid fibrosis and eventually biliary cirrhosis with end-stage liver disease [136–140].

IFALD develops frequently at very early ages, especially in premature infants in whom liver immaturity, frequent sepsis and necrotizing enterocolitis (NEC) facilitate liver inflammation and severe damages. At this young age PN is most often administered continuously over 24 h and CRBSIs is common. High risk situations for developing liver disease are summarized in Table 3. The combination of those factors makes the onset of cholestatic liver disease likely. The current use of taurolidine lock procedure decreased dramatically the rate of CRBSIs [141].

Table 2 Factors causing liver disease

Patient and intestinal failure related factors
• **Prematurity and low birth weight**
• **Lack of enteral feeding**
– *Total parenteral nutrition*
• **Dysruption of entero-hepatic biliary acid cycle**
– *Proximal stoma, ileal resection*
• **Intestinal stasis and bacterial overgrowth**
– *Obstruction, dysmotility, lack of ileo-caecal valve, over-tube feeding*
Parenteral nutrition related factors
• **Duration of PN**
• **Recurrent catheter related sepsis**
• **Unadapted protein energy delivery**
– Excessive or unadapted amino acid intake
– Continuous versus cyclic infusion
– Excessive glucose intake
– Unappropriate use of lipid emulsion
Phytosterols
Lipoperoxidation
Excess of omega-6 fatty acids
Essential fatty acid deficiency
• **Potential toxic components of PN**
Iron
Aluminium
Chromium
Manganese
• **Deficiencies**
Taurine
Chlorine

Table 3 High risk situations for developing liver disease

• Premature and young infants
• NEC or gastroschisis ± atresia
• Protracted bowel rest/intestinal stasis
• Bacterial overgrowth/gram negative sepsis
• Recurrent catheter-related sepsis
• Unadapted and/or continuous PN

The combination of these factors makes cholestatic liver disease likely

Intravenous Lipid Emulsions and Liver Disease

Frequently cited observational studies suggested a link between intravenous lipid emulsions (ILE) and liver disease [142, 143]. It has been reported that the improvement of cholestasis depends also on maintaining an appropriate protein/energy ratio in PN, achieving cyclic rather than continuous PN infusion, using medium-chain triglycerides (MCT) based lLE and adding α-tocopherol in ILE [144].

IFALD is a multifactorial disease in which the use of soybean oil-based ILE in PN may represent the major culprit [145]. Several factors should be taken into consideration when choosing an ILE for parenteral use: the content in essential fatty acids (EFAs), the ratio of ω-6/ω-3, the polyunsaturated fatty acid (PUFAs) content, the amount of medium chain triglycerides (MCTs), the quantity of α-tocopherol and phytosterols [146]. The probable detrimental effect (pro-inflammatory) of ω-6 FAs on liver function is provided by studies that showed fat emulsions based on pure fish oil (containing ω-3 FAs) being successful as rescue therapy in pediatric patients with SBS affected by severe liver disease. The infusion of exclusively ω-3 FAs ultimately changed the management of these patients since it allowed the reduction of intake of pro-inflammatory ω-6 and phytosterols while increasing the amounts of alpha-tocopherol, a powerful antioxidant agent [146].

The evidence gathered on the beneficial effects of fish-oil in these patients has led to its use in clinical practice. However, two different approaches have been developed in North America as compared to Europe. In North America, following the paper by Gura et al. or Cowles et al., a pure fish oil based lipid emulsion (Omegaven®) has been promoted and has been, until recently was the unique emulsion to be available on the market [147–149]. In Europe it has become early possible to use a composite lipid emulsion containing a mixture of soybean oil (30%), coconut oil (30%), olive oil (25%) and fish oil (15%) (SMOF-lipid®). Both ILEs contain 200 mg/L of alpha-tocopherol. Clayton compared the level of phytosterols in plasma of healthy subjects, patients with mild hepatic dysfunction and those with severe dysfunction who received soybean oil emulsion - rich in sterols, and found a link between liver damage and phytosterols plasma levels [150]. Phytosterols contained in soybean oil have been found to be associated with liver disease progression and their exclusion from ILE may also be beneficial in children on PN [151].

Regarding the presence of tocopherol in lipid emulsions, one should emphasize that there are different preparations of tocopherol: alpha-tocopherol is the form with far greater antioxidant activity [152]. While soybean oil emulsions contain a high amount of gamma-tocopherol (which has 25% of the antioxidant power as compared to alpha-tocopherol), lipids based on fish oil are rich of the most powerful antioxidant vitamin E, alpha-tocopherol [153]. To ensure a proper antioxidant power in lipid preparations it is advisable to add 0.5 mg of alpha-tocopherol per gram of PUFAs.

Some concerns have been raised on providing fish oil as the sole source of lipids over a long period of time. Pure fish oil provides less essential ω-6 fatty acids than that currently recommended in infants and young children. Furthermore, Omegaven® (pure fish oil) can only be given at lower infusion rates compared to SMOF-lipid®). Omegaven® may not be able to provide enough calories to sustain growth. Thus, the combination of several types of oil by mixing soybean oil (rich in ω-6 FAs), coconut oil (rich in MCTs), olive oil (rich in MUFAs) and fish oil (rich in ω-3 FAs) appears to promote better growth while limiting hepatic toxicity [145]. A ran-

domized, double-blind, controlled trial on 60 preterm babies stratified by body weight has analyzed a set of parameters (clinical data, laboratory data, fatty acids in plasma and red blood cells, plasma levels of alpha-tocopherol and-phospholipids) after infusion of PN with SMOF-lipid® or soybean oil based emulsion [154]. The SMOF-lipid® emulsion increased the content of eicosapentaenoic EPA and docosahexaenoic (DHA) acids and reduced the ω-6 / ω-3 ratio, improving also liver function tests).

Another study evaluated the long-term effects of the lipid mixture SMOF-lipid® versus a soybean oil based preparation in pediatric patients on home PN [155]. This randomized, double blind study involved 28 children who received more than 4 infusions of PN per week for 4 consecutive weeks. The infusion was administered in 12–14 h overnight. At the end of the study no differences between biochemical and nutritional outcomes were recorded, but there was a clear association between the use of SMOF-lipid® and a significant decrease of bilirubin levels, that conversely increased in the soybean oil based group.

A confirmation of these findings comes from the study of Muhammed et al. who examined the effect of the switch from a soybean based lipid emulsion to SMOF-lipid® in 17 children with cholestasis [156]. The subjects were assigned to a treatment group receiving SMOF-lipid® and a group receiving soy based lipids. Over a period of 6 months the use of SMOF-lipid® was associated with a marked statistically significant reduction in the levels of bilirubin when compared with the soy based lipid group [156].

Finally, recent studies have emphasized the "superiority" of fish-oil derived lipid emulsions as a major advance for the management of patients on long-term PN. Preparations with pure fish oil are effective in decreasing cholestasis but their use as the sole source of lipids may not meet essential fatty acids requirements especially in the long-term [145]. Nevertheless, while some randomized controlled trials have demonstrated the beneficial effect of SMOF-lipid® versus soy-based lipid emulsion, no studies have compared SMOF-lipid® to Omegaven® in these patients The last ESPGHAN/ESPEN guidelines make the following recommandations [157]: As part of measures to reverse IFALD in paediatric patients, a discontinuation of Soy based ILE, a reduction of other ILE dosage and/or the use of composite ILE with FO, should be considered along with the treatment and management of other risk factors (LoE 2þ, RG B, strong recommendation for).

R 4.19 The use of pure FO ILE is not recommended for general use in paediatric patients but may be used for short-term rescue treatment in patients with progression to severe IFALD, based on case reports. (LoE 3e4, GPP, conditional recommendation for, strong consensus).

A recent study of the long-term use of the composite ILE SMOF-lipid® at a dose of 1.5–2 g/kg/day for more than 2 years, concluded that the Long-term use of the composite fish oil based ILE was well tolerated in home PN-dependent children. The RBC-FA profile alterations were consistent with the ω-3 PUFA-enriched composition of this emulsion without evidence of essential FA deficiency [158].

Long Term Management of Intestinal Failure

Home Parenteral Nutrition

Long-term PN administration is best achieved at home. Home PN, first used in the early 1980s, allows for full nutritional support of children and adults with temporary or permanent IF at home [8, 94, 159, 160]. Survival of children receiving prolonged PN depends mainly on the underlying diagnosis and has increased dramatically during the last three decades; nevertheless complications such as CRBSIs, IFALD and loss of venous access can seriously challenge the clinical stability of patients with IF [8, 94, 159–165].

The expertise required to prescribe PN both at home and in the hospital usually comes from a dedicated hospital-based nutritional team who has a thorough knowledge of energy expenditure, nutrients and trace-elements requirements by age, appropriate central catheter handling, and awareness of the risk and complications of long-term PN. Home PN must be tailored to the single patient and its family, always maintaining the goal of counteracting the deleterious aspects of intestinal failure. Official guidelines and position statements on central catheter handling and PN prescription have been published [135].

One of the largest cohort from a single center has been recently reported [8]. It involves 251 children referred to the Paris-Necker Intestinal Rehabilitation Center and discharged on HPN between January first 2000 and December 31st 2013. In this survey, 217 children (86%) had a primary digestive diseases (PDD). The mean age at HPN onset was 0.7 ± 0.3 year with a mean duration of 1.9 ± 0.4 years. The major indication for HPN was SBS (59%) secondary to midgut volvulus (16.7%), necrotizing enterocolitis (12.3%), gastroschisis (12%), extensive Hirschsprung Disease (10%) and intestinal atresia (6.4%). Other PDD were congenital enteropathies (10%), CIPOS, (9.1%) and Inflammatory Bowel Diseases (IBD, 5.1%). At the end of the study period, 56% of children were weaned off HPN, 8% had intestinal transplantation and 9.6% of children died - most of them had immune deficiency. The major complications of HPN were catheter-related blood stream infections (CRBSI, 1.7 per 1000 days of catheter) and IFALD, 51 children, (20% of the cohort). Children with congenital enteropathies had the highest rates of IFALD (44% of the sub-group). Children on HPN in this cohort have a shorter HPN duration to weaning, lower death rate and longer interval to catheter replacement than other

studies. One of the most important advances for long term PN dependent patients has been the onset of antiseptic catheter locking [92, 166].

The European data on the long-term management of IF on HPN need to be compared with other continent, especially North America. Several papers from the US, report "intestinal rehabilitation centers" including early management of intestinal failure (IF), especially short bowel syndrome in both neonatalogy and surgical wards, with the aim of the earliest PN weaning [87, 88, 167–170]. Some patients get severe complications and become candidates for ITx. Some others fail to be weaned off PN and are discharged on home-PN when suitable. The organization and follow-up of home PN is supposed to be shared between paediatric gastroenterology-nutrition teams and home care-giver companies according to the local facilities. Unfortunately, there is almost no report in the literature about the prevalence and results of paediatric home PN programs making a comparison with North-America management almost impossible. One of the reasons is linked to the organization and the management of IF. In France, patients suffering from IF, especially those with SBS, are managed by specialized medico-surgical departments, including paediatric surgeons and paediatric gastroenterologists-nutritionists or neonatology units. The decision of discharging the child on home PN and the follow-up are fully dependent on paediatric gastroenterology and nutrition teams. The French network is organized regionally. Patients are referred to the closest of the 7 reference centres for HPN. The world largest cross-sectional study included all children enrolled in any of the 7 French HPN certified centres from January 1st, 2014 to December 31st, 2019 [165]. The number of patients increased by 43.6% between 2014 and 2019. According to the year of follow up, the indications for HPN were short bowel syndrome (SBS) (42.3–46.6%), congenital enteropathies (CE) (18.5–22.8%), chronic intestinal pseudo-obstruction syndrome (CIPOS) (13.0–16.3%), long segment Hirschsprung's disease (LSHD) (9.7–13.3%), Crohn's disease (CD) (1.6–2.6%) and other non-primary digestive diseases (NPDD) such as immune deficiency, cancer or metabolic disease (4.0–9.2%). The median age at discharge on HPN decreased from 11.7 months in 2014 to 8.3 months in 2019 ($p < .001$). By December 31st, 2019, 44.8% of children had left the HPN program after a median duration ranging between 39.9 and 66.4 months. Among these patients, 192 (74.2%) were weaned off PN (94.7% SBS), 41 (15.8%) were transferred to adult centers for CIPOS (42%), SBS (31%) or CE (27%), 21 died (8.1%) - mostly in relation to cancer or immune deficiency - and 5 were transplanted (1.9%): 4 underwent combined liver-intestine transplantation for LSHD (n = 2), SBS, CE and one multivisceral Tx for CIPOS. The use of a composite fish-oil based ILE increased from 67.4% in 2014 to 88.3% in 2019 ($p < 0.001$). With the use of taurolidine lock procedure (TLP) the rate of CRBSIs dropped from 1.04 CRSBIs per 1000 days HPN in 2014 to 0.61 in 2019 ($p < 0.001$) while in meantime, the percentage of children receiving TLP increased from 29.4% to 63.0% ($p < 0.001$). The prevalence of cholestasis (conjugated bilirubin ≥20 μmol/l) was low and stable between 4.1 and 5.9% of children during the study period.

Intestinal Rehabilitation Centers and Multidisciplinary Team

Paediatric IF is a multifaceted condition requiring the competent contributions of several medical and allied health professionals both for inpatient and outpatient care. Therefore, the formation of a multidisciplinary team is crucial to achieve optimal results [165, 167–170].

The IF team should ideally include staff specialised in surgery, neonatalogy, gastroenterology and nutrition, a paediatric dietician and nurses experienced in central venous catheters handling and parenteral nutrition infusion. Special consideration should be given to the link between the hospital team and the home care team. Fostering coordination of surgical, medical, and nutritional management is mandatory to provide high quality, integrated care of patients with IF, thus improving remarkably the survival of these patients [8]. The three most important issues in the management of children with IF include:

1. A good and early link between primary care givers and intestinal failure programs.
2. The presence in the program of both intestinal rehabilitation and intestinal transplantation expertise.
3. The participation in the network of the organisations providing home PN bags.

Collaborative strategies must be developed in order to reduce mortality and morbidity in patients with IF, especially for those who are referred for permanent IF or intestinal transplantation [144].

Intestinal Transplantation

Although a large percentage of children with IF can survive with long-term PN, a proportion of patients develop life-threatening complications such as severe septic episodes (CRBSIs and/or SIBO related), fluid and electrolytes imbalance with renal disease, loss of venous access for PN and end stage liver disease. In these patients, nutrition has failed both in the enteral and the parenteral routes. These patients are considered to have "nutritional failure" [9, 144, 171]. They should be referred for intestinal transplantation (ITx). Successful ITx were first reported in the late 1980s and pro-

posed for the treatment of patients affected by irreversible intestinal failure [172, 173]. In 2001 the American Society of Transplantation defined irreversible liver disease, exhaustion of central venous access sites, and recurrence of life-threatening situations (recurrent sepsis or dehydration) as indications to consider ITx for patients with IF [174]. Despite important surgical and medical advances in the transplant techniques, reported long term patients' and grafts' survival rates remains around 50% at 5 years for children [175]. As an example, from a series of children with ultra-SBS referred to our institution some of them underwent ITx for nutritional failure while the others were maintained on HPN. With 5 years follow up, all children on HPN (100%) survived while those who have died anyway from nutritional failure survived in only 60% of cases [26]. This suggests that ITx has been a life saving procedure for 60%.

There is probably a different threshold for ITx on both sides of the Atlantic Ocean. The European approach is more inclined to support long-term home PN, which is cost-effective and provides a better quality of life, rather than to refer a child for ITx. Support for this view comes from Pironi et al. who have performed a 3-year prospective study including both adults and children on long-term PN for IF [176]. They compared 'non-candidates' for ITx (no indications nor contraindications), with 'candidates' who had an indication according to the USA Medicare and Medicaid Services definitions, and a high risk of death or morbidity according to the American Society of Transplantation position paper [177, 178]. The results showed that only patients with nutritional failure due to IFALD or major catheter complications had an increased risk of death on home PN, thus supporting its use as the primary treatment for IF. Those results were confirmed by another 3 years prospective follow-up study on potential paediatric candidates to ITx in Japan [179]. Bilirubin levels >100 μmol/l seem to negatively impact on post ITx survival. It is an important observation that a quarter of patients referred to an IF multidisciplinary team for ITx work up for irreversible IFALD, eventually reversed their cholestasis with an appropriate nutritional management [144].

Therefore it was suggested that ITx should be used only as a life-saving procedure. Although experienced transplantation centers have suggested that the role of ITx should be expanded to a pre-emptive/rehabilitative procedure applicable to all patients with irreversible IF, the recent findings have shown that home PN is the treatment of choice for IF in adults as well as in children. An early referral to IRC is essential to prevent or optimize the long-term management of IFALD. Central venous-catheter-related major complications might be indications for a pre-emptive ITx in selected patients. As a matter of fact, "nutritional failure" should be regarded mostly or even only as a clear indication to ITx [9].

In certain patients with other major organ failure in addition to SBS-IF, both long-term home PN and ITx may prolong suffering without improving quality of life. In such cases a wide-ranging ethical discussion should be performed to establish the best course of further treatment for the individual child. If home PN and ITx are not considered in the child's best interests it is important to involve a symptom care/palliative care team and if necessary make an end of life care plan [180].

Isolated liver Tx has been performed for IFALD in patients with SBS. Taha et al. reported a group of children with SBS and IFALD who have the potential for adaptation in the residual bowel underwent isolated LTx [181, 182]. The prognosis remains poor after this procedure, 8 survivors out of 14 [181]. This procedure should be avoided by preventing liver disease. If performed, it should be exercised with extreme caution. These children need careful assessment before isolated LTx and close follow-up with an experienced multidisciplinary team to monitor nutritional outcomes and may need consideration for transplant or non-transplant surgery in the long term (Fig. 5).

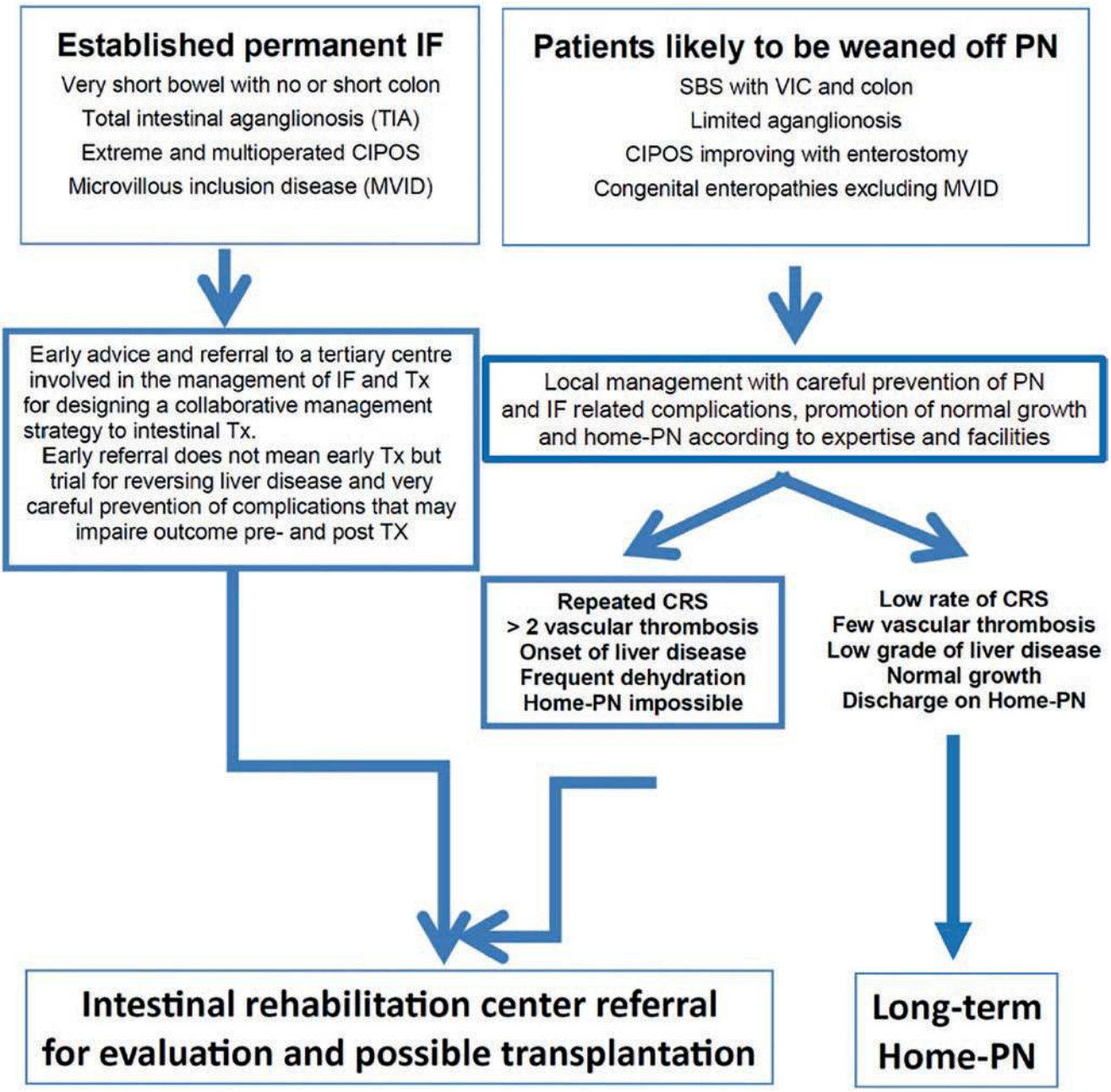

Fig. 5 Algorithm for managing intestinal failure from referral to possible intestinal transplantation

Conclusion

Intestinal failure requires specialized and individualized medical therapy that includes surgery, medical equipment, nutritional products, and standard nursing care. Intestinal rehabilitation programs provide such complex care with the goal of achieving enteral autonomy and oral feeding with or without intestinal transplantation. The treatment of permanent IF has made remarkable strides in the past decades. The establishment of multi-disciplinary intestinal rehabilitation programs at leading centers has improved the survival of children with IF while the morbidity associated with both IF and PN has significantly decreased. These programs almost all include neonatalogists, pediatric surgeons, pediatric gastroenterologists, specialized nurses, and dietitians; many also include a variety of other medical and allied medical specialists, providing integrated interdisciplinary care.

Recent advances in the knowledge of factors implicated in PN and IF complications and improvements in the medi-

cal and surgical management of SBS result in better outcomes for these patients. Isolated liver Tx for SBS patients who have the potential of bowel adaptation should be no longer required. It is interesting to note that the most recent International Intestinal Transplantation Registry report showed early evidence of a world-wide trend of reduction in the number of pediatric ITx. This might be explained by at least four factors:

- the provision of guidelines and training
- the development of intestinal rehabilitation centers with increasing IF expertise
- the enlarged use of non-transplant surgery
- the better prevention of IFALD, with fish oil based lipid emulsions playing a role
- the improved prevention of catheter related sepsis by using taurolidine or ethanol locks
- the onset of hormonal treatment for SBS

The combined and coordinated talents and skills of multiple types of health care practitioners have the potential to ameliorate the impact of intestinal failure and improve health outcomes and quality of life.

Major efforts are needed to improve the outcome of ITx that will likely remain part of the armamentarium required to prolong the survival of children with life-threatening complications of IF. Nevertheless the European experience has led to support a more conservative approach more inclined to home PN, limiting referrals for ITx only to children with nutritional failure.

References

1. Goulet O, Ruemmele F. Causes and management of intestinal failure in children. Gastroenterology. 2006;130(2 Suppl 1):S16–28.
2. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R. 1. Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005;41(Suppl 2):S1–87.
3. Mihatsch W, Shamir R, van Goudoever JB, Fewtrell M, Lapillonne A, Lohner S, et al. ESPEN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Guideline development process for the updated guidelines. Clin Nutr. 2018;37(6 Pt B):2306–8. https://doi.org/10.1016/j.clnu.2018.06.943.
4. Abi Nader E, Lambe C, Talbotec C, Dong L, Pigneur B, Goulet O. A new concept to achieve optimal weight gain in malnourished infants on total parenteral nutrition. J Parenter Enter Nutr. 2018;42:78–86.
5. Crenn P, Coudray-Lucas C, Thuillier F, Cynober L, Messing B. Postabsorptive plasma citrulline concentration is a marker of absorptive enterocyte mass and intestinal failure in humans. Gastroenterology. 2000;119:1496–505.
6. Konstantinos C, Fragkos AF. Citrulline as a marker of intestinal function and absorption in clinical settings: a systematic review and meta-analysis. Eur J Gastroenterol. 2018;6:181–91.
7. Proli F, Faragalli A, Talbotec C, Bucci A, Zemrani B, Chardot C, Abi Nader E, Goulet O, Lambe C. Variation of plasma citrulline as a predictive factor for weaning off long-term parenteral nutrition in children with neonatal short bowel syndrome. Clin Nutr. 2021;40(8):4941–7. https://doi.org/10.1016/j.clnu.2021.07.017; Epub 2021 Jul 18.
8. Abi Nader E, Lambe C, Talbotec C, Pigneur B, Lacaille F, Garnier-Lengline H, et al. Outcome of home parenteral nutrition in 251 children over a 14-y period: report of a single center. Am J Clin Nutr. 2016;103:1327–36.
9. D'Antiga L, Goulet O. Intestinal failure in children: the European view. J Pediatr Gastroenterol Nutr. 2013;56:118–26.
10. Goulet O, Joly F, Corriol O, Colomb-Jung V. Some new insights in intestinal failure-associated liver disease. Curr Opin Organ Transplant. 2009;14:256–61.
11. Kaufman SS, Pehlivanova M, Fennelly EM, et al. Predicting liver failure in parenteral nutrition-dependent short bowel syndrome of infancy. J Pediatr. 2010;156:580–5.
12. Pichler J, Horn V, Macdonald S, Hill S. Intestinal failure-associated liver disease in hospitalised children. Arch Dis Child. 2012;97:211–4.
13. Goulet O, Lambe C. Intravenous lipid emulsions in pediatric patients with intestinal failure. Curr Opin Organ Transplant. 2017;22:142–8.
14. Velazco CS, Fullerton BS, Brazzo JA, Hong CR, Jaksic T, BarnewoltCE. Radiographic measurement of intestinal length among children with short bowel syndrome: retrospective determination remains problematic. J Pediatr Surg. 2017;52:1921–4.
15. Weaver LT, Austin S, Cole TJ. Small intestinal length: a factor essential for gut adaptation. Gut. 1991;32:1321–3.
16. Struijs MC, Diamond IR, de Silva N, WalesPW. Establishing norms for intestinal length in children. J Pediatr Surg. 2009;44:933–8.
17. Ricour C, Duhamel JF, Arnaud-Battandier F, Collard Y, Revillon Y, Nihoul-Fekete C. Enteral and parenteral nutrition in the short bowel syndrome in children. World J Surg. 1985;9:310–5.
18. Goulet OJ, Revillon Y, Jan D, et al. Neonatal short bowel syndrome. J Pediatr. 1991;119:18–23.
19. Iacono G, Carroccio A, Montalto G, et al. Extreme short bowel syndrome: a case for reviewing the guidelines for predicting survival. J Pediatr Gastroenterol Nutr. 1993;16:216–9.
20. Andorsky DJ, Lund DP, Lillehei CW, et al. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr. 2001;139:27–33.
21. Quiros-Tejeira RE, Ament ME, Reyen L, et al. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. J Pediatr. 2004;145(2):157–63.
22. Goulet O, Baglin-Gobet S, Talbotec C, Fourcade L, Colomb V, Sauvat F, et al. Outcome and long-term growth after extensive small bowel resection in the neonatal period: a survey of 87 children. Eur J Pediatr Surg. 2005;15:95–101.
23. Sala D, Chomto S, Hill S. Long-term outcomes of short bowel syndrome requiring long-term/home intravenous nutrition compared in children with gastroschisis and those with volvulus. Transplant Proc. 2010;42:5–8.
24. Nusinovich Y, Revenis M, Torres C. Long-term outcomes for infants with intestinal atresia studied at Children's National Medical Center. J Pediatr Gastroenterol Nutr. 2013;57:324–9.
25. Diamanti A, Conforti A, Panetta F, Torre G, Candusso M, Bagolan P, Papa RE, Grimaldi C, Fusaro F, Capriati T, et al. Long-term outcome of home parenteral nutrition in patients with ultra-short bowel syndrome. J Pediatr Gastroenterol Nutr. 2014;58:438–42.

26. Norsa L, Artru S, Lambe C, Talbotec C, Pigneur B, Ruemmele F, et al. Long term outcomes of intestinal rehabilitation in children with neonatal very short bowel syndrome: parenteral nutrition or intestinal transplantation. Clin Nutr. 2019;38(2):926–33.
27. Goulet O, Olieman J, Ksiazyk J, Spolidoro J, Tibboe D, Köhler H, Yagci RV, Falconer J, Grimble G, Beattie RM. Neonatal short bowel syndrome as a model of intestinal failure: physiological background for enteral feeding. Clin Nutr. 2013;32:162–71.
28. Boctor DL, Hassen Jutteau W, Fenton TR, Shourounis J, Galante GJ, Eicher I, Goulet O, Lambe C. The prevalence of feeding difficulties and potential risk factors in pediatric intestinal failure: time to consider promoting oral feeds? Clin Nutr. 2021;40:5399–406. https://doi.org/10.1016/j.clnu.2021.08.018; Epub 2021 Sep 6.
29. Parvadia JK, Keswani SG, Vaikunth S, et al. Role of VEGF in small bowel adaptation after resection: the adaptive response is angiogenesis dependent. Am J Physiol Gastrointest Liver Physiol. 2007;293:G591–8.
30. Helmrath MA, Shin CE, Fox JW, et al. Adaptation after small bowel resection is attenuated by sialoadenectomy: the role for endogenous epidermal growth factor. Surgery. 1998;124:848–54.
31. Olieman JF, Penning C, Ijsselstijn H, et al. Enteral nutrition in children with short-bowel syndrome: current evidence and recommendations for the clinician. J Am Diet Assoc. 2010;110:420–6.
32. Cummins AG, Thompson FM. Effect of breast milk and weaning on epithelial growth of the small intestine in humans. Gut. 2002;51:748–54.
33. Capriati T, Nobili V, Stronati L, Cucchiara S, Laureti F, Liguori A, Tyndall E, Diamanti A. Enteral nutrition in pediatric intestinal failure: does initial feeding impact on intestinal adaptation? Expert Rev Gastroenterol Hepatol. 2017;11:741–8.
34. Mezoff EA, Hawkins JA, Ollberding NJ, Karns R, Morrow AL, Helmrath MA. The human milk oligosaccharide 2′-fucosyllactose augments the adaptive response to extensive intestinal. Am J Physiol Gastrointest Liver Physiol. 2016;310:G427–38.
35. de Boissieu D, Dupont C. Allergy to extensively hydrolyzed cow's milk proteins in infants: safety and duration of amino acid-based formula. J Pediatr. 2002;141:271–3.
36. Diamanti A, Fiocchi AG, Capriati T, Panetta F, Pucci N, Bellucci F, Torre G. Cow's milk allergy and neonatal short bowel syndrome: comorbidity or true association? Eur J Clin Nutr. 2015;69:102–6.
37. Bines J, Francis D, Hill D. Reducing parenteral requirement in children with short bowel syndrome: impact of an amino acid-based complete infant formula. J Pediatr Gastroenterol Nutr. 1998;26:123–8.
38. De Greef E, Mahler T, Janssen A, et al. The influence of neocate in paediatric short bowel syndrome on PN weaning. J Nutr Metab. 2010;2010:297575.
39. Goulet O, Colomb-Jung V, Joly F. Role of the colon in short bowel syndrome and intestinal transplantation. J Pediatr Gastroenterol Nutr. 2009;48(Suppl 2):S66–71.
40. Goulet O, Joly F. Intestinal microbiota in short bowel syndrome. Gastroenterol Clin Biol. 2010;34(Suppl 1):S37–43. https://doi.org/10.1016/S0399-8320(10)70019-1. PMID: 20889003.
41. Tappenden KA, Thomson AB, Wild GE, McBurney MI. Short-chain fatty acid-supplemented total parenteral nutrition enhances functional adaptation to intestinal resection in rats. Gastroenterology. 1997;112:792–802.
42. Bartholome AL, Albin DM, Baker DH, Holst JJ, Tappenden KA. Supplementation of total parenteral nutrition with butyrate acutely increases structural aspects of intestinal adaptation after an 80% jejunoileal resection in neonatal piglets. JPEN J Parenter Enteral Nutr. 2004;28:210–22.
43. Reigstad CS, Salmonson CE, Rainey JF 3rd, Szurszewski JH, Linden DR, Sonnenburg JL, Farrugia G, Kashyap PC. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. FASEB J. 2015;29:1395–403.
44. Koruda MJ, Rolandelli RH, Settle RG, Zimmaro DM, Rombeau JL. Effect of parenteral nutrition supplemented with short-chain fatty acids on adaptation to massive small bowel resection. Gastroenterology. 1988;95:715–20.
45. Mayeur C, Gratadoux JJ, Bridonneau C, Chegdani F, Larroque B, Kapel N, Corcos O, Thomas M, Joly F. Faecal D/L lactate ratio is a metabolic signature of microbiota imbalance in patients with short bowel syndrome. PLoS One. 2013;8(1):e54335. https://doi.org/10.1371/journal.pone.0054335; Epub 2013 Jan 23.
46. Joly F, Mayeur C, Messing B, Lavergne-Slove A, Cazals-Hatem D, Noordine ML, et al. Morphological adaptation with preserved proliferation/transporter content in the colon of patients with short bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2009;297:G116–23.
47. Kaneko T, Bando Y, Kurihara H, Satomi K, Nonoyama K, Matsuura N. Fecal microflora in a patient with short-bowel syndrome and identification of dominant lactobacilli. J Clin Microbiol. 1997;35:3181–5.
48. Engstrand Lilja H, Wefer H, Nyström N, Finkel Y, Engstrand L. Intestinal dysbiosis in children with short bowel syndrome is associated with impaired outcome. Microbiome. 2015;3:18. https://doi.org/10.1186/s40168-015-0084-7.
49. Davidovics ZH, Carter BA, Luna RA, Hollister EB, Shulman RJ, Versalovic J. The fecal microbiome in pediatric patients with short bowel syndrome. JPEN J Parenter Enteral Nutr. 2016;40(8):1106–13. https://doi.org/10.1177/0148607115591216.
50. Kadakia SC. D-lactic acidosis in a patient with jejunoileal bypass. J Clin Gastroenterol. 1995;20:154–6.
51. Petersen C. D-lactic acidosis. Nutr Clin Pract. 2005;20:634–45.
52. Hudson M, Pocknee R, Mowat NA. D-lactic acidosis in short bowel syndrome--an examination of possible mechanisms. Q J Med. 1990;74:157–63.
53. Mayeur C, Gratadoux JJ, Bridonneau C, et al. Faecal D/L lactate ratio is a metabolic signature of microbiota imbalance in patients with short bowel syndrome. PLoS One. 2013;8(1):e54335.
54. Uchida H, Yamamoto H, Kisaki Y, Fujino J, Ishimaru Y, Ikeda H. D-lactic acidosis in short-bowel syndrome managed with antibiotics and probiotics. J Pediatr Surg. 2004;39:634–6.
55. Takahashi K, Terashima H, Kohno K, Ohkohchi N. A standalone synbiotic treatment for the prevention of D-lactic acidosis in short bowel syndrome. Int Surg. 2013;98:110–3.
56. Coronado BE, Opal SM, Yoburn DC. Antibiotic-induced D-lactic acidosis. Ann Intern Med. 1995;122:839–42.
57. Wales PW, de Silva N, Kim JH, Lecce L, Sandhu A, Moore AM. Neonatal short bowel syndrome: a cohort study. J Pediatr Surg. 2005;40:755–62.
58. Squires RH, Duggan C, Teitelbaum DH, Wales PW, Balint J, Venick R, et al. Pediatric Intestinal Failure Consortium. Natural history of pediatric intestinal failure: initial report from the pediatric intestinal failure consortium. J Pediatr. 2012;16:723–8.
59. Hukkinen M, Mutanen A, Pakarinen MP. Small bowel dilation in children with short bowel syndrome is associated with mucosal damage, bowel-derived bloodstream infections, and hepatic injury. Surgery. 2017;162:670–9.
60. Husebye E. The patterns of small bowel motility: physiology and implications in organic disease and functional disorders. Neurogastroenterol Motil. 1999;11:141–61.
61. Willis TC, Carter BA, Rogers SP, Hawthorne KM, Hicks PD, Abrams SA. High rates of mortality and morbidity occur in infants with parenteral nutrition-associated cholestasis. JPEN J Parenter Enteral Nutr. 2010;34:32–7; Comment in:JPEN J Parenter Enteral Nutr. 2010; 34: 94–5.
62. Cole CR, Frem JC, Schmotzer B, et al. The rate of bloodstream infection is high in infants with short bowel syndrome: relation-

ship with small bowel bacterial overgrowth, enteral feeding, and inflammatory and immune responses. J Pediatr. 2010;156:941–7.
63. Moseley RH. Sepsis and cholestasis. Clin Liver Dis. 2004;8:83–94.
64. Jones A, Selby PJ, Viner C, Hobbs S, Gore ME, McElwain TJ. Tumour necrosis factor, cholestatic jaundice, and chronic liver disease. Gut. 1990;31:938–9.
65. Charbit-Henrion F, Chardot C, Ruemmele F, Talbotec C, Morali A, Goulet O, Colomb V. Anastomotic ulcerations after intestinal resection in infancy. J Pediatr Gastroenterol Nutr. 2014;59:531–6.
66. Frémond ML, Viala J, Tréton X, Roy M, Berrebi D, Gottrand F, Bonnard A, Martinez-Vinson C, Hugot JP. Digestive peri-anastomotic ulcerations and Crohn's disease. J Crohns Colitis. 2014;8:1624–31.
67. Madre C, Mašić M, Prlenda-Touilleux D, Brueckne A, Koletzko S, Fabre A, et al. A European survey on digestive perianastomotic ulcerations, a rare Crohn-like disorder occurring in children and young adults. J Pediatr Gastroenterol Nutr. 2021;73(3):333–7. https://doi.org/10.1097/MPG.0000000000003200.
68. Bianchi A. Intestinal loop lengthening--a technique for increasing small intestinal length. J Pediatr Surg. 1980;15:145–51.
69. Kim HB, Lee PW, Garza J, Duggan C, Fauza D, Jaksic T. Serial transverse enteroplasty for short bowel syndrome: a case report. J Pediatr Surg. 2003;38:881–5.
70. Sudan D, Thompson J, Botha J, Grant W, Antonson D, Raynor S, Langnas A. Comparison of intestinal lengthening procedures for patients with short bowel syndrome. Ann Surg. 2007;246:593–601.
71. Bianchi A, Morabito A. The dilated bowel: a liability and an asset. Semin Pediatr Surg. 2009;18:249–57.
72. Modi BP, Javid PJ, Jaksic T, et al. International STEP Data Registry. First report of the international serial transverse enteroplasty data registry: indications, efficacy, and complications. J Am Coll Surg. 2007;204:365–7.
73. Thompson J, Sudan D. Intestinal lengthening for short bowel syndrome. Adv Surg. 2008;42:49–61.
74. Barrett M, Demehri FR, Ives GC, Schaedig K, Arnold MA, Teitelbaum DH. Taking a STEP back: assessing the outcomes of multiple STEP procedures. J Pediatr Surg. 2017;52:69–73.
75. Mutanen A, Barrett M, Feng Y, Lohi J, Rabah R, Teitelbaum DH, Pakarinen MP. Short bowel mucosal morphology, proliferation and inflammation at first and repeat STEPprocedures. J Pediatr Surg. 2019;54(3):511–6. https://doi.org/10.1016/j.jpedsurg.2018.04.016.
76. Oliveira C, de Silva N, Wales PW. Five-year outcomes after serial transverse enteroplasty in children with short bowel syndrome. J Pediatr Surg. 2012;47:931–7.
77. Coletta R, Aldeiri B, Morabito A. Institutional experience with spiral intestinal lengthening and tailoring. Eur J Pediatr Surg. 2019;29:412–6. https://doi.org/10.1055/s-0038-1660850.
78. Matarese LE, Abu-Elmagd K. Somatropin for the treatment of short bowel syndrome in adults. Expert Opin Pharmacother. 2005;6:1741–50.
79. Goulet O, Dabbas-Tyan M, Talbotec C, et al. Effect of recombinant human growth hormone on intestinal absorption and body composition in children with short bowel syndrome. JPEN J Parent Enter Nutr. 2010;34:513–20.
80. Peretti N, Loras-Duclaux I, Kassai B, et al. Growth hormone to improve short bowel syndrome intestinal autonomy: a pediatric randomized open-label clinical trial. J Parenter Enter Nutr. 2011;35:723–31.
81. Wales PW, Nasr A, de Silva N, et al. Human growth hormone and glutamine for patients with short bowel syndrome. Cochrane Database Syst Rev. 2010;6:CD006321.
82. Wilhelm SM, Lipari M, Kulik JK, Kale-Pradhan PB. Teduglutide for the treatment of short bowel syndrome. Ann Pharmacother. 2014;48:1209–13.
83. Carter BA, Cohran VC, Cole CR, Corkins MR, Dimmitt RA, Duggan C, et al. Outcomes from a 12-week, open-label, multicenter clinical trial of teduglutide in pediatric short bowel syndrome. J Pediatr. 2017;181:102–11.
84. Kocoshis SA, Merritt RJ, Hill S, Protheroe S, Carter BA, Horslen S, Hu S, Kaufman SS, Mercer DF, Pakarinen MP, Venick RS, Wales PW. Grimm AA safety and efficacy of teduglutide in pediatric patients with intestinal failure due to short bowel syndrome: a 24-week, phase III study. JPEN J Parenter Enteral Nutr. 2020;44:621–31. https://doi.org/10.1002/jpen.1690.
85. Jeppesen PB. Gut hormones in the treatment of short-bowel syndrome and intestinal failure. Curr Opin Endocrinol Diabetes Obes. 2015;22:14–20.
86. Spencer AU, Neaga A, West B, et al. Pediatric short bowel syndrome: redefining predictors of success. Ann Surg. 2005;242:403–9.
87. Nucci A, Burns RC, Armah T, Lowery K, Yaworski JA, Strohm S, Bond G, Mazariegos G, Squires R. Interdisciplinary management of pediatric intestinal failure: a 10-year review of rehabilitation and transplantation. J Gastrointest Surg. 2008;12:429–35.
88. Sigalet D, Boctor D, Robertson M, Lam V, Brindle M, Sarkhosh K, Driedger L, Sajedi M. Improved outcomes in paediatric intestinal failure with aggressive prevention of liver disease. Eur J Pediatr Surg. 2009;19:348–53.
89. Fullerton BS, Hong CR, Jaksic T. Long-term outcomes of pediatric intestinal failure. Semin Pediatr Surg. 2017;26:328–35.
90. Merritt RJ, Cohran V, Raphael BP, Sentongo T, Volpert D, Warner BW, Goday PS, Nutrition Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Intestinal rehabilitation programs in the management of pediatric intestinal failure and short bowel syndrome. J Pediatr Gastroenterol Nutr. 2017;65:588–96.
91. Totonelli G, Tambucci R, Boscarelli A, Hermans D, Dall'Oglio L, Diamanti A, et al. Pediatric intestinal rehabilitation and transplantation registry: initial report from a European Collaborative Registry. Eur J Pediatr Surg. 2018;28:75–80.
92. Lambe C, Poisson C, Talbotec C, Goulet O. Strategies to reduce catheter-related bloodstream infections in pediatric patients receiving home parenteral nutrition: the efficacy of taurolidine-citrate prophylactic-locking. JPEN J Parenter Enteral Nutr. 2018;42:1017–25.
93. Smith JM, Weaver T, Skeans MA, Horslen SP, Harper AM, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2016 annual data report: intestine. Am J Transplant. 2018;18(Suppl 1):254–90.
94. Leonberg B, Chuang E, Eicher P, Tershakovec AM, Leonard L, Stallings VA. Long-term growth and development in children after home parenteral nutrition. J Pediatr. 1998;132:461–6.
95. Olieman JF, Tibboel D, Penning C. Growth and nutritional aspects of infantile short bowel syndrome for the past 2 decades. J Pediatr Surg. 2008;43:2061–9.
96. Wu J, Tang Q, Feng Y, Huang J, Tao Y, Wang Y, Cai W, Shi C. Nutrition assessment in children with short bowel syndrome weaned off parenteral nutrition: a long-term follow-up study. J Pediatr Surg. 2007;42:1372–6.
97. Kimura O, Ono S, Furukawa T, Higuchi K, Deguchi E, Iwai N. Management strategies for infants with total intestinal aganglionosis. J Pediatr Surg. 2009;44:1564–7.
98. Ziegler MM, Royal RE, Brandt J, Drasnin J, Martin LW, Extended myectomy-myotomy. A therapeutic alternative for total intestinal aganglionosis. Ann Surg. 1993;218:504–9.
99. Fusaro F, Morini F, Mutanen A, De Angelis P, Tambucci R, Capriati T, et al. Autologous intestinal reconstructive surgery in the management of total intestinal aganglionosis. J Pediatr Gastroenterol Nutr. 2019;68:635–41.

100. Sauvat F, Grimaldi C, Lacaille F, Ruemmele F, Dupic L, Bourdaud N, Fusaro F, Colomb V, Jan D, Cezard JP, Aigrain Y, Revillon Y, Goulet O. Intestinal transplantation for total intestinal aganglionosis: a series of 12 consecutive children. J Pediatr Surg. 2008;43:1833–8.
101. Lacaille F, Irtan S, Dupic L, Talbotec C, Lesage F, Colomb V, Salvi N, Moulin F, Sauvat F, Aigrain Y, Revillon Y, Goulet O, Chardot C. Twenty-eight years of intestinal transplantation in Paris: experience of the oldest European center. Transpl Int. 2017;30:178–86.
102. Norsa L, Gupte G, Ramos Boluda E, Joly F, Corcos O, Pirenne J, Herlenius G, Lacaille F. Life of patients 10 years after a successful pediatric intestinal transplantation in Europe. Am J Transplant. 2018;18:1489–93.
103. Payen E, Talbotec C, Cherdot C, Capito C, Khen-Dunlop N, Sarnacki S, Lacaille F, Lambe C, Goulet O. Outcome of total colonic Aganglionosis involving the small bowel depends on bowel length, liver disease, and enterocolitis. J Pediatr Gastroenterol Nutr. 2022;74:582–7. https://doi.org/10.1097/MPG.0000000000003415.
104. Thapar N, Saliakellis E, Benninga MA, Borrelli O, Curry J, Faure C, De Giorgio R, Gupte G, Knowles CH, Staiano A, Vandenplas Y, Di Lorenzo C. Paediatric intestinal pseudo-obstruction: evidence and consensus-based recommendations from an ESPGHAN-Led Expert Group. J Pediatr Gastroenterol Nutr. 2018;66:991–1019.
105. Goulet O, Sauvat F, Jan D. Surgery for pediatric patients with chronic intestinal pseudo-obstruction syndrome. J Pediatr Gastroenterol Nutr. 2005;41(Suppl 1):S66–8.
106. Lapointe SP, Rivet C, Goulet O, et al. Urological manifestations associated with chronic intestinal pseudo-obstructions in children. J Urol. 2002;168:1768–70.
107. Galmiche L, Jaubert F, Sauvat F, et al. Normal oxidative phosphorylation in intestinal smooth muscle of childhood chronic intestinal pseudo-obstruction. Neurogastroenterol Motil. 2011;23:24–9.
108. De Giorgio R, Cogliandro RF, Barbara G, et al. Chronic intestinal pseudo-obstruction: clinical features, diagnosis, and therapy. Gastroenterol Clin N Am. 2011;40:787–807.
109. Lapointe R. Chronic idiopathic intestinal pseudo-obstruction treated by near total small bowel resection: a 20-year experience. J Gastrointest Surg. 2010;14:1937–42.
110. Goulet O, Talbotec C, Jan D, et al. Nutritional management of pediatric patients with chronic intestinal pseudo-obstruction syndrome. J Pediatr Gastroenterol Nutr. 2001;32(Suppl 1):S44–7.
111. Di Lorenzo C, Youssef NN. Diagnosis and management of intestinal motility disorders. Semin Pediatr Surg. 2010;19:50–8.
112. Faure C, Goulet O, Ategbo S, et al. Chronic intestinal pseudoobstruction syndrome: clinical analysis, outcome, and prognosis in 105 children. French-Speaking Group of Pediatric Gastroenterology. Dig Dis Sci. 1999;44:953–9.
113. Abu-Elmagd K. The concept of gut rehabilitation and the future of visceral transplantation. Nat Rev Gastroenterol Hepatol. 2015;12:108–20.
114. Goulet OJ, Brousse N, Canioni D, et al. Syndrome of intractable diarrhoea with persistent villous atrophy in early childhood: a clinicopathological survey of 47 cases. J Pediatr Gastroenterol Nutr. 1998;26:151–61.
115. Canani RB, Castaldo G, Bacchetta R, Martín MG, Goulet O. Congenital diarrhoeal disorders: advances in this evolving web of inherited enteropathies. Nat Rev Gastroenterol Hepatol. 2015;12:293–302.
116. Goulet O, Pigneur B, Charbit-Henrion F. Congenital enteropathies involving defects in enterocyte structure or differentiation. Best Pract Res Clin Gastroenterol. 2022;56-57:101784. https://doi.org/10.1016/j.bpg.2021.101784.
117. Halac U, Lacaille F, Joly F, et al. Microvillous inclusion disease: how to improve the prognosis of a severe congenital enterocyte disorder. J Pediatr Gastroenterol Nutr. 2011;52:460–5.
118. Girard M, Lacaille F, Verkarre V, Mategot R, Feldmann G, Grodet A, Sauvat F, Irtan S, Davit-Spraul A, Jacquemin E, Ruemmele F, Rainteau D, Goulet O, Colomb V, Chardot C, Henrion-Caude A, Debray D. MYO5B and bile salt export pump contribute to cholestatic liver disorder in microvillous inclusion disease. Hepatology. 2014;60:301–10.
119. Ruemmele FM, Jan D, Lacaille F, Cézard JP, Canioni D, Phillips AD, Peuchmaur M, Aigrain Y, Brousse N, Schmitz J, Revillon Y, Goulet O. New perspectives for children with microvillous inclusion disease: early small bowel transplantation. Transplantation. 2004;77:1024–8.
120. Wiegerinck CL, Janecke AR, Schneeberger K, Vogel GF, van Haaften-Visser DY, Escher JC, et al. Loss of syntaxin 3 causes variant microvillus inclusion disease. Gastroenterology. 2014;147:65–8.
121. Janecke AR, Schneeberger K, et al. Loss of syntaxin 3 causes variant microvillus inclusion disease. Gastroenterology. 2014;147:65–8.
122. van der Velde KJ, Dhekne HS, Swertz MA, Sirigu S, Ropars V, Vinke PC, et al. An overview and online registry of microvillus inclusion disease patients and their MYO5B mutations. Hum Mutat. 2013;34:1597–605.
123. Goulet O, Salomon J, Ruemmele F, et al. Intestinal epithelial dysplasia (tufting enteropathy). Orphanet J Rare Dis. 2007;2:20.
124. Salomon J, Goulet O, Canioni D, Brousse N, Lemale J, Tounian P, et al. Genetic characterization of congenital tufting enteropathy: epcam associated phenotype and involvement of SPINT2 in the syndromic form. Hum Genet. 2014;133:299–310.
125. Salomon J, Espinosa-Parrilla Y, Goulet O, et al. A founder effect at the EPCAM locus in congenital tufting enteropathy in the Arabic Gulf. Eur J Med Genet. 2011;54:319–22.
126. Müller T, Rasool I, Heinz-Erian P, Mildenberger E, Hülstrunk C, Müller A, et al. Congenital secretory diarrhoea caused by activating germline mutations Congenital secretory diarrhoea caused by activating germline mutations in GUCY2C. Gut. 2015;65(8):1306–13. https://doi.org/10.1136/gutjnl-2015-309441.
127. Salomon J, Gaston C, Magescas J, Duvauchelle B, Canioni D, Sengmanivong L, et al. Contractile forces at tricellular contacts modulate epithelial organization and monolayer integrity. Nat Commun. 2017;8:13998.
128. Ashworth I, Wilson A, Aquilina S, Parascandalo R, Mercieca V, Gerada J, Macdonald S, Simchowitz V, Hill S. Reversal of intestinal failure in children with tufting enteropathy supported with parenteral nutrition at home. J Pediatr Gastroenterol Nutr. 2018;66:967–71.
129. Goulet O, Vinson C, Roquelaure B, et al. Syndromic (phenotypic) diarrhea in early infancy. Orphanet J Rare Dis. 2008;3:6.
130. Fabre A, Martinez-Vinson C, Goulet O, Badens C. Syndromic diarrhea/Tricho-hepato-enteric syndrome. Orphanet J Rare Dis. 2013;8:5. https://doi.org/10.1186/1750-1172-8-5.
131. Vély F, Barlogis V, Marinier E, Coste ME, Dubern B, Dugelay E, et al. Combined immunodeficiency in patients with Trichohepatoenteric syndrome. Front Immunol. 2018;9:1036. https://doi.org/10.3389/fimmu.2018.01036; eCollection 2018.
132. Esteve C, Francescatto L, Tan PL, Bourchany A, De Leusse C, Marinier E, et al. Loss-of-function mutations in UNC45A cause a syndrome associating cholestasis, diarrhea, impaired hearing, and bone fragility. Am J Hum Genet. 2018;102:364–74.
133. Oz-Levi D, Olender T, Bar-Joseph I, Zhu Y, Marek-Yagel D, Barozzi I, et al. Noncoding deletions reveal a gene that is critical for intestinal function. Nature. 2019;571:107–11.

134. Goulet OJ. Intestinal failure-associated liver disease and the use of fish oil-based lipid emulsions. World Rev Nutr Diet. 2015;112:90–114.
135. Marschall J, Mermel L, Fakih M, Hadaway L, Kallen A, O'Grady N, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35:753–71.
136. Geier A, Fickert P, Trauner M. Mechanisms of disease: mechanisms and clinical implications of cholestasis in sepsis. Nat Clin Pract Gastroenterol Hepatol. 2006;3:574–85.
137. Hermans D, Talbotec C, Lacaille F, Goulet O, Ricour C, Colomb V. Early central catheter infections may contribute to hepatic fibrosis in children receiving long-term parenteral nutrition. J Pediatr Gastroenterol Nutr. 2007;44:459–63.
138. Wagner M, Zollner G, Trauner M. New molecular insights into the mechanisms of cholestasis. J Hepatol. 2009;51:565–80.
139. El Kasmi KC, Anderson AL, Devereaux MW, et al. Toll-like receptor 4-dependent Kupffer cell activation and liver injury in a novel mouse model of parenteral nutrition and intestinal injury. Hepatology. 2012;55:1518–28.
140. McKenna S, Gossling M, Bugarini A, Hill E, Anderson AL, Rancourt RC, Balasubramaniyan N, El Kasmi KC, Wright CJ. Endotoxemia induces IκBβ/NF-κB-dependent endothelin-1 expression in hepatic macrophages. J Immunol. 2015;195:3866–79.
141. Kolaček S, Puntis JWL, Hojsak I, ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: venous access. Clin Nutr. 2018;37(6 Pt B):2379–91. https://doi.org/10.1016/j.clnu.2018.06.952; Epub 2018 Jun 18.
142. Colomb V, Jobert-Giraud A, Lacaille F, et al. Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. J Parenter Enter Nutr. 2000;24:345–50.
143. Cavicchi M, Beau P, Crenn P, et al. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med. 2000;132:525–32.
144. Ganousse-Mazeron S, Lacaille F, Colomb-Jung V, Talbotec C, Ruemmele F, Sauvat F, Chardot C, Canioni D, Jan D, Revillon Y, Goulet O. Assessment and outcome of children with intestinal failure referred for intestinal transplantation. Clin Nutr. 2015;34:428–35.
145. Goulet OJ, Cai W, Seo JM. Lipid emulsion use in pediatric patients requiring long-term parenteral nutrition. JPEN J Parenter Enteral Nutr. 2020;44(Suppl 1):S55–67. https://doi.org/10.1002/jpen.1762.
146. Linseisen J, Hoffmann J, Lienhard S, et al. Antioxidant status of surgical patients receiving TPN with an omega-3-fatty acid-containing lipid emulsion supplemented with alpha-tocopherol. Clin Nutr. 2000;19:177–84.
147. Gura KM, Duggan CP, Collier SB, et al. Reversal of parenteral nutrition- associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. Pediatrics. 2006;118:e197–201.
148. Cowles RA, Ventura KA, Martinez M, Lobritto SJ, Harren PA, Brodlie S, Carroll J, Jan DM. Reversal of intestinal failure-associated liver disease in infants and children on parenteral nutrition: experience with 93 patients at a referral center for intestinal rehabilitation. J Pediatr Surg. 2010;45:84–7.
149. Nandivada P, Fell GL, Gura KM, Puder M. Lipid emulsions in the treatment and prevention of parenteral nutrition-associated liver disease in infants and children. Am J Clin Nutr. 2016;103:629S–34S.
150. Clayton PT, Whitfield P, Lyer K. The role of phytosterols in the pathogenesis of liver complications of pediatric parenteral nutrition. Nutrition. 1998;14:158–64.
151. Forchielli ML, Bersani G, Tala S, et al. The spectrum of plant and animal sterols in different oil-derived intravenous emulsions. Lipids. 2010;45:63–71.
152. Wanten G, Beunk J, Naber A, et al. Tocopherol isoforms in parenteral lipid emulsions and neutrophil activation. Clin Nutr. 2002;21:417–22.
153. Mertes N, Grimm H, Furst P, et al. Safety and efficacy of a new parenteral lipid emulsion (SMOFlipid) in surgical patients: a randomized, double-blind, multicenter study. Ann Nutr Metab. 2006;50:253–9.
154. Tomsits E, Tolgysi A, Fekete G, et al. Safety and efficacy of a lipid emulsion containing a mixture of soybean, olive, coconut and fish oils: a randomized double blind trial in premature infants requiring parenteral nutrition. J Pediatr Gastroenterol Nutr. 2010;51:514–21.
155. Goulet O, Antebi H, Wolf C, et al. A new intravenous fat emulsion containing fish oil: a single center, double-blind randomized study on long-term efficacy and safety in pediatric patients. J Parenter Enter Nutr. 2010;34:485–95.
156. Muhammed R, Bremner R, Protheroe S, Johnson T, Holden C, Murphy MS. Resolution of parenteral nutrition-associated jaundice on changing from a soybean oil emulsion to a complex mixed-lipid emulsion. J Pediatr Gastroenterol Nutr. 2012;54:797–802.
157. Lapillonne A, Fidler Mis N, Goulet O, van den Akker CHP, Wu J, Koletzko B, ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: lipids. Clin Nutr. 2018;37(6 Pt B):2324–36.
158. Goulet O, Lamazière A, Abi Nader E, Talbotec C, Wolf C, Lambe C. Erythrocyte fatty acid membrane composition in children on long-term parenteral nutrition enriched with ω-3 fatty acids. Am J Clin Nutr. 2022;115:422–31. https://doi.org/10.1093/ajcn/nqab263.
159. Colomb V, Dabbas-Tyan M, et al. Long-term outcome of children receiving home parenteral nutrition: a 20-year single-center experience in 302 patients. J Pediatr Gastroenterol Nutr. 2007;44:347–53.
160. Gandullia P, Lugani F, Costabello L, Arrigo S, Calvi A, Castellano E, Vignola S, Pistorio A, Barabino AV. Long-term home parenteral nutrition in children with chronic intestinal failure: a 15-year experience at a single Italian centre. Dig Liver Dis. 2011;43:28–33.
161. Pironi L, Joly F, Forbes A, et al. Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. Gut. 2011;60:17–25.
162. Wiskin A, Cole C, Owens D, Morgan M, Burge DM, Beattie RM. Ten-year experience of home parenteral nutrition in a single Centre. Acta Paediatr. 2012;101:524–7.
163. Barclay A, Henderson P, Gowen H, Puntis J, BIFS collaborators. The continued rise of paediatric home parenteral nutrition use: implications for service and the improvement of longitudinal data collection. Clin Nutr. 2014;14:290–8.
164. Diamanti A, Capriati T, Gandullia P, Di Leo G, Lezo A, Lacitignola L, et al. Pediatric chronic intestinal failure in Italy: report from the 2016 survey on behalf of Italian Society for Gastroenterology, Hepatology and Nutrition (SIGENP). Nutrients. 2017;9(11):1217. https://doi.org/10.3390/nu9111217.
165. Goulet O, Breton A, Coste ME, Dubern B, Ecochard-Dugelay E, Guimber D, Loras-Duclaux I, Abi Nader E, Marinier E, Peretti N, Lambe C. Pediatric home parenteral nutrition in France: a six years national survey. Clin Nutr. 2021;40:5278–87. https://doi.org/10.1016/j.clnu.2021.08.002.
166. Kawano T, Kaji T, Onishi S, Yamada K, Yamada W, Nakame K, Mukai M, Ieiri S. Efficacy of ethanol locks to reduce the incidence of catheter-related bloodstream infections for home parenteral nutrition pediatric patients: comparison of therapeutic treatment with prophylactic treatment. Pediatr Surg Int. 2016;32:863–7.

167. Sudan D, DiBaise J, Torres C, Thompson J, Raynor S, Gilroy R, et al. A multidisciplinary approach to the treatment of intestinal failure. J Gastrointest Surg. 2005;9:165–76.
168. Torres C, Sudan D, Vanderhoof J, Grant W, Botha J, Raynor S, Langnas A. Role of an intestinal rehabilitation program in the treatment of advanced intestinal failure. J Pediatr Gastroenterol Nutr. 2007;45:204–12.
169. Beath S, Pironi L, Gabe S, et al. Collaborative strategies to reduce mortality and morbidity in patients with chronic intestinal failure including those who are referred for small bowel transplantation. Transplantation. 2008;85:1378–84.
170. Javid PJ, Malone FR, Reyes J, et al. The experience of a regional pediatric intestinal failure program: successful outcomes from intestinal rehabilitation. Am J Surg. 2010;199:676–9.
171. Rodrigues AF, van Mourik IDM, Sharif K, et al. Management of end-stage central venous access in children referred for possible small bowel transplantation. J Pediatr Gastroenterol Nutr. 2006;42:427–33. https://doi.org/10.1097/01.mpg.0000215311.71040.89.
172. Goulet O, Révillon Y, Jan D, et al. Small-bowel transplantation in children. Transplant Proc. 1990;22:2499–500.
173. Grant D, Abu-Elmagd K, Mazariegos G, Vianna R, Langnas A, Mangus R, et al. Intestinal transplant association. Intestinal transplant registry report: global activity and trends. Am J Transplant. 2015;15:210–9.
174. Kaufman SS, Atkinson JB, Bianchi A, et al. Indications for pediatric intestinal transplantation: a position paper of the American Society of Transplantation. Pediatr Transplant. 2001;5:80–7. https://doi.org/10.1034/j.1399-3046.2001.005002080.x.
175. Raghu VK, Beaumont JL, Everly MJ, et al. Pediatric intestinal transplantation: analysis of the intestinal transplant registry. Pediatr Transplant. 2019;23:e13580. https://doi.org/10.1111/petr.13580.
176. Pironi L, Forbes A, Joly F, et al. Survival of patients identified as candidates for intestinal transplantation: a 3-year prospective follow-up. Gastroenterology. 2008;135:61e71.
177. Pironi L, Joly F, Forbes A, Colomb V, Lyszkowska M, Baxter J, et al. Home Artificial Nutrition & Chronic Intestinal Failure Working Group of the European Society for Clinical Nutrition and Metabolism (ESPEN). Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. Gut. 2011;60:17–25.
178. Pironi L, Goulet O, Buchman A, et al. Home Artificial Nutrition and Chronic Intestinal Failure Working Group of ESPEN. Outcome on home parenteral nutrition for benign intestinal failure: a review of the literature and benchmarking with the European prospective survey of ESPEN. Clin Nutr. 2012;31:831–45.
179. Ueno T, Wada M, Hoshino K, et al. Three-year prospective follow-up of potential pediatric candidate for intestinal transplantation. Transplant Proc. 2018;50:2779–82. https://doi.org/10.1016/j.transproceed.2018.03.067.
180. Ribeiro-Mourão F, Bertaud S, Brierley J, et al. Use of home parenteral nutrition in severely neurologically impaired children. Arch Dis Child. 2022;107:365–70. https://doi.org/10.1136/archdischild-2021-321850.
181. Botha JF, Grant WJ, Torres C, et al. Isolated liver transplantation in infants with end-stage liver disease due to short bowel syndrome. Liver Transpl. 2006;12:1062–6. https://doi.org/10.1002/lt.20763.
182. Taha AM, Sharif K, Johnson T, Clarke S, Murphy MS, Gupte GL. Long-term outcomes of isolated liver transplantation for short bowel syndrome and intestinal failure-associated liver disease. J Pediatr Gastroenterol Nutr. 2012;54:547–51.

Part IV

Consequences of Intestinal Failure

Consequences of Undernutrition and Dehydration

Pete Turner, Simon Alison, and Jeremy M.D. Nightingale

Key Points

1. Undernutrition is common in all patient groups and affects all body systems.
2. Undernutrition adversely affects all disease processes resulting in longer hospital admissions with increased nursing dependency, higher morbidity and mortality.
3. Severe malnutrition impairs thermoregulation so that patients with a severe sepsis may not be identified.
4. Albumin is generally not a marker of nutritional status.
5. Patients who have been obese can have a high body mass index (BMI) yet be severely undernourished (sarcopenic obesity).
6. With no food (oral intake) but with water a healthy adult may be expected to live 2 months. This time is reduced in the presence of sepsis/inflammation.
7. With no water intake (oral, enteral or intravenous) an adult may be expected to survive for up to 2 weeks. This depends upon activity, ambient temperature and fluid losses.

Introduction

The European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) (ESPEN) have stated that the terms undernutrition and malnutrition can be considered synonymous and can be defined as 'a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function, and clinical outcome from disease' [1]. Gastrointestinal disease gives rise to undernutrition by reduction of appetite, oral intake, digestion and/or absorption, and increased metabolic demands.

The physical and mental consequences of starvation and undernutrition have been known since ancient times. An ancient Egyptian royal tomb of more than 2000 years BC bears the inscription:

> *I am mourning on my high throne for the vast misfortune, because the Nile flood in my time has not come for seven years! Light is the grain; there is lack of crops and of all kinds of food. Each man has become a thief to his neighbours. They desire to hasten and cannot walk. The child cries, the youth creeps along as does the old man; their souls are bowed down, their legs are bent together and drag along the ground and their hands rest in their bosoms. The counsel of the great ones in the court is but emptiness. Torn open are the chests of provisions, but instead of contents there is air. Everything is exhausted.*

During the twentieth century, a number of studies of normal and obese individuals undergoing prolonged starvation, [2, 3] of populations under famine conditions, [4] and of patients suffering from disease-related undernutrition, [5] have given us a clearer picture of the relationship between weight loss or, more particularly, loss of body cell mass and deteriorating mental and physical function. The relationship between structure and function is not always linear [6] with some functions beginning to deteriorate early in the process of starvation, whereas others are relatively unimpaired until later. In some cases there may be a threshold above, which function is largely maintained but below which it falls rapidly [7]. Much depends upon the initial nutritional state of the subject and also on the rate at which tissue is lost [8]. Total starvation may have different effects from partial starvation, and there may also be a process of adaptation to chronically low intakes, as seen among the lean subsistence farmers of Asia. The relative proportions of energy and protein deficiency, the development of single or multiple deficiencies of minerals, trace elements and vitamins, and the

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presence of disease may all modify the consequences of partial starvation.

This chapter mainly outlines the consequences of disease-related undernutrition consequent upon intestinal failure, with supportive and relevant evidence from other studies of starvation. Much data about the consequences of undernutrition come from paediatric reports from developing countries and from work on young people with anorexia nervosa. The chapter also summarises the consequences of dehydration which are known to most clinicians but for which there are few publications to reference.

Survival

Hunger strikes have occurred since Roman times, and the suffragettes brought this method of protest to public attention in Britain in the early twentieth century. Mahatma Gandhi fasted at least 14 times but never for more than 21 days. The most striking example of total starvation in previously healthy young men without disease was provided by the 30 Irish Republican Army (IRA) hunger strikers of Northern Ireland [8]. In 60–70 days, they lost 38% of their body weight and one-third of them had died, allowing us to conclude that, in the absence of disease, previously normally nourished adults may survive weight loss of 35%, or approximately 60 days of total starvation (Fig. 1). Beyond this point mortality rises steeply. This time point is considerably reduced if a patient has already lost weight or has underlying sepsis or malignancy. One of the hunger strikers, who was suffering from a gunshot wound, survived for only 45 days, emphasizing the cumulative effect of illness and starvation. Studley in 1936 showed that if patients had lost more than

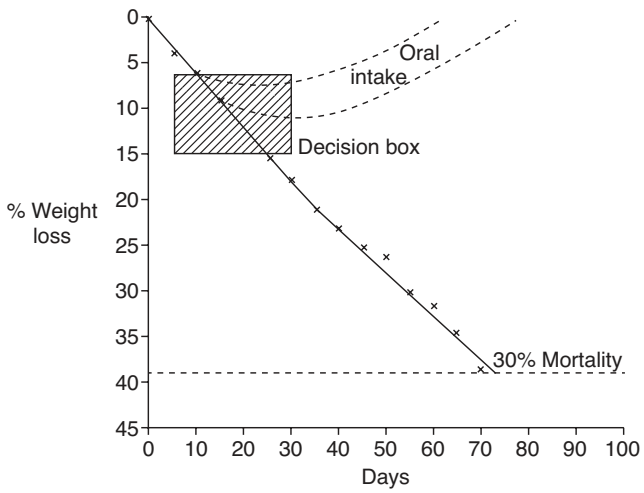

Fig. 1 Percentage weight loss and days after starting to starve. The decision box indicates the time when an oral intake will lead to a rapid recovery

20% of their body weight prior to surgery for peptic ulcers, they had a 33% mortality compared with 4% if less than 20% body weight had been lost [9].

Children are even more vulnerable because of the demands of growth and development and, during infancy, because of their high metabolic rate in relation to body size and high surface to volume ratio. The survival of a totally starved neonate may be no more than a few days. Studies among undernourished Asian children by Pelletier et al. suggested that their odds of dying from disease and undernutrition increased by a compound rate of more than 7% for each percentage point deterioration in weight for age [10]. There was also an exponentially increasing probability of morbidity as weight fell below 80% of normal for age.

The protective effect of obesity is illustrated by reports of survival by fat adults undergoing periods of starvation of 130–382 days [3]. This protective effect is not only due to greater fuel reserves, but also to the lower daily losses of nitrogen in relation to lean mass, implying a metabolic control mechanism. Whether obesity is similarly protective in the presence of intercurrent illness is unclear.

The extraordinary studies carried out by the Jewish physicians in the Warsaw ghetto in 1942 gives us further insight [4]. Most of the inhabitants had been on 800 kcal a day or less for many months and at the point where they were studied had already lost between 20% and 50% of their pre-war weight and weighed between 30 and 40 kg. One woman, for example, with a height of 1.52 m weighed 24 kg, giving a body mass index (BMI) of 10.3 kg/m^2. Many were suffering from intercurrent infections and most died within 3 weeks of the studies, although there were clearly some variations in the ability to survive starvation. A review suggests that the lower limit of BMI compatible with survival is approximately 10 kg/m^2 in women and 12 kg/m^2 in men [11]. These observations have important implications for clinical work. The MEED guidelines suggest admitting anyone with a BMI of less than 13 kg/m^2 [12]. It is not uncommon to be referred patients for nutritional support who have lost 20–35% of their body weight and in whom not only function but also survival is at stake. It can also be argued that, if parenteral nutrition is required for a total of 60 days or more because of continuing gastrointestinal dysfunction, such treatment is life-saving in the same sense that dialysis is life-saving in renal failure and ventilation in respiratory failure. The difference between these situations is not one of principle but of time-scale.

Undernutrition in Intestinal Failure

Undernutrition in intestinal failure (IF) can be considered as disease related malnutrition that occurs not only due to reduced intake/loss of appetite but through malabsorption, high GI losses, multiple surgical procedures, immobilisa-

tion and sepsis/inflammation all of which result in a loss of body mass. This is classified by ESPEN as 'disease related malnutrition with inflammation' [1]. A further subcategory 'chronic disease related malnutrition with inflammation' is considered synonymous with cachexia and can include that caused by inflammatory bowel diseases [1]. In this a less severe inflammatory response (CRP ≤40 mg/L) due to the disease itself over a prolonged period can lead to significant muscle wasting. A detailed nutritional assessment taking into account the degree and cause of inflammation is imperative for successful management of malnutrition in IF. In the presence of sepsis/inflammation nutritional status may not improve despite adequate energy being given. A study of 1950 medical patients found that those with a CRP level <100 mg/L did not respond well to nutrition support in terms of improvements in 30 day mortality or functional measures, whereas those with moderate (CRP 10–100 mg/mL) or low inflammation (CRP <10 mg/L) did [13]. This phenomenon forms a key part of the SNAP (Sepsis, Nutrition, Anatomy, Plan) principle of treating IF (chapter "Acute Surgical Intestinal Failure. Sepsis and Enterocutaneous Fistula(s)").

Due to malabsorption and high GI losses, IF patients are at a high risk of multiple micronutrient deficiencies. These have been demonstrated in paediatric studies and are likely to occur in adults. A study of long term paediatric IF patients having undergone transition from PN to oral nutrition demonstrated a high incidence of vitamin, mineral and trace element deficiencies, despite most (101 of the 138) children studied being on micronutrient supplements (Table 1) [14].

Zinc and copper are excreted in bile and deficiencies can therefore easily occur in patients with high output fistulas and stomas. Their levels should be interpreted with caution in acutely unwell patients; zinc is a negative acute phase reactant being bound to albumin and copper a positive one being bound to caeruloplasmin [15].

Table 1 Micronutrient deficiencies in children with IF [14]

Micronutrient	Deficiency %	p-value
Vitamin A	19.1	0.046
Vitamin B12	12.4	0.41
Vitamin D	30.1	0.56
Vitamin E	6.2	<0.001
Folate	0	1
Copper	7.7	0.14
Iron	61	0.003
Selenium	4.3	0.26
Magnesium	10.9	0.71
Phosphorus	8.8	0.88
Zinc	22.9	0.73
Anaemia	43.2	<0.001
Iron deficiency anaemia	29	0.21

Consequences of Undernutrition

General

A clear description of undernutrition/starvation comes from data in Western Holland in 1945. Complaints were of backache, aching legs, tingling of fingers and toes, periods of diarrhoea, nocturnal urinary frequency. Superficial haemorrhages, on skin on the back of the hands and on the face, hunger oedema, cyanosis of the skin of the extremities and rarely gangrene of the toes. A low temperature down to 35 °C was recorded, the heart rate was usually slow at 40 beats per min, the systolic blood pressure was down to 80 mmHg. There was often a red tender tip of tongue. The reflexes were normal, the urine testing showed no albumin, acetone or glucose. Anaemia was common (Hb 110 g/L) as was a leucopenia. Osteoporosis and kyphoscoliosis of the upper spine was observed [16].

Observations from hunger strikers state that they feel faint and dizzy. They learn to stand up very slowly and may become bed bound. Bradycardia and drop in blood pressure occur after even relatively short fasting. Orthostatic hypotension is present by about day 20 and may be disabling. Weakness and light headedness are common. Although thyroxine concentrations are maintained in fasting, triiodothyronine is converted rapidly to an inactive metabolite, thus reducing effective thyroid function. This will lead to weakness and a sensation of feeling cold. Abdominal pain has been described in around three quarters of hunger strikers [17–19].

Undernourished patients in hospital require high-dependency nursing, having an increased hospital stay with an increased morbidity and mortality compared with patients of normal weight having similar underlying clinical problems [20–24]. The consequences of undernutrition are summarised in Table 2.

Biochemical

In uncomplicated starvation, hepatic gluceonogenesis maintains blood glucose for use by the brain, blood cells and renal medulla. Muscle, some neural tissue, adrenal cortex and adipose tissue switch from using glucose to using fatty acids and ketones, derived from lipolysis, for energy. Muscle supplies alanine, glycine and lactate for hepatic gluceonogenesis, and glutamine as a source of energy to intestinal and lymphoid tissue. The glycogen reserves are rapidly utilised (6 h–3 days). As there is no carbohydrate for energy insulin levels fall and glucagon levels rise. The increased plasma glucagon levels (like GLP-1) induce a naturesis and thus weight loss. Energy starts (day 3 onwards) to be derived mainly from lipid via ketones. The sodium/potassium pump fails. Whole body phosphate, potassium and magnesium fall.

Table 2 Consequences of undernutrition

System with reduced function	Consequence
Psychological/neurological	Apathy/depression/anxiety/psychosis
Depletion of water soluble vitamins e.g. thiamine	Increased sleep time
	Reduced recent memory
	Loss of appetite
Muscle	Weakness, impaired rehabilitation
Skeletal	Chest infections
	Pressure sores
	DVT/pulmonary emboli
Cardiac	Bradycardia/low BP/orthostatic hypotension
	Cardiac failure, Cardiac atrophy
	Long QT interval, T wave abnormalities, sudden death
Gastrointestinal	Parotid hypertrophy, reduced gastric acid and pancreatic enzymes Mucosal atrophy with inflammatory infiltrate Gastric dilatation and slow gastric emptying, colonic stony Bacterial overgrowth/change in microbiota Increased translocation
	Reduced gut associated lymphoid tissue
	Reduced colonic sodium and water absorption Diarrhoea
	Sepsis/multi-organ failure
Liver	Steatosis, abnormal nuclear receptor PPARalpha signaling, synthetic function reduced (e.g. conjugated bile acids, complement proteins and albumin)
Endocrine (low sex, thyroid and growth hormones)	Poor growth
	Delayed puberty
	Amenorrhoea
	Infertility
	Osteopaenia/osteoporosis
Thermoregulation	Hypothermia
Repair mechanisms	Slow wound healing
	Pressure sores
Immune	Reduced lymphocyte count
	Infections
Fluid and electrolytes	Oedema
Metabolic	Low creatinine, urea, glucose, phosphate and potassium Faecal alpha 1 antitrypsin increased
Haematological	Anaemia, neutropaenia, thrombocytopaenia
Bone	Osteopaenia/osteoporosis

In the presence of sepsis, lipolysis is impaired and a further increase in muscle protein catabolism occurs. Protein is initially protected (making up only about 10% of the energy source) but in the latter stages, when fat stores have been exhausted there is catastrophic protein catabolism including from cardiac muscle and ultimately death [19].

Psychological and Neurological

Apathy/Depression

The mental changes associated with starvation, noted by the ancient Egyptians, were a striking feature of the studies carried out by the Warsaw physicians [4]. They reported: 'The most striking psychiatric finding is the prevalence of depression, even in young people. There is complete apathy, lack of interest, poor thinking, and even incoherence.'

In his introduction to the *Biology of Human Starvation*, [2] Sir Jack Drummond wrote of the famine in Holland in 1945:

> *Two impressions dominated: firstly the immense importance of the psychological aspects of inanition; secondly the comparative simplicity of the nutritional and biochemical problem. One of the curious and rather disconcerting psychological manifestations of starvation, seen repeatedly in Western Europe, was the unresponsive and uncooperative attitude of those to whom relief was brought. It disappeared without trace when calorie intakes rose above 1500 to 1800 a day…. An outstanding impression gained in Western Holland in 1945 was the importance and significance of the psychological consequences of food shortage…. From the grumbling and grousing that are inevitably provoked when the energy intake is deficient to the extent of 15–20%, to the apathy and dissolution of higher human qualities that come with severe starvation, there is a wide variety of psychological reactions to hunger, many of which are almost of themselves diagnostic of the level of calorie intake.*

In their study of normal young male volunteers undergoing semi-starvation for 24 weeks, Ancel Keys and his colleagues described not only the diminished physical powers which were associated with a loss of up to 23% of the body weight during that time, but also a rise in a depression score of 30% [2, 25]. This was slow to recover during the process of re-feeding. Indeed it took up to 4 months to return to normal. Similar observations have been made in prisoner of war camps, during the Russian famine of 1918–1921, among undernourished children in the Indian subcontinent and in Africa.

It is important to remember that patients suffering from disease-related undernutrition are often apathetic, depressed and awkward. These difficulties soon dissolve with appropriate nutritional care. The fatigue, which follows illness, may also be prolonged by undernutrition.

Intellectual Performance/Sleep

Intellectual performance changes little though short-term memory is reduced and sleep-time increased [2, 11, 26].

Appetite

Undernutrition causes a reduction in appetite. A vicious circle is thereby created which needs to be broken if normal oral intake is to be resumed. After 1–2 weeks of overnight nasogastric tube feeding, the appetite may be restored so that voluntary oral intake by day is increased [26]. This is sometimes very striking in some cases of inflammatory bowel disease. Once a certain weight has been reached, the appetite appears to be self-perpetuating and nutritional support may be discontinued. Interestingly it has been demonstrated that patients undoing upper gastrointestinal surgery such as oesophagectomy may have decreased appetite similar to that seen following bariatric surgery, mediated by enhanced release of satiety hormones [27].

Skeletal Muscle Function

Protein/energy malnutrition is characterized by muscle wasting with particular loss of the Type II fast-twitch fibres, which are prevalent in the respiratory muscles, including the diaphragm [28–33]. The poor function of skeletal muscle in the chest increases the risk of developing chest infections [34] including tuberculosis, and the resulting reduction in mobility increases the risk of deep venous thrombosis, pulmonary emboli and pressure sores [33–37].

In a study of ten patients with various gastrointestinal disorders, Lopez et al. [28] measured the function of the adductor pollicis muscle by electrical stimulation of the ulnar nerve and found that undernutrition resulted in increased muscle fatiguability and an altered pattern of muscle contraction and relaxation, all of which were reversible by nutritional supplementation. In a study of five morbidly obese female subjects, on a 400 kcal/day carbohydrate diet, Russell et al. [29, 30] showed similar changes in muscle function, significant reductions in muscle enzymes and a change in muscle histochemistry with type II fibre atrophy. Comparing the effect of undernutrition with the effects of surgery and sepsis, Brough et al. [31] found abnormal muscle function consequent upon sepsis, but the changes were easily distinguishable from subjects taking an inadequate diet. They found no effect on muscle function following trauma, surgery or steroid administration. They also showed that, following the initiation of parenteral nutritional support, there was a rapid initial improvement in muscle function within days, which occurred before any change in anthropometric variables or plasma proteins. Hill found similar changes in undernourished patients with inflammatory bowel disease [5, 6]. Measuring whole body protein by neutron activation techniques, he showed that a 20% reduction in total body protein, reflecting lean mass, was associated with little change in respiratory muscle strength, but beyond this there was a steep deterioration.

Over the first 5 days of nutritional support, both grip strength and peak expiratory flow rate rose from a mean of 65–75% of normal [5, 6]. This was followed by a much more gradual and sustained improvement over the ensuing weeks as body composition was restored. This again illustrates the two-phase response to refeeding. The first is associated with a rapid improvement in cellular function and the second with the much more gradual process of the restoration of body cell mass. Muscle function may also be seriously impaired with single or multiple electrolyte, mineral or micronutrient deficiencies, conditions that are not uncommon in patients with gastrointestinal disease. Hypokalaemia may be responsible for muscle weakness or even paralysis; selenium deficiency causes impairment of both myocardial and skeletal muscle function. Deficiencies of magnesium and of calcium decrease peristalsis but increase skeletal neuromuscular excitability and may cause fits.

Respiratory

Undernutrition impairs respiratory function, chiefly through its effect on respiratory muscles, impairing ventilation and the ability to cough and clear secretions [38–44]. It also reduces respiratory response to hypoxia [45, 46] and the ability to wean from ventilators [43]. In contrast, nutritional support improves ventilatory function and has facilitated weaning from ventilators. Respiratory complications of surgery, trauma or acute illness are one of the major consequences of under-nutrition. The terminal event in progressive starvation is nearly always bronchopneumonia [16].

One corollary of weak respiratory muscles is the inability to cope with the additional respiratory demands imposed by excessive caloric feeding, particularly of carbohydrate. Such patients may be rendered breathless by carbohydrate loads in

excess of 5 mg/kg/min or total energy intakes in excess of 40 kcal/kg/day, owing to increased oxygen consumption and CO_2 production [47, 48].

Cardiovascular and Sympathetic Nervous System

The Warsaw studies of advanced starvation [4] showed that this was associated with lower systolic and diastolic blood pressures at rest and in response to exercise. Bennett et al. showed that starvation, with sodium supplementation, for 48 h in healthy men was associated with a small drop in supine blood pressure, but after 10 min standing, there was a fall in systolic blood pressure of 15 mmHg with no change in the non-starved controls [49]. There is a reduction in heart rate, blood pressure and cardiac muscle mass; although this reduction in cardiac muscle is considerably less than that of skeletal muscle, it could predispose to cardiac failure [50, 51]. A prolonged QT interval may lead to ventricular arrhythmias [52]. The long QT interval is a function that takes the longest to recover on refeeding. Patients who have a postural fall in BP greater than 20 mmHg (or syncope), a bradycardia less than 40 bpm, and or a long QT internal are at risk of sudden death [12].

As sympathetic nervous system function is a major determinant of metabolic rate and as its function is reduced in undernourished patients, it is not surprising to find a markedly reduced resting metabolic expenditure in these patients. This must be borne in mind when estimating the nutritional requirements of depleted patients.

Gastrointestinal

The effects of undernutrition upon the gastrointestinal tract are complex and depend upon its severity. The Warsaw studies [4] demonstrated, in patients with more than 30% weight loss, an impairment of gastric acid secretion. Lack of luminal nutrition during parenteral nutrition, in studies on normal subjects or associated with undernutrition, may result in villous atrophy, impaired small bowel mucosal function and increased intestinal permeability [53–56]. Gut mucosal atrophy may be responsible for mucosal barrier dysfunction and bacterial translocation which may gives rise to an endotoxaemia, which with immune impairment, in turn may contribute to multi-organ failure [57]. The addition of antibiotics to therapeutic regimens for uncomplicated severe acute malnutrition in children is associated with a significant improvement in recovery and mortality rates [58]. The colon can be affected, losing its ability to reabsorb water and electrolytes, so diarrhoea may result [59, 60]. There may be altered intestinal flora with migration of bacteria proximally into the small bowel, thereby exacerbating malabsorption [61].

These changes may be seen during parenteral feeding when there is a lack of oral/enteral intake, or in segments of bowel that have been by-passed. The introduction of food, by the oral or enteral route, reverses these changes and accelerates adaptation of a retained ileum in patients with a short bowel. Particular substrates may be important. Soluble fibre and prebiotics such fructo-oligosaccharides, giving rise to short-chain fatty acids, may enhance both small and large bowel mucosal growth and function. Glutamine is an essential fuel for the mucosal epithelium and may enhance the protective effect of the gut-associated lymphatic tissue.

Pancreatic function has been studied in undernourished infants and in adults, and been shown to be impaired. Winter and colleagues [62–64] studied a series of patients with a mean BMI of 13.6 kg/m^2 before treatment and 16.5 kg/m^2 after nutritional support. They found that before treatment, pancreatic protein synthesis and enzyme production was reduced, so that 70% of gastric and pancreatic secretion was lost with consequent impairment of xylose and fat absorption. All parameters were restored towards normal by refeeding. They confirmed findings of impaired gastric acid secretion, as well as pancreatic amylase and trypsin secretion.

Malnutrition-related enteropathy is well described though can be difficult to differentiate from environmental enteric dysfunction (EED) ("tropical sprue"). It is characterised by villous atrophy, crypt hyperplasia, loss of tight junctions, and an influx of inflammatory cells into the intestinal mucosa [65]. This is why care must be taken in interpreting small bowel biopsies (usually to determine if there is an enteric myopathy or neuropathy) in the presence of severe malnutrition.

Gastric emptying for liquid and solid is delayed in undernourished patients with anorexia nervosa [66, 67]. Gastric dilatation, peptic ulcer, acid reflux and colonic atony leading to constipation have been reported.

Malnourished patients with Crohn's have a worse disease progression than those who are normally nourished and indeed feeding and increasing the weight of malnourished patients with Crohn's disease reduces the inflammation [68].

The microbiota of malnourished children change to being less diverse and there being an increased relative abundance of pathogenic genera within the phylum Proteobacteria (*Enterobacter, Escherichia, Klebsiella,* and *Shigella*), and a decreased relative abundance of genera containing beneficial bacteria (*Bifidobacterium, Butyrivibrio, Faecalibacterium, Lactobacillus*, and *Roseburia*) [69].

Immunological

In undernutrition, many aspects of immune function, particularly of cell-mediated immunity, are impaired and increased susceptibility to infection is well documented in adults, [4,

70–73] children [74, 75] and the elderly [76]. Conversely, one of the consistent features of positive trials of nutritional support is a reduction in postoperative and other infections [74–80]. Much of the tissue involved in immune responses lies in the gastrointestinal tract and the gut-associated lymphatic tissue. The provision of luminal nutrients and special substrates such as glutamine may have their beneficial effects partly through providing essential nutrients to this tissue. It is important, however, not to over-simplify the situation, since the relationship between nutritional status and immune competence is a complex one and may vary according to the clinical condition and the nutritional deficiencies involved. As well as protein-energy undernutrition, mineral and micronutrient deficiencies may also impair immunity. Good et al. [73] for example, found zinc to be an important factor for the maintenance of cell-mediated immunity.

Immune competence, as measured by delayed cutaneous hypersensitivity (DCH), is affected by severe protein-energy malnutrition. While it is true that immune competence as measured by DCH is reduced in protein-energy malnutrition, several diseases [53] and drugs influence this measurement making it a poor predictor of protein-energy malnutrition in sick patients. The following factors non-specifically alter DCH in the absence of protein-energy malnutrition:

1. Infections (viral, bacterial and granulomatous)
2. Uraemia, cirrhosis, hepatitis, trauma, burns and haemorrhage
3. Steroids, immunosupressants, cimetidine, warfarin and perhaps aspirin
4. General anaesthesia and surgery.

Hence in the critically sick patient many factors can alter DCH and render it valueless in assessing the state of nutrition. Meakins et al. [54] have shown that simply draining an abscess can reverse anergy. Immunity is therefore neither a specific indicator of protein-energy malnutrition nor is it easily studied [55].

Thermoregulation

The Warsaw physicians observed lower than normal body temperatures in their patients, as well as failure to develop a fever in response to typhoid or tuberculosis [3]. Similar changes may be seen among the undernourished and the elderly in routine hospital practice. Bastow et al. [81] observed low core temperatures in winter (<36 °C) among elderly women admitted with fractured femur, whose anthropometric indices were more than two standard deviations below the reference range. In contrast, the normally nourished fractured femur patients had core temperatures in excess of 36 °C on admission. When undernourished individuals were put in a cooling suit, Fellows et al. [82] found normal vasoconstriction but no increase in thermogenesis in response to the challenge. Mansell et al. [83] showed, in younger subjects, that the thermogenic response to cooling was restored when body composition was returned to normal by nutritional support. They also showed [84] that the vasoconstrictor response to cooling was impaired in normal subjects who fasted for 48 h. Both short-term starvation and weight loss, therefore, impair thermoregulation but by different mechanisms.

In adults, with a temperature of 34–36 °C: they will feel cold and will move around more, but may become withdrawn or aggressive. At a temperature of 33–34 °C: they may stagger and become confused and drowsy, but strangely the patient may feel warm and remove clothes. At a temperature of 26–32 °C, coma may occur and at less than 26 °C death may occur (sometimes after ventricular fibrillation) [12].

Thus undernourished patients are prone to hypothermia and the recognition of sepsis/fever may be difficult as their temperature tends to be lower than normal.

Wound Healing

The metabolic response to injury in which energy and substrates are mobilized from within the body to meet the demands of illness and injury must have a survival value to have evolved at all. The paradox is that, when taken to extremes, it may threaten survival. One of the crucial features of the response is the mobilization of nitrogen from muscle to meet metabolic requirements. This feature was blunted in traumatized rats that had previously been exposed to a low protein diet [85].

There is an impairment of wound healing [86–92]. Windsor et al. [86] showed, in man, that a low preoperative food intake impaired wound healing. Haydock and Hill [87] also documented impaired wound healing in undernourished surgical patients and further observed that this can occur with quite modest degrees of undernutrition. Pressure sores are also more likely to develop in undernourished patients and are slower to heal [88]. Nutritional support may contribute to more rapid healing. An adequate supply of minerals and micronutrients is necessary for wound healing, including vitamins A, B, C, D, E and K [89]. Zinc is a cofactor for collagen formation, [89] and zinc deficiency has been associated with failed wound healing which is restored to normal by zinc supplementation [90, 91].

Endocrine and Bone

Anorexia nervosa with a BMI below 17 kg/m^2 is characterized by amenorrhoea with subdued hypothalamic function

and secondary effects upon the pituitary and the ovaries or testes. Exactly the same changes are seen in patients who are cachectic as a result of gastrointestinal disease. Low sex and growth hormone coupled with increased cortisol and glucagon levels reduce muscle mass, strength and energy, as well as reducing bone density. We have observed a young patient with Crohn's disease to have a bone density three standard deviations below the mean for his age and a low serum testosterone. These were both restored to normal within 2 years, once his chronic state of undernutrition had been adequately treated. Protein/energy malnutrition may also affect bone structure; osteoporosis is characteristically more prevalent in the undernourished. Malabsorption of fat-soluble vitamins may result in vitamin D deficiency and osteomalacia.

Growth and Development

Undernutrition in childhood leads to reduced growth velocity which may be restored by nutritional intervention. However, prolonged undernutrition permanently impairs achievement of genetic potential for height, which cannot be recovered even with optimal nutrition [93, 94]. Puberty is also delayed since the pituitary gonadal axis fails to function normally and it is a common experience to find impaired growth and development among adolescents with severe gastrointestinal disease and malabsorption.

Fluid and Electrolytes

Starvation and subsequent refeeding have profound effects on fluid and electrolyte balances. Intracellular concentrations of key ions such as sodium and potassium are maintained by cell membrane pumps. Since cell membrane pumps are activated by insulin and account for approximately a third of resting energy expenditure [95], there is likely to be a significant reduction in their activity during starvation which is responsible for depletion of intracellular ions such as potassium, magnesium and phosphate. 98% of body potassium is intracellular [96] and starvation can lead to a significant reduction in whole body potassium that is not reflected in plasma levels which may remain normal [97].

Oedema has been observed during refeeding [4, 98] and may partially be due to reactivation of cell membrane pumps leading to a loss of accumulated sodium and water from cells, with subsequent failure to excrete this load due to the effects of insulin and potassium depletion on the kidney [99]. Since sodium excretion more or less ceases in refeeding [100] it has been recommended that sodium provision be restricted to <1 mmol/kg and fluid to around 20 mL/kg/day, [101] especially as malnourished patients who may have cardiac atrophy and risk of cardiac failure [102]. Extreme caution should be taken when providing electrolytes or medicines in 0.9% saline as the sodium load and constriction of renal arteries caused by hyperchloraemia increase the risk fluid overload and oedema [103, 104]. Bowel oedema may lead to ileus and poor healing of anastomoses and fistulae [104, 105]. However since IF patients may have high GI losses of fluid, sodium, chloride, potassium and magnesium, a careful daily assessment of fluid and electrolyte requirements is imperative to ensure the correct composition of maintenance fluids and those used to replace GI losses [106].

Resistant oedema can be encountered in acutely unwell IF patients and unusual causes such as beri beri may need to be excluded. A slightly negative sodium and fluid balance should be the target with provision of adequate potassium [107]. Whole body potassium depletion can lead difficultly in excreting sodium if there is insufficient potassium to exchange in the kidney, thus ensuring patients get adequate amounts is imperative and at least maintenance amounts should be given even if plasma levels are normal [106, 107]. Strict fluid balance recording is essential and is important to take into account the effect of fluid balance, including GI losses, on body weight and its use for nutritional assessment.

Albumin

In the past a low serum albumin has been considered a marker of malnutrition. Although oedema is often seen in hospitalised malnourished patients it is a common misconception that this is due to starvation or low protein intake leading to hypoalbuminaemia [107]. Starvation does not cause hypoalbuminaemia, [108, 109] a point illustrated by patients with anorexia nervosa who may have a very low BMI but neither low albumin nor oedema [110, 111].

The concentration of serum albumin represents the net summation of many events—albumin synthesis, albumin degradation, albumin losses from the body, exchange between intra- and extravascular albumin compartments, and the volume in which albumin is distributed. Albumin is highly water-soluble and resides in the extracellular space. The total body pool of albumin in a normal 70 kg man is about 300 g (3.5–5.3 g/kg). Approximately one-third of the total pool constitutes the intravascular compartment and two-thirds the extravascular compartment [112]. The concentration of albumin in blood is greater than that in lymph or other extracellular fluids, and the ratio of intravascular to extravascular albumin concentration varies from tissue to tissue. Within 30 min of initiating albumin synthesis, the hepatocyte secretes albumin into the bloodstream [113]. Once albumin is released into plasma, its half-life is 20 days. During steady state conditions ~14 g of albumin (200 mg/kg) are produced and degraded daily. Thus, each day about 5% of the total albumin pool is degraded and replaced by newly synthesized albumin. Equilibration of albumin in the intra-

vascular compartment is rapid and occurs within minutes after albumin enters the bloodstream. Equilibration between intra- and extravascular albumin occurs more slowly. Every hour about 5% of the plasma albumin pool exchanges with extravascular albumin so that the total plasma albumin mass exchanges with extravascular albumin each day. Because the rate of equilibration varies among tissues complete equilibration may take 7–10 days.

Protein-calorie malnutrition causes a decrease in the rate of albumin synthesis because adequate nutrient intake is important for polysomal aggregation and maintenance of cellular RNA levels needed for protein synthesis. Within 24 h of fasting, the rate of albumin synthesis decreases markedly [114]. However, a short-term reduction in albumin synthesis has little impact on albumin levels because of a large pool size, compensatory decrease in the rate of degradation, a transfer of extravascular albumin to the intravascular compartment and an increase in colonic urea salvage [115]. Indeed, plasma albumin concentration may actually increase during short-term fasting largely because of contraction of intravascular water [116].

Prolonged protein-calorie restriction induced experimentally in human volunteers [2] or observed clinically in patients with anorexia nervosa [111] causes marked reductions in body weight but little change in plasma albumin concentration. A protein-deficient diet with adequate calories in elderly persons causes a decrease in lean body mass and muscle function without a change in plasma albumin concentration [117].

Hospitalized patients may have low levels of plasma albumin for several reasons. Inflammatory disorders cause a decrease in albumin synthesis, [118] an increase in albumin degradation, [119] and an increase in albumin transcapillary losses [120]. Gastrointestinal and some cardiac diseases increase albumin losses through the gut, while renal diseases may cause considerable albuminuria. Wounds, burns and peritonitis cause major losses from the injured surface and in certain circumstances an increase in albumin losses through the gut, kidneys, or damaged tissues. Because the exchange between intra-and extravascular albumin is so large, even small changes in the percentage of exchange can cause significant changes in plasma albumin levels. The normal rate of albumin exchange between intra- and extravascular compartments is more than ten times the rate of albumin synthesis or degradation. During serious illness vascular permeability increases dramatically. Albumin losses from plasma to the extravascular space were increased twofold in patients with cancer cachexia and threefold in patients with septic shock. Plasma albumin levels will not increase in stressed patients until the inflammatory stress remits and is not affected by nutritional intake. For example, albumin levels fail to increase in patients with cancer after 21 days of intensive nutritional therapy [121] and in nursing home patients after enteral feeding through a gastrostomy [122]. Rapid drops in plasma levels can be seen in sick individuals due to the inflammatory response leading to increased vascular permeability and loss of albumin to the extravascular compartment [108, 109]. In hospital excessive provision of high sodium and chloride IV fluids may contribute to this. Lobo et al found that the rapid IV infusion of 2000 mL 0.9 saline led to a 20% drop in serum albumin that did not recover over the 6 h study period (indeed it took 2 weeks to return to normal), with the authors concluding that this was not only due to dilution but to increased loss of albumin to the extravascular compartment [123].

While a very poor nutritional marker, albumin is a good marker of disease severity, and moves inversely as the as the acute phase reactants (e.g. CRP) rise [124]. In a recent Malaysian IF study, low BMI and serum albumin and correlated with poor healing of enterocutaneous fistulae and increased mortality [125]. It is also a good marker of saline excess.

Prealbumin

Prealbumin is a transport protein for thyroid hormones and exists in the circulation as a retinol-binding–prealbumin complex [126]. The turnover rate of this protein is rapid with a half-life of 2–3 days. It is synthesized by the liver and is catabolized partly in the kidneys. Protein-energy malnutrition reduces the levels of prealbumin and refeeding restores levels [127]. However, prealbumin levels fall without protein-energy malnutrition in infections [128, 129] and in response to cytokine [130] and hormone infusion [131]. Renal failure increases [132] while liver failure may cause decreased levels. Although, prealbumin is responsive to nutritional changes it is influenced by several disease-related factors making it unreliable as an index of nutritional status in patients.

Serum Cholesterol

Low levels are seen in undernourished patients. However, very low levels are seen in patients with liver disease, renal disease and malabsorption. In addition, low levels correlate with mortality [133, 134].

Refeeding

Functional improvements in cell function occurs long before any gain in tissue mass. Muscle function may improve rapidly (15% over the first 5 days) with refeeding, but the restoration of muscle mass, unlike that of adipose tissue, is very slow [2, 8]. Functional improvements should be seen as the initial goal of nutrition support, with restoration of body

composition a longer term aim that can be achieved once inflammatory issues have been treated (chapter "Refeeding Problems").

Under Hydration/Dehydration

Most of the human body (65%) is water which is needed for almost every physiological process. These include regulating body temperature (through sweating and breathing), aiding digestion (through secretions), lubrication/moistening functions and helping eliminate waste products/toxins. When exercising in a hot environment, the human body can lose 1.5–3 L of water every hour from sweating. Another 0.2–1.5 L can be lost as moisture in exhaled breath, depending on the humidity of the surrounding air.

Survival with Dehydration

Survival is often quoted as 2 weeks but will vary according to ambient temperature, degree of activity, illness/losses (including sepsis) (sweating). In a previously healthy adult, death follows the loss of 12–15 L of body water. In the very young, the very old, or the debilitated, death occurs at a lower level of dehydration. As it is unethical to perform experiments on normal subjects going without water, the only information about survival time can be gained from newspaper reports of survival times after people are trapped or buried alive without water. From this it appears that it is possible to survive without food and drink for 8–21 days [135, 136].

Symptoms and Signs of Dehydration

Initially with mild dehydration a person feels thirsty (occurs when cells have lost about 1% of their intracellular water), and has a dry mouth (may not be the case in the elderly). They may complain of sluggishness, lack of energy, difficulty swallowing, stiff joints, cramps, headache, dizziness, syncope and confusion.

The signs of dehydration include dry wrinkled skin, sunken eyes often with a dark ring around them, dry mucus membranes, a tachycardia, postural fall in systolic blood pressure. Urine output may be low but as long as more than 30 mL per hour the kidneys can excrete nitrogenous and non-nitrogenous molecules. If however 8% of the total body water has been lost (about 4 L) then the blood urea and creatinine are likely to rise. Blood viscosity also increases. As dehydration progresses sweating stops and body temperature rises, as blood pressure reduces due to low blood volume cardiogenic shock may occur. Because of their relatively larger skin surface-to-volume ratio, children are especially susceptible to rapid overheating and dehydration.

References

1. Cederholm, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017;36(1):49–64.
2. Keys A, Brozek J, Henschel A, Michelsen O, Taylor HL. The biology of human starvation. Minneapolis, MN: University of Minnesota Press; 1950.
3. Elia M. Effect of starvation and very low calorie diets on protein-energy interrelationships in lean and obese subjects. In: Scrimshaw NS, Schürch B, editors. Protein-energy interactions. Lausanne: Nestlé Foundation; 1992.
4. Winick M, editor. Hunger disease: studies by the Jewish physicians in the Warsaw Ghetto. New York: Wiley; 1979.
5. Hill GL. Disorders of nutrition and metabolism in clinical surgery. Edinburgh: Churchill Livingstone; 1993.
6. Kinney JM. The influence of calorie and nitrogen balance on weight loss. Br J Clin Pract. 1988;42(Suppl 63):114–20.
7. Hill GL. Body composition research: implications for the practice of clinical nutrition. J Parenter Enteral Nutr. 1992;16:197–218.
8. Allison SP. The uses and limitations of nutritional support. Clin Nutr. 1992;11:319–30.
9. Studley HO. Percentage of weight loss. A basic indicator of surgical risk in patients with chronic peptic ulcer. JAMA. 1936;106:458–60.
10. Pelletier DL, Frongillo EA, Habicht JP. Epidemiological evidences for a potentiating effect of malnutrition on childhood mortality. Am J Public Health. 1993;83:1130–3.
11. Henry CJK. Body mass index and the limits of human survival. Eur J Clin Nutr. 1990;44:329–35.
12. Nicholls D (chair). Medical emergencies in eating disorders: guidance on recognition and management (replacing MARSIPAN and Junior MARSIPAN) 2 May 2022. The Royal College of Psychiatrists College report CR233.
13. Merker M, Felder M, Gueissaz L, Bolliger R, Tribolet P, Kägi-Braun N, Gomes F, Hoess C, Pavlicek V, Bilz S, Sigrist S, Brändle M, Henzen C, Thomann R, Rutishauser J, Aujesky D, Rodondi N, Donzé J, Stanga Z, Mueller B, Schuetz P. Association of baseline inflammation with effectiveness of nutritional support among patients with disease-related malnutrition: a secondary analysis of a randomized clinical trial. JAMA Netw Open. 2020;3(3):e200663.
14. Ubesie AC, Kocoshis SA, Mezoff AG, Henderson CJ, Helmrath MA, Cole CR. Multiple micronutrient deficiencies among patients with intestinal failure during and after transition to enteral nutrition. J Pediatr. 2013;163(6):1692–6.
15. Shenkin. Trace elements and inflammatory response: implications for nutritional support. Nutrition. 1995;11(1 Suppl):100–5.
16. Burger GCE, Sandstead HR, Drummond J. Starvation in West Holland: 1945. Lancet. 1945;246:282–3.
17. Frommel D, Gautier M, Questiaux E, Schwarzenberg L. Voluntary total fasting: a challenge for the medical community. Lancet. 1984;1:1451–2.
18. Kalk WJ, Felix M, Snoey ER, Veriawa Y. Voluntary total fasting in political prisoners: clinical and biochemical observations. S Afr Med J. 1993;83:391–4.
19. Peel M. Hunger strikes. BMJ. 1997;315:829.
20. Weinsier RL, Hunker EM, Krumdieck CL, Butterworth CE Jr. A prospective evaluation of general medical patients during the course of hospitalization. Am J Clin Nutr. 1979;32:418–26.
21. Walesby RK, Goode AW, Spinks TJ, Herring A, Ranicar ASO, Bentall HH. Nutritional status of patients requiring cardiac surgery. J Thorac Cardiovasc Surg. 1979;77:570–6.

22. Warnold I, Lundholm K. Clinical significance of preoperative nutritional status in 215 noncancer patients. Ann Surg. 1984;199:299–305.
23. Windsor JA, Hill GL. Weight loss with physiologic impairment: a basic indicator of surgical risk. Ann Surg. 1988;207:290–6.
24. Sullivan DH, Patch GA, Walls RC, Lipschitz DA. Impact of nutrition status on morbidity and mortality in a select population of geriatric rehabilitation patients. Am J Clin Nutr. 1990;51:749–58.
25. Brozek J. Effects of generalised malnutrition on personality. Nutrition. 1990;6:389–95.
26. Leyton GB. Effects of slow starvation. Lancet. 1946;2(6412):73–9.
27. Elliott JA, Docherty NG, Murphy CF, Eckhardt HG, Doyle SL, Guinan EM, Ravi N, Reynolds JV, le Roux CW. Changes in gut hormones, glycaemic response and symptoms after oesophagectomy. Br J Surg. 2019;106(6):735–46.
28. Lopez J, Russell DM, Whitwell J, Jeejeebhoy KN. Skeletal muscle function in malnutrition. Am J Clin Nutr. 1982;36:602–10.
29. Russell DM, Leiter LA, Whitwell J, Marliss EB, Jeejeebhoy KN. Skeletal muscle function during hypocaloric dieting and fasting: a comparison with standard nutritional assessment parameters. Am J Clin Nutr. 1983;37:133–8.
30. Russell DM, Walker PM, Leiter LA, et al. Metabolic and structural changes in muscle during hypocaloric dieting. Am J Clin Nutr. 1984;39:503–13.
31. Brough W, Horne G, Blount A, Irving MH, Jeejeebhoy KN. Effects of nutrient intake, surgery, sepsis, and long term administration of steroids on muscle function. Br Med J. 1986;293:983–8.
32. Russell DM, Pendergast PJ, Darby PL, Garfinkel PE, Whitwell J, Jeejeebhoy KN. A comparison between muscle function and body composition in anorexia nervosa: the effect of refeeding. Am J Clin Nutr. 1983;38:229–37.
33. Pichard C, Jeejeebhoy KN. Muscle dysfunction in malnourished patients. Q J Med. 1988;260:1021–45.
34. Windsor JA, Hill GL. Risk factors for post-operative pneumonia: the importance of protein depletion. Ann Surg. 1988;208:209–14.
35. Allman RM, Laprade CA, Noel LB, Walker JM, Moorer CA, Dear MR, Smith CR. Pressure sores among hospitalized patients. Ann Intern Med. 1986;105:337–42.
36. Pinchcofsky-Devin GD, Kaminski MV. Correlation of pressure sores and nutritional status. J Am Geriatr Soc. 1986;34:435–40.
37. Holmes R, MacChiano K, Jhangiani SS, Agarwal NR, Savino JA. Combating pressure sores—nutritionally. Am J Nurs. 1987;87:1301–3.
38. Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. Am Rev Respir Dis. 1982;126:5–8.
39. Arora NS, Rochester DF. Effect of body weight and muscularity on human diaphragm muscle mass, thickness and area. J Appl Physiol Resp Envir Exerc Physiol. 1982;52:64–70.
40. Kelsen SG, Ference M, Kapoor S. Effects of prolonged undernutrition on structure and function of the diaphragm. J Appl Physiol. 1985;58:1354–9.
41. Lewis MI, Sieck GC, Fournier M, Belman MJ. Effect of nutritional deprivation on diaphragm contractility and muscle fibre size. J Appl Physiol. 1986;60:596–603.
42. Lewis MI, Sieck GC. Effect of acute nutritional deprivation on diaphragm structure and function. J Appl Physiol. 1990;68:1938–44.
43. Kelly SM, Rosa A, Field S, Coughlin M, Shizgal HM, Macklem PT. Inspiratory muscle strength and body composition in patients receiving total parenteral nutrition therapy. Am Rev Respir Dis. 1984;130:33–7.
44. Murciano D, Armengaud MH, Rigaud D, Pariente R, Aubier M. Effect of renutrition on respiratory and diaphragmatic function in patients with severe mental anorexia. Am Rev Resp Dis. 1990;141:A547.
45. Doekel RC Jr, Zwillich CW, Scroggin CH. Clinical semistarvation: depression of hypoxic ventilatory response. N Engl J Med. 1976;295:358–61.
46. Bassili HR, Deitel M. Effect of nutritional support on weaning patients off mechanical ventilation. J Parenter Enteral Nutr. 1981;5:161–3.
47. Askanazi J, Carpentier YA, Elwyn DH, et al. Influence of total parenteral nutrition on fuel utilisation in injury and sepsis. Ann Surg. 1980;191:40–6.
48. Burke JF, Wolfe RR, Mullany CJ, Mathews DE, Bier SM. Glucose requirements following burn injury. Parameters of optimal glucose infusion and possible hepatic and respiratory abnormalities following excessive glucose intake. Ann Surg. 1979;190:274–85.
49. Bennett T, MacDonald IA, Sainsbury R. The influence of acute starvation on the cardiovascular responses to lower body sub-atmospheric pressure or to standing in man. Clin Sci. 1984;66:141–6.
50. Heymsfield SB, Bethel RA, Ansley JD, Gibbs DM, Felner JM, Nutter DO. Cardiac abnormalities in cachectic patients before and during nutritional repletion. Am Heart J. 1978;95:584–94.
51. Gottdiener JS, Gross HA, Henry WL, Borer JS, Ebert MH. Effects of self-induced starvation on cardiac size and function in anorexia nervosa. Circulation. 1978;58:425–33.
52. Isner JM, Sours HE, Paris AL, Ferrans VJ, Roberts WC. Sudden, unexpected death in avid dieters using the liquid-protein-modified-fast diet. Observations in 17 patients and the role of the prolonged QT interval. Circulation. 1979;60:1401–12.
53. Elia M, Goren A, Behrens R, Barber RW, Neale G. Effect of total starvation and very low calorie diets on intestinal permeability in man. Clin Sci. 1987;73:205–10.
54. Jackson WD, Grand RJ. The human intestinal response to enteral nutrients: a review. J Am Coll Nutr. 1991;10:500–9.
55. Buchman AL, Moukarzel AA, Bhuta S, et al. Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. J Parenter Enteral Nutr. 1995;19:453–60.
56. Groos S, Hunefeld G, Luciano L. Parenteral versus enteral nutrition; morphological changes in adult human intestinal mucosa. J Submicrosc Cytol Pathol. 1996;28:61–74.
57. Deitch EA, Winterton J, Li M, Berg R. The gut as a portal of entry for bacteremia: role of protein malnutrition. Ann Surg. 1987;205:681–90.
58. Trehan I, Goldbach HS, LaGrone LN, Meuli GJ, Wang RJ, Maleta KM, Manary MJ. Antibiotics as part of the management of severe acute malnutrition. N Engl J Med. 2013;368(5):425–35.
59. Roediger WEW. Famine, fibre, fatty acids and failed colonic absorption: does fibre fermentation ameliorate diarrhoea? J Parenter Enteral Nutr. 1994;18:4–8.
60. Roediger WEW. Metabolic basis of starvation diarrhoea: implications for treatment. Lancet. 1986;I:1082–4.
61. Berg RD. Translocation of indigenous bacteria from the intestinal tract. In: Hentges DJ, editor. Human intestinal microflora in health and disease. New York: Academic Press; 1983.
62. Winter TA, Ogden JM, Lemmer E, Bridger SA, Tigler-Wybrandi NA, Young GO, O'Keefe SJD. Assessment of entero-pancreatic function in normal and malnourished subjects during enteral feed stimulation. S Afr Med J. 1994;84:440.
63. Winter TA, De Coito P, O'Keefe SJD, Bridger S, Marks T. Entero-pancreatic function in patients with severe malnutrition due to anorexia. Gut. 1997;41(Suppl 3):A14.
64. Winter TA, Ogden JM, De Coito P, O'Keefe SJD, Marks T. The vicious circle of malnutrition, mal-digestion and malabsorption: response to refeeding. S Afr Med J. 1997;87:1245.
65. Attia S, Feenstra M, Swain N, Cuesta M, Bandsma RHJ. Starved guts: morphologic and functional intestinal changes in malnutrition. J Pediatr Gastroenterol Nutr. 2017;65(5):491–5.

66. Robinson PH, Clarke M, Barrett J. Determinants of delayed gastric emptying in anorexia nervosa and bulimia nervosa. Gut. 1988;29(4):458–64.
67. Norris ML, Harrison ME, Isserlin L, Robinson A, Feder S, Sampson M. Gastrointestinal complications associated with anorexia nervosa: a systematic review. Int J Eat Disord. 2016;49(3):216–37.
68. Harries AD, Jones LA, Danis V, Fifield R, Heatley RV, Newcombe RG, Rhodes J. Controlled trial of supplemented oral nutrition in Crohn's disease. Lancet. 1983;1(8330):887–90.
69. Velly H, Britton RA, Preidis GA. Mechanisms of cross-talk between the diet, the intestinal microbiome, and the undernourished host. Gut Microbes. 2017;8(2):98–112.
70. Chandra RK. Immunodeficiency in undernutrition and overnutrition. Nutr Rev. 1981;39:225–31.
71. Dominioni L, Dionigi R. Immunological function and nutritional assessment. J Parenter Enteral Nutr. 1987;11(Suppl):70S–2S.
72. Brookes GB, Clifford P. Nutritional status and general immune competence in patients with head and neck cancer. J R Soc Med. 1981;74:132–9.
73. Good RA, Lorenz E. Nutrition and cellular immunity. Int J Immunopharmacol. 1992;14:361–6.
74. Abbassy AS, el-Din MK, Hassan AI, et al. Studies of cell mediated immunity and allergy in protein-energy malnutrition. I: cell-mediated delayed hypersensitivity. J Trop Med Hyg. 1974;77:13–7.
75. Abbassy AS, el-Din MK, Hassan AI, Aref GH, Hammad SA, el-Araby II, el-Din AA. Studies of cell mediated immunity and allergy in protein-energy malnutrition: II. Immediate hypersensitivity. J Trop Med Hyg. 1974;77:18–21.
76. Lesourd B. Protein undernutrition as the major cause of decreased immune function in the elderly: clinical and functional implications. Nutr Rev. 1995;53:S86–94.
77. Collins JP, Oxby CB, Hill GL. Intravenous amino acids and intravenous hyperalimentation as protein sparing therapy after major surgery. Lancet. 1978;1:788–91.
78. Kudsk KA, Minard G, Croce MA, et al. A randomized trial of isonitrogenous enteral diets after severe trauma. An immune-enhancing diet reduces septic complications. Ann Surg. 1996;224:531–43.
79. Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. Gut. 1996;39:833–5.
80. Von Meyenfeldt MF, Meijerink WJHJ, Rouflart MMJ, Buil-Maassen MTHJ, Soeters PB. Perioperative nutritional support: a randomised clinical trial. Clin Nutr. 1992;11:180–6.
81. Bastow MD, Rawlings J, Allison SP. Undernutrition, hypothermia and injury in elderly women with fractured femur: an injury response to altered metabolism? Lancet. 1983;1:143–6.
82. Fellows IW, Macdonald IA, Bennett T, Allison SP. The effect of undernutrition on thermoregulation in the elderly. Clin Sci. 1985;69:525–32.
83. Mansell PI, Fellows IW, Macdonald IA, Allison SP. Defect in thermoregulation in malnutrition reversed by weight gain. Physiological mechanisms and clinical importance. Q J Med. 1990;280:817–29.
84. Macdonald IA, Bennett T, Sainsbury R. The effect of a 24-hour fast on the thermoregulatory responses to graded cooling in man. Clin Sci. 1984;67:445–52.
85. Munro HN. In: Munro HN, Allison JB, editors. Mammalian protein metabolism. New York: Academic Press; 1964.
86. Windsor JA, Knight GS, Hill GL. Wound healing response in surgical patients: recent food intake is more important than nutritional status. Br J Surg. 1988;75:135–7.
87. Haydock DA, Hill GL. Impaired wound healing in surgical patients with varying degrees of malnutrition. J Parenter Enteral Nut. 1986;10:550–4.
88. Ek AC, Unosson M, Larsson J, von Schenck H, Bjurulf P. The development and healing of pressure sores related to the nutritional state. Clin Nutr. 1991;10:245–50.
89. Goodson WH, Hunt TK. Wound healing. In: Kinney JM, Jeejeebhoy KN, Hill GL, Owen OE, editors. Nutrition and metabolism in patient care. Philadelphia: WB Saunders; 1988. p. 635–42.
90. Sandstead HH, Henriksen LK, Greger JL, Prasad AS, Good RA. Zinc nutriture in the elderly in relation to taste activity, immune response and wound healing. Am J Clin Nutr. 1982;36:1046–59.
91. Pories WJ, Henzel JH, Rob CG, Strain WH. Acceleration of wound healing in man with zinc sulphate given by mouth. Lancet. 1967;1:121–4.
92. Shukla VK, Roy SK, Kumar J, Vaidya MP. Correlation of immune and nutritional status with wound complications in patients undergoing abdominal surgery. Am Surg. 1985;51:442–5.
93. Widdowson EM. Intra-uterine growth retardation in the pig. 1. Organ size and cellular development at birth and after growth to maturity. Biol Neonate. 1971;19:329–40.
94. Moy RJD, Smallman S, Booth IW. Malnutrition in a UK children's hospital. J Hum Nutr Dietet. 1990;3:93–100.
95. Rolfe DF, Brown GC. Cellular energy utilization and molecular origin of standard metabolic rate in mammals. Physiol Rev. 1997;77:731–58.
96. Walker HK, Hall WD, Hurst JW, editors. Clinical methods: the history, physical, and laboratory examinations. Chapter 195 Serum potassium. 3rd edition. Boston: Butterworths; 1990. www.ncbi.nlm.nih.gov/books/NBK307.
97. National Collaborating Centre for Acute Care. Guideline 32. Nutrition support in adults. Oral nutrition support, enteral tube feeding and parenteral nutrition. 2006. www.nice.org.uk/guidance/cg32/evidence/full-guideline-194889853.
98. Tey HL, Lim SC, Snodgrass AM. Refeeding oedema in anorexia nervosa. Singapore Med J. 2005;46(6):308–10.
99. Friedberg CE, van Buren M, Bijlsma JA, Koomans HA. Insulin increases sodium reabsorption in diluting segment in humans: evidence for indirect mediation through hypokalaemia. Kidney Int. 1991;40(2):251–6.
100. Gozansky DM, Herman RH. Water and sodium retention in the fasted and refed human. Am J Clin Nutr. 1971;24:869–71.
101. Stanga Z. Nutrition in clinical practice-the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr. 2008;62(6):687–94.
102. Solomon SM, Kirby DF. The refeeding syndrome: a review. JPEN J Parenter Enteral Nutr. 1990;14(1):90–7.
103. Nightingale J, Turner P, De Silva A, and the BIFA Committee. Top tips for preventing and managing refeeding syndrome. www.bapen.org.uk/pdfs/bifa/bifa-top-tips-series-7.pdf.
104. Li H, Sun SR, Yap JQ, Chen JH, Qian Q. 0.9% saline is neither normal nor physiological. J Zhejiang Univ Sci B. 2016;17(3):181–7.
105. Lobo DN, Awad S. Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent 'pre-renal' acute kidney injury?: con. Kidney Int. 2014;86(6):1096–105.
106. NICE Clinical Guideline 174. Intravenous fluid therapy in adults in hospital. 2013. www.nice.org.uk/guidance/cg174.
107. Powell-Tuck J, Gosling P, Lobo DN, Simon P, Allison SP, Carlson GL, Gore M, Lewington AJ, Pearse RM, Mythen MG. British consensus guidelines on intravenous fluid therapy for adult surgical patients. GIFTASUP. 2011. www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf.
108. Klein S. The myth of serum albumin as a measure of nutritional status. Gastroenterology. 1990;99:1845–6.
109. Evans DC, Corkins MR, Malone A, Miller S, Mogensen KM, Guenter P, Jensen GL, ASPEN Malnutrition Committee. The use of visceral proteins as nutrition markers: an ASPEN position paper. Nutr Clin Pract. 2021;36(1):22–8.
110. Krantz MJ, Lee D, Donahoo WT, Mehler PS. The paradox of normal serum albumin in anorexia nervosa: a case report. Int J Eat Disord. 2005;37(3):278–80.
111. Russell DMcR, Prendergast PJ, Darby PL, Garfinkel PE, Whitwell J, Jeejeebhoy KN. A comparison between muscle function and

body composition in anorexia nervosa: the effect of refeeding. Am J Clin Nutr. 1983;38:229–37.
112. Jeejeebhoy KN. Cause of hypoalbuminaemia in patients with gastrointestinal and cardiac disease. Lancet. 1962;1:343.
113. Rothschild MA, Oratz M, Schreiber SS. Albumin synthesis. N Engl J Med. 1972;286:748–57.
114. James WPT, Hay AM. Albumin metabolism: effect of the nutritional state and the dietary protein intake. J Clin Invest. 1968;47:1958–72.
115. Jackson AA. Salvage of urea-nitrogen in the large bowel: functional significance in metabolic control and adaptation. Biochem Soc Trans. 1998;26(2):231–6.
116. Broom J, Fraser MH, McKenzie K, et al. The protein metabolic response to short-term starvation in man. Clin Nutr. 1986;5:63.
117. Castaneda C, Charnley JM, Evans WJ, Crim MC. Elderly women accommodate to a low-protein diet with losses of body cell mass, muscle function, and immune response. Am J Clin Nutr. 1995;62:30–9.
118. Moshage HJ, Janssen JAM, Franssen JH, Hafkenscheid JCM, Yap SH. Study of the molecular mechanism of decreased liver synthesis of albumin in inflammation. J Clin Invest. 1987;79:1635–41.
119. Cohen S, Hansen JDL. Metabolism of albumin and gammaglobulin in Kwashiorkor. Clin Sci. 1962;23:411.
120. Fleck A, Hawker F, Wallace PI, Raines G, Trotters J, Ledingham I, Calman KC. Increase vascular permeability: a major cause of hypoalbuminemia in disease and injury. Lancet. 1985;1:781–4.
121. Gray GE, Meguid MM. Can total parenteral nutrition reverse hypoalbuminemia in oncology patients? Nutrition. 1990;6:225–8.
122. Kaw M, Seka G. Long-term follow up of consequences of percutaneous endoscopic gastrostomy (PEG) in nursing home patients. Dig Dis Sci. 1994;39:738–43.
123. Lobo DN, Stanga Z, Simpson JA, Anderson JA, Rowlands BJ, Allison SP. Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. Clin Sci (Lond). 2001;101(2):173–9.
124. Fleck A. Plasma proteins as nutritional indicators in the perioperative period. Br J Clin Pract. 1988;42(Suppl 63):20–4. Allison SP, Kinney JM, editors. Perioperative nutrition.
125. Badrasawi MM, Shahar S, Sagap I. Nutritional management of enterocutaneous fistula: a retrospective study at a Malaysian university medical center. J Multidiscip Healthc. 2014;7:365–70.
126. Waits RP, Yamada T, Uemichi T, Benson MD. Low plasma concentrations of retinol-binding protein in individuals with mutations affecting position 84 of the transthyretin molecule. Clin Chem. 1995;41:1288–91.
127. Measurement of visceral protein status in assessing protein and energy malnutrition: standard of care. Prealbumin in Nutritional Care Consensus Group. Nutrition. 1995;11(2):169–71.
128. Hedlund JU, Hansson LO, Ortqvist AB. Hypoalbuminemia in hospitalized patients with community-acquired pneumonia. Arch Intern Med. 1995;155:1438–42.
129. Winkler MF, Gerrior SA, Pomp A, Albina JE. Use of retinol-binding protein and prealbumin as indicators of response to nutrition therapy. J Am Diet Assoc. 1989;89:684–7.
130. Nieken J, Mulder NH, Buter J, Vellenga E, Limburg PC, Piers DA, de Vries EG. Recombinant human interleukin-6 induces a rapid and reversible anemia in cancer patients. Blood. 1995;86:900–5.
131. O'Riordain MG, Ross JA, Fearon KC, Maingay J, Farouk M, Garden OJ, Carter DC. Insulin and counterregulatory hormones influence acute-phase protein production in human hepatocytes. Am J Physiol. 1995;269:E323–30.
132. Cano N, Di Costanzo-Dufetel J, Calaf R, et al. Prealbumin retinol binding protein-retinol complex in hemodialysis patients. Am J Clin Nutr. 1988;47:664–7.
133. Lowrie EG, Lew N. Death risk in hemodialysis patients: the predictive value of commonly measured variables and the evaluation of death rate differences between facilities. Am J Kidney Dis. 1990;15:458–82.
134. Degoulet P, Legrain M, Reach I, et al. Mortality risk factors in patients treated by hemodialysis. Nephron. 1983;31:103–10.
135. Kottusch P, Tillmann M, Püschel K. Oberlebenszeit bei Nahrungs- und Flüssigkeitskarenz [Survival time without food and drink]. Arch Kriminol. 2009;224(5–6):184–91. German.
136. Malpas PJ. Dying is much more difficult than you'd think: a death by dehydration. Perm J. 2017;21:16–148.

Refeeding Problems

Aminda De Silva and Jeremy M.D. Nightingale

Key Points

1. Refeeding syndrome (RFS) describes the adverse clinical and biochemical problems that may result from feeding severely malnourished patients via any route, be it oral, enteral or parenteral.
2. Clinicians need to be aware of it and assume most malnourished patients are at risk.
3. Hypophosphataemia is the most commonly used marker of refeeding syndrome and it commonly occurs when artificial nutritional support is started (especially with carhohydrate) and can rarely cause death. Hypomagnesaemia, hypokalaemia and hypo (or hyper) glycaemia may also occur.
4. More enterally fed patients have refeeding hypophosphataemia than those given parenteral nutrition.
5. Sodium and water retention is common as the cell membrane sodium/potassium pump reactivates and can lead to oedema and cardiac failure.
6. Confusion can be due to thiamine deficiency (Wernicke's encephalopathy) which if untreated may lead to a permanent loss of short term memory (Korsakoff psychosis)
7. United Kingdom NICE guidelines are are helpful but not a reliable predictor of high risk patients. Low magnesium or Insulin like growth factor-1 (IGF-1) may improve them.
8. When feeding malnourished patients carbohydrate must be introduced slowly (non-protein energy usually 50% carbohydrate and 50% lipid). Additional phophate, B vitamins, potassium and magnesium may be given before starting and when feeding commences. Little or occasionally no sodium is given.
9. Nutritional support to the high risk patient should start at no more than 50% of estimated needs for the first 24–48 h.
10. Monitor phosphate, potassium and magnesium regularly (especially after the first feed).
11. Hypothermia and low blood glucose are often an indication of co-existing sepsis and must be treated.
12. These patients should be cared for by healthcare professionals with skills, training and knowledge about nutritional requirements and nutritional support.

Definition

There are wide variations in what is defined as refeeding syndrome (RFS) [1]; hence in this chapter the phrase "refeeding problems" is mostly used. RFS is a potentially fatal condition commonly characterised by rapid changes in fluid and electrolyte balance leading to problems of cardiac arrthymias, cardiac and respiratory failure. There are also a wide variety of other manifestations that can occur, including hidden sepsis, acute fatty liver, endocrine & haematological abnormalities along with acute thiamine deficiency (which can lead to Wernike's syndrome and possibly Korsakoff's psychosis) and other neurological syndromes such as delirium and centropontine myelinolysis.

RFS is thus best described as the adverse clinical and biochemical problems that can result from feeding malnourished patients via any route, be it oral, enteral or parenteral.

History

The first records of the problems of refeeding come from when towns/cities were surrounded and the inhabitants starved into surrendering. In AD 70 after the Seige of Jerusalem by the Romans, written about by Flavius Josephus: "they all on the sudden overfilled those bodies that were before empty, and so burst asunder, excepting such only as

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were skillful enough to restrain their appetites, and by degrees took in their food", "death was observed in those who overindulged but not in those who restrained their appetite" [2], Then in AD 543 after the Siege of Naples by the Ostrogoths, Totila "exhibited a considerable humanity." "He knew that if an abundance of food were at once supplied, the famished inhabitants would gorge themselves to death. He posted sentinels at the gates and in the harbour and allowed no one to leave the city. Then he dealt out small rations, gradually increasing the quantity every day until the people had recovered their strength" [3].

While many associate the problems of refeeding with the Second World War, the scientific literature for this is sparse. There are reports stating that "Untold thousands of the liberated starved prisoners from the Nazi concentration camps died immediately after liberation, after having been given some food by well-meaning soldiers. According to an oral testimony a woman died after eating just a few sugar packets." The three scientific papers that relate to the second world war are from the Leningrad siege of 1940 [4], freed Japanese prisoners of war [5] and from when the Netherlands was liberated towards the end of the Second World War (1944–1945) [6]. The information from the Lenningrad siege is surprisingly scarce; in the 2 years following the siege of Leningrad there were a high number of hospital admissions for hypertension (BP > 140/90), oedema and cardiac failure. The observations in 1945 of 24 Japanese prisoners of war who typically weighed 35 kg having lost 30% of their body weight in the preceeding 6 months reported that an intervention of a diet containing approximately 3500 kcal/day was made and it was observed that 5 of the 24 died. However they all had a serum albumin of less than 20 g/L, indicating that there were other medical issues in addition to simple malnutrition (e.g. infection or inflammation). It was observed that an attack of malaria made their oedema worse. The large informative publication from when the Netherlands was liberated towards the end of the Second World war (1944–1945) reported that deaths in severely malnourished people occurred in 3 ways; Firstly suddenly shortly after admission. Secondly after seeming to recover then a low blood pressure and tachycardia occurred with death within 1 h. Thirdly a slow death preceded by coma taking days. While there is much haematological and biochemical detail regular phosphate/magnesium measurements were not made. The overall death rate was 10% and it was noted that "obstinate diarrhoea" had a particularly poor prognosis. Many of the subjects had increased pigmentation though the cause was not clear.

Towards the end of the second world war (19 November 1944 to 20 December 1945) Ancel Keys performed studies upon 36 men (22–33 years) who were all conscientious objectors at the University of Minnesota, USA [7]. They were put on a semi-starvation diet for 24 weeks (1560 kcal/day) and during this time they had to walk 22 miles per week. and on this they lost more than 25% of their body weight. No deaths occurred on refeeding with 4 regimens (400, 800, 1200, 1600 kcal more than in semi-starvation).

Evidence for RFS in Clinical Practice

The lack of a uniform definition of RFS hampers all studies. The evidence of refeeding problems from oral, enteral and parenteral feeding is poor. Two patients (1 anorexia nervosa, 1 alcohol excess) were described as having a low phosphate after oral refeeding [8]. A low phosphate was observed in a study of 25 post-operative patients [9]. With parenteral nutrition 3 patients are described with paraesthesia, weakness seizures 4–5 days after starting and a low serum phosphate was observed [10]. The paper that brought attention to the problems of refeeding was entitled "Death resulting from overzealous total parenteral nutrition" [11] in which 2 deaths were described associated with hypophosphataemia; yet both were being given large amounts of intravenous glucose (500 and 700 g glucose in 24 h). Hypophosphatemic respiratory failure has been described in patients given post-operative total parenteral nutrition [12].

The UK NCEPOD report of 2010 showed that 60% (455/877) of patients given parenteral nutrition were at risk of refeeding problems with hypophosphataemia occurring in 18%. Hypokalaemia, hypomagnesaemia and hyperglycaemia were also common [13].

A retrospective study by Zeki et al. showed that a phosphate fall to less than 0.6 mmol/l occurred in 36/168 21% fed nasogastrically and 23/153 8% fed parenterally within a week of starting feeding [14]. Rio et al. using more strict criteria ($K^+ < 2.5$, $P < 0.32$, $Mg < 0.5$ mmol/l, oedema/circulatory fluid overload or disturbance to organ function) showed only 3/243 patients met these criteria within 15 days of starting to feed though 6% had a phosphate less than 0.5 mmol/l on day 3 [15].

Pathophysiology and Biochemistry of Refeeding

Biochemistry of Starvation

With reduced glucose levels resulting from starvation, insulin secretion drops and glucagon levels increase, resulting in higher glycogenolysis to generate energy from carbohydrate sources. However as starvation continues glycogen stores become depleted, typically within 6 h to 3 days, then the body shifts to using fat and eventually muscle to produce energy resulting in a high production of ketone bodies which are in turn used for energy instead of glucose.

Other changes include reducing basal metabolic rate and down-regulating energy consuming processes. This includes down-regulating the activity of ATP pumps such as the sodium/potassium ATP-pump. Down-regulation of these pumps results in changes of electrolyte handling causing leakage of mainly-intracellular cations such as potassium, magnesium and phosphate into the circulation where they are lost in urine. Down-regulation of cell membrane Na^+/K^+-ATP pump also allows sodium and water to leak into cells.

Despite poor dietary intake of electrolytes, serum levels of these cations during starvation could remain normal during starvation (or could even be high if there is a degree of renal failure) as these electrolytes move from the intracellular to the extracellular space [16], so measuring electrolyte levels as a one off investigation at this point gives littles or no useful information to the risk of refeeding syndrome occurring.

Severe starvation may lead to hepatic steatosis through various mechanisms. Protein deficiency can result in decreased apolipoprotein synthesis, leading to decreased very low density lipoprotein (VLDL) synthesis and inhibited VLDL transport. Reduced VLDL transport plays a significant role in lipid accumulation in the liver during starvation [17].

Biochemical Changes of Refeeding

Two key events happen on feeding glucose to patients who have been starving (Fig. 1).

Insulin levels increase which drives glucose and phosphate into cells. This leads to an increased uptake of glucose, phosphate and thiamine (needed for glycolysis and thus ATP manufacture). As a result, serum levels of phosphate along with other cations such as potassium, magnesium, calcium may fall, as will thiamine. Thiamine is a co-factor in many metabolic processes including its essential role in cerebral energy utilization, it will already be depleted in starvation so refeeding with glucose will result in rapid depletion of the already low stores of thiamine [18].

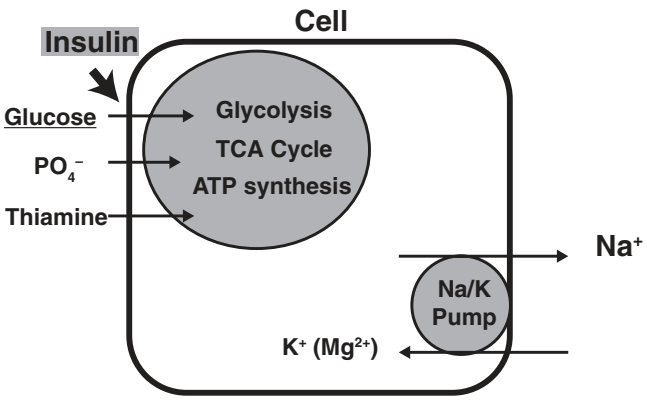

Fig. 1 Diagragm to show key events in RFS

Secondly the cell membrane sodium/potassium pump starts actively pumping sodium out of the cell and taking potassium and magnesium into the cell thus furthering the deficit in circulating electrolytes. In addition to this insulin stimulates sodium reabsorption from the distal nephron [19]. Water and sodium efflux into circulation also results and may result in fluid overload and heart failure [20]. This combination of a sudden fluid load into the circulation in to a system where the heart (like all other muscles) has been weakened and atrophied due to starvation, along with low circulating electrolytes (causing a propensity to cardiac arrhythmias) can easily lead to pulmonary oedema or signs of heart failure and potentially death (Fig. 2) [20].

Clinical Manifestations of Refeeding

Hypophosphataemia

This is often considered the hallmark feature of the refeeding "syndrome" (Table 1) though there are many other reasons for hypophosphataemia than just refeeding syndrome (Table 2). Within the cell phosphate is vital for many cellular pathways including glycolysis and the decarboxcylic acid cycle. Hypophosphataemia results in reduced ATP so many metabolic pathways are slowed/stopped. The low phosphate also reduces the levels of 2,3-diphosphoglycerate so causing the RBCs to be less able to give up oxygen (shifting the oxygen dissociation curve to the right). Hypophosphataemia is common in the critically ill but may not be associated with adverse outcomes [22]. The normal adult range of phosphate is 0.8–1.5 mmol/l. About 3% of patients admitted to hospital will have a phosphate below 0.85 mmol/l. Blood levels below 0.32 mmol/l are considered severe in the literature.

Thiamine Deficiency

The body stores of thiamine (vitamin B1) are sufficient for up to 7 days. It is a co-factor in aerobic glucose consumption. In thiamine deficiency, a combined enzyme defect results in aerobic metabolism impairment and isufficient ATP generation. Furthermore, pyruvate is converted into lactate, resulting in hyperlactaemia and lactic acidosis. As thiamine dependent metabolic pathways are present in almost all human cells, deficiency can affect many organ systems. It can also exacerbate the hypmagnesaemia, hypokalaemia and hypophosphataemia associated with increased renal losses due to oxidative stress that has damaged the renal tubules [23]. Thiamine deficiency can lead to the development of Wernicke's encephalopathy which is a triad of encephalopathy, ataxia and ocular dysfunction (nystagmus). Other features include hypothermia, peripheral neuropathy and heart failure [18]. Wernicke's encephalopathy can progress to the

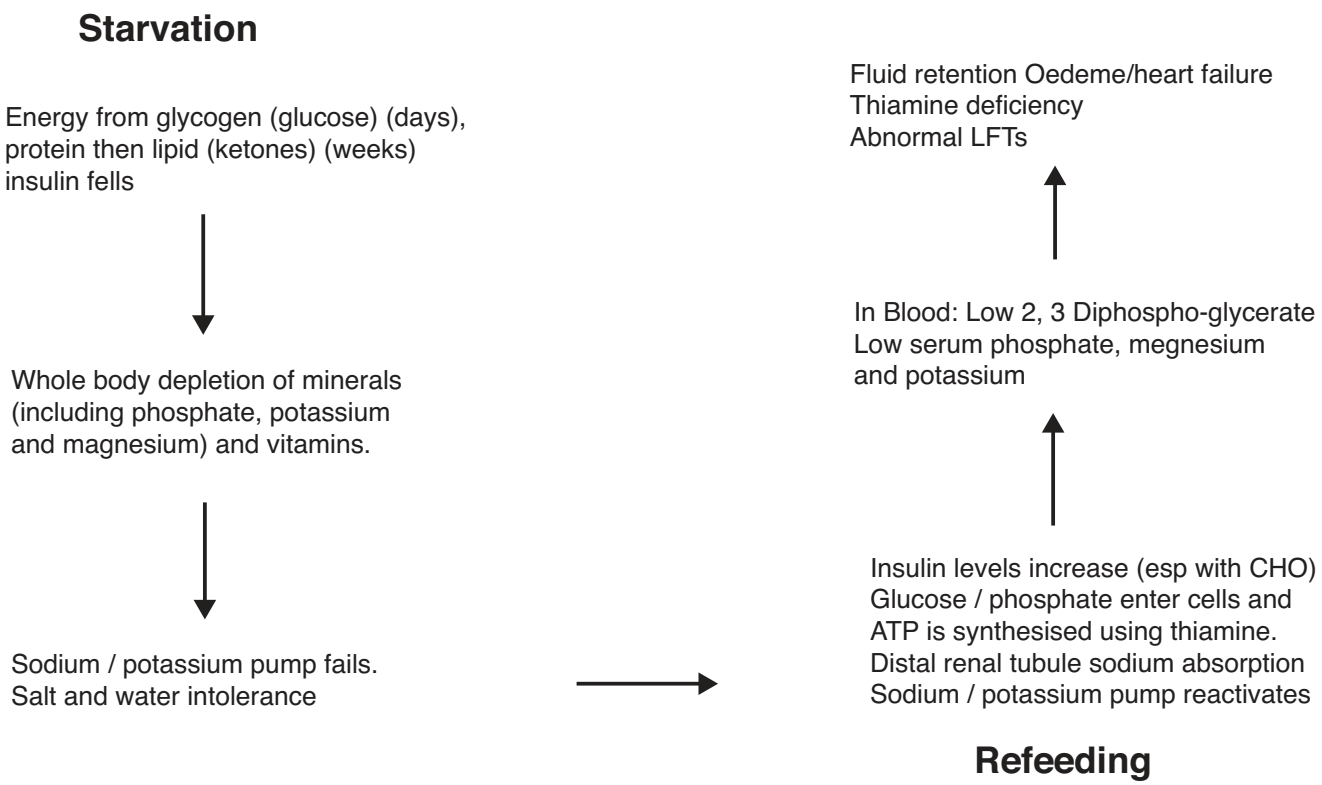

Fig. 2 Diagram summarising events in RFS. Based upon [21]

Table 1 Effects of hypophosphatemia

Muscular	Weakness (diaphragm), respiratory failure
	Rhabdomyolysis
Cardiac	Biventricular failure, low blood pressure
	Arrhythmias, sudden death
Haematological	Low and dysfunctional white blood cells, red blood cells and platelets
	Haemolysis
Neurological	Weakness, lower motor neurone type paralysis (loss of reflexes)
	Cranial nerve palsies
	Confusion, ataxia, tremors, fits, coma
Hepatic	Dysfunction (esp alcohol excess)

Table 2 Causes of hypophosphataemia other than refeeding

Sepsis
Post op/trauma/burns
Recovery from acidosis (e.g. diabetic ketoacidosis)
Alcohol withdrawal
Insulin (±glucose) treatment
Drugs—chemotherapy, diuretics, biphosphonates, phosphate binding antacids
Renal dialysis/transplantation
Hyperparathyroidism
Respiratory alkalosis

irreversible Korsakoff's syndrome which is an amnesic syndrome consisting of retrograde and antegrade amnesia (short term memory loss) but preservation of long-term memory. A substantial percentage of patients suffer from confabulation. Patients with Korsakoff syndrome often lack insight into their problem.

Return of Activity to the Cell Membrane Sodium/Potassium Pump

As the cell membrane sodium/potassium (Na^+/K^+) pump returns to activity the osmotically active sodium enters the interstitial space and circulation so giving rise to oedema and occasionally cardiac failure. This effect is compounded by insulin causing sodium retention in the kidney [19], dysregulation of anti-diuretic hormone and aldosterone secretion, and the addition of carbohydrate into the diet which leads to a rapid decrease in renal excretion of sodium and water [19]. This sudden fluid flux into the circulation and the inability to excrete it, particularly in the presence of a heart that may well be functioning less well in the context of poor nutrition, along with the possibility of low circulating elctrolytes giving a predisposition to cardiac arrhythmia, can lead to oedema, left ventricular failure and hypertension. Thus, the first clinical manifestions of refeeding problems may be a raised pulse and respiratory rate. In patients with low BMIs, one would often expect a sinus bradycardia, so even a pulse of above 60 beats/min might indicate a relative tachycardia and should alert the clinician to a potential problem.

Hypokalaemia

Potassium is the main intracellular cation. Depletion in starvation and malnutrition is mainly driven by low intake and/or excessive losses (e.g. hyperemesis). Serum potassium levels may remain normal in starvation because of movement of potassium along chemical gradients to the extracellular space. Insulin is important in stimulation of potassium influx into cells through the cell membrane Na^+/K^+-ATP pump. With initiation of nutrition the resulting increased secretion of insulin precipitates potassium influx into cells causing a fall in serum potassium levels. Hypokalaemia can cause muscle weakness including the respiratory muscles, atrial and ventricular arrhythmias (QT prolongation), atrioventricular block, a U wave on the electocardiogram and can cause/prolong an ileus.

Hypomagnesaimia

Magnesium is a predominantly intracellular cation. Deficiency in malnutrition and starvation stem from poor intake and redistribution. Upon refeeding, magnesium moves into cells with resultant drop of serum levels. While clinicians usually treat low serum magnesium levels patients with high stomal outputs are often seen with very low levels and apparently no symptoms or signs. The literature suggests that hypomagnesaemia alone (in the absence of hypocalcaemia) may cause a tremor, poor memory and precipitate arrhythmias in susceptible patients [24].

Moderate Abnormalities of Liver Function

Liver enzyme abnormalities are commonly found both in periods of starvation as well as during the refeeding phase. Excess glucose administered in the early phase of refeeding, particularly after prolonged periods of starvation leads to lipogenesis, again as a result of insulin stimulation. Deposition of fatty acids and triglycerides (hypertriglyceridaemia may occur) in the liver can lead to an acute fatty liver often being detected through raised liver transaminases. Moderate abnormalities of liver function (e.g. alanine transaminase up to 10 times the upper limit of the normal range) should not delay feeding [25].

Other Metabolic/Clinical Abnormalities

Both hyperglycaemia or hypoglycaemia can occur. Glucose intake after a period starvation, can suppress gluconeogenesis through the release of insulin. Excessive administration of glucose can therefore lead to hyperglycaemia and its sequelae including osmotic diuresis, dehydration, metabolic acidosis and ketoacidosis. Conversely, hypoglycaemia can also occur, particularly in the presence of sepsis [26]. This may relate to depleted glycogen stores, impaired gluconeogenesis and increased peripheral glucose utilization. Hypoglycaemia must be detected and corrected quickly as if prolonged can lead to perminant cerebral damage. Symptoms of bloating / constipation have been reported [25].

Infection

Hypothermia and low blood glucose are often an indication of sepsis and these must be urgently treated. Studies have documented significantly elevated rates of infection and leukopenia among hospitalized patients with anorexia nervosa [27]. In a case series of 14 patients, two patients developed occult sepsis that proved fatal, in one case despite of ITU treatment. Two patients in the same series had severe leukopenia with WBC of less than 0.5×10^9/l [28]. While infection and sepsis are not classical presentations of refeeding syndrome, it is important to monitor for these during the initial period of refeeding as patients with significant malnutrition are at higher risk of developing severe infections. These patients often don't develop the usual signs of sepsis (eg pyrexia, neutrophilia or increased CRP). In fact, their temperatures often fall, and blood sugars can be high or low. The combination of low BMI, hypoglycaemia and hypothermia is often termed the deadly triad and is a marker for severe infection and should always trigger consideration of antibacterial treatment [21].

Who Is at Risk of Refeeding Problems

Not only gastroenterological patients who have become severely malnourished often with IF or pancreatic disease are at risk of refeeding problems; but also patients with anorexia nervosa, classic kwashiorkor/marasmus, prolonged fasting (greater than 7–10 days including hunger strikers), some critical care patients, elderly patients (particularly those who are depressed), patients with cancer and those who are post bariatric surgery [29, 30]. It is especially common to find patients who look obese (BMI within the normal range) but who have lost much of their muscle mass (sarcopenic obesity) due to a poor intake of food and/or an inflammatory process (e.g. sepsis, surgery etc) and thus become relatively immobile and so are at a high risk of hospital acquired complications (e.g. sepsis, DVT etc).

How to Detect a Patient at Risk of Refeeding Problems

The current United Kingdom (UK) guidelines for nutrition support [29] identify criteria as risk factors for developing refeeding syndrome (Table 3). These criteria are not always reliable in predicting RFS as an accurate history regarding weight and recent nutritional intake may not be available. Moreover, the sensitivity of NICE guidelines (i.e. the proportion of those who developed refeeding hypophosphataemia who were correctly identified) was poor; scoring just 0.5 for enteral nutrition and 0.38 for parenteral nutrition but the specificity was better 0.76 for nasogastric tube feeding and

Table 3 UK NICE risk factors for developing refeeding problems [29]

One or more of the following
• BMI <16 kg/m^2
• Unintentional weight loss >15% within last 3–6 months
• Little or no nutritional intake for more than 10 days
• Low potassium, magnesium or phosphate prior to feeding
Two or more of the following
• BMI <18.5 kg/m^2
• Unintentional weight loss >10% within last 3–6 months
• Little or no nutritional intake for more than 5 days
• A history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics

0.73 for parental nutrition [14]. There are a variety of other risk factors identified in other studies that have identified those at risk of refeeding syndrome including, age, higher nutritional intake during feeding and nutritional risk feeding score >3 [1] however there are no data on their sensitivity or specificity. A baseline low serum Mg^{2+} was a predictor in one study [15]. Refeeding Index (a score generated from baseline insulin-like growth factor and leptin) has been proposed as a useful biochemical marker for predicting those at risk of RFS [31]. A study in 2015 has shown that using highly sensitive baseline IGF-1 alone is an objective, sensitive and specific biochemical marker in identifying patients who are at high risk of developing refeeding hypophosphataemia in patients starting parenteral nutrition (a ≥30% drop in PO_4 during the first 36-h of PN administration) [32].

Why Is Refeeding Hypophosphataemia More Common with Oral/Enteral Feeding Than with Parenteral Feeding?

Zeki et al. showed that the occurance of refeeding hypophotaemia in adult patients fed enterally vs those fed parenterally was more common in those fed enterally (21 vs 8%, $p < 0.05$) [14]. The reason for the more significant fall in phosphate after enteral rather than intravenous feeding was not due to more phosphate being in the parenteral feed rather than the enteral one (both had about 20–30 mmol). It does not relate to a difference in the lipid or carhohydrate amount in enteral and parenteral feeds (generally the lipid and carbohydrate energy were the same). The main reason is likely to relate enteral feeding stimulating a greater insulin secretion than parenteral feeding and so the mechanism that drives refeeding hypophospahtaemia is amplified. This "incretin effect" was first recognised in the 1960s and describes the descibes the greater insulin secretion after a patient is given the same amount of glucoses orally as intravenously [33]. This response has subsequently been related to the release of two upper gut peptide hornones gastroinsulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1) which both act to increase/exaggerate insulin secretion from the pancreatic islet β cells. It is for this same reason that hyperglycaemia is more common with parenteral than enteral feeding. Refeeding problems must be considered very seriously when starting enteral feeding.

Treatment of Patients at Risk of Refeeding Problems

Circulatory volume (dehydration) should be restored and fluid balance monitored. Hypothermia and sepsis must be treated [34]. In the acute phase cardiac monitoring is advised. It is also recommended for inpatients with cardiac manifestations and/or ECG changes secondary to hypokalaemia, patients with a QTc >450 ns or where intravenous correction of potassium is needed at a rate of more than 10 mmol/h is deemed necessary [21].

There is varied opinion about giving vitamins/minerals (including phosphate) before starting to give feeding. It can be argued that without the necessary energy to switch the celluar homestatic mechanisms back on, thereby enabling them to move vitamins/minerals (including phosphate) from the circulation to the intracellular compartment, there is a concern that any administered may simply be excreted via the kidneys. This argument is especially around phosphate and pre treating with it. Most institutions would give supplementation prior to feeding if serum electrolyte levels are low or low normal before feeding.

Energy

When the UK NICE guidelines were published there were no good quality trials to enable evidence based management protocols to be developed so reliance was upon expert opinion (Level D evidence considered a Good Practice Point) [29]. It suggested that people who had eaten little or nothing for more than 5 days should have nutrition support introduced at no more than 50% of requirements for the first 2 days; that the prescription for people at high risk of developing refeeding problems could be giving nutritional support at a maximum of 10 kcal/kg/day, increasing levels slowly to meet or exceed full needs by 4–7 days. It even controversially went on to suggest using only 5 kcal/kg/day in extreme cases (for example, BMI less than 14 kg/m^2 or a negligible intake for more than 15 days). A survey in 2008 showed 39% felt the guidance was appropriate and 36% felt it was too cautious [30].

Subsequent to this there have been two trials in intensive care units to show that a hypocaloric diet given to patients with refeeding hypophosphataemia in ITU do have a better survival than in those fed without restriction [35, 36]. Most nutrition support teams in UK do give reduced amounts of energy and gradually increase the energy to requirements

over 4–7 days. The Parenteral and Enteral Nutrition Group (PENG) which is a specialist group within the British Dietetic Association now recommends 10–20 kcal/kg feeding for the severely malnourished [37]. Some however, are bolder and start the parenteral feed to meet the requirements of the BMI and after taking into account the protein energy, give the lipid and carbohydrate energy as half each.

Refeeding of adolescents with anorexia nervosa at 1200 kcal/day versus 500 kcal/day resulted in improved weight gain but no other adverse effect, including on QTc interval [38]. Within 48 h of feeding commencing, 28% of high calorie and 11% of low calorie developed hypophosphataemia but in the absence of other electrolyte abnormality

Phosphate Replacement

Most authorities suggest that in patients with mild to moderate hypophosphataemia (phosphate above >0.32 mmol/dl) oral replacement should be initiated unless there are concerns about absorption from the gastrointestinal tract. However in RFS, it could be argued that in the context of multiple electrolyte disturbances, a lower threshold for starting intravenous correction should be employed and most advocate IV replacement for patients at high risk of RFS at PO4 levels of <0.6 mmol.

Intravenous phosphate supplements could be in the form of monbasic potassium phosphate or the more-widely used phosphate infusion, Polyfusor. Electrolytes need to be closely monitored as the latter contains significant amounts of sodium and potassium. One litre of Polyfusor contains 100 mmol of PO_4^{3-}, 162 mmol of sodium and 19 mmol of potassium. Excessive doses should also be avoided as they can result in hypocalcaemia and metastatic calcification. The BNF defines maximal dose as 500 µml/kg. Maximal dose is 50 mmol/24 h i.e. 500 ml of polyfuser [39]. We would advocate smaller infusions of 10–20 mmol phosphate i.e. 100–200 ml of polyfuser repeated if necessary to reduce the risk of metastatic calcification. The UK NICE guidelines suggest the likely requirement for potassium is 0.3–0.6 mmol/kg/day.

A study showed 36.8% of critically ill, mechanically ventilated patients developed hypophosphataemia and those fed at 50% target rate had improved 6 month outcomes [36].

There is no doubt that phosphate must be administered concurrently with a low rate feeding.

Thiamine, Other Vitamins and Trace Elements

It is crucial that thiamine supplementation is started prior to and continued during nutrition support and glucose administration. Oral thiamine can be given at a dose of 200–300 mg daily. One to two tablets of vitamin B co strong can be given three times a day. A daily intravenous vitamin B preparation such as Pabrinex can be given intravenously (usually for 3–5 days) in addition to oral multivitamin supplements. A balanced multivitamin/trace element supplement once daily for 10 days is recommended by UK NICE guidelines [29]. If signs of Wernicke's encephalopathy are present the B vitamins need to be given intravenously.

Electrolytes (Potassium and Magnesium)

Severely abnormal blood electrolytes (e.g. phosphate, potassium or magnesium are corrected prior to feeding. A drop of serum potassium by 1 mmol/L is equivalent to a total deficit of approximately 200–400 mmol. Mild asymptomatic hypokalaemia is ideally be corrected orally with potassium chloride used to provide up to 50 mmol/day. However, many patients suffer from gastrointestinal side effects that limit compliance [39]. Intravenous potassium can be used to treat significant hypokalaemia with potassium levels less than 3.0 mmol/l. Intravenous infusion with potassium chloride concentration of 40 mmol/l are used when using peripheral veins [39]. This can be administered at a rate of 10–20 mmol/h. Higher concentrations of intravenous potassium delivered into a central vein can be used with close cardiac monitoring after specialist advice. Some authorities accept up to 40 mmol/dl administered into a large central vein. The UK NICE quideline recommends providing oral, enteral or intravenous supplements of potassium with the likely requirements being 2–4 mmol/kg/day [29].

About 80% of plasma magnesium is filtered through glomeruli. 20% is reabsorbed by the proximal tubules and about 80% is reabsorbed by Loop of Henle, a process influenced by the plasma concentration of magnesium. Intravenous infusion of magnesium will result in a transient increase in magnesium levels and consequently renal wasting of a substantial proportion of that magnesium. So, in more severe hypomagnesaemia where higher magnesium supplements are required, these should be administered over longer hours to avoid sudden increases in magnesium levels [39]. In mild hypomagnesaemia 4–8 mmol of magnesium sulphate can be given over 1–2 h [39]. Oral formulas like magnesium glycerophosphate, oxide or aspartate can be used to prevent recurrence of the deficit. The UK NICE quideline recommends providing oral, enteral or intravenous supplements of magnesium with the likely requirements being 0.2 mmol/kg/day intravenous, 0.4 mmol/kg/day orally [29].

Fluid

Should problems with fluid overload occur an 'ABC' approach to resuscitation should be taken and transfer to ICU should be considered. If absolutely necessary, diuretics may be required but may have the effect of lowering circulating electrolytes further. If this occurs, central access should be sought and administration of concentrated electrolytes in ICU may be appropriate. The feed should be slowed further whilst these issues are being managed. Sodium administration at first is very reduced. Patients at high risk of refeeding prob-

lems should receive about 20 ml fluid/kg and <1 mmol/kg sodium. Sodium excretion is limited in refeeding and excess provision combined with that liberated from cells can lead to circulatory overload (heart failure and severe oedema) which is dangerous in combination with cardiac atrophy from malnutrition / arrhythmias from electrolyte imbalances. Extreme caution should be observed when giving electrolytes in 0.9% NaCl (154 mmol Na/l) due to the risk of sodium and fluid overload and if using 5% dextrose the energy content needs to be taken into consideration (200 kcal/l). Ideally electrolytes should be added to the PN bag and oral preparations in water should be used where possible for oral and enteral tube feeding. However it is important to remember that intestinal failure patients may need additional sodium and fluid to replace gastrointestinal losses from stomas/ fistulas.

Conclusion

Refeeding problems are common however are less likely to occur if patients are identified as at risk and if precautions are taken (14 vs 46%) [13]. Electrolyte (especially hypophosphataemis), sodium and water and thiamine deficiency are common and can be life threatening/life changing so need to be prevented and treated. The "Start low, go slow" approach-for energy provision recommended by UK NICE guidelines may risk underfeeding which is linked to poor weight gain and the risk of the underlying clinical condition deteriorating leading to organ dysfunction, poor wound healing, increased rates of infection and prolonged hospitalisation [29]. In this review we have advocated an equally cautious start to energy provision but would highlight the importance of a more rapid increase in energy, particularly during the first couple of days, linked to careful blood monitoring and electrolyte/vitamin provision. Experienced healthcare workers should manage these patients [40–43].

References

1. Friedli N, Stanga Z, Sobotka L, Culkin A, Kondrup J, Laviano A, Mueller B, Schuetz P. Revisiting the refeeding syndrome: results of a systematic review. Nutrition. 2017;35:151–60.
2. Josephus F. The wars of the Jews or history of the destruction of Jerusalem. Translated by William Whiston 2009. Book V, chapter XIII, paragraph 4.
3. Bury JB. The first successes of Totila (AD 541-543), The reconquest of Italy in the History of the later Roman empire. 1923 (Dover Books reprint 1958). Chapter 19; S2.
4. Brozek J, Chapman CB, Keys A. Drastic food restriction. Effect on cardiovascular dynamics in normotensive and hypertensive conditions. JAMA. 1948;137:1569–74.
5. Schnitker MA, Mattman PE, Bliss TL. A clinical study of malnutrition in Japanese prisoners of war. Ann Intern Med. 1951;35:69–96.
6. Burger GCE, Drummond JC, Sanstread HR. Malnutrition and starvation in Estern Netherlands. September 1944-July 1945. The Hague General State Printing Office 1948. Part I and II.
7. Keys A, Brozek J, Mickelsen O, Taylor HL. The biology of human starvation. Minneapolis: University of Minnesota Press; 1950.
8. Cumming AD, Farquhar JR, Bouchier IA. Refeeding hypophosphataemia in anorexia nervosa and alcoholism. Br Med J. 1987;295:490–1.
9. Hayek ME, Eisenberg PG. Severe hypophosphatemia following the institution of enteral feedings. Arch Surg. 1989;124:1325–8.
10. Silvis SE, Paragas PD Jr. Paresthesias, weakness, seizures, and hypophosphatemia in patients receiving hyperalimentation. Gastroenterology. 1972;62:513–20.
11. Weinsier RL, Krumdieck CL. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. Am J Clin Nutr. 1981;34:393–9.
12. Youssef HA. Hypophosphatemic respiratory failure complicating total parenteral nutrition: a potentially lethal iatrogenic hazard. Int Surg. 1982;67:371–2.
13. Stewart JAD, Mason DG, Smith N, Protopapa K, Mason M. A mixed bag. An enquiry into the care of hospital patients receiving parenteral nutrition. A report by the National Confidential Enquiry into Patient Outcome and Death, 2010.
14. Zeki S, Culkin A, Gabe SM, Nightingale JM. Refeeding hypophosphataemia is more common in enteral than parenteral feeding in adult in patients. Clin Nutr. 2011;30:365–8.
15. Rio A, Whelan K, Goff L, Reidlinger DP, Smeeton N. Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. BMJ Open. 2013;3:e002173.
16. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition. 2001;17:632–7.
17. Kneeman JM, Misdraji J, Corey KE. Secondary causes of nonalcoholic fatty liver disease. Ther Adv Gastroenterol. 2012;5:199–207.
18. Victor M, Adams RD, Collins GH. The Wernicke Korsakoff syndrome. Philadelphia: F.A. Davis; 1989.
19. Gozansky DM, Herman RH. Water and sodium retention in the fasted and refed human. Am J Clin Nutr. 1971;24:869–71.
20. Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, Lobo DN. Nutrition in clinical practice-the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr. 2008;62:687–94.
21. Jackson AA. Severe malnutrition chapter 10.4 1054. In: Oxford textbook of medicine. 4th ed. Oxford: Oxford University Press; 2005.
22. Fuentes E, et al. Hypophosphatemia in enterally fed patients in the surgical intensive care unit. Nutr Clin Pract. 2017;32:252–7. https://doi.org/10.1177/0884533616662988.
23. Maiorana A, Vergine G, Coletti V, Luciani M, Rizzo C, Emma F, Dionisi-Vici C. Acute thiamine deficiency and refeeding syndrome: similar findings but different pathogenesis. Nutrition. 2014;30:948–52.
24. Nightingale JMD, Woodward J, Small Bowel/Nutrition Committee of BSG. Guidelines for the management of patients with a short bowel. Gut. 2006;55:1–12.
25. Robinson P. Marsipan: management of really sick patients with anorexia nervosa. 2nd ed. Cambridge: Cambridge University Press; 2014.
26. Miller SI, Wallace RJ Jr, Musher DM, Septimus EJ, Kohl S, Baughn RE. Hypoglycemia as a manifestation of sepsis. Am J Med. 1980;68:649–54.
27. Devuyst O, Lambert M, Rodhain J, Lefebvre C, Coche E. Haematological changes and infectious complications in anorexia nervosa: a case-control study. Q J Med. 1993;86:791–9.

28. Webb GJ, Smith K, Thursby-Pelham F, Smith T, Stroud MA, De Silva AN. Complications of emergency refeeding in Anorexia Nervosa: case series and review. Acute Med. 2011;10(2):69–76.
29. National Institute for Health en Clinical Excellence. Nutrition support in adults. Clinical guidelines, 2006.
30. De Silva A, Smith T, Stroud M. Attitudes to NICE guidance on refeeding syndrome. BMJ. 2008;337:a680.
31. Elnenaei MO, Alaghband-Zadeh J, Sherwood R, Awara MA, Moniz C, le Roux CW. Leptin and insulin growth factor 1: diagnostic markers of the refeeding syndrome and mortality. Br J Nutr. 2011;106:906–12.
32. Goyale A, Ashley SL, Taylor DR, Elnenaei MO, Alaghband-Zadeh J, Sherwood RA, le Roux CW, Vincent RP. Predicting refeeding hypophosphataemia: insulin growth factor 1 (IGF-1) as a diagnostic biochemical marker for clinical practice. Ann Clin Biochem. 2015;52:82–7.
33. McIntyre N, Holdsworth C, Turner D. New interpretation of oral glucose tolerance. Lancet. 1964;2:20–1.
34. Ashworth A, Khanum S, Jackson A, Schofield C. Guidelines for the inpatient treatment of severely malnourished children. Geneva: World Health Organization; 2003.
35. Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, Reade MC, Harrigan PW. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015;3:943–52.
36. Olthof LE, Koekkoek WACK, van Setten C, Kars JCN, van Blokland D, van Zanten ARH. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: a retrospective study. Clin Nutr. 2018;37:1609–17.
37. Culkin A, White R. Refeeding syndrome. In: A pocket guide to clinical nutrition. 5th ed. Birmingham: British Dietetic Association; 2018.
38. O'Connor G, Nicholls D, Hudson L, Singhal A. Refeeding low weight hospitalized adolescents with anorexia nervosa: a multicenter randomized controlled trial. Nutr Clin Pract. 2016;31:681–9.
39. British National Formulary (BNF). bnf.nice.org.uk.
40. De Silva A, Nightingale JMD. Refeeding problems/syndrome: physiological background and practical management. Frontline Gastroenterol. 2019;11(5):404–9.
41. Nightingale J, Turner P, De Silva A; BIFA Committee. Top tips for preventing and managing refeeding syndrome. www.bapen.org.uk.
42. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ. 2008;336(7659):1495–8.
43. Medical Emergencies in Eating Disorders (MEED): Guidance on Recognition and Management (Replacing MARSIPAN and Junior MARSIPAN) May 2022. Royal College of Psychiatrists Report CR233; 2022. www.rcpsych.ac.uk/cr233.

Intestinal Failure Associated Liver Disease

Sue V. Beath and Alan L. Buchman

Key Points

1. Intestinal failure-associated liver disease (IFALD) is a stand-alone disease that may have multiple aetiologies, but develops exclusively in patients with dysfunctional gastrointestinal tracts, namely short bowel syndrome, intestinal dysmotility and various malabsorptive disorders.
2. Paediatric patients often present with cholestatic liver function tests (LFTs).
3. In acute intestinal failure abnormal liver function is most commonly due to sepsis, drug therapy or pre-existing liver disease, rather than due to the parenteral nutrition.
4. An excess of any of the macronutrient components of parenteral nutrition (PN) can cause abnormal LFTs. In particular first-generation, soya bean-based lipid preparations are associated abnormal liver function.
5. An excess of copper, manganese, or aluminium and deficiencies of choline, taurine, carnitine or essential fatty acids may all cause abnormal LFTs.
6. Treatment involves treating sepsis, reviewing medication and parenteral nutrition prescription, maximising oral/enteral feeding, giving cyclical PN and changing bile composition (e.g. ursodeoxycholic acid (URSO)).
7. Bacterial overgrowth should be evaluated and treated with antibiotics and small bowel dilation sub-acute obstruction should be actively managed by a multidisciplinary team (MDT) which includes gastrointestinal surgeons.
8. Severe IFALD-associated liver failure is an indication for small bowel transplantation.

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Introduction

Intestinal Failure-Associated Liver Disease (IFALD), formerly known as parenteral nutrition-associated liver disease (PNALD) develops in a significant percentage of patients who cannot maintain nutritional autonomy and thereby require the infusion of parenteral nutrients. It must be recognized that the assimilation of nutrients when delivered to the body intravenously differ, at least for some nutrients, when they are consumed via the oral or enteral route [1] The bypassing of the enterohepatic circulation and associated homeostatic mechanisms, combined with different presentations of nutrients across the sinusoids explains the tendency to hepatic steatosis in patients who are committed to extended periods of PN [2, 3].

The History of IFALD, Epidemiology and Outcome

First recognized in 1971 in an infant [4], for many years IFALD was described as one cause for non-alcoholic steatohepatitis (NASH) [5]. Although NASH has many aetiologies, IFALD is an unrelated disease with different pathophysiology, histology, and outcomes [6]. Transient biochemical abnormalities in hepatic aminotransferases and alkaline phosphatase have been reported in over 90% of adults within 1–6 weeks of starting parenteral nutrition [7]. These reports, however, came from an era of overfeeding wherein excess carbohydrate energy was often provided to patients (often >50 kcal/kg/day) [8]. With longer term use (home parenteral nutrition) Aspartate aminotransferase (AST) and alkaline phosphatase (ALP) become progressively more elevated [9]. It should be recognized however, that biochemical indices of liver injury provide little information with regards to hepatic function and specifically, serum aminotransferase concentrations are often insensitive and nonspecific indicators of hepatic histopathology [10]. This is equally true of IFALD in children [11, 12].

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The frequency of clinically-significant IFALD remains substantial, but is much less when compared to the 1980s [13]. In the Cavicchi study of adults, at least two of three enzymes (ALT, AST or alkaline phosphatase) were elevated in 55% of patients at 2 years, 64% at 4 years, and 72% at 6 years in a group of 90 (57 with histologic data) patients that had received home parenteral nutrition (HPN) [13]. However, modern cohorts differ from this historic group in which half the patients developed clinically significant liver disease; when defined by a serum total bilirubin concentration exceeding 60 μmol/L (3.5 mg/dl) for at least one month, the presence of ascites, hepatic encephalopathy, variceal haemorrhage, a serum factor V concentration less than 50% or portal fibrosis or cirrhosis on biopsy, the percentage of patients was 26% at 2 years, 39% at 4 years, 50% at 6 years and 53% at 8 years.

In adults, the elevation of serum bilirubin is an ominous sign, with a mean lifespan of only 10.8 months following this observation and death in all once the total serum bilirubin concentration exceeded 61 ± 20 μmol/L (3.6 ± 1.2 mg/dl) for 6–12 months [14]. IFALD is the complication in patients with intestinal failure with the greatest risk of death [15], and impending hepatic failure is the most common indication for isolated small bowel transplantation [16]. Chan et al. reported 15% of their 42 adult patients that received long-term PN at the Beth Israel Deaconess program in Boston developed IFALD that progressed to end stage liver disease; all died shortly thereafter [14]. Should the liver fail, a combined liver-small bowel transplant is necessary given that continued malabsorption will result in continued hepatic insult. Timely isolated intestinal transplant carried out before end stage liver disease has developed has lead to the reversal of IFALD [17–19].

Children, especially pre-term infants are particularly susceptible to IFALD [20]. A study which recruited pre-term babies born between 28 weeks gestation and 37 weeks week found that lower gestational age (<34 weeks) was associated with higher serum bilirubin and that episodes of sepsis were on average responsible for 30% increase in serum bilirubin [21]. Physiologically babies are less robust because the immaturity of liver canalicular membranes reduced glutathione reserves and dependency on exogenous taurine, choline [2, 20, 22]. Fifty percent of children become jaundiced (bilirubin in excess of 70 μmol/L) at some point during the administration of PN [23]. In addition to immature homeostatic mechanisms, infants and children are exposed to relatively higher toxic impact of intravenous nutrition intakes because of the greater calories requirement per kg to account for growth requirement. As in adults the development of persistent jaundice was associated with mortality, and in the early phase of intestinal transplantation in the 1990s approximately twice as many children as adults were transplanted for end stage IFALD, despite the difficulties in finding size matched donors for young recipients typically weighing 10–20 kg.

The improved awareness of IFALD and willingness to ameliorate risk factors such as over provision of nutrients and a more active approach to supplemental enteral nutrition has led to a reduction in severe IFALD in children and adults the past three decades [24, 25].

Definitions

Intestinal failure is defined as a condition where an individual is unable to absorb sufficient nutrients and/or fluid to maintain nutritional autonomy. The European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) (ESPEN) has defined intestinal failure as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth" [26]. The International Small Bowel Transplant Association (ISBTA), now known as the Intestinal Rehabilitation and Transplant Association (IRTA), a subdivision of The Transplantation Society, has defined IFALD as "a persistent elevation of liver enzymes, alkaline phosphatase and γ-glutamyl transferase 1.5 times the upper limit reference range which persist for more than or equal to 6 months in adults and more than or equal to 6 weeks in children" [27]. This definition of IFALD includes pragmatic definitions of severity—clinically described as mild/early IFALD; moderate IFALD; advanced/end stage IFALD. And acknowledges that IFALD is a disease with a spectrum of responses by the liver to a variety of biological provocations including: abnormal route of nutrient administration causing greater glucose uptake (PN versus EN) [3]; excess nutrient provision [13, 28]; bacterial overgrowth; systemic sepsis, especially originating from the bowel [29, 30].

Histopathology

Steatocholestasis (combination of steatosis and cholestasis) is the hallmark of IFALD, and a histologic finding that differentiates it from non-alcoholic fatty liver disease (NAFLD), which includes non-alcoholic steatohepatitis (NASH) [6], although steatosis tends to predominate in most adults. Steatosis generally develops initially as macrosteatosis in zone 1 (periportal) (Fig. 1). Microvesicular steatosis is seen in the majority of adults, and in some patients a combination of both macro- and microsteatosis is observed [13] (Fig. 2). Steatohepatitis is uncommon and is rare in the absence of cholestasis [13, 31]. Therefore, although IFALD is a unique liver disease unto itself, in children it is often

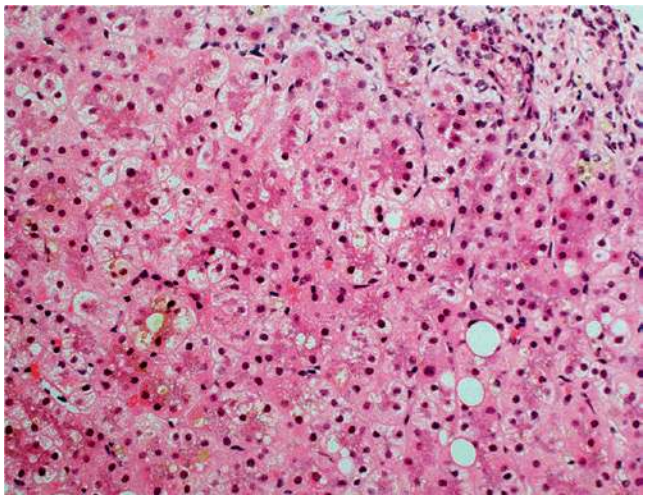

Fig. 1 Macrosteatosis with steatosis (steatocholestasis) in zone 1 (periportal)

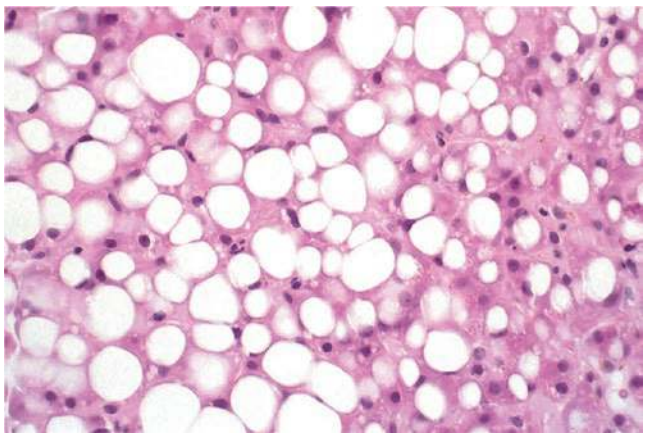

Fig. 2 Macro-and microsteatosis

noted to resemble numerous other diseases such as extra hepatic biliary atresia, α1anti-trypsin deficiency, or cystic fibrosis, and thus careful clinical pathological correlation is required. It is to be noted cholestasis may be evident biochemically (1.5× the normal upper value for at least 2 of 3 livers tests including alkaline phosphatase, conjugated bilirubin and γ-glutamyl transferase as defined by Cavicchi et al. or the ISBTA [13, 27]. Other histologic findings may include features of biliary obstruction with portal inflammation, edema and ductular proliferation, although ductopenia (the absence of bile ducts in >50% of portal tracts) may also occur uncommonly [6] (Fig. 3), this is important as it illustrates how IFALD can mimic other diseases histologically. Fibrosis begins with portal expansion and may progress to cirrhosis, often in a characteristic "jig-saw" pattern) although hepatic failure may occur prior to development of cirrhosis (Fig. 4).

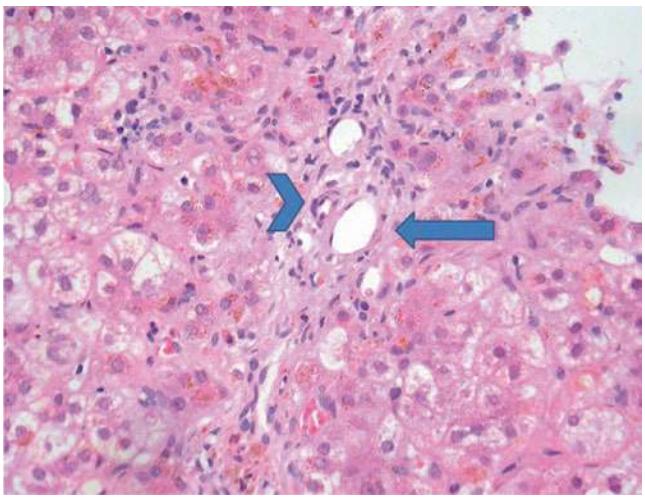

Fig. 3 Ductopenia (the absence of bile ducts in >50% of portal tracts) found in a 4 months old baby who has been on parenteral nutrition since being born prematurely. Slide H&E × 200. Arrow head = artery, arrow = vein branch, but no accompanying bile duct. Kindly supplied Dr. Rachel M. Brown Consultant Histopathologist Queen Elizabeth Hospital Birmingham, UK

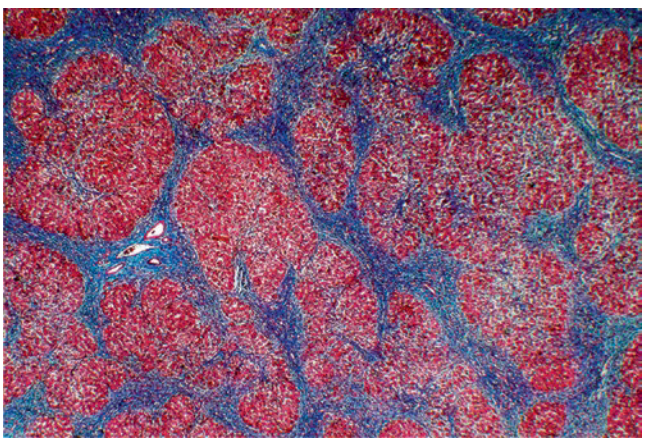

Fig. 4 Fibrosis begins with portal expansion and may progress to cirrhosis, often in a characteristic "jig-saw" pattern)

In young children, cholestasis dominates the histopathology, with steatosis being relatively inconspicuous [32, 33]. A peri-cellular pattern of fibrosis is often seen in early cases of IFALD in children along with Mallory-Denk bodies which are often seen with toxic insults. The combination of perivenular and portal fibrosis is especially characteristic of IFALD [31]. Although cirrhosis is not common in IFALD, when it occurs there is a risk of hepatocellular carcinoma development [34]. Ischaemic hepatitis has also been reported in an acute case of intestinal failure caused by mid-gut volvulus and septic shock—this child developed rapidly progressive liver disease but did well after combined liver and bowel transplant [35].

Pathophysiology of IFALD in Adults

Adult patients with the least functional residual intestine and thereby the most significant nutrient malabsorption and most dependent on PN are at the greatest risk for development of IFALD [36]. Normally, upon ingestion of food, nutrient digestion begins in the mouth and continue into the stomach and small bowel, with absorption in those organs with transport to the liver via the portal vein. When nutrients are intravenously infused, they are infused directly into the vena cava at the cardiocaval junction. After passing through the heart, the nutrient-enriched blood eventually makes its way to the liver via the hepatic artery. As such, first pass metabolism is effectively bypassed. In 1972 Stegink and Den Besten showed that orally-administered methionine was metabolized via the hepatic transulfuration pathway to cystine [1]. Choline is a product of the same hepatic pathway, which is incompletely functional when presented with intravenously-infused substrate, resulting in deficient choline biosynthesis [37–39]. As a result of impaired methionine metabolism, plasma methionine concentrations ranges from high normal or elevated in patients that receive PN [37, 40, 41]. In such circumstances, choline deficiency develops in patients fed intravenously because there is minimal choline supplied in PN (chiefly via lipids) and hepatic biosynthesis is impaired. Plasma free choline concentration is decreased below normal in 85–90% of PN patients, and negatively correlates with serum hepatic aminotransferase concentrations and the degree of hepatic steatosis [42, 43]. Steatosis develops due to decreased very low-density lipoprotein (VLDL) synthesis and a subsequent reduction in transport of triglycerides from hepatocytes; choline is required for VLDL biosynthesis. Small, but placebo-controlled studies have shown IFALD can be improved or ameliorated with choline supplementation in adults [42, 44]. Animal data have suggested choline also improves bile flow [45], which is decreased during PN infusion [46–48], and thereby reduce cholestasis as noted by a fall in the serum alkaline phosphatase [44]. Choline deficiency may be necessary for the development of IFALD, but not sufficient. A second "hit" such as lipid peroxidation [49, 50], or the presence of endotoxin may be required [51].

There are however a myriad of other proposed etiologies for IFALD in adults (Table 1), some of have not been substantiated by investigational studies (carnitine deficiency), but others clearly contribute (carbohydrate overfeeding, essential fatty acid deficiency, generalized malnutrition, lipid overload), Others proposed etiologies have little human or animal data currently (glutamine, taurine and bile salt deficiencies, bacterial overgrowth and endotoxin, aluminum and bile salt toxicities).

Both severe protein undernutrition [52], and essential fatty acid deficiency (EFAD) [53–56] have been associated with the development of hepatic steatosis. The undernutrition presumably would be corrected with PN although a minimum of 2–4% of total energy must be supplied as linoleic fatty acid via lipid emulsion to prevent development of EFAD. Like choline, carnitine is also a product of the hepatic transsulfuration pathway and blood concentrations are decreased in patients that receive PN, although not to the level generally seen in congenital carnitine deficiency [41, 57, 58]; Carnitine supplementation however has not been useful in the treatment of IFALD [59].

Table 1 Factors associated with the development of IFALD

Malnutrition	Excessive dextrose calories
Essential fatty acid deficiency	Excessive omega-6 fatty acids
Glutamine deficiency	Toxic effects of protein hydrolysates
Choline deficiency	Carnitine deficiency
Taurine deficiency	Differential metabolism of intravenously-infused nutrients
Hyperglycemia	Increased portal insulin: glucagon ratio
Bacterial overgrowth	Bacterial endotoxin
Bile salt deficiency	Toxic bile salts
Lithocholic acid toxicity	Aluminum and heavy metal toxicity

Nutrient toxicity has also been implicated in the development of IFALD. These include dextrose overfeeding (>50 kcal/kg/day), which leads to an increase in the portal insulin: glucagon ratio [60]. Mitochondrial carnitine acyltransferase is then inhibited and thereby fatty acid oxidation impaired since it is the rate-limiting step [61]. Hepatic acetyl-coenzyme A is increased and acetyl-coenzyme A carboxylase is induced, which stimulates hepatic fatty acid synthesis [62]. Case reports indicate lipid overload (>2.5–3.0 g/kg/day also causes severe cholestasis and even death [63, 64]. It has been suggested that phyotosterols (plant sterols) present in soyabean based lipid infusions may decrease bile secretion and contribute to cholesatasis [65]. What remains unclear is whether the increase in serum phytosterols is a result of impaired hepatic function or a cause of impaired hepatic function. There is limited data for the treatment of IFALD in adults short of intravenous lipid reduction (to a maximum of 1 g/kg/day) [13], and even here there is no prospectively-controlled data to support this practice. Two single retrospective case reports suggest some potential value of the use of a fish oil-based lipid emulsion in adults with IFALD [66, 67].

Manganese toxicity has been described in association with hepatic abnormalities during PN in case reports [68–70] although it is not clear whether these heavy metals, which are eliminated in bile, accumulate in the liver because of cholestasis, or whether they directly contribute to the exacerbation of IFALD. There is concern that the amount of manganese in PN is excessive [71], although there is no data currently that the dose of copper typically provided causes liver disease outside of the presence of IFALD or other liver disease.

Pathophysiology of IFALD in Children

As in adults, the abnormal route of administration whereby nutrients reach the hepatic sinusoial bed via the hepatic artery rather than the portal vein must adversly affect the liver—but observations have focused more on the effect on the canalicular membrane and the liver's capacity to take up glucose from PN solutions in the absence of enteral feeds [2, 3]. The role of choline in restoring bile flow and reducing steatosis has not been proven in children, although choline concentrations in blood are low [38]. However, taurine may be important in reducing serum bilirubin: in a study of 236 premature infants with NEC—those who were supplemented with taurine had a significant reduction of peak bilirubin (70 μmol/L versus 140 μmol/L) [72]. Vitamin E has been shown to protect against liver injury when given pre-operatively to adults undergoing partial hepatectomy for tumour surgery [73], and the positive effects on liver biochemistry of the multisource lipid emulsion SMOFlipid (SMOFlipid™ Fresenius-Kabi, Uppsala, Sweden) reported by Goulet et al. [74] may in fact be a function of vitamin E which was found to be significantly increased in the SMOFlipid 20% when compared to Intralipid 20%, although definitive studies in IFALD are lacking.

The role of fish oils which contain relatively greater ratio of omega 3 lipids to omega 6 lipid (either multisource oils or Omegaven, Frenius-Kabi, Bad Homburg, Germany) in long term PN has been debated vigorously for two decades and opinion remains divided as to whether the the omega 3 lipids have a protective effect on sinusoidal/cholangiocyte function or whether a reduction in the pro-inflammatory omega 6 lipids is the key. An important caveat to the claims around the value of the mulitsource lipid SMOF (Fresenius-Kabi, Bad Homburg, Germany; contains soya oil; medium chain fatty acids; olive oil and fish oil) is that although many studies have demonstrated a an improvement in serum bilirubin concentration, improvement has not generally been seen in alkaline phosphatase and improvement is variable for hepatic aminotransferases [11]. More importantly, the long term outcomes are unknown and there are publications calling attention to the development of fibrosis and cirrhosis despite the use of this lipid emulsion in children who have normal or close to normal hepatic aminotransferases [11–13]. This lack of concordance between hepatic aminotransferases tests and liver histology is of concern and shows that improved means of monitoring and detecting IFALD are needed (see later section).

Perhaps because of the obvious immaturity of organ function (liver and intestine) of infants and children, the concept of toxic stress (excess calories/hypertonic glucose/phytosterols/w6 fats) as an important driver of IFALD has gained particular traction in the paediatric literature [33]. This, combined with deficiency of protective factors (vitamin E, taurine and choline) and amplification by endogenous factors such as abdominal sepsis especially NEC and VAP-1 released by inflammed bowel [29, 30], and the role of bacterial overgrowth have resulted in IFALD being regarded as a multi-stage condition requiring multiple triggers [75–77]. See Fig. 5 processes leading to steatosis and fibrosis.

There is increasing acknowledgement of role of bacterial overgrowth especially in dilated and/or, obstructed bowel. Hukkinen et al. [78] reported a relationship between degree of dilatation of bowel and blood stream infections. The small bowel diammeter (sbd) was standardised to vertebral height (vh) and a ratio of sbd to vh was derived: ratio of >2.71 predicted PN dependency. Dilatation of the bowel also correlated with: increased faecal calprotectin; serum bilirubin; and gamma glutamyl transferase (GGT); pre-albumin and inversely correlated with citrulline [78]. Patients with dilated bowel were also more likely to demonstrate abnormal liver histology (i.e. increased portal inflammation and cholestastis).

The importance of the intestinal microbiome in a wide range of diseases is well described and has led to the notion that a "fibrogenic microbiome" exists [76, 77]. Rifaximin was found in rodent study to significantly reduce portal pressure, fibrosis, and angiogenesis and a follow up study in TLR4 mutant mice confirmed that the effect of rifaximin was dependent on lipolysachharide acting via the TLR4 pathway [77]. In a study of 21 children with intestinal failure the loss of bacterial diversity in the colon and an overabundence of Lactobacilli, Proteobacteria, and Actinobacteria correlated with steatosis and fibrosis, which was noted to be a stronger association with steatosis than duration of PN or bowel length [75]. These studies point to the loss of barrier function as being the key link between abnormal bowel; bacterial overgrowth, the "fibrogenic microbiome" and the development of IFALD in children [79] and adults [80]. There are only few human studies published as yet but this is an expanding field and the excellent review of the literature by Cahova et al. [81] is a good source of further information.

It is appreciated that the Gut-Liver axis is fundamental to health with many examples of the impact of disease in the bowel leading to liver dysfunction (e.g. inflammatory bowel disease and autoimmune hepatitis) and the most obvious example in intestinal failure is the adverse impact of necrotising enterocolitis on the liver [20]. Disruption to the enterohepatic circulation is inevitable in short bowel syndrome especially if the distal ileum is affected as this is the region of the bowel which contains cell surface active transporter channels for the re-absorption of bile acids. Furthermore reduced bowel mass leads to less ileal fibroblast growth factor-19 (FGF-19) [81, 82] and, since FGF-19 activates the nuclear transcription factor frasenoid X (FXR) in hepato-

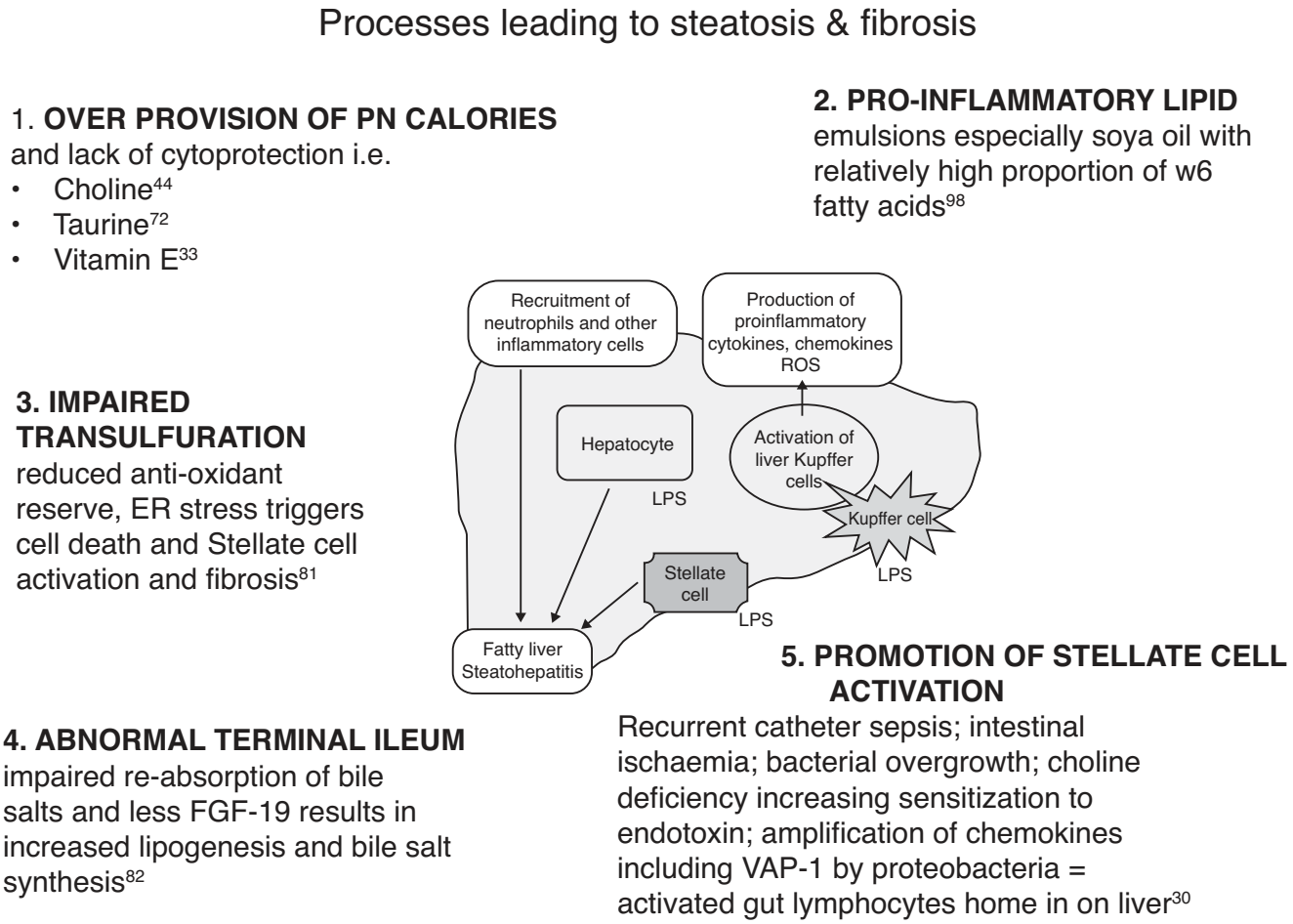

Fig. 5 Processes leading to steatosis and fibrosis in IFALD

cytes, a lack of FXR ensues. The lack of FXR in short bowel syndrome permits excess lipogenesis and bile salt synthesis [83, 84] and this leads on to the observed development of steatosis and fibrosis reported in IFALD [85]. See Fig. 6 liver-gut axis in IFALD. However, recent investigation suggests the residual bowel ina model of short bowel syndrome in fetal pigs is unable to respond to FXR activation, casting doubt for FXR as a treatment for IFALD [86].

Detecting IFALD

The monitoring of patients on PN is routine and rightly includes measures of anthropometry and biochemical stability. Normal liver function and transaminases do not necessarily correlate with a healthy liver as is clear from reports of hepatic fibrosis and cirrhosis in adults and children with normal LFTs [10–12]. In addition, the haemodynamics of the splanchnic circulatory system are different in intestinal failure: typically lower portal blood flow ensues, and this may result in lesser varices and trivial ascites except in advanced cases. This means that fibrosis and cirrhosis can be easily overlooked. However, regular abdominal ultrasound every 6–12 months may be valuable [87]: changes in hepatic parenchyma reflectivity and the size of spleen may give early warning of steatosis and fibrosis. Biliary sludge and obstruction to the biliary tree may also be detected prior to frank jaundice. See Fig. 7—impacted gall stones in a young adult with gastroschisis who required PN for first 12 months of life.

In addition to spleen size on ultrasonography, hypersplenism may be tracked by regular measurements of the platelet count [88], but it is often unclear whether thrombocytopaenia it is acting as a surrogate marker for portal hypertension or inflammation, or both.

Specific tests for IFALD are not available—detection depends on the exclusion of primary liver pathologies (e.g. heterozygote or homozygous alpha 1 antitrypsin deficiency; thyroid disease; viral hepatitis; autoimmune disease) and a baseline abdominal ultrasound, CT or MR, which are especially useful for the detection of steatosis, which may be diffuse. Liver biopsy is not usually necessary in mild IFALD, except when staging of liver disease is helpful or where there is persisting diagnostic uncertainty. Other less invasive tests

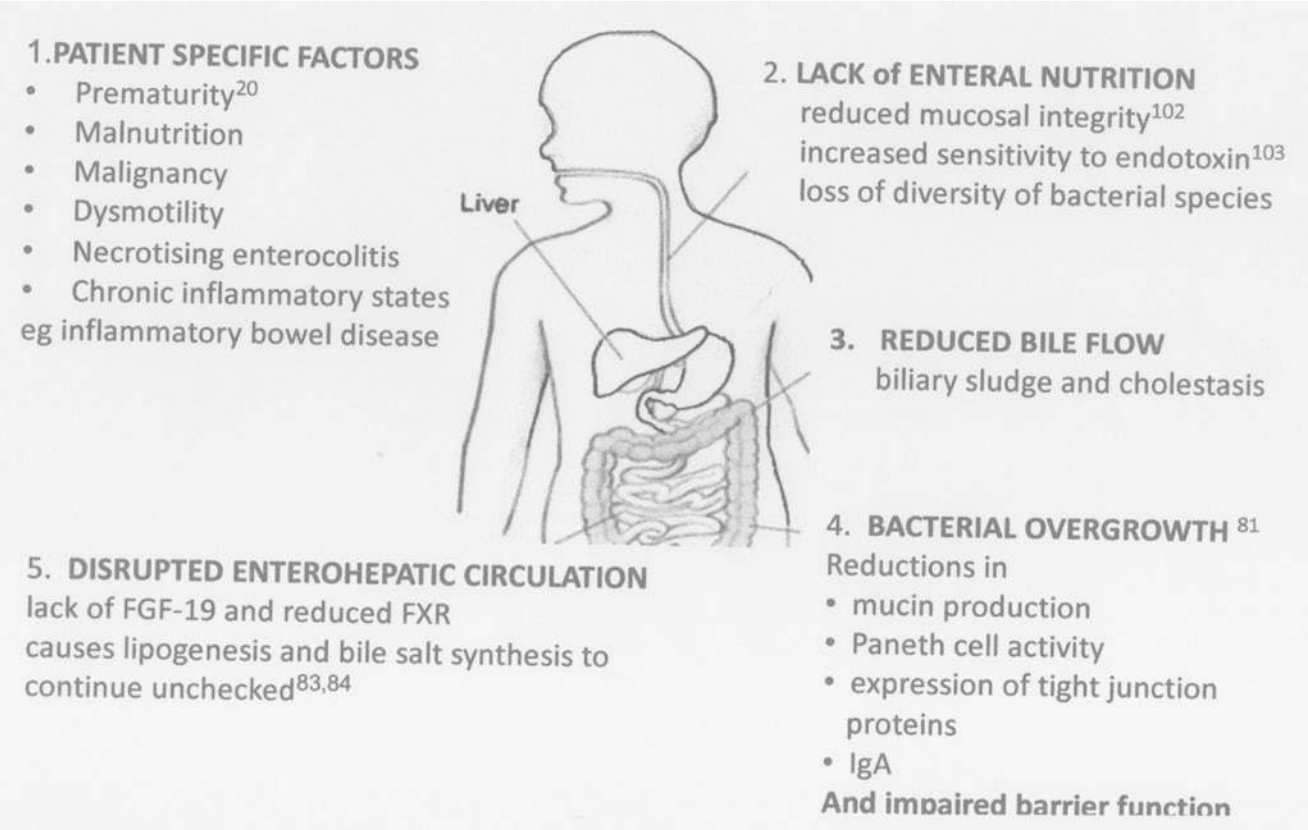

Fig. 6 Liver–Gut axis in IFALD

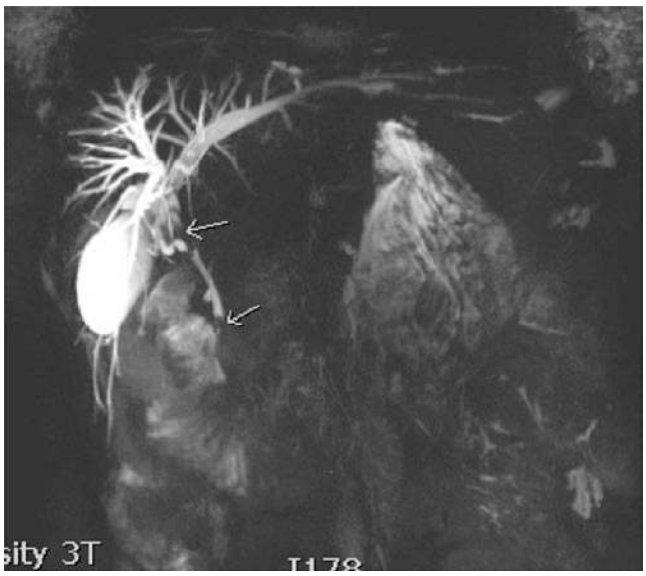

Fig. 7 Illustration of biliary disease in a child with short bowel syndrome—MRCP arrows show areas of filling defect caused by bilary sludge and impacted gall stone

such as the AST to platelet ratio (APRI) score have been used to predict cholestasis in children but doe not correlate with fibrosis. Hukkinen et al. in a retrospective study [89] reported on 57 children who receive PN ≥3 months and found raised AST and bilirubin levels were found in 51%, splenomegaly in 26%, and oesophageal varices in 3.5%. All the children had at least one liver biopsy and histological fibrosis was present in 61% (Metavir stage F1; 27%, F2; 26%, F3-4; 9%), cholestasis and steatosis was noted in a quarter. This group found that transient elastography was superior to APRI in predicting fibrosis Metavir F2 0.73 (95% CI 0.59–0.88). However, in adults, elastography appears to correlate better with cholestasis then it does with fibrosis [90].

Other non-invasive tests include: serum markers of collagen synthesis (cytokeratin 18 fragment levels, hyaluronic acid, matrix metalloproteinase [75]; and [13 C] methionine breath test [91]). Duro et al. found that intravenous. administration of the stable isotope [C]-Met was straight forward and, in five patients who were studied serially, the [C]-Met breath sampling reflected changing paediatric end stage liver disease (PELD) scores [91]. These tests are very interesting and may provide a more dynamic measure of liver dysfunction in IFALD than other measures, but the number of patients studied is small and not yet validated with long term outcomes. See Fig. 8 algorithm to evaluate abnormal liver function in children and adults with intestinal failure.

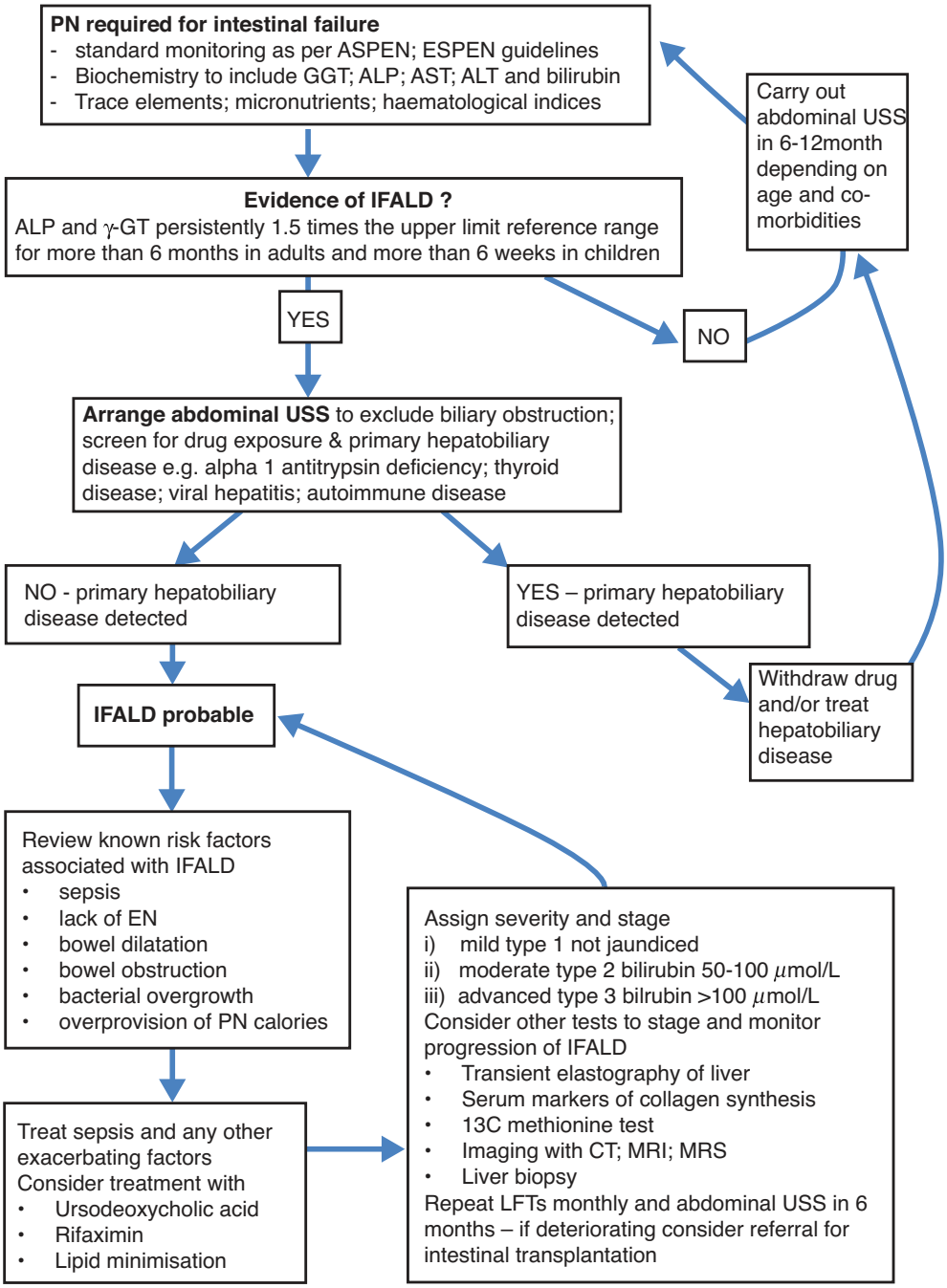

Fig. 8 Algorithm for detecting IFALD

Managing IFALD in Children and Adults

The management of IFALD in children and adults has common principles which include scrupulous attention to the PN prescription which should avoid excess calories in the form of carbohydrates [8] and minimisation of lipids [13, 92–94]. There is long history of the use of substrates with cytoprotective properties e.g. choline [42, 44] and taurine [72] and and more recently the role of vitamin E which is added in high concentrations in newer lipids to prevent peri-oxidation, but may have a cytoprotective role equal to the use of fish oils [33, 73, 74].

Lipid management strategies is a term which covers a huge range of approaches to mitigate the the pro-inflammtory nature of soyabean oil and its role in IFALD. The term includes: reduction or removal altogether of soya oil lipid infusions (usually for limited periods only in order to avoid development of essential fatty acid deficiency); the use of mixed source lipid emulsions containing another of lipids

added to Soya oil lipid such olive oil (Clinolipid®, Baxter Healthcare Corporation, Deerfield, IL) or medium chain triglyceride (Lipofundin® MCT/LCT; B Braun, Mesungen, Germany), and multisource lipid emulsions containing soyabean oil; medium chain triglyeride (from coconut oil); olive oil and fish oil (SMOFlipid™ Fresenius-Kabi, Uppsala, Sweden). Omegaven (Frenius-Kabi, Bad Homburg, Germany) is also used especially in the United states of America—this last lipid consists entirely of fish oil as a 10% emulsion. There are some significant claims for SMOF and Omegaven but although cholestasis improves, there are reports that these lipid sources do not arrest the development of fibrosis [11, 12, 95–97]. Whilst most agree that lipids can contribute to the pro-infammatory signal coming from the bowel or septic states, there is no clear agreement about which type of lipid, if any, is best for prevent hepatic deterioration in patients on long term PN [97]. A pragmatic approach is to substitute at least half the soya bean oil with any other [33, 98].

Enteral feeding in short bowel syndrome should be promoted and started as soon as possible as it may improve function of the residual bowel and is associated with beneficial effects on gut permeability [99]. A study of patients in critical care randomly allocated to recive either EN or TPN found that permeability was increased in both groups initially compared to controls, but only in the EN group did the recovery of lactulose relative to rhannose start to fall, suggesting that mucosal integrity is better maintained by the institution of EN [100] although the clinical ramifications of this observation are unknown. The hypothesis that excluding EN and relying on TPN can adversely affect response to endotoxin was tested in small group of human volunteers who were given either TPN or EN and then challenged with endotoxin—the TPN group had an exaggerated physiological response with twice as much tumor necrosis factor detected and significantly increased serum lactate and C-reactive protein [101].

It is not certain what component of EN, if any specific component(s), is beneficial in improving the mucosal integrity of stressed GI tracts: it could be the role of nutrients in the bowel acting locally on the mucosa, or EN may be influencing the microbiome. The lack of EN is associated with a loss of diversity of bacterial species combied with overabundance of Lactobacilli, Proteobacteria, and Actinobacteria is linked with reduced mucin production by Goblet cells; reduced Paneth cell activity; reduced expression of proteins associated with tight junctions and reduced IgA - all of which contribute to reduced intestinal epithelia barrier function [81]. The microbiome in children with IFALD and short bowel has been reported to show less diversity than in healthy children although it is not clear whether this directly leads to liver disease or whether it is and epiphenomenon of the short bowel syndrome causing an abnormal microbiome [75]. Overabundance of Lactobacilli and decreased abundance of Ruminococcus has also been reported in children with short bowel syndrome and increased bowel frequency [102].

Ursodeoxycholic acid may be helpful in preventing biliary sludge gall stones especially in babies with low enteral intake. In a prospective, double-blind, placebo-controlled study of ursodeoxycholic acid in preterm infants, fecal fat excretion decreased and achievement of full enteral feeding was slightly earlier in the UDCA group, but these differences did not quite reach significance, although the gamma-glutamyl transferase activity was significantly lower in the UDCA treated group for the duration of the study [103]. A smaller study in very low birth weight babies showed some benefits of ursodeoxycholic acid: the group given ursodeoxycholic acid had a shorter period of jaundice than the control group [104]. However, there is no prospective data to support the role of ursodeoxycholic acid in adults.

Multidisciplinary nutrition support teams faciliate monitoring (as per algorithm in Fig. 8) and staff training [105] in the care of feeding catheters, and are well established approaches for minimising liver disease in intestinal failure [106]. Dedicated multidisciplinary expert teams not only improve staff training but the increasing prevalance of such teams is thought to be behind the overall improvements in long term outcomes of intestinal failure and the reduction in IFALD [25]. These teams allow timely management of dilated/obstructed/bowel with tapering surgery [78, 107]. Dedicated vascular access teams have been shown to have good long term results for vessel patency [108] and are especially important for children and adults who may need PN for years.

The relationship between induction of inflamatory states by sepsis especially the role of endotoxin and other products of gram negative bacteria is well known and thus attempts to minimise infection from the bowel and/or catheter related blood stream infections (CRBSI) are now part of the management of IFALD. Octenisan skin washes have been shown to reduce CRBSI [109] and a study of 200 adult patients the use of taurolidine line locks was associated with a five-fold reduction in the incidence of CRBSI [110].

Intestinal Transplantation for IFALD

Patients who demonstrate signs of worsening liver disease despite the measures above should be considered for isolated intestinal transplantation before irreresible liver disease supervenes. But the timing of referral can be difficult as depending on liver function tests alone can provide false re-assurance. Regular liaison with an intestinal transplant centre and professional collaborations are key to identifying that point where a patient could benefit from an isolated small bowel transplant [27, 98]. This topic has been reviewed recently [99] and based on reports that sustained but mild hyperbilirubinaemia can be reversed once enteral feeding is re-established after successful small bowel trans-

plant [19], the following criteria based on degree of hepatic fibrosis and markers of portal hypertension/hypersplenism are proposed: (1) Total plasma bilirubin <100–120 mmol/L. (2) Minimal hepatosplenomegaly. (3) Platelet count >150,000 × 10^9/L. (4) Stage 1 or 2 fibrosis on biopsy. Once patients are listed for isolated intestine transplant, it is important they are re-evaluated if they wait longer than a few months for a donor, and especially after any septic episode given the likelihood of progression of IFALD. Combined liver-small bowel transplantation should not be necessary if isolated intestinal transplantation is performed at an appropriate time.

References

1. Stegink LD, Den Besten L. Synthesis of cysteine from methionine in normal adult subjects: effects of route of alimentation. Science. 1972;178:514–6.
2. Black DD, Suttle EA, Whitington PF, Whitington GL, Korones SD. The effect of short-term total parenteral nutrition on hepatic function in the human neonate: a prospective randomized study demonstrating alteration of hepatic canalicular function. J Pediatr. 1981;99(3):445–9.
3. Chen SS, Torres-Snachez CJ, Hosein N, Zhang Y, Brooks Lacy D, Change C, McGuinness OP. Route-dependent effect of nutritional support on liver glucose uptake. AJP Regul Integr Comp Physiol. 2005;289:1319–27. https://doi.org/10.1152/ajpregu.00175.2005.
4. Pendon VH, Witzeleben CL, Skelton MA. Total parenteral nutrition. J Peds. 1971;78:180–1.
5. James OFW. Nonalcoholic fatty liver disease. In: Yamada T, Alpers DH, Kaplowitz N, Laine L, Owyang O, Powell DW, editors. Textbook of gastroenterology. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2003. p. 2437–44.
6. Buchman AL, Naini BV, Spilker B. The differentiation of intestine failure-associated liver disease from nonalcoholic fatty liver and nonalcoholic steatohepatitis. Semin Liver Dis. 2017;37:33–44.
7. Grant JP, Cox CE, Kleinman LM, et al. Serum hepatic enzyme and bilirubin elevations during parenteral nutrition. Surg Gynecol Obstet. 1977;145:573–80.
8. Burke JF, Wolfe RR, Mullany CJ, et al. Glucose requirements following burn injury. Parameters of optimal glucose infusion and possible hepatic and respiratory abnormalities following excessive glucose intake. Ann Surg. 1979;190:274–85.
9. Clarke PJ, Ball MJ, Kettlewell MGW. Liver function tests in patients receiving parenteral nutrition. JPEN. 1991;15:54–9.
10. Sax HC, Talamini MA, Brackett K, Fischer JE. Hepatic steatosis in parenteral nutrition: failure of fatty infiltration to correlate with abnormal serum hepatic enzyme levels. Surgery. 1986;100:697–704.
11. Mercer DF, et al. Hepatic fibrosis persists and progresses despite biochemical improvement in children treated with intravenous fish oil emulsion. J Pediatr Gastroenterol Nutr. 2013;56:364–9.
12. Matsumoto CS, Kaufman SS, Island ER, Kallakury B, Yazigi NA, Khan KM, Fishbein TM. Hepatic explant pathology of pediatric intestinal transplant recipients previously treated with omega-3 fatty acid lipid emulsion. J Pediatr. 2014;165:59–64.
13. Cavicchi M, Beau P, Crenn P, et al. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med. 2000;132:525–32.
14. Chan S, McCowen KC, Bistrian BC, et al. Incidence, prognosis, and etiology of end-stage liver disease in patients receiving home total parenteral nutrition. Surgery. 1999;126:28–34.
15. Pironi L, Goulet O, Buchman AL, et al. Outcome on home parenteral nutrition for benign intestinal failure: a review of the literature and benchmarking with the European prospective survey of ESPEN. Clin Nutr. 2012;31:831–45.
16. Buchman AL. Short bowel syndrome. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fortran's gastrointestinal disease. 9th ed. Philadelphia: Saunders; 2010. p. 1779–95.
17. Buchman AL, Iyer K, Fryer J. Parenteral nutrition-associated liver disease and the role for isolated intestine and intestine/liver transplantation. Hepatology. 2006;43:9–19.
18. Fiel MI, Wu HS, Iyer K, et al. Rapid reversal of parenteral nutrition-associated cirrhosis following isolated intestinal transplantation. J Gastrointest Surg. 2009;13:1717–23.
19. Fishbein TM, Kaufman SS, Florman SS, et al. Isolated intestinal transplantation: proof of clinical efficacy. Transplantation. 2003;76(4):636–40.
20. Hsieh MH, et al. Parenteral nutrition-associated cholestasis in premature babies: risk factors and predictors. Pediatr Neonatol. 2009;50:202–7.
21. Beath SV, Davies P, Papadopoulou A, Khan AR, Buick RG, Corkery JJ, Gornall P, Booth IW. Parenteral nutrition-related cholestasis in postsurgical neonates: multivariate analysis of risk factors. J Pediatr Surg. 1996;31(4):604–6.
22. Vina J, Vento M, Garcia-Sale F, et al. L-cysteine and glutathione metabolism are impaired in premature infants due to cystathionase deficiency. Am J Clin Nutr. 1995;61:1067–9.
23. Lauriti G, et al. Incidence, prevention, and treatment of parenteral nutrition-associated cholestasis and intestinal failure-associated liver disease in infants and children: a systematic review. JPEN J Parenter Enteral Nutr. 2014;38:70–85.
24. Hess RA, et al. Survival outcomes of pediatric intestinal failure patients: analysis of factors contributing to improved survival over the past two decades. J Surg Res. 2011;170:27–31.
25. Grant D, et al. Intestinal transplant registry report: global activity and trends. Am J Transplant. 2015;15:210–9.
26. Pironi L, Arends J, Baxter J, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34:171–80.
27. Beath S, Pironi L, Gabe S, et al. Collaborative strategies to reduce mortality and morbidity in patients with chronic intestinal failure including those who are referred for small bowel transplantation. Transplantation. 2008;85:1378–84.
28. European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPID) supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005;41(Suppl 2):1–87.
29. Welham ML. VAP-1: a new anti-inflammatory target? Blood. 2004;103:3250–1.
30. Lalor PF, et al. Activation of vascular adhesion protein-1 on liver endothelium results in an NF-kappa B-dependent increase in lymphocyte adhesion. Hepatology. 2007;45:465–74.
31. Naini BV, Lassman CR. Total parenteral nutrition therapy and liver injury: a histopathologic study with clinical correlation. Hum Pathol. 2012;43:826–33.
32. Beath SV, Needham SJ, Kelly DA, Booth IW, Raafat F, Buick RG, Buckels JAC, Mayer AD. Clinical features and prognosis of children assessed for isolated small bowel (ISBTx) or combined small bowel and liver transplantation (CSBLTx). J Pediatr Surg. 1997;32:459–61.

33. Lee WS, Sokol RJ. Intestinal microbiota, lipids, and the pathogenesis of intestinal failure-associated liver disease. J Pediatr. 2015;167:519–26.
34. Yeop I, Taylor CJ, Narula P, Johnson L, Bowen C, Gupte GL. Hepatocellular carcinoma in a child with intestinal failure-associated liver disease. J Pediatr Gastroenterol Nutr. 2012;54(5):695–7.
35. Santra S, McKiernan P, Lander A, Dalzell AM, Baillie C, Beath S, Gupte GL. Ischemic hepatitis is a risk factor for progression of liver disease associated with parenteral nutrition in intestinal failure. J Pediatr Gastroenterol Nutr. 2008;47(3):367–9.
36. Stanko RT, Nathan G, Mendelow H, et al. Development of hepatic cholestasis and fibrosis in patients with massive loss of intestine supported by prolonged parenteral nutrition. Gastroenterology. 1987;92:197–202.
37. Chawla RK, Berry CJ, Kutner MH, Rudman D. Plasma concentrations of transsuluration pathway products during nasoenteral and intravenous hyperalimentation of malnourished patients. Am J Clin Nutr. 1985;42:577–84.
38. Sentongo TA, Kumar P, Karza K, et al. Whole blood free choline and choline metabolites in infants who require chronic parenteral nutrition therapy. J Pediatr Gastroenterol Nutr. 2010;50: 194–9.
39. Riedijk MA, Stoll B, Chacko S, et al. Methionine transmythelation and transsulfuration in the piglet gastrointestinal tract. Proc Natl Acad Sci U S A. 2007;104:3408–13.
40. Waterhouse C, Clarke EF, Heinig RE, et al. Free amino acid levels in the blood stream of patients undergoing parenteral alimentation. Am J Clin Nutr. 1979;32:2423–9.
41. Dahlstrom KA, Ament ME, Laidlaw SA, Kopple JD. Plasma amino acid concentrations in children receiving long-term parenteral nutrition. J Pediatr Gastroenterol Nutr. 1988;7:748–54.
42. Buchman AL, Dubin M, Jenden D, et al. Lecithin increases plasma free choline and decreases hepatic steatosis in long-term parenteral nutrition patients. Gastroenterology. 1992;102:1363–70.
43. Compher CW, Kinosian BP, Stoner NE, et al. Choline and vitamin B12 deficiencies are interrelated in folate-replete parenteral nutrition-dependent patients. JPEN. 2002;26:57–62.
44. Buchman AL, Ament ME, Sohel M, et al. Choline causes reversible hepatic abnormalities in patients receiving parenteral nutrition: proof of a human choline requirement: a placebo-controlled trial. JPEN. 2001;25:260–8.
45. LeBlanc MJ, Gavino V, Perea A, et al. The role of dietary choline on the role of beneficial effects of lecithin on the secretion of biliary lipids in rats. Biochim Biophys Acta. 1998;1393:223–34.
46. Rivera A Jr, Bhatia J, Rassin DK, et al. In vivo biliary function in the adult rat: the effect of parenteral glucose and amino acids. JPEN. 1989;13:240–5.
47. Duerksen DR, Van Aerde JE, Chan G, et al. Total parenteral nutrition impairs bile flow and alters bile composition in newborn piglet. Dig Dis Sci. 1996;41:1864–70.
48. Vanwijngaerden YM, Langouche L, Derde S, et al. Impact of parenteral nutrition versus fasting on hepatic bile acid production and transport in a rabbit model of prolonged critical illness. Shock. 2014;41:48–54.
49. MacDonald GA, Bridle KR, Ward PJ, et al. Lipid peroxidation in hepatic steatosis in humans is associated with hepatic fibrosis and occurs predominately in acinar zone 3. J Gastroenterol Hepatol. 2001;16:599–606.
50. Massarenti P, Biasi F, De Francesco A, et al. 4-hydroxynonenal is markedly higher in patients on a standard long-term home parenteral nutrition. Free Radic Res. 2004;38:73–80.
51. Eastin CE, McClain CJ, Lee EY, et al. Choline deficiency augments and antibody to tumor necrosis factor attenuates endotoxin-induced hepatic injury. Alcohol Clin Exp Res. 1997;21: 1037–41.
52. Cook GC, Hutt MSR. The liver after kwashiorkor. BMJ. 1967;3:454.
53. Richardson TJ, Sgoutas D. Essential fatty acid deficiency in four adult patients during total parenteral nutrition. Am J Clin Nutr. 1975;28:258–63.
54. Rielia MC, Broviac JW, Wells M, Scribner BH. Essential fatty acid deficiency in human adults during total parenteral nutrition. Ann Intern Med. 1975;83:786–9.
55. Reif S, Tano M, Oliveio R, et al. Total parenteral nutrition-induced steatosis: reversal by parenteral lipid infusion. JPEN. 1991;15:102–4.
56. Faulkner WJ, Flint LM. Essential fatty acid deficiency associated with total parenteral nutrition. Surg Gynecol Obstet. 1977;144:665–7.
57. Karpati G, Carpenter S, Engel AG, et al. The syndrome of systemic carnitine deficiency: clinical, morphologic, biochemical, and pathologic features. Neurology. 1975;25:16–24.
58. Moukarzel AA, Dahlstrom KA, Buchman AL, et al. Carnitine status of children receiving long-term total parenteral nutrition: a longitudinal prospective study. J Pediatr. 1992;20:759–62.
59. Bowyer BA, Mils JM, Haymond MW, et al. L-carnitine therapy in home parenteral nutrition patients with abnormal liver tests and low plasma carnitine concentration. Gastroenterology. 1988;94:434–8.
60. Meduit MM, Akahoshi MF, Jeffers S, et al. Amelioration of metabolic complications of conventional parenteral nutrition. Arch Surg. 1984;119:1294–8.
61. Kaminski DL, Adams A, Jellinck M. The effect of hyperalimentation on hepatic lipid content and lipogenic enzyme activity in rats and man. Surgery. 1980;88:93–100.
62. Hwang TL, Lue MC, Chen LL. Early use of cyclic TPN prevents further detioration of liver functions for the TPN patients with impaired liver function. Hepato-Gastroenterology. 2000;47:1347–50.
63. Salvian AJ, Allardyce DB. Impaired bilirubin secretion during total parenteral nutrition. J Surg Res. 1980;28:547–55.
64. Allardyce DB. Cholestasis caused by lipid emulsions. Surg Gynecol Obstet. 1982;154:641–7.
65. Iyer KR, Spitz L, Clayton P. BAPS prize lecture: new insight into mechanisms of parenteral nutrition-associated cholestasis; role of plant sterols. J Pediatr Surg. 1998;33:1–6.
66. Burns DL, Gill BM. Reversal of parenteral nutrition-associated liver disease with a fish oil-based lipid emulsion (Omegaven) in an adult dependent on home parenteral nutrition. JPEN. 2013;37:274–80.
67. Venecourt-Jackson E, Hill SJ, Walmsley RS. Successful treatment of parenteral nutrition-associated liver disease in an adult by use of a fish oil-based lipid source. Nutrition. 2013;29:365–8.
68. Ejima A, Imaamura T, Nakamura S, et al. Manganese intoxication during parenteral nutrition (letter). Lancet. 1992;339:426.
69. Taylor S, Manara AT. Manganese toxicity in a patient with cholestasis receiving total parenteral nutrition (letter). Anaethesia. 1994;19:1013.
70. Azaz A, Thomas A, Miller V, et al. Manganese in long term pediatric parenteral nutrition (letter). Arch Dis Child. 1995;73:89.
71. Vanek VW, Borum P, Buchman AL, et al. A.S.P.E.N. position paper: recommendations for changes in commercially-available parenteral multivitamin and multi-trace element products. Nutr Clin Pract. 2012;27:440–91.
72. Spencer AU, et al. Parenteral nutrition-associated cholestasis in neonates: multivariate analysis of the potential protective effect of taurine. JPEN J Parenter Enteral Nutr. 2005;29:337–43.
73. Bartels M, Biesalski HK, Engelhart K, Sendlhofer G, Rehak P, Nagel E. Pilot study on the effect of parenteral vitamin E on ischemia and reperfusion induced liver injury: a double blind, randomized, placebo-controlled trial. Clin Nutr. 2004;23(6):1360–70.

74. Goulet O, Antébi H, Wolf C, Talbotec C, Alcindor LG, Corriol O, Lamor M, Colomb-Jung V. A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2010;34(5):485–95.
75. Korpela K, Mutanen A, Salonen A, Savilahti E, de Vos WM, Pakarinen MP. Intestinal microbiota signatures associated with histological liver steatosis in pediatric-onset intestinal failure. JPEN J Parenter Enteral Nutr. 2017;41:238–48. https://doi.org/10.1177/0148607115584388. Epub 2016 Sep 30.
76. De Minicis S, Rychlicki C, Agostinelli L, Saccomanno S, Candelaresi C, Trozzi L, Mingarelli E, Facinelli B, Magi G. Dysbiosis contributes to fibrogenesis in the course of chronic liverinjury in mice. Hepatology. 2014;59:1738–49.
77. Zhu Q, Zou L, Jagavelu K, Simonetto DA, Huebert RC, Jiang ZD, DuPont HL, Shah VH. Intestinal decontamination inhibits TLR4 dependent fibronectin-mediated cross-talk between stellate cells and endothelial cells in liver fibrosis in mice. J Hepatol. 2012;56:893–9.
78. Hukkinen M, Mutanen A, Pakarinen MP. Small bowel dilation in children with short bowel syndrome is associated with mucosal damage, bowel-derived bloodstream infections, and hepatic injury. Surgery. 2017;162:670–9.
79. Parm U, Metsvaht T, Ilmoja ML, Lutsar I. Gut colonization by aerobic microorganisms is associated with route and type of nutrition in premature neonates. Nutr Res. 2015;35:496–503.
80. Joly F, Mayeur C, Bruneau A, Noordine ML, Meylheuc T, Langella P, Messing B, Duée PH, Cherbuy C, Thomas M. Drastic changes in fecal and mucosa-associated microbiota in adult patients with short bowel syndrome. Biochimie. 2010;92:753–61.
81. Cahova M, Bratova M, Wohl P. Parenteral nutrition-associated liver disease: the role of the gut microbiota nutrients. Nutrients. 2017;9:987–106. https://doi.org/10.3390/nu9090987.
82. Mutanen A, Lohi J, Heikkilä P, Jalanko H, Pakarinen MP. Loss of ileum decreases serum fibroblast growth factor 19 in relation to liver inflammation and fibrosis in pediatric onset intestinal failure. J Hepatol. 2015;62:1391–7.
83. Ali AH, et al. Recent advances in the development of farnesoid X receptor agonists. Ann Transl Med. 2015;3:5.
84. Legry V, et al. Yin Yang 1 and farsenoid X receptor: a balancing act in non-alcoholic fatty liver disease. Gut. 2014;63:1–2.
85. Pereira-Fantini PM, Lapthorne S, Joyce SA, Dellios NL, Wilson G, Fouhy F, Thomas SL, Scurr M, Hill C, Gahan CG, Cotter PD, Fuller PJ, Hardikar W, Bines JE. Altered FXR signalling is associated with bile acid dysmetabolism in short bowel syndrome-associated liver disease. J Hepatol. 2014;61:1115–25.
86. Pereira-Fantini PM, Lapthorne S, Gahan CGM, Joyce SA, Charles J, Fuller PJ. Farnesoid X receptor agonist treatment alters bile acid metabolism but exacerbates liver damage in a piglet model of Short-Bowel syndrome. Cell Mol Gastroenterol Hepatol. 2017;4:65–74.
87. Pichler J, Watson T, McHugh K, Hill S. Prevalence of gallstones compared in children with different intravenous lipids. J Pediatr Gastroenterol Nutr. 2015;61(2):253–9.
88. Kaufman SS, Pehlivanova M, Fennelly EM, Rekhtman YM, Gondolesi GE, Little CA, Matsumoto CS, Fishbein TM. Predicting liver failure in parenteral nutrition-dependent short bowel syndrome of infancy. J Peds. 2010;156:580–5.
89. Hukkinen M, Kivisaari R, Lohi J, Heikkilä P, Mutanen A, Merras-Salmio L, Pakarinen MP. Transient elastography and aspartate aminotransferase to platelet ratio predict liver injury in paediatric intestinal failure. Liver Int. 2016;36:361–9.
90. Van Gossum A, Pironi L, Messing B, et al. Transient elastography (FibroScan) is not correlated with liver fibrosis but with cholestasis in patients with long-term home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2015;39:719–24.
91. Duro D, Fitizgibbons S, Valim C, Yang CFJ, Zurakowski D, Dolan M, Bechard L, Yu LM, Duggan C, Jaksic T. [13C]Methionine breath test to assess intestinal failure-associated liver disease. Pediatr Res. 2010;68:349–54.
92. Lumen W, Shaffer JL. Prevalence, outcome and associated factors of deranged liver function tests in patients on home parenteral nutrition. Clin Nutr. 2002;21:337–43.
93. Wales PW, et al. Clinical guidelines: support of pediatric patients with intestinal failure at risk of parenteral nutrition-associated liver disease. J Parenter Enter Nutr. 2014;38:538–57.
94. Lacaille F, et al. A position paper by the ESPGHAN Working Group of intestinal failure and intestinal transplantation. J Pediatr Gastroenterol Nutr. 2015;60:272–83.
95. Belza C, Thompson R, Somers GR, de Silva N, Fitzgerald K, Steinberg K, Courtney-Martin G, Wales PW, Avitzur Y. Persistence of hepatic fibrosis in pediatric intestinal failure patients treated with intravenous fish oil lipid emulsion. J Pediatr Surg. 2017;52:795–801.
96. Teng J, Arnell H, Bohlin K, Nemeth A, Fischler B. Impact of Parenteral Fat composition on cholestasis in pre-term neonates. J Pediatr Gastroenterol Nutr. 2015;60:703–7.
97. Anez-Bustillos L, Dao DT, Baker MA, Fell GL, Puder M, Gura KM. Intravenous fat emulsion formulations for the adult and pediatric patient: understanding the differences. Nutr Clin Pract. 2016;31(5):596–609. https://doi.org/10.1177/0884533616662996.
98. Hojsak I, Colomb V, Braegger C, Bronsky J, Campoy C, Domellöf M, Embleton N, Fidler Mis N, Hulst JM, Indrio F, Lapillonne A, Mihatsch W, Molgaard C, van Goudoever J, Fewtrell M. Intravenous lipid emulsions and risk of hepatotoxicity in infants and children: a systematic review and meta-analysis. J Pediatr Gastroenterol Nutr. 2016;62:776–92.
99. Hawksworth JS, Desai CS, Khan KM, Kaufman SS, Yazigi N, Girlanda R, Kroemer A, Fishbein TM, Matsumoto CS. Visceral transplantation in patients with intestinal-failure associated liver disease: evolving indications, graft selection, and outcomes. Am J Transplant. 2018;18(6):1312–20. https://doi.org/10.1111/ajt.14715.
100. Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. Am J Respir Crit Care Med. 1995;152(5):1545–8.
101. Fong YM, Marano MA, Barber A, He W, Moldawer LL, Bushman ED, Coyle SM, Shires GT, Lowry SF. Total parenteral nutrition and bowel rest modify the metabolic response to endotoxin in humans. Ann Surg. 1989;210(4):449–56.
102. Davidovics ZH, Carter BA, Luna RA, Hollister EB, Shulman RJ, Versalovic J. The fecal microbiome in pediatric patients with Short Bowel syndrome. JPEN J Parenter Enteral Nutr. 2016;40:1106–13.
103. Arslanoglu S, Moro GE, Tauschel HD, Boehm G. Ursodeoxycholic acid treatment in preterm infants: a pilot study for the prevention of cholestasis associated with total parenteral nutrition. J Pediatr Gastroenterol Nutr. 2008;46:228–31.
104. Chen CY, Tsao PN, Chen HL, Chou HC, Hsieh WS, Chang MH. Ursodeoxycholic acid (UDCA) therapy in very-low-birth-weight infants with parenteral nutrition-associated cholestasis. J Pediatr. 2004;145(3):317–21.
105. Puntis JWL, et al. Staff training: a key factor in reducing intravascular catheter sepsis. Arch Dis Child. 1991;66:335–7.
106. Sudan D, DiBaise J, Torres C, Thompson J, Raynor S, Gilroy R, Horslen S, Grant W, Botha J, Langnas A. A multidisciplinary

approach to the treatment of intestinal failure. J Gastrointest Surg. 2005;9:165–76.
107. Hukkinen M, Kivisaari R, Koivusalo A, Pakarinen MP. Risk factors and outcomes of tapering surgery for small intestinal dilatation in pediatric short bowel syndrome. J Pediatr Surg. 2017;52:1121–7.
108. Arul GS, et al. Ultrasound-guided percutaneous insertion of Hickman lines in children. Prospective study of 500 consecutive procedures. J Pediatr Surg. 2009;44:1371–6.
109. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep. 2011;51:1–82.
110. Olthof ED, Versleijen MW, Huisman de Waal G, Feuth T, Kievit W, Wanten GJ. Taurolidine lock is superior to heparin lock in the prevention of catheter related bloodstream infections and occlusions. PLoS One. 2014;9(11):e111216. https://doi.org/10.1371/journal.pone.0111216. eCollection 2014.

Acid-Base Disturbances

Barry J. M. Jones

Key Points

1. Acid-base disturbances (ABD) should be expected from the changes to anatomy and physiology in Intestinal Failure, even when the gastrointestinal tract is intact. They may be exacerbated by intravenous nutrition or saline, oral rehydration solutions, acid suppressing treatments, urinary diversion, thiamine and phosphate deficiencies, refeeding syndrome, L- or D-lactic acidosis and renal or respiratory disease.
2. Serum bicarbonate and chloride should be regularly measured in intestinal failure (IF) patients and the serum anion gap calculated as recommended by international guidelines. Blood gas measurements are occasionally needed to give further information.
3. Metabolic high anion gap acidosis occurs with renal failure, ketosis, L-lactic acidosis, thiamine deficiency and D-lactic acidosis. Coexistent impaired renal function is the most important contributory factor, tolerance of which is further impaired by respiratory disease.
4. Metabolic hyperchloraemic acidosis with a normal anion gap is common and due to bowel bicarbonate loss, sodium chloride infusions (or oral rehydration solutions) and acid suppression therapy (also urinary diversion and phosphate deficiency).
5. Metabolic alkalosis reflects loss of acid through vomiting, and/or potassium and magnesium deficiencies (often consequent upon diuretics, hypovolaemia and hyperaldosteronism) and is associated with cardiac, intestinal, muscular and neurological symptoms.
6. Respiratory acidosis results from excessive glucose infusion, particularly if respiratory disease is present.
7. Chronic acidosis leads to bone mineral loss resulting in osteoporosis.
8. Acetate (which is metabolisable) may replace chloride in parenteral nutrition (PN) infusions to reduce acidosis. Rehydration solutions not based on sodium chloride should be considered in intestinal failure patients at risk of acidosis. Additionally stopping a patients proton pump inhibitor (PPI)H_2 antagonist may also reduce acidosis.
9. Patients with a short bowel and a functioning colon in continuity may develop a high anion gap acidosis due to D-lactate (worse if thiamine deficiency and/or liver disease); this may cause profound cerebellar signs, behavioural changes and coma.
10. Patients with a jejunostomy may develop chronic renal failure from dehydration. If dialysed they should not have fluid removed (no weight loss), with additional fluid being given at the time (weight gain).
11. Muscle cramps during PN infusion are an enigma but possibly relate to acute acid-base changes or electrolyte fluxes across cell membranes. Slower infusion rates appear to relieve symptoms.

Introduction

Survival of our species depends upon maintenance of the "milieu interieur" within boundaries permitting normal metabolism. Mammals including humans have evolved to be able to cope with the production within their bodies of highly acidic and alkaline fluids without detriment to local structures or the wider metabolic balance of the body—an extraordinary and finely balanced feat of evolution. It takes very little to disturb this equilibrium yet the body is able to compensate for most of such disturbances—provided that those compensatory mechanisms are intact and the demands upon them are not excessive. The function of the gastrointestinal system depends upon the interactions between its anatomy and physiology. The gastrointestinal tract has been likened to "a sleeping bear" with regard to acid-base homeostasis [1]. It should not be surprising that disturbed anatomy leads to dis-

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ordered physiology. *In the context of intestinal failure, the gut should be considered a critical part of the acid-base metabolic system* [1]. Hitherto, the contributions of acid-base disturbances (ABD) to the complications associated with intestinal failure have not received the attention they deserve compared to other major organ failures.

The purpose of this chapter is to aid understanding, detection, treatment and avoidance of ABD in intestinal failure (IF), especially in patients with a short bowel (SB). ABD can cause profound short and long term consequences in these most complex patients.

The major contributors to acid base equilibrium are the kidneys, lungs and buffering systems within the extracellular fluids including blood and the intracellular compartment. The metabolic and excretory roles of the liver should not be forgotten with regard to metabolism of ketones, lactate, amino acids and other potentially acid substances with onward transport via blood or bile. The roles of the kidneys and lungs in the overall control of acid-base balance (ABB) are well known but the role of the gut is not. Unlike the kidneys and lungs, the gut has no role in normal acid-base homeostasis and under normal conditions, the fluxes of acid and alkali within the gut do not lead to metabolic stresses on the buffering systems or the final arbiters of acid–base balance—the kidneys and lungs. However, in patients with a SB and other causes of IF, this is not so as ABB can become severely imbalanced. The patient then becomes precariously dependent on renal and respiratory function which are often insufficient to maintain homeostasis leading to ABD. Other causes of disturbed ABB include urinary diversion to the gut, abnormal intraluminal fermentation and specific nutritional deficiencies. Parenteral nutrition and hydration with saline are major contributors to acid load. Treatment with acid suppressing agents may also prove critical in leading to metabolic acidosis. The common scenario of inadequate fluid balance places IF patients at great risk of ABD—either metabolic acidosis or alkalosis.

To adequately consider acid-base disturbances in the human suffering from intestinal failure, and in particular patients with a SB, we must first observe the main influences on acid-base balance under normal physiological conditions.

Normal Acid-Base Balance

Large amounts of H^+ and HCO_3^- traverse the gut epithelia daily and facilitate digestion and absorption of nutrients and water. When normal, only 40 mmol HCO_3^- are lost in the stool which does not stress acid-base homeostasis [1]. To the daily production of intrinsic acid production by cellular metabolism and digestion of diet, must be added the impact of fluxes of acid and alkali associated with gastric, hepatobiliary, pancreatic and ileocolonic function. Acid base equilibrium is maintained and finely controlled within the body principally by buffering systems. These include the ubiquitous carbonic anhydrase and plasma proteins such as albumin. Any net excess of acid (H^+) or alkali (HCO_3^-) from cellular metabolism must then be dealt with by the homeostatic functions of the kidneys, lungs and liver.

The production of 2 l of gastric fluid containing hydrochloric acid (HCl) in the stomach to a pH of 1–3 [1] means that a corresponding amount of alkali is left behind during the synthesis of gastric acid. There is potential for major acid-base disequilibrium if acid secretion is interrupted or absent in IF/SB and if corresponding bicarbonate production elsewhere in the gut is lost through diarrhoea or a stoma.

The buffering effect of diet, the dilution effect of oral fluid intake and alkaline saliva reduce the acidity of gastric contents which then come into contact with alkaline secretions from the duodenal ampulla. This leads to a rise in luminal pH to 6 [2] in the proximal jejunum and an average pH over the small bowel of 7 [3]. Small bowel intraluminal bicarbonate rapidly disappears [4] partly due to an active transport system but also with a rise in pCO_2 [5]. This reflects carbonic anhydrase activity in the mucosa with fluxes of hydrogen ions across the mucosa [5]. The overall impact of acid and alkaline fluxes across the length of the gut are probably neutral under normal circumstances but not so when IF is present.

The production of bicarbonate by the pancreas, hepatobiliary system and salivary glands is also a potential metabolic strain leaving behind net acid. The volume of these fluids is approximately 2.5 l/day [1] but the pH of 7.6–8.6 is not equivalent to that of gastric acid pH. Thus there must be a net residuum of acid in the gut at the level of the duodenal ampulla and proximal jejunum with a corresponding level of alkali (bicarbonate) in the extra—alimentary compartments of blood/extracellular fluids. Under normal conditions, this extraluminal excess is dealt with in the distal duodenum and jejunum by buffer systems including carbonic anhydrase and plasma proteins, notably albumin. Intraluminal pH falls again to 5.7 in the caecum but rises towards 6–7 in the rectum. Any intraluminal excess of acid is normally removed by ileal and colonic exchange of intraluminal chloride for bicarbonate [1, 4, 5]. Further influences on acid-base balance occur in the colon from the formation and absorption of acetate and other short chain fatty acids (SCFA) which are metabolised with consumption of hydrogen ions to bicarbonate, thus reducing the impact of ileocolonic secretion of bicarbonate [6].

Assuming normal buffering capacity, any net imbalances of H^+ or HCO_3^- are easily dealt with in the bowel mucosa or vascular compartments and any residual excesses of H^+ or HCO_3^- are dealt with by normal respiratory and renal function along with the usual products of cellular metabolism.

Normality also assumes normal body stores of potassium, magnesium, sodium and water and normal urinary drainage via bladder, none of which may apply in IF/SB.

Armed with an understanding of normal acid base balance and gut physiology, it should be possible to predict ABD when IF/SB is present [1] but each individual differs with regard to the quantitative impact of losses of bowel and qualitative function of the remaining bowel, as well as day to day fluid balance, oral dietary and fluid intake and renal function. The impact of dehydration on renal function and aldosterone secretion on both renal and gut function must also be factored in as well as potassium and magnesium deficiencies.

Physiology of Acid-Base Balance in IF/SB patients

The metabolic stresses of dehydration, lactic acidosis, ketoacidosis, renal impairment and infusion of acid PN regimes or "normal saline" are a challenge to the otherwise normal patient. In IF, these challenges are amplified by the metabolic stresses associated with reduced bowel length and function.

These metabolic stresses caused by IF/SB are predictable and have considerable consequences. Even when normal compensatory mechanisms are intact, ABD may occur in IF/SB [7]. ABD does not only occur in patients with a SB, but in other causes of IF in which the gut remains structurally intact but functionally incompetent, as in dysmotility syndromes in which vomiting may predominate [7]. In addition, urinary diversion to colon or ileum, and loss of gastric acid production (acid suppressing drugs, achlorhydria, gastric or vagal surgery, radiation or vomiting) may influence ABB.

To the above causes must be added the impact of the nutritional support required for treatment of IF/SB, whether it be enteral or parenteral [8]. Parenteral nutrition (PN) [9] and some enteral nutrition (EN) solutions are acid. Elemental or semi-elemental diets are usually acid and are the types of EN often used in borderline intestinal failure. So called "normal saline" is itself an acid promoting infusion [10] and saline is often the mainstay of replacing intestinal losses in "net secretors" [11]. The influence of oral rehydration solutions should also be considered [12, 13]. All IF/SB patients are as much at risk of the causes of ABD as normal patients plus those causes related to the disturbed physiology associated with IF/SB.

Net alimentary losses of acid or bicarbonate pose metabolic stresses leading to metabolic acidosis or alkalosis unless compensatory mechanisms are intact and sufficient to cope [1].

Negative water balance may cause either metabolic acidosis or alkalosis or a mixture of both linked by renal impairment [1]. Normally stable long term HPN patients can develop ABD with acute changes in hydration as a result of hot weather, intercurrent infections or increases in stomal losses, and hydration may be precarious even with full supportive measures [11].

To these disturbances can be added other causes such as D-lactic acidosis, sepsis related L-acidosis, hepatic causes (thiamine efficiency), phosphate deficiency and the metabolic impact of refeeding syndrome, potassium and magnesium deficiencies.

The scene is therefore set for extreme disturbances of the metabolic norms enjoyed by healthy individuals. These problems will be discussed further below.

Detection of ABD

Although simple in principal, ABD often goes unnoticed or undetected in IF. There are several reasons for this.

1. The possibility of acid-base disturbance is not considered as part of normal monitoring.
2. Arterial blood gas analysis is not routine in chronic IF patients and regarded as painful by many patients. Blood pH may be normal but not reflective of underlying ABD if compensatory mechanisms are functioning adequately. Thus metabolic acidosis may be masked by respiratory compensation but careful inspection of all of the blood gas parameters including pCO_2 and bicarbonate should elicit the true picture. This is especially important in high anion gap acidosis due to L- or D-lactic acidosis.
3. Many units do not monitor venous bicarbonate and chloride levels as part of a routine electrolyte profile. The reasons for this failure may lie in economic pressures to reduce laboratory costs incurred with assays with low overall utility due to low rates of abnormality detection. In IF, this can lead to chronic failure to detect metabolic acidosis and alkalosis with serious consequences for the individual patient in terms of bone disease, intestinal function or cardiac abnormalities. Until recently, neither textbooks nor national and international guidelines included recommendations to monitor ABD using bicarbonate and chloride estimations [6] so IF/HPN units did not monitor these parameters. ESPEN and ASPEN have now issued such guidance (see below).
4. Calculation of the serum and urinary anion gaps (SAG and UAG) is not routine.
5. An increased anion gap should lead to measurement of L- and D-lactate. D-lactic acidosis should be suspected in the presence of an increased anion gap and normal L-lactate in any patient with colon in continuity with residual small bowel [14].

6. Compensatory or mixed metabolic acidosis and alkalosis may mask underlying ABD [15].
7. Serum potassium levels are often not indicative of total body potassium and may be normal even in the presence of total body K^+ deficiency. Raised bicarbonate levels with a normal potassium may indicate metabolic alkalosis due to potassium deficiency. K^+ deficiency often accompanies magnesium deficiency so the presence of metabolic alkalosis as indicated by a high bicarbonate will highlight the need for potassium supplementation as well as magnesium [16].
8. The acid pH of PN solutions should be made clear on the labelling of PN bags [9].

Anion Gap and Types of Metabolic Acidosis

Metabolic acidosis can be subdivided according to the presence or absence of a serum anion gap (SAG) [17, 18], also now known as Strong Ion Difference or SID. Calculation of serum anion gap differs from centre to centre with differing normal ranges. Two methods are commonly used;

$$\left[Na^+ + K^+\right] - \left[Cl^- + HCO_3^-\right] = \text{Serum anion gap} > 20\,\text{mmol/l} = \text{positive abnormal anion gap}$$

$$Na^+ - \left[Cl^- + HCO_3^-\right] = \text{Serum anion gap} > 15\,\text{mmol/l} = \text{positive abnormal anion gap}$$

Calculation of Urinary anion gap (UAG) excludes bicarbonate [19];

$$\left[Na^+ + K^+\right] - Cl^- = \text{UAG} > 5\,\text{mmol/l} = \text{positive gap}, < 5\,\text{mmol/l} = \text{negative UAG}$$

Normal Serum Anion Gap (Non gap) Acidosis: Table 1

Hyperchloraemic acidosis is associated with a normal anion gap as bicarbonate levels fall reciprocally as chloride rises. Causes fall into 3 main groups which can be distinguished by use of the UAG [18]:

Loss of base (bicarbonate) via the gut: negative UAG of −27 ± 10 mmol/l

Loss of base via kidneys/reduction in ammonium excretion as in Renal tubular acidosis: positive UAG of >5 mmol/l

Infusion of acid solutions such as parenteral nutrition or acidosis inducing solutions such as sodium chloride: positive UAG.

High Serum Anion Gap Acidosis: Table 2

A high SAG is caused by accumulation of unmeasured anions [17, 18].

L-lactic or D-lactic acidosis patients have a high SAG due to accumulation of lactate as do ketoacidotic and renal failure patients.

Renal control of acid excretion depends on excretion of hydrions via ammonium ions (NH_4^+) and phosphates together with bicarbonate reclaim. Renal tubular acidosis should be suspected if a normal serum anion gap acidosis is detected with hyperchloraemia, low serum bicarbonate and hypokalaemia. An increased UAG with normal SAG indicates decreased ammonium excretion due to renal tubular acidosis [19]. A negative UAG with normal SAG indicates increased ammonium excretion due to extra renal causes such as gut bicarbonate losses together with potassium [19]. Interestingly, renal ammonium excretion is derived from tubular metabolism of glutamine [20], an amino acid which is often depleted in malnutrition and which is not routinely added to PN solutions in chronic IF.

To make matters more complicated, combined metabolic acidosis and metabolic alkalosis can occur simultaneously [15]. For example, excessive bicarbonate losses from a jejunostomy lead to metabolic acidosis but the combination of gut potassium losses and hyperaldosteronism due to the vascular contraction lead to metabolic alkalosis. The interpretation of such complex metabolic situations [15] is beyond the scope of this chapter but use of the "delta gap" [21] can help explain the presence of mixed ABD.

One of the principle mechanisms for controlling acid-base equilibrium is the buffering system of blood and extra cellular fluid. The major extracellular buffer is serum albumin. In low albumin states, during the early phase of treatment of IF, or during intercurrent illness, interpretation of SAG requires adjustment for the low albumin which may mask high SAG [22]. Such patients are also more likely to be susceptible to acidosis induced by endogenous or extraneous sources of acid or bicarbonate loss.

Table 1 Non anion gap acidosis; hyperchloraemic metabolic acidosis

Cause	Mechanism	Comments
Diarrhoea	Loss of bicarbonate and Na^+	Worse with gastroenteritis
Stomal losses	Loss of bicarbonate	Net secretors most at risk
Urinary diversion	Ileocolonic exchange of chloride for bicarbonate	More likely with colonic diversion and continent pouch than ileal conduit
Oral rehydration solutions	High chloride content. Lack of bicarbonate or citrate.	Bicarbonate or citrate based ORS may prevent acidosis
Normal saline and sodium chloride in PN solutions	Causes greater changes in ECF chloride than Na^+. Cl^- is not a buffer	Most common iatrogenic cause of Metabolic acidosis in critical care
PN/HPN	Amino acids and acid pH for stability. NaCl content	Acetate preferable to HCl and NaCl
PPI/achlorhydria/gastric resection/vagotomy	Loss of H^+ secretion into gut	PPI used to suppress fluid losses in SB
Phosphate deficiency	Reduced H^+ elimination from tubules with chloride retention	Phosphate is a major factor in renal H^+ excretion
Refeeding syndrome	Hypophosphataemia	May occur after intercurrent illness

Table 2 High anion gap metabolic acidosis

Cause	Mechanism	Comment
Renal impairment/failure	Retention of acidic ions, sulphate, chloride	Respiratory compensation may be inadequate.
L-lactic acidosis	Sepsis	Worse in liver disease, thiamine deficiency
Ketosis	Diabetic or starvation	Associated with renal acidosis due to dehydration
D-lactic acidosis	Colonic fermentation. Poor metabolic capacity for D-lactate	Colon continuity required but possible in dysmotility syndromes due to small bowel bacterial overgrowth
Vitamin B1 deficiency	L-lactate accumulation	Worse if hepatic dysfunction
Drugs	Ethanol, methanol, salicylates	Rare in IF

Acid-Base Disturbances in Intestinal Failure

ABD, particularly metabolic acidosis, has long been recognised as a complication of PN and saline infusion in hospital and critical care units [10]. The now obsolete practice of hyperalimentation led not only to uraemia and dehydration but to metabolic and respiratory acidosis [23, 24]. There is little to be found in the literature on ABD during long term management of IF with HPN [7]. In the context of IF with or without PN, respiratory alkalosis is the only ABD not to be represented, except as part of the acute compensatory response to metabolic acidosis or sepsis. Metabolic acidosis and alkalosis, and respiratory alkalosis occur frequently enough for every clinician involved in managing IF/HPN to be fully aware of how to avoid, detect and treat such problems [7]. No one patient with IF is the same as another in view of the wide variation in underlying causation, complications and anatomical impact of loss of intestinal length or function, together with concomitant renal or respiratory impairment. Intercurrent illness leading to sudden loss of circulating volume, dehydration, sepsis, respiratory or renal failure can lead to rapid deterioration with acute acidosis or even alkalosis. IF patients are at particular risk of being unable to respond to metabolic stresses caused by acute illness such as gastroenteritis [7] as the compensatory processes are already under duress before the addition of further stress.

Metabolic Acidosis in IF

Historically, metabolic acidosis was a well recognised cause of acidosis and confusion in the early days of PN [25]. Fructose and ethanol were both used as main energy sources until superseded by glucose and lipid sources and interest in ABD seems to have waned. However, metabolic acidosis is still a significant complication of PN in IF patients [7, 26–28]. In the experience of one UK HPN centre with apparently stable Type 3 IF patients on HPN, normal anion gap acidosis is more common than positive anion gap acidosis due to D-lactic acidosis [7]. In the acutely ill IF patient, perhaps admitted with negative fluid balance due to excessive intestinal losses, L-lactic acidosis should be considered as the result of underlying sepsis, especially line related or intra-abdominal. Measurement of serum lactate and arterial blood gases should be part of the investigation of such patients who may have both hyperchloraemic acidosis and high anion gap acidosis. In IF patients with underlying renal impairment or diabetes mellitus, lactic acidosis or ketoacidosis with a high anion gap may be compounded by hyperchloraemic acidosis due to excessive bicarbonate losses and/or replacement therapy with normal saline. Arterial blood gases AND serum chloride and bicarbonate should be measured and resuscitation with solutions other than sodium chloride considered, including sodium bicarbonate [29]. In those with a SB but some colon in continuity, D-lactic acidosis should be considered if confusion, cerebellar signs and a high serum SAG are detected [14]. The high SAG is associ-

ated with low plasma pH although compensatory respiratory alkalosis may mask the low pH. A low bicarbonate and pCO_2 but normal chloride would be characteristic.

The commonest cause of metabolic acidosis in IF is hyperchloraemic acidosis with low bicarbonate and normal SAG [7] and elevated potassium [1]. Bicarbonate losses from the gut, failure of gastric acid secretion, sodium chloride infusion or PN are the most likely causes. High serum potassium levels accompany acidosis due to displacement of K^+ from cells and impaired renal function [1]. However, concomitant renal impairment due to excessive losses of fluid from the gut (high stoma/diarrhoea) may lead to a combination of hyperchloraemic acidosis and high SAG acidosis due to retention of anions usually excreted via the kidneys (L-lactate, sulphate, phosphate, ketones) [8, 30].

Since both negative fluid balance and sepsis are common in patients with a SB and replacement fluids most usually include "normal saline", the above scenario is common.

Oral Treatments in IF

Patients with <1200 ml stomal losses/day can usually maintain sodium balance by adding salt (sodium chloride - NaCl) to their food at the table [11]. With increased stomal losses of 1200–2000 ml, salt capsules (NaCl) or glucose—saline solutions may permit sodium balance to be maintained except when ambient temperatures are high. Many require an oral rehydration solution (ORS) of which the commonest in use is based on the World Health Organisation (WHO) cholera solution without the potassium chloride. This contains NaCl 60 mmol/L $NaHCO_3$ (or citrate) 30 mmol/L and glucose 110 mmol/L. This reflects the high concentration of sodium lost from jejunostomies. Sodium losses from short jejunostomies average 88 mmol/l but rise with longer residual jejunum and terminal ileal stoma sodium losses rise to 140 mmol/L [11]. Colostomy losses can be closer to plasma levels but the lower volumes lost mean that this is less of a problem. In the human jejunum, sodium balance breaks even at 90 mmol/L [31, 32] but solutions containing much higher concentrations of NaCl (136 mmol/L) have been used [33]. Use of high sodium chloride concentrations in ORS may therefore exacerbate metabolic acidosis [8, 12, 13] especially if a solution without bicarbonate or citrate is used (NaCl 120 mmol, glucose 44 mmol/L) [34].

The potential for acidosis or alkalosis to occur in patients receiving ORS [12, 13] may be exacerbated by the high chloride, low bicarbonate content (acidosis) or absent potassium (alkalosis). Oral sodium bicarbonate or citrate based solutions can be used to treat hyperchloraemic metabolic acidosis [35]. Again, this emphasises that monitoring for ABD should be conducted in such IF patients.

Enteral Feeds

There is no data on the occurrence of ABD in patients with borderline SB who can be managed using oral supplements or enteral feeds. However, it should be noted that some enteral feeds are themselves acidic, particularly peptide based feeds. Since the degree of intestinal failure and the intensity of treatment are only moderate in the absence of parenteral nutrition, serious episodes of ABD are unlikely but sub clinical ABD may be present nevertheless.

However, when oral measures fail to maintain fluid and sodium balance, intravenous 0.9% saline 1–2 L/day is often used [11], perhaps supplemented with magnesium [11] or potassium. Such patients are at risk of saline induced acidosis.

Metabolic Acidosis Caused by Infusion Fluids

Parenteral nutrition solutions must be titrated to a pH at which the constituents can remain stable under conditions of storage and usage. This is typically 5–5.5 but pH as low as 4.36 has been used [9]. Thus the interaction between amino acids and glucose (the Maillard reaction) and the stability of calcium salts and lipids depends on an acid pH achieved by use of hydrochloric acid (non metabolisable) or acetate (metabolisable), both of which are added to PN bags during their preparation [9, 27]. Evidence suggests that titratable acidity due to non-metabolisable acid (hydrochloric acid) rather than metabolisable acid (acetate) is the principal cause of acidosis associated with PN infusions [9, 36]. When IF patients already have a tendency to metabolic acidosis due to bicarbonate losses, infusion of hydrions with chloride may precipitate acute or chronic acidosis, particularly if renal impairment is present. Metabolism of acetate involves consumption of hydrions hence the improvement seen in acidosis when this acid is used to acidify PN solutions [28].

PN solutions are also formulated with sodium chloride in sufficient quantities to prevent dehydration and sodium depletion in those unable to maintain hydration due to a SB. Once infused, sodium chloride also induces metabolic acidosis although it is not itself acidic, nor does it contribute to the acid pH of PN solutions [10].

Lessons from critical care and surgery provide a background for changes in the management of IF patients requiring fluid resuscitation. Normal saline solutions have been implicated in metabolic acidosis during treatment of critically ill patients with a variety of diagnoses [29, 37] and by inference, also contribute to the acidosis seen in IF patients on PN or during resuscitation when hypovolaemic. More importantly, saline has been shown to increase mortality in critical care whereas use of balanced salt solutions improved both metabolic acidosis [38] and mortality [39]. Chloride based crystalloids may not be the most appropriate solutions for rehydration, especially when other causes of metabolic

acidosis such as stomal bicarbonate loss or renal impairment are present [29, 40].

Since NaCl solutions are neutral, it is important to understand why NaCl causes or exacerbates acidosis. The *concentration* of Na Cl in solution is not the reason—any concentration may precipitate acidosis because it is the *imbalance between ECF concentrations of* Cl^- *and* Na^+ which provokes acidosis. Unlike bicarbonate, chloride does not act as a buffer. The equimolar concentrations of Na^+ and Cl^- in infusion solutions lead to further imbalances between Na^+ and Cl^- in the blood and ECF as a whole. Thus so called normal saline 0.9% contains 154 mmol/l of Na^+ and Cl^-. Blood and ECF contain Na^+ at 140 mmol/and Cl^- at 100–110 mmol/l. Although the concentration of Na^+ and Cl^- both exceed the ECF concentrations and therefore increase the concentrations of Na^+ and Cl^- they do so to different degrees. Chloride pairs with H^+ to form hydrochloric acid, and sodium pairs with OH^- and HCO_3^- to form base but less so as the increment in sodium is less than for chloride.

When sodium chloride is present in more dilute solutions as in PN, it is again the influence of the imbalance between ECF Na^+ and Cl^- which determines the final balance between Na^+ and Cl^- which still contributes towards acidosis but less so than with normal saline. It follows that the greater the concentration of saline added to PN solutions, the greater effect on acidosis. In those who need large quantities of sodium to replace gut losses which usually include bicarbonate, use of chloride exacerbates the tendency to acidosis. Hence the use of sodium acetate to replace not only HCl but sodium chloride in PN solutions [28]. This permits a reduction in chloride infusion and each acetate molecule consumes one H^+ during its metabolism in vivo [26]. Use of acetate therefore achieves 2 aims—the reduction in chloride infusion and a reduction in the non-metabolisable acid load of the PN solution required for stability purposes as described earlier. The burden on buffering capacity and renal or respiratory compensation on infusion of PN can therefore be offset by use of acetate. It has been suggested that when renal impairment is present chloride based PN solutions should be avoided [28].

This strategy has been shown to improve measures of acid-base balance in a retrospective study [28] and a prospective randomised controlled study [9].

The use of acetate does not come without some adverse consequences. Acetate has been shown to inhibit osteoblast activity [41] thus offsetting some of the benefits of avoiding acidosis although acidosis itself also inhibits osteoblasts and enhances osteoclast activity.

The amino acid content of PN solutions may also contribute to acidosis as a result of sulphur containing amino acids such as methionine and cysteine, and cationic amino acids such as arginine, lysine and histidine, metabolism of which may contribute to ABD. Sulphates are excreted by the renal tubules in exchange for chloride and oxidation of cationic amino acids generates hydrions thus contributing to hyperchloraemic acidosis [8].

Loss of Gastric Acid Production: Effect on Acidosis

The integrated acid-base functions of the gut depend on production of acid and bicarbonate as already discussed. If acid is not produced, bicarbonate is not generated in the gastric mucosa to balance the acid produced during secretion of bicarbonate from liver and pancreas. If bicarbonate losses occur due to SB from a high stoma, acidosis may occur even if gastric acid production is normal but if gastric acid production fails for any reason, acidosis is promoted further. In the presence of achlorhydria (due to gastritis or pernicious anaemia), gastric surgery (complete or partial gastrectomy, vagotomy) or drug inhibition of gastric secretions (H_2 receptor antagonists, PPI or somatostatin analogues), acidosis is likely to occur if bicarbonate losses are high. If renal compensation fails, acidosis is inevitable. Omeprazole has been used clinically to correct metabolic alkalosis [42]. There is anecdotal evidence that PPI induce metabolic acidosis in SB/IF and that withdrawal of the drug leads to correction of metabolic acidosis [7]. Since PPIs are used to reduce stomal fluid losses in IF [11, 43], and since those losses themselves predispose to acidosis, any patient on a PPI should have appropriate monitoring to detect onset of acidosis.

Urinary Diversion to Colon or Ileum

Urinary diversion to the ileum or colon can both lead to metabolic acidosis which is more common in those with uretero-colonic diversions (50% or more) than with uretero-ileal (2–20%) [44]. The tendency to acidosis does not prevent the occurrence of alkalosis from other causes [7]. Deficiencies of potassium and magnesium leading to alkalosis may also occur. The impact on bone metabolism has also been highlighted, partly as a result of the sub clinical acidosis which routinely accompanies urinary diversion [44]. This appears to decline over time [45].

The colonic exchange of chloride for bicarbonate and slower transit explain the occurrence of acidosis with urinary diversion to the colon. Clinical presentation may be influenced by hyperammonaemic encephalopathy [46, 47]. If acidosis occurs with an ileal conduit, stenosis or obstruction of the conduit should be considered [48].

Thiamine Deficiency

Acidosis caused by thiamine deficiency is a well recognised feature of alcoholics presenting with withdrawal symptoms and Wernicke–Korsakoff syndrome. High anion gap acidosis requiring thiamine treatment has also been described during parenteral nutrition [49]. Thiamine is essential to the correct functioning of the Krebs cycle and metabolism of lactic acid to pyruvate and alpha keto butyrate which then enter the Krebs cycle. L-lactic acid accumulates in the absence of this vitamin cofactor, particularly in septic and critically ill patients [50]. Malnourished patients including those with IF are at risk of this complication if thiamine is not included in their nutritional regime. The practice of feeding patients with incomplete "off the shelf" nutritional regimes, particularly PN can precipitate acute metabolic acidosis and should be discouraged. Indeed the metabolic consequences of providing an incomplete regime containing no vitamins, trace elements, phosphate or potassium can be a catastrophic form of refeeding syndrome. PN should never be administered in such form and the use of PN solutions as an emergency out of hours by inexperienced clinicians should be avoided. Thiamine deficiency has also been shown to precipitate L-lactic acidosis even in the absence of liver dysfunction in ICU patients [50]. Many IF patients have liver disease consequent upon the long-term use of PN and a SB. Although less frequent now, especially in children with the introduction of newer lipid sources and prevention of line sepsis, liver disease is not uncommon in IF so avoidance of L-lactic acidosis is important. Thiamine deficiency may also precipitate D-lactic acidosis as discussed below [50].

Hypophosphataemia

Failure to provide adequate phosphate in PN solutions to the malnourished (for example–anorexia nervosa) or acutely sick IF patient can precipitate metabolic acidosis, acute psychiatric disturbances and muscle dysfunction [8]. Phosphate is required as part of the renal elimination of hydrogen ions together with the bicarbonate and ammonia systems. Renal tubular excretion of H^+ is impaired in phosphate deficiency and therefore predisposes to acidosis. At tissue level, phosphate deficiency impairs oxygen release and leads to lactic acid accumulation [8]. These problems are most commonly found in the refeeding syndrome and when incomplete PN solutions are used "off the shelf".

D-lactic Acidosis

This is a rare but serious complication of SB with colon in line, occurring in <5% [6] but more commonly in jejuno–ileal bypass for obesity. It is possible that dysmotility syndromes may also be complicated by D-lactic acidosis from small bowel bacterial overgrowth [51, 52]. It may be acute, subacute or recurrent. It is characterised by confusion, ataxia, slurred speech, ophthalmoplegia, nystagmus and behavioural disturbances such as aggression. In severe cases, stupor may progress to coma. The exact pathophysiology is unclear. Messing [6] states that only a few mmols of D-lactate are required to cause cerebellar signs and pseudo-ebriety or drunkenness. However, D-lactate levels do not correlate with symptoms and administration of D-lactate to the levels seen in D-lactic acidosis or above does not cause symptoms [53, 54]. To further confuse the picture, the syndrome can occur in the absence of acidosis [6] and could be due to other products of colonic metabolism such as mercaptans, aldehydes, amines and alcohols acting as false neurotransmitters [55]. It was thought that no enzyme capable of metabolizing D-lactate existed in humans but it is now known that humans do have an enzyme capable of metabolising D-lactate to pyruvate (D-2-hydroxy acid dehydrogenase) in liver and kidney [56] and that most D-lactate is excreted via the kidneys. The enzyme is inhibited by low blood pH. Similarly, in the gut, a low pH favours greater D-lactate production.

Diagnosis requires low pH, hypocapnia, an increased serum anion gap with low bicarbonate, elevated D-lactate and normal L-lactate [56].

Symptoms appear after ingestion of carbohydrate loads including those in enteral tube feeds, particularly monosaccharides or disaccharides including sucrose and lactose. Pickles, yoghourt, sour milk, tomatoes, apples, beer and wine should be avoided as they contain D-lactate. Colonic bacteria are required to metabolise these sugars to produce the syndrome [54].

B1 deficiency may also provoke D-lactic acidosis [51] as may broad spectrum antibiotics [57]. Changes to colonic flora with a reduction in gram-negative anaerobes and an increase in gram-positive anaerobes, especially Lactobacillus, Eubacterium and Bifidobacterium [58] lead to an increase in D-lactate [59].

Treatment Options in D-lactic Acidosis

Initial: Rehydrate and give IV bicarbonate with nil by mouth for 24 h. Haemodialysis has been used in serious cases.

Prevention of future attacks: include nil by mouth with introduction of enteral diet under supervision avoiding mono and oligo saccharides and rapidly digestible glucose polymers in favour of slow digesting complex starches [56, 60]. Since medium chain triglycerides may also provoke D-lactic acidosis they should be omitted from the oral intake [61].

Antibiotics such as metronidazole, neomycin or vancomycin may improve symptoms presumably by suppressing colonic flora but rifaxamin has proved most effective [14, 56].

Recently, faecal transplant has been used to treat D-Lactic acidosis successfully [62, 63].

Probiotics containing B Breve (Yakult®) or L Casei (Shirota®) producing L-lactate not D-lactate may help reset the microbiome after a course of antibiotics but care should be taken when choosing a probiotic containing lactobacillus as some may precipitate D-lactic acidosis [64].

The role of oral rehydration solutions containing bicarbonate to prevent recurrence by raising intestinal pH or moderating the systemic acidosis is unclear.

Metabolic Alkalosis: Table 3

This is typically associated with potassium deficiency and hypochloraemia, often compounded by magnesium deficiency, especially if intestinal losses are great as in net secretors. Hyperaldosteronism, as in chronically underfilled patients, leads to increased renal potassium wastage and also causes increased colonic potassium excretion [65]. Without replenishment of magnesium, potassium levels will remain low with consequent muscle weakness, cardiac arrhythmias and ileus, the latter compounding potassium and acid losses through vomiting. Metabolic alkalosis should be regarded as a surrogate for total body deficiency of potassium, hence the importance of monitoring bicarbonate levels as well as potassium. Mortality associated with severe alkalosis is high [65].

The main causes of metabolic alkalosis are:

- Vomiting or drainage of gastric contents (by NGT or drainage PEG) leading to loss of HCL. This scenario may occur in patients on palliative PN for small bowel obstruction due to cancer if palliative gastric drainage is utilised. IF due to dysmotility of the gut leads to recurrent vomiting of either gastric or small bowel contents or both. If gastroparesis predominates, metabolic alkalosis may occur due to loss of gastric acid and increased aldosterone activity leading to a low serum potassium. Cimetidine has been used successfully to treat severe metabolic alkalosis in gastric hypersecretion in patients with a SB [66]. Omeprazole may be protective [42].

Table 3 Metabolic alkalosis

Cause	Mechanism	Comment
Loss of K+	Diarrhoea, vomiting, stomal losses, diuretics	May be resistant if low magnesium too
Loss of Mg++	Stomal losses; Vit D deficiency	May require vitamin D to replete stores
ORS solutions	Potassium free ORS	Taste and compliance a problem
Contraction alkalosis	Hyper aldosteronism. renal and intestinal chloride loss	Now called chloride depletion alkalosis
Refeeding syndrome	Hypokalaemia	May be masked by acidosis

- Vomiting of small bowel contents leading to losses of potassium and sodium with secondary hyperaldosteronism and further potassium losses from the kidneys and gut. Spironolactone may have a role as an aldosterone antagonist in severe cases [65].
- Activation of the renin—angiotensin—aldosterone system by reduction in plasma volume/dehydration leading to loss of potassium from kidneys and gut—so called constriction alkalosis (see below).
- Hypokalaemia leads to alkalosis as hydrogen ions enter cells to replace lost potassium, leaving bicarbonate in the ECF. Any cause of hypokalaemia may lead to alkalosis including use of loop and thiazide diuretics leading to tubular losses of potassium and magnesium. These diuretics also promote alkalosis through renal chloride excretion [65]
- Loss of sodium chloride in sweat as in cystic fibrotics or hot climates leading to contraction alkalosis.
- Magnesium losses occur in stomal effluent in SB independent of the length of residual small bowel, together with potassium losses. Aldosterone increases both potassium and magnesium losses from the kidneys. Since magnesium deficiency inhibits Na^+/K^+/ATPase leading to K^+ loss from cells and excretion via the kidneys, potassium deficiency is resistant to repletion until magnesium stores have been repleted [16] but this can only be achieved if underfilling due to dehydration and sodium depletion are corrected first, thereby removing the influence of aldosterone. Magnesium deficiency quickly leads to a 25% reduction in total body stores of potassium [67]. Potassium deficiency cannot be remedied without repletion of magnesium stores [16] which are best assessed using 24 h urinary excretion studies. Care should be taken to monitor magnesium levels during octreotide therapy. Magnesium repletion may require oral 1 alpha-hydroxycholecalciferol treatment [68].
- Inadequate replacement of potassium, often due to misleading serum K^+ levels, is exacerbated by infusion of glucose (as in refeeding syndrome) and more so if insulin is given too. As cells return to an anabolic phase, K^+ requirements increase so adequate replacement is essential if metabolic alkalosis is to be avoided.
- Contraction alkalosis or chloride depletion alkalosis?
- This term reflects the contraction of the vascular compartment caused by fluid losses insufficient to reduce glomerular filtration but adequate to stimulate the renin—angiotensin—aldosterone secretion system. Renal tubular exchange of potassium for sodium leads to potassium deficiency and alkalosis. Aldosterone also has a role in sodium and potassium exchange in the small bowel and colon, promoting alkalosis. Chronically fluid depleted patients can thereby develop metabolic alkalosis. This can even be enough to overwhelm the tendency to metabolic

acidosis associated with ureteric diversion in our experience [7].

However, more recent publications have challenged the concept of contraction alkalosis [65, 69] emphasising the role of chloride repletion in hypochloraemic alkalosis but this is beyond the scope of this article.

Respiratory Acidosis

It has long been recognised that infusions of glucose lead to an increase in CO_2 production with concomitant increases in respiratory excretion. If respiratory function is normal, this does not present a problem and CO_2 is exhaled sufficiently. When respiratory reserve is impaired due to pulmonary infection, trauma or underlying disease, CO_2 can accumulate to cause respiratory acidosis [23, 24, 70]. If other causes of metabolic acidosis are present, infusion of glucose may impose a rise in total body CO_2 which contributes to an overall fall in pH due to a combination of metabolic acidosis and respiratory acidosis, leaving the kidneys as the sole means of readjusting pH. Since the use of glucose is essential in PN solutions, it follows that avoidance of metabolic causes of acidosis are essential if compensatory mechanisms are not to be overwhelmed, particularly because many causes of metabolic acidosis impact upon renal function (loss of intestinal fluid, vomiting, sepsis).

Respiratory Alkalosis

This is never chronic in IF but can occur acutely as part of the response to sepsis or haemorrhage. Hyperventilation together with confusion and a low pCO_2 should alert the clinician to the possibility of line sepsis or intraabdominal causes.

Drug Therapy During IF

Potassium sparing diuretics have been implicated in precipitating metabolic hyperchloraemic acidosis during PN [71] by opposing renal aldosterone response and impairing tubular function. Intracellular transfer of potassium leads to loss of intracellular hydrions to the ECF [71]. The carbonic anhydrase inhibitor, acetazolamide, has been used to treat alkalosis and may cause acidosis by inducing renal bicarbonate secretion [72].

The role of acid suppressing agents has already been discussed above.

Octreotide and other somatostatin analogues may in theory affect ABB by influencing gastric or pancreatic secretions and there a few reports of metabolic acidosis in patients on octreotide [73] with pancreatic fistula but no evidence that octreotide is either causal or therapeutic.

Cholestyramine used to treat bile acid related diarrhoea in patients with resected ileum has also caused metabolic hyperchloraemic acidosis [74].

Consequences of ABD

These may be life threatening or lead to chronic morbidity.

Metabolic Acidosis

Short term metabolic acidosis due to lactic acidosis is better understood than hyperchloraemic non gap acidosis or chronic metabolic acidosis. Metabolic acidosis impacts upon cardiac function with hyperventilation, arrhythmias, vasodilatation, and hypotension and may also increase inflammation and impair immune responses [75]. Hyperkalaemia is common and potentially fatal [1]. Some studies have shown that high anion gap acidosis adversely affects mortality whereas non gap acidosis does not [10]. Other studies have shown increased mortality with non-gap hyperchloraemic acidosis [10, 37, 38]. Many studies have shown increased mortality with the use of normal saline as a resuscitative fluid compared to solutions with lower chloride content [10, 37, 38] and others have shown improved acid-base parameters with alternatives to 0.9% saline solutions [29].

It should be clear that prevention of metabolic acidosis is of paramount importance and that modification of PN, intravenous and oral rehydration solutions offers the best opportunity to do so. The treatment of acute severe acidosis is beyond the remit of this chapter.

Acidosis and Metabolic Bone Disease

In the context of chronic IF on HPN, the long term effect of acidosis on bone metabolism cannot be ignored. The impact of chronic metabolic acidosis on bone metabolism and the benefits to muscles, bones and growth with treatment of acidosis have long been recognised in renal failure [76–78]. Acidosis increases bone resorption by increasing osteoclast and decreasing osteoblast activity [79, 80]. Acidosis also impairs renal vitamin D activation. Mobilisation of bone calcium leads to nephrocalcinosis and nephrolithiasis.

Although acidosis has not featured strongly in texts or guidelines until recently, the importance of treating acidosis to prevent metabolic bone disease in IF during HPN has been highlighted [13, 41].

Metabolic acidosis is considered to be an important contributor to metabolic bone disease in chronic renal failure. Improvements in bone metabolism follow treatment of acidosis [81]. Impaired bone metabolism has also been documented in D-lactic acidosis [82], treatment of which improves bone metabolism. Subclinical acidosis is most likely to contribute to long term bone disease, hence the importance of monitoring acid-base balance and preventing acidosis by incorporating acetate in PN formulations. Pironi [41] advises 160 mmol/day of acetate to avoid acidosis and maintain bicarbonate within normal range.

Metabolic Alkalosis

Clinical features are those of hypokalaemia, low magnesium and the decrease in ionised calcium caused by alkalosis itself. With increasing pH, ionised calcium increasingly binds to albumen leading to further falls in ionised calcium and tetany. Convulsions, muscular irritability and cramps or tetany, paraesthesia, psychosis and coma may occur. Cardiac arrhythmias, gastroparesis or paralytic Ileus reflect hypokalaemia. Mortality is high in severe cases [65].

Alkalosis may also affect bone metabolism when associated with low magnesium stores which reduce parathormone secretion and renal activation of vitamin D [83].

Incidence of ABD

Little has been published on ABD in IF on HPN. This author's group described their experience in a small UK referral centre for Type 3 IF and HPN [7]. Of 39 patients, there were 11 episodes of ABD in 10 patients (25%). In 5/11 episodes, the presentation was after many years on HPN with severe ABD and renal impairment as a prominent feature. The remaining 6 episodes were subclinical detected on routine screening and only 1 of these had renal impairment.

Symptomatic hyperchloraemic acidosis (e.g. lethargy, rapid breathing, confusion) was present in 3/5 severe presentations. Jejunostomy was present in 2 and jejunocolonic anastomosis in one. All had impaired renal function, 2 were on a PPI and all were taking modified WHO oral rehydration solutions without potassium. Withdrawal of PPI in one case led to improvement in the acidosis. None had D-lactic acidosis. Interestingly, 2 had a raised anion gap but both had elevated serum creatinine. Smoking related chronic obstructive airways disease was present in one case with Crohn's disease.

There were 2 severe symptomatic metabolic alkaloses, one of which had also suffered from severe metabolic acidosis which resolved on withdrawal of PPI and supplementary IV saline infusions at home. On this occasion, she suffered acute delusional psychosis. Both cases had hypochloraemia, hypokalaemia, hypomagnesaemia and elevated creatinine suggesting contraction alkalosis and hyperaldosteronism. Neither were taking a PPI. Both had high stomas but one had urinary diversion to an ileal conduit.

There were 6 cases of subclinical metabolic acidosis, none of which had a raised anion gap or detectable D-lactate. All were detected on implementation of routine monitoring of serum bicarbonate and chloride for ABD. The PN formulations were altered to include sodium acetate instead of sodium chloride and the incidence of metabolic acidosis declined. There was no colon in continuity in 6/9 acidotic patients. One case had a dysmotility syndrome due to scleroderma with the entire gastrointestinal tract intact.

Refeeding Syndrome Scenarios Leading to ABD

Instigating nutritional support in the malnourished or metabolically challenged patient without attention to providing adequate amounts of all essential nutrients can lead to a refeeding syndrome. Typically, provision of energy sources creates demands for other basic nutrients and exposes deficiency states if those nutrients are in short supply. This applies particularly to potassium, phosphate, thiamine, zinc and selenium. Acidosis may result if insufficient thiamine or phosphate are provided [8, 49–52] as in a case on HPN [84]. Stable HPN patients could be exposed to this risk after intercurrent illness such as line sepsis or surgery when the catabolic phase gives way to the anabolic recovery phase.

Vitamin B1 thiamine deficiency is well recognised, particularly in alcoholics with the onset of Wernicke–Korsakov syndrome. The associated acidosis may contribute to the overall malaise of this condition but if acidosis is detected in such patients, B1 deficiency should be suspected and treated urgently.

Phosphate deficiency is seen at its worst in anorexia nervosa. The contribution of acidosis is unclear but impaired oxygen release at tissue level due to 2,3-diphosphoglycerate deficiency and ATP in red blood cells probably explains the symptoms of confusion, seizures, muscle weakness, paraesthesia, hyperventilation and coma [8].

Cramps During PN Infusions

Muscle cramps occurring during HPN infusions represent the commonest side effect of HPN according to a multicentre report [85] from the UK. These cramps should be distinguished from the tetanic cramps associated with calcium or magnesium deficiencies which occur independent of PN infusions. The cause of PN related muscle cramps is unclear

but some theoretical possibilities can be entertained on the basis that PN solutions are acid (pH 4.4) and contain sodium at lower concentrations than in blood and extracellular fluid.

One particular observation stands out to direct investigation into this problem. It is generally agreed that reduction in flow rates of PN infusions either reduces the intensity and duration of cramps but may help avoid them altogether [86]. This would suggest that it is the rate of infusion of fluid and some constituent or property of that PN which causes the cramps. There is no clear evidence that quinine reduces the cramps although this treatment is often deployed.

The suggestion that some cases may prove to be due to sodium deficiency does not explain why symptoms occur during infusion of sodium. Similarly, one would expect cramps due to underlying calcium, magnesium or phosphate deficiencies to be corrected during infusion of PN solutions. Some other cause must explain these cramps. On the other hand, infusion of 3 l PN solution over 12 h may cause dilution of serum sodium or other electrolytes sufficient to trigger cramps. However, increasing the sodium content of HPN solutions does not improve the cramps in this author's experience.

Transport of ions across muscle cell membranes during glucose and amino acid infusions could create temporary ionic transmembrane gradients as in the refeeding syndrome but no evidence exists to support this theory.

The infusion of large volumes of PN solutions with an acid pH may alter acid—base balance sufficiently for polarisation of muscle membranes to be affected adversely, thus triggering cramps. To this theory may be added the dilutional effect of infusing solutions with sodium concentrations well below those of serum and extracellular fluid bathing nerve membranes. A sudden drop in sodium concentration coupled with a transient but rapid fall in pH of extracellular fluids could precipitate cramps. However, this theory requires further investigation. Meanwhile, reduction in flow rate of PN solutions is the most effective treatment, albeit at the expense of time online. Patients are willing to accept this trade off if they can avoid the extremely painful cramps associated with their PN in my experience. This is a subject requiring further investigation.

Guidelines and ABD

Until recent iterations of ASPEN and ESPEN guidelines, acid-base disturbances were not highlighted. However, the latest ASPEN recommendations and ESPEN guidelines now include clear advice on detection of ABD.

ASPEN Recommendations 2014

These recommendations state [87] that safe PN should start with a clear understanding of acid-base equilibrium and that monitoring the major electrolytes involved in nutritional metabolism and fluid homeostasis, blood glucose concentrations and acid-base balance is important. They state categorically that laboratory testing should include measures of acid-base balance.

ESPEN Guidelines 2016

Recommendation 19 [13] recommends regular monitoring of acid-base status in patients on long term HPN (serum chloride and bicarbonate) because both metabolic acidosis and alkalosis can occur. The guidance also states that chloride and bicarbonate levels should be monitored frequently until stable.

Renal Impairment in IF

Renal impairment in patients with intestinal failure is most commonly due to chronic dehydration in patients with a jejunostomy and due to oxalosis in patients with a jejunum in continuity with a functioning colon (chapter "Nephrolithiasis and Nephrocalcinosis"). In addition parenteral chloride may cause renal vasoconstriction so further impairing renal function [88].

Acute renal impairment due to hypovolaemia can often be treated with intravenous fluids but if a patient is allowed to be chronically dehydrated (often an insidious process) then permanent renal dysfunction will ensure. Persisting dehydration is a reason for starting or increasing parenteral support.

Patients with acute kidney injury secondary to a high output from a small bowel stoma may need dialysis (if acidotic or hyperkalaemic), however during dialysis fluid must not be removed, in fact they must continue to be rehydrated and ideally gain 1–4 kg in weight depending upon how dehydrated they are at the commencement of dialysis. If an already dehydrated patient is dialysed and fluid removed their kidney injury may become irreversible.

If a patient is prone to acute kidney injury due to dehydration then it is important to avoid or closely monitor them if they take a potassium containing rehydration solution (e.g. dioralyte®). While omeprazole and loperamide are relatively safe in patients with renal impairment the dose of codeine phosphate which has active renally excreted metabolites, must be reduced.

References

1. Gennari FJ, Weise WJ. Acid-base disturbances in gastrointestinal disease. CJASN. 2008;3:1861–8. Adamson R, Swenson ER. Acetazolamide use in severe chronic obstructive pulmonary disease pros and cons. Annals Am Thorac Soc. 2017;14:1086–93.
2. Watson WC, Paton E. Studies on intestinal pH by radiotelemetry. Gut. 1965;6:606–12.

3. Wang YT, Mohammed SD, Farmer AD, Wang D, Hobson AR, Hellstrom PM, et al. Regional gastrointestinal transit and pH studied in 215 healthy volunteers using the wireless motility capsule: influence of age, gender, study country and testing protocol. Aliment Pharmacol Ther. 2015;42:761–72.
4. Sladen GE. Absorption of fluid and electrolyte in health and disease. In: MacColl I, Sladen GE, editors. Intestinal absorption in man. London: Academic Press; 1975. p. 81–98.
5. Turnberg LA, Bieberdorf FA, Morawski SG, Fordtran JS. Interrelationships of chloride, bicarbonate, sodium and hydrogen transport in the human ileum. J Clin Invest. 1970;49:557–67.
6. Messing B, Joly F, Jeppesen P. Short bowel syndrome. In: Bozzetti F, Staun M, Van Gossum A, editors. Home parenteral nutrition. Cambridge: Cab International; 2006. p. 57–77.
7. Jones BJM, Chopra P, Groning J, Deel-Smith P. Acid-base disturbance during home parenteral nutrition- an observational cohort study. e-SPEN. 2011;6:31–5.
8. Dounousi E, Kikou X, Koulouras V, Katopodis K. Metabolic acidosis during parenteral nutrition: pathophysiological mechanisms. Indian J Crit Care Med. 2015;19:270–4.
9. Kato K, Sugiura S, Yano K, Fukuoka T, Itoh A, Nagino M, et al. The latent risk of acidosis in commercially available total parenteral nutrition (TPN) products: a randomised clinical trial in post operative patients. J Clin Biochem Nutr. 2009;45:68–73.
10. Handy JM, Soni N. Physiological effects of hyperchloraemia and acidosis. Br J Anaesth. 2008;101:141–50.
11. Nightingale JMD. Management of a high output jejunostomy. In: Nightingale JMD, editor. Intestinal failure. Greenwich Medical Media Limited: London; 2001. p. 373–92.
12. Btaiche IF, Khalidi N. Metabolic complications of parenteral nutrition in adults, part 2 acid-base disturbances. Am J Health Syst Pharm. 2004;61:2050–9.
13. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PD, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35:247–307.
14. Stanciu S, De Silva A. Metabolic acidosis in short bowel syndrome: think D-lactic acid acidosis. BMJ Case Rep. 2018. https://doi.org/10.1136/bcr-2018-224221.
15. Walmsley RN, White GH. Mixed acid – base disorders. Clin Chem. 1985;31:321–5.
16. Huang C, Kuo E. Mechanism of hypokalaemia in magnesium deficiency. J Am Soc Nephrol. 2007;18:2649–52.
17. Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. Clin J Am Soc Nephrol. 2007;2:162–74.
18. Kraut JA, Nagami GT. The serum anion gap in the evaluation of acid-base disorders: what are its limitations and can its effectiveness be improved? CJASN. 2013;8:2018–24.
19. Wikipedia. Urine anion gap. 2018. https://en.wikipedia.org/wiki/urine_anion_gap.
20. Weiner ID, Verlander JW. Renal ammonia metabolism and transport. Compr Physiol. 2013;3:201–20.
21. Wikipedia. Delta ratio. 2018. https://en.wikipedia.org/wiki/Delta_ratio. Accessed 16 May 2018.
22. Hatherill M, Waggie Z, Purves L, Reynolds L, Argent A. Correction of the anion gap for albumin in order to detect occult tissue anions in shock. Arch Dis Child. 2002;87:526–9.
23. Jih KS, Wang MF, Chow JH, Yen CC. Hypercapnic respiratory acidosis precipitated by hypercaloric carbohydrate infusion in resolving septic acute respiratory distress syndrome: a case report. Zhonghua Yi Xue Za Zhi. 1996;58:359–65.
24. Klein CJ, Stanek GS, Wiles CE. Overfeeding macronutrients to critically ill adults: metabolic complications. J Am Diet Assoc. 1998;98:795–806.
25. Chan JC, Asch MJ, Lin S, Hays D. Hyperalimentation with amino acid and casein hydrolysate solutions: mechanisms of acidosis. JAMA. 1972;220:1700–5.
26. Kushner RF, Sitrin MD. Metabolic acidosis: development in two patients receiving a potassium-sparing diuretic and total parenteral nutrition. Arch Intern Med. 1986;146:343–5.
27. Sugiera S, Inagaki K, Noda Y, Nagai T, Nabeshima T. Acid load during total nutrition: comparison of hydrochloric acid and acetic acid on plasma base balance. Nutrition. 2000;16:260–3.
28. Tsai I, Huang J, Chu T, Wu K, Tsai T. Factors associated with metabolic acidosis in patients receiving parenteral nutrition. Nephrology. 2007;12:3–7.
29. Kraut JA, Kurtz I. Treatment of acute non-anion gap metabolic acidosis. Clin Kidney J. 2015;8:93–9.
30. Banerjee A, Warwicker P. Acute renal failure and metabolic disturbances in short bowel syndrome. Quart J Med. 2002;95:37–40.
31. Jones BJM. Glucose polymer absorption from the human jejunum. MD Thesis, London, 1985.
32. Spiller RC, Jones BJM, Silk DBA. Jejunal water and electrolyte absorption from 2 proprietary enteral feeds in man: the importance of sodium content. Gut. 1987;28:681–7.
33. Beaugerie L, Cosnes J, Verwaerde F, Dupas H, Lamy P, Gendre J, et al. Isotonic high-sodium oral rehydration solution for increasing sodium absorption in patients with short-bowel syndrome. Am J Clin Nutr. 1991;53:769–72.
34. Nightingale JMD, Lennard-Jones JE, Walker ER, Farthing MJG. Oral supplements to compensate for jejunostomy losses: comparison of sodium chloride capsules, glucose electrolyte solution and glucose polymer electrolyte solution (Maxijul). Gut. 1992;33:759–61.
35. Atia AN, Buchman AL. Oral rehydration solutions in non-cholera diarrhoea: a review. Am J Gastroenterol. 2009;104:2596–604.
36. Terashima H, Miura O, Hatakeyama K, Hirayama K, Ohkubo S. Hyperchloraemic metabolic acidosis associated with TPN solutions. JPEN. 1998;20:359–68.
37. Noritomi DT, Soriano FG, Kellum JA, Cappi SB, Biselli PJ, Liborio AB, et al. Metabolic acidosis in patients with severe sepsis and septic shock: longitudinal study. Crit Care Med. 2009;37:2733–9.
38. Yunos NM, Kim IB, Bellomo R, Bailey M, Story D, Gutteridge GA, et al. The biochemical effects of restricting chloride-rich fluids in intensive care. Crit Care Med. 2011;39:2419–24.
39. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications, mortality, and resource utilisation after open abdominal surgery: 0.9% saline compared to Plasma-lyte. Ann Surg. 2012;255:821–9.
40. Lobo DN, Awad S. Should chloride rich crystalloids remain the mainstay of fluid resuscitation to prevent pre-renal acute kidney injury. Kidney Int. 2014;86:1096–105.
41. Pironi L. Metabolic bone disease in long term HPN in adults. In: Bozzetti F, Staun M, Gossum V, editors. Home parenteral nutrition. Cambridge: CAB International; 2006. p. 159–74.
42. Hixson R, Christmas D. Use of omeprazole in life threatening metabolic alkalosis. Intensive Care Med. 1999;25:1201.
43. Nightingale JMD, Walker ER, Farthing MJG, Lennard-Jones JE. Effect of omeprazole on intestinal output in the short bowel syndrome. Aliment Pharmacol Ther. 1991;5:405–12.
44. Van der Aa F, Joniau S, Van Den Branden M, Van Poppel H. Metabolic changes after urinary diversion. Adv Urol. 2011. https://doi.org/10.1155/2011/764325.
45. Kim KH, Yoon HS, Yoon H, Chung WS, Sim BS, Ryu D-R, et al. Risk factors for developing metabolic acidosis after radical cystectomy and ileal neobladder. PLoS ONE. 2016;11(7):e0158220. https://doi.org/10.1371/journal.pone.0158220. Accessed 6 July 2016.
46. Hampel DJ, Stoll J, Nibbe L, Golllasch M. Hyperammonaemic encephalopathy and severe metabolic acidosis in a patient with chronic renal insufficiency years after ureterosigmoidoscopy. Nephrol Dial Transplant. 2007;22:2713–9.

47. Weise WJ, Serrano FA, Fought J, Gennari FJ. Acute electrolyte and acid-base disorders in patients with ileostomies: a case series. Am J Kidney Dis. 2008;52:494–500.
48. Hall MC, Koch MO, McDougal WS. Metabolic consequences of urinary diversion through intestinal segments. Urol Clin North Am. 1991;18:725–35.
49. Nakasaki H, Ohta M, Soeda J, Makuuchi H, Tsuda M, Tajima T, et al. Clinical and biochemical aspects of thiamine treatment for metabolic acidosis during total parenteral nutrition. Nutrition. 1997;13:110–7.
50. Donnino MW, Carney E, Cocchi MN, Barbash I, Chase M, Joyce N, et al. Thiamine deficiency in critically ill patients with sepsis. J Crit Care. 2010;25:576–81.
51. Rao SSC, Rehman A, Yu S, de Andino NM. Brain fogginess, gas and bloating: a link between SIBO, probiotics and metabolic acidosis. Clin Transl Gastroenterol. 2018;9:162. https://doi.org/10.1038/s41424-018-0030-7.
52. Hudson M, Pocknee R, Mowat NA. D-lactic acidosis in short bowel syndrome – an examination of possible mechanisms. Quart J Med. 1990;74:157–63.
53. de Vrese M, Koppenhoefer B, Barth CA. D-lactic acid metabolism after an oral load of d-lactate. Clin Nutr. 1990;9:23–8.
54. Connor H, Woods HF, Ledingham JGG. Comparision of the kinetics and utilisation of D(-) and L(-) sodium lactate in normal man. Ann Nutr Metab. 1983;27:481–7.
55. Halperin ML, Kamel KS. D-lactic acidosis: turning sugar into acids in the gastrointestinal tract. Kidney Int. 1996;49:1–8. https://doi.org/10.1038/ki.1996.1.
56. Kowlgi GN, Chabra L. D-lactic acidosis: an under recognized complication of short Bowel syndrome. Gastroenterol Res Pract. 2015;2015:476215. https://doi.org/10.1155/2015/476215.
57. Flourie B, Messing B, Bismuth E, Etanchaud F, Thuillier F, Rambaud J. D-lactic acidosis and encephalopathy in short bowel syndrome occurring during antibiotic treatment. Gastroenterol Clin Biol. 1990;14:596–8.
58. Stolberg L, Rolfe R, Gittlin N, Merritt J, Mann L, Linder J, et al. Lactic acidosis due to abnormal gut flora: diagnosis and treatment of two cases. N Engl J Med. 1982;306:1344–8.
59. Hove H, Mortensen PB. Colonic lactate metabolism and D-lactic acidosis. Dig Dis Sci. 1995;40:320–33.
60. Mayne AJ, Handy DJ, Preece MA, George RH, Booth IW. Dietary management of D-lactic acidosis in short bowel syndrome. Arch Dis Child. 1990;65:229–31.
61. Jover R, Leon J, Palazon JM, Dominguez JR. D-lactic acidosis associated with the use of medium chain triglycerides. Lancet. 1995;346:314.
62. Davidovics ZH, Vance K, Etienne N, Hyams JS. Fecal transplantation successfully treats recurrent D-lactic acidosis in a child with short bowel syndrome. J Parenter Enter Nutr. 2017;41:896–7.
63. Bulik-Sullivan EC, Roy S, Elliott RJ, Lichtman SN, Carroll IM, Gulati AS. Intestinal microbial and metabolic alterations following successful fecal microbiota transplant for D-lactic acidosis. J Pediatr Gastroenterol Nutr. 2018;67(4):483–7. https://doi.org/10.1097/MPG.0000000000002043.
64. Ku WH, Lau DCY, Huen KF. Probiotics provoked D-lactic acidosis in short bowel syndrome: case report and literature review. Hong Kong J Paediatr. 2006;11:246–54.
65. Galla J. Metabolic alkalosis. J Am Soc Nephrol. 2000;11:369–75.
66. Doherty NJ, Sufian S, Pavlides CA, Matsumoto T. Cimetidine in the treatment of severe metabolic alkalosis secondary to short bowel syndrome. Int Surg. 1978;63:140–2.
67. Shils ME. Experimental production of magnesium deficiency in man. Ann N Y Acad Sci. 1969;162:847–55.
68. Selby PL, Peacock M, Bambach CP. Hypomagnesiumaemia after small bowel resection: treatment with 1 alpha-hydroxylated vitamin D metabolites. Br J Surg. 1984;71:334–7.
69. Luke RG, Galla JH. It is chloride depletion alkalosis, not contraction alkalosis. J Am Soc Nephrol. 2012;23:204–7.
70. Covelli HD, Black JW, Olsen MS, Jerome F. Respiratory failure precipitated by high carbohydrate loads. Ann Intern Med. 1981;85:579–81.
71. Kushner RF. Total parenteral nutrition associated metabolic acidosis. J Parenter Enter Nutr. 1986;10:306–10.
72. Adamson R, Swenson ER. Acetazolamide use in severe chronic obstructive pulmonary disease pros and cons. Ann Am Thorac Soc. 2017;14:1086–93.
73. eHealthme. Sandostatin and metabolic acidosis –from FDA reports. 2018. https://www.ehealthme.com/ds/sandostatin/metabolic-acidosis/.
74. Scheel PJ, Whelton A, Rossiter K, Watson A. Cholestyramine induced hyperchloraemic acidosis. J Clin Pharmacol. 1992;32:536–8.
75. Kraut JA, Madias NE. Treatment of acute metabolic acidosis: a pathophysiological approach. Nat Rev Nephrol. 2012;8:589–601.
76. Mitch WE. Metabolic and clinical consequences of metabolic acidosis. J Nephrol. 2006;19:S70–5.
77. McSherry E, Morris RC. Attainment and maintenance of normal stature with alkali therapy in infants and children with classic renal tubular acidosis. J Clin Invest. 1978;61:509–27.
78. Roderick P, Willis NS, Blakeley S, Jones C, Tomson C. Correction of chronic metabolic acidosis for chronic kidney disease patients. Cochrane Database Syst Rev. 2007;1:CD001890. https://doi.org/10.1002/14651858.CD001890.pub3.
79. Klein CJ, Coburn JW. Parenteral nutrition: effect on bone and mineral homeostasis. Annu Rev Nutr. 1991;11:93–119.
80. Koo WWK. Parenteral nutrition related bone disease. JPEN. 1992;16:386–94.
81. Cunningham J, Fraher LJ, Clemens TL, Reveil PA, Papapoulos SE. Chronic acidosis with metabolic bone disease. Effect of alkali on bone morphology and vitamin D metabolism. Am J Med. 1982;73:199–204.
82. Karton MA, Rettmer R, Lipkin EW, Ott SM, Chait A. D-lactate and metabolic bone disease in patients receiving long term parenteral nutrition. JPEN. 1989;13:132–5.
83. Jeejeebhoy KN. Short bowel syndrome: a nutritional and medical approach. Can Med Assoc J. 2002;166:1297–302.
84. Romanski SA, McMahon MM. Metabolic acidosis and thiamine deficiency. Mayo Clin Proc. 1999;74:259–63.
85. Elphick DA, Baker M, Baxter JP, Nightingale JM, Bowling T, Page KB, et al. Muscle cramps are the commonest side effect of home parenteral nutrition. Clin Nutr. 2009;28:351–4.
86. Jones BJM. Muscle cramps on HPN. Published by PINNT 2017. http://www.pinnt.com.
87. Ayers P, Adams S, Boullata J, Gervasio J, Holcombe B, Kraft MD, et al. ASPEN parenteral nutrition safety consensus recommendations. JPEN. 2014;38:296–333.
88. Iacone R, Scanzano C, D'Isanto A, Vitalone A, Frangipane I, D'Angeli SL, Contaldo F. Prediction of renal acid load in adult patients on parenteral nutrition. Pharmaceutics. 2018;10(2):43.

Gallstones in Intestinal Failure

Jeremy M.D. Nightingale and Mattias Soop

Key Points

1. Gallstones are more common in patients with intestinal failure (IF) 38% at 20 years of parenteral nutrition at home. They are also common in patients with a short bowel (21% over 10 years).
2. Most (76%) patients receiving home parenteral nutrition (PN) with gallstones develop complications.
3. Gallstone formation may relate to a high-calorie and/or lipid parenteral nutrition, a lack of oral intake, an ileal resection or disease, and certain medications (anticholinergics, opioids or octreotide).
4. Supersaturation of bile, nucleation, crystallization and reduced gall bladder contractility are the key factors that contribute to gallstone formation. In IF patients biliary stasis is most relevant and leads to gall bladder sludge and the formation of gallstones containing calcium bilirubinate.
5. Medical therapy is rarely used to prevent or dissolve gallstones in IF patients due to unpredictable absorption of medication and a lack of proven benefit.
6. Gallstones might be prevented changing the bile composition directly (e.g. ursodeoxycholic acid) or indirectly by increasing gut transit (e.g. cisapride) or changing the bowel flora (e.g. metronidazole).
7. Prevention could also be by maintaining regular gall bladder contraction with oral diet, cholecystokinin injections, rapid amino acid infusions, non-steroidal anti-inflammatory drugs (NSAID's) and avoiding octreotide.
8. Cholecystectomy is recommended if there are gallstones present and surgery is being performed for another reason.
9. Prophylactic cholecystectomy and/or sphincterotomy are not recommended if there are no gallstones.

Introduction

Gallstones (stones in the gallbladder or biliary ducts or both) are a major public health issue and are present in 10–15% of adults in the Western world and are overall more common in women [1]. Of those with gallstones (mainly cholesterol ones) about 25% will develop symptoms, in particular women [2]. Gallstones are of three main types: cholesterol stones, comprising about 75% of stones; pigment stones; and mixed. While pigment stones may predominate in patients with intestinal failure (IF), all types of stones can occur [3]. Gallstones may cause severe and life-endangering complications from cholecystitis (typically large stones >10 mm), biliary colic, obstructive jaundice (often multiple stones), pancreatitis (small stones), bowel obstruction (a large stone which passes from the gallbladder through a choledocho-duodenal fistula into the small bowel, where it may cause obstruction in the duodenum or terminal ileum) and rarely gallbladder cancer or a cholangiocarcinoma. Generally, gallstones greater than 1–1.5 cm and of a high number are most likely to cause symptoms.

(a) *Cholesterol gallstones* are composed of cholesterol, mucin, bile pigments, calcium salts and other compounds. The pathogenetic factors for cholesterol gallstones include a genetic background, female, older age, sedentary life style, high fat diet, lack of fibre, pregnancy (high number of childbirths), hormone replacement therapy. Insulin resistance, as occurs with obesity, metabolic syndrome and type 2 diabetes is a common aetiological component. A further contribution may be from factors within the gallbladder: hepatic hypersecretion of cholesterol, supersaturation of bile (precipitation of cholesterol

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Fig. 1 Pigment type gallstone of 1 cm from a patient with a short bowel

crystals), a sluggish gallbladder, mucin and inflammatory changes in the gallbladder. Factors outside the gallbladder include slowing intestinal motility, increased intestinal absorption of cholesterol, and altered gut microbiota [4, 5].

In patients with IF (having PN or with a short bowel) however, the predominant type of gallstones found are pigment stones. Cholesterol may also play a part in gallstone formation in this group.

(b) Pigment gallstones (Fig. 1) are composed of calcium bilirubinate and are classically associated with haemolytic anaemia but do occur in other circumstances. In North India, where obesity is common, gallstones are primarily (>80%) cholesterol stones whereas in south India where most are vegetarian (less spices and fat) and non-obese, most (>60%) are pigment stones [1]. Liver disease (non-alcoholic fatty liver disease and cirrhosis) are also associated with pigment gallstones. Patients with cirrhosis have an incidence of 2–5% per year (most common if an alcoholic aetiology, a more severe cirrhosis and a longer duration of cirrhosis), which is four times that of the general population [5].

Epidemiology of Gallstones in Intestinal Failure

Gallstones are prevalent in patients with acute or chronic intestinal failure, and in chronic illnesses such as Crohn's disease, after intestinal resections and with the long-term use of parenteral nutrition (PN). Increased rates of cholelithiasis and cholecystitis have been shown also following trauma, burns, truncal vagotomy and pregnancy.

Inflammatory Bowel Disease

There is an increased prevalence of gallstones (25%) (detected by cholecystography and ultrasonography) in patients with Crohn's ileitis or ileo-colitis [6–9] and these occur with equal frequency in men and women [8, 10]. These stones often appear calcified on a plain abdominal radiograph [7]. Gallstones are more common in patients with ileitis than in those with ileo-colitis or colitis [11] and the likelihood may increase with the length of bowel resected [10], the duration of disease, previous surgery and the age of the patient [8, 12].

Patients with loss of functioning distal ileum due to disease or surgical excision have a disruption to the normal enterohepatic circulation of bile salts. It was estimated that the frequency of gallstones in patients with an ileal resection greater than 50 cm in length was 33%, compared to 17% in those who had undergone a lesser resection [10]. However, some studies suggest that the likelihood of gallstone formation is not related to the site of disease or resection but to the duration of disease and previous surgery [12].

Patients with ulcerative colitis (without operation) have on average a 7–14% prevalence of gallstones, marginally more than controls [9, 12, 13]. The risk of stones is higher after a panproctocolectomy and ileostomy formation [6, 14]. A large series of patients (180) who had an ileostomy following a panproctocolectomy showed gallstones in 24–25%, (three times the incidence that might have been expected in a population of this age and sex distribution), it was higher if more than 10 cm terminal ileum had been removed [15].

Short Bowel

Work at St Mark's Hospital showed that 17/27 (63%) men and 15/47 (32%) women with less than 200 cm small bowel remaining had either had a cholecystectomy or were found to have gall stones on an ultrasound examination. This study included subjects who were nutritionally autonomous and subjects who required parenteral nutrition (PN). There was no difference between those with a colon in continuity (15 (44%)) and those with a jejunostomy (17 (43%)) [16]. Another study showed that 72 of 345 patients (21%) who had a total small bowel length less than 104 cm (19% had a jejunostomy) developed gallstones over a 10 year period. PN dependence (34% of patients) and a very short length of

remaining jejunum were independent risk factors. 39% developed symptoms (23/28 (82%) acute cholecystitis/cholangitis and 5/28 (18%) acute pancreatitis) [15].

Parenteral Nutrition

Anecdotal reports in the 1970s suggested that PN might be associated with an increased incidence of both acalculous cholecystitis and cholelithiasis [17]. There were also descriptions of massively dilated gallbladders in patients receiving PN [18]. Later studies confirmed the association between PN and gallstone formation. In one study of patients receiving PN for a minimum of 3 months, 23% developed gallbladder disease after commencement of PN [19]. There was a 40% incidence of gallbladder disease in this group receiving PN, which is significantly greater than that in Crohn's disease or ileal resection patients not receiving PN. The same researchers also found that the risk of development of gallstones whilst on PN was greater in patients of less than 30 years old and in patients whose ileal resection had been performed less than 15 years previously. Research on a population of children on PN showed that 43% of children on long-term PN (mean duration 20 months) developed gallstones [20].

Subsequent studies also showed that long-term parenteral nutrition in both adults and children is commonly associated with gallstones (40%) [19–25], which in patients with a short bowel are often symptomatic [24]. Acalculous cholecystitis may occur but is less common [17, 23]. Gallstones were more common in men than women in one study [22].

Patients receiving PN frequently develop sludge and may go on to develop gallstones [21]. Dray et al. prospectively followed adult patients with a gallbladder in situ receiving HPN and 45/119 (38%) developed gallstones and/or biliary sludge (14 sludge alone), the probability of developing them was 21% at 1 year and 39% at 2 years. Eight of the 45 developed biliary complications. It was estimated that the incidence of biliary complications was 5% at 1 year and 10% at 2 years. No or negligible oral intake was associated with the development of gallstones. There was no difference in incidence between the sexes in this study [26].

Appleton showed that 17/63 (27%) of patients with no previous gallstones developed them over a median of 11 years of HPN. The cumulative incidence was 21% at 10 years, 38% at 20 years and 47% at 30 years. No less than thirteen of the 17 (76%) had symptoms (4 biliary colic, 4 acute pancreatitis, 2 common bile duct (CBD) stones, 1 cholangitis, 1 empyema/abscess) and 10 of these required surgical or endoscopic interventions. Increased energy content and the provision of lipid were predictors for cholelithiasis [27]. The authors concluded that complications from gallstones were so common that en-passent cholecystectomy is warranted when gallstones are present; in other words, during abdominal surgery for other reasons, the gallbladder should be removed if safe [27].

Biliary Sludge in PN and Crohn's Disease

Biliary sludge formation is an important stage in gallstone development and is associated with PN. Messing et al. reported a progressive increase in the incidence of biliary sludge from 6% after 3 weeks of PN to 50% between 4 and 6 weeks, and reaching 100% in patients receiving intravenous nutritional therapy for more than 6 weeks [21]. Sludge appears to precede gallstone formation; gallstones were then noted in six of 14 patients who developed sludge, while none of the patients without sludge developed gallstones. Interestingly, five of seven patients who earlier had sludge or gallstones were found to be free of both after a short period of oral refeeding [21].

There are considerably less data available on the prevalence of sludge in Crohn's disease itself without the concomitant use of PN but reduced gallbladder contractility, which predisposes to biliary sludge, has been demonstrated especially in those who have undergone ileal resection [28].

Biliary sludge also commonly develops rapidly in patients on an intensive care unit. Some of these patients had a previously recognized risk factor such as abdominal surgery or PN but neurosurgical procedures were also associated with sludge formation [29].

Pathogenesis of Gallstone Disease

Supersaturation of bile, nucleation and crystallisation, and reduced gall bladder contractility are the traditional factors that produce "lithogenic bile". In patients with IF the stones, while containing some cholesterol, are mainly of pigment type composed of calcium bilirubinate. The stones develop within biliary sludge, which has formed due to gallbladder stasis often due to a period of no or reduced oral intake. Biliary sludge contains calcium bilirubinate or unconjugated bilirubin, cholesterol monohydrate crystals and increased amounts of mucin glycoproteins [30]. Biliary sludge may disappear spontaneously but frequently evolves into gallstones [31]. Sludge may persist or recur in 50% of cases and gallstones may form in up to 14% of affected subjects over 3 years [25]. Calcium bilirubinate crystals, within biliary sludge, are more commonly found in men than women [32].

Supersaturation of Bile

While pigment stones are most common, cholesterol supersaturation is well researched and may occur and contribute to the genesis of gallstones [3]. Cholesterol is secreted into the bile canalicular lumina and subsequently taken up by biliary lipid vesicles with a cholesterol: phospholipid ratio of 0.34: 0.38, but the ratio is higher in lithogenic bile [33, 34]. Cholesterol, lecithin (the most abundant biliary phospholipid) and bile salts aggregate to produce mixed micelles and

vesicles in bile, in which the hydrophilic portions of these lipids are located peripherally with the hydrophobic portions orientated centrally in a hydrophobic domain, thus permitting lipid solubility in an aqueous environment [35]. Cholesterol solubility in bile has been defined using a triangular coordinate map comprising cholesterol, bile salts and phospholipids [36, 37]. Bile supersaturated with cholesterol may be a result of increased cholesterol secretion or decreased phospholipid or bile salt secretion. Cholesterol-rich vesicles play an important part in the formation of cholesterol crystals [38].

Nucleation and Crystallization

Bile contains both anti-nucleating and pronucleating factors, the balance of which is important in determining the likelihood of gallstone formation. Apolipoprotein A-1 and A-2, and a glycoprotein (120 kDa), all found in human bile, have been identified as anti-nucleating factors [39]. Pro-nucleating factors include both mucin glycoproteins [40] and non-mucin glycoproteins [41]. Mucin is thought to play a significant role in crystallization of cholesterol. The evidence for this comes from three main sources. First, mucin glycoproteins have been found in the matrix of cholesterol gallstones [42]. Second, mucin hypersecretion precedes crystallization of cholesterol in animal models [43] and probably humans [44]. Third, mucin has been shown to promote crystal nucleation in cholesterol supersaturated bile *in vitro*. Mucin may act as a nidus for crystal aggregation by entrapping cholesterol crystals or calcium bilirubin on non-glycosylated hydrophobic domains of the peptide chain of the mucin glycoprotein molecule [45].

In addition to mucin, several other non-mucin pronucleating factors have been identified *in vitro* such as amino peptidase N, a low-density lipoprotein particle, and haptoglobins.

Crystal growth in bile follows nucleation. Cholesterol monohydrate crystals are composed of bilayers of cholesterol bonded to a water layer. Rapid growth occurs as these crystals pack side-by-side in their long axis, resulting in plate-like monohydrate crystals. Cholesterol also precipitates in other forms such as helical, tubular and filamentous forms of non-hydrated cholesterol [46].

Gallbladder Contractility

As well as cholesterol supersaturation and mucin hypersecretion, reduced gallbladder contractility appears crucially important in cholelithiasis by allowing the cholesterol crystals entrapped in mucin to grow to a sufficient size to allow them to remain in the gallbladder. Early cholesterol crystals are likely to develop into macroscopic stones only if formed in the mucus layer adherent to the epithelium in gallbladders with reduced contractility.

It would appear that all three requirements—cholesterol/calcium bilirubinate supersaturation, increased nucleation rate mediated by mucin hypersecretion, and reduced gallbladder contractility—occurring simultaneously allow cholelithiasis to occur (the "triple defect of gallstone formation").

Pigment stones have been shown to be largely composed of calcium bilirubinate and other calcium salts. Less is known about the process of pigment stone formation than about cholesterol gallstones, but biliary stasis appears to play a major role. Unconjugated bilirubin concentration is higher in gallbladder bile in patients with pigment gallstones than in controls and it is likely that unconjugated bilirubin forms gallstones by precipitation in a similar fashion to that of cholesterol [47].

Biliary Sludge

Biliary sludge may be an important intermediate factor in the formation of gallstones [45]. Sludge was initially identified by ultrasonography as low amplitude echoes without acoustic shadowing which layered in the most dependent portion of the gallbladder [48] (Fig. 2). Biliary sludge is an amorphous precipitant of mucin glycoproteins, bile pigment granules (calcium bilirubinate), cholesterol crystals, small stones, protein and lipids. An ever-present constituent of biliary sludge in humans is calcium bilirubinate or unconjugated bilirubin. Cholesterol monohydrate crystals and a marked increase in the amount of mucin are found in biliary sludge [45]. They also noted that the cholesterol and phospholipid concentration in bile from sludge-forming patients was no different to that of normal controls and gallstone patients [45].

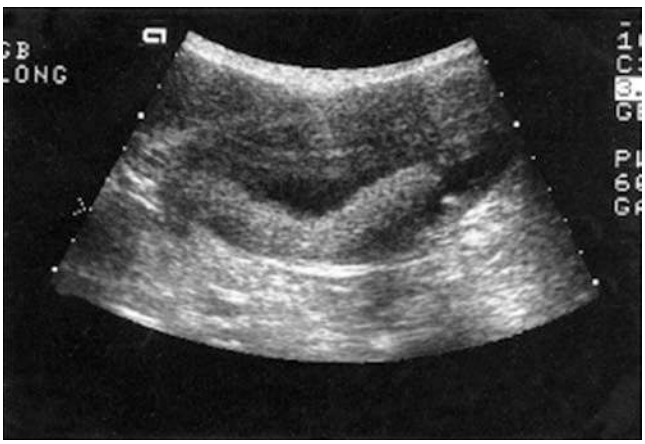

Fig. 2 Ultrasound image of the gallbladder in longitudinal section showing layering of sludge without acoustic shadowing (courtesy of Professor M. J. Lee, Radiology Department, Beaumont Hospital, Dublin 9)

Several possible factors leading to biliary sludge formation are cited in the literature including biliary stasis (due to no or little oral intake), use of total parenteral nutrition, mucin hypersecretion, bile infection and acute illness. A definite association between development of biliary sludge and gallbladder stasis has been noted especially in patients receiving total PN with no oral intake [24].

The exact mechanism of sludge formation has not yet been elucidated but one theory is that decreased gallbladder contractility leads to bile becoming progressively more concentrated due to water absorption and the cholesterol vesicular carriers becoming enriched in cholesterol content and depleted of lecithin and other phospholipids. Crystals of cholesterol are thus formed, and calcium salts (especially bilirubinate) precipitate secondary to stasis as well. Thus, sludge may form. Prolonged stasis and further growth may lead to the development of gallstones [49]. Biliary sludge may disappear spontaneously or have a fluctuating course but it frequently evolves into gallstones [50]. It would appear that sludge may persist or recur in at least 50% of cases and that gallstones may form in up to 14% of affected subjects over 3 years [51]. Biliary sludge always represents a pathological process and cholecystitis is common [52].

Intestinal Microbiota

Bile acids are cholesterol-derived molecules that can be modified by the gut microbiota and can act as signaling molecules to regulate metabolic and physiological processes. The gut microbiota releases many enzymes that can modify the bile acids such as bile salt hydrolases (7α-dehydroxylase, and hydroxysteroid dehydrogenase). These enzymes can change the gut microbiota composition, and thus alter the bile acids (more secondary bile acids) and so predispose to gallstone formation. A slower gut transit time also allows more secondary bile acids to be manufactured.

Pathogenesis of Gallstones in Intestinal Failure

Gallstones in IF patients may occur due to ileal disease/resection, fasting, PN, surgery, rapid weight loss or drug treatments (Fig. 3). Bacterial overgrowth may have a role.

Surgery, weight loss and parenteral nutrition may all involve prolonged fasting. The main drugs that are causative are anticholinergic agents, opioid analgesics or octreotide. Other factors may include poor cholecystokinin secretion and less physical activity.

Ileal Disease/Resection

While disruption of the enterohepatic circulation and consequent loss of bile salts should lead to an increase in cholesterol saturation (relates to concentrations of cholesterol, bile salts and phospholipids); this was the case in some studies of patients with "ileal dysfunction or resection" [53, 54] but not in others [53]. A reduced amount of deoxycholic acid and an increased amount of ursodeoxycholic acid are found in the bile of patients with ileal Crohn's disease [54, 55]. Bilirubin concentrations are two- to threefold higher in patients with ileal disease compared to those with no ileal disease [54, 55] while phosphatidylcholine levels are not different [54]. The majority of patients (children and adults) who undergo ileal resection and require long-term PN develop pigment gallstones [56]. Of note, some researchers have found normal or even low cholesterol saturation of bile after resection of ileum [55]. In patients with Crohn's disease gallbladder contractility is reduced after a fatty meal [31, 57], which may contribute to the formation of biliary stasis. The fasting gallbladder volume is decreased and fasting plasma cholecystokinin levels are surprisingly increased in patients with Crohn's disease of the large bowel and patients after an ileocecal resection) [58].

Much data suggests that ileal resection results in alteration of bilirubin rather than cholesterol metabolism so resulting in pigment gallstone formation (Table 1). Ileal resection

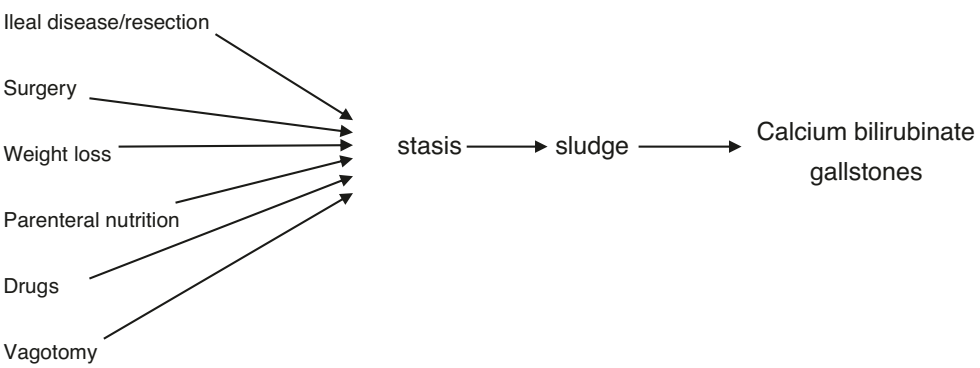

Fig. 3 Pathogenesis of gallstones in patients with intestinal failure

Table 1 Gallstones in Crohn's disease: disturbance of cholesterol or bilirubin metabolism?

Researchers	Year	Subjects	Main findings
Dowling RH, Bell GD, White J [53]	1972	Patients with Crohn's disease	Increased cholesterol saturation index
Dowling RH, Mack E, Small DM [59]	1971	Rhesus monkey's ileal resection	Cholesterol supersaturation Lithogenic bile model
Kelly TR, Klein RL, Woodford JW [60]	1972	Prairie dog's ileal resection	Increased cholesterol/ phospholipid ratio
Pitt HA, Lewinski MA, Muller EL, Porter-Fink V, Den Besten L [61]	1984	Prairie dog's Ileal resection	Pigment gallstones Increased bilirubin concentration in bile
Brink MA, Slors FM, Keulemans YCA, et al. [62]	1999	Patients with Crohn's disease or ileal resection	Increased bilirubin levels in bile, probably secondary to enhanced colonic uptake of bilirubin

in the prairie dog led to the development of pigment gallstones in 44% of animals compared to none in the control group [61]. Calcium bilirubinate crystals were found in up to 94% of animals who underwent ileal resection and in none of the control groups. It was noted that calcium and total bilirubin concentrations in bile were significantly greater in ileal-resected animals.

Data from patients with ileal resection receiving TPN have shown that there is a predisposition to development of pigment gallstones. Analysis of stones from adults and children who have had significant ileal resection necessitating long-term parenteral nutrition shows that pigment rather than cholesterol stones form in the majority of these patients [56].

Research in humans has shown that there is a three- to tenfold increase in bilirubin levels (unconjugated and conjugated) in gallbladder bile in patients with ileal disease and/or resection for Crohn's disease compared to patients with ulcerative colitis or Crohn's colitis [62]. Biliary bilirubin concentrations correlated positively with the anatomic length of resection and duration of ileal disease. This shows that there is an increase in the enterohepatic cycling of bilirubin secondary to enhanced uptake of bilirubin in the colon. This may explain the increased risk of pigment gallstone formation in patients with terminal ileal Crohn's disease and after an ileal resection.

There are several proposed mechanisms for reduced gallbladder contractility in Crohn's patients. Reduction in intestinal release of cholecystokinin or other peptides due to proximal small bowel disease may be a factor [63]. The number of argentaffin cells in colonic mucosa in patients with ulcerative colitis is reduced [64]. Reduction in levels of peptide YY concentration in the colonic mucosa of patients with ulcerative colitis and Crohn's disease has also been demonstrated [65]. Thus, changes in peptide secretion by small and large bowel may occur in Crohn's disease and may influence gallbladder contractility.

In contrast to the increased prevalence of gallstones in women compared to men in the general population, female sex does not seem to be a risk factor for gallstones in Crohn's disease [10]. In fact, some data suggest a higher prevalence of gallstones in men receiving PN compared to women [22]. Men with a short bowel with or without a retained colon have a much higher prevalence of gallstones than women [16].

A diagnosis of CD, intestinal surgery, prolonged NSAID use, disease activity and duration and bowel stenosis have been associated with cholecystonephrolithiasis in IBD [66].

Fasting and Parenteral Nutrition

Patients who have a reduced or absent oral intake (e.g. if having total PN) may experience long periods when food-stimulated intestinal hormone secretion (e.g. cholecystokinin) is not activated. Cholecystokinin secretion in response to a meal is significantly decreased in short bowel patients [67]. This may result in gallbladder stasis and the rapid formation of biliary sludge [21, 50, 68]. As reviewed above, the incidence of biliary sludge rapidly increases from 6% at three weeks of TPN to 50% between four and six weeks, and 100% after 6 weeks [21]. The sludge gradually disappears when oral refeeding is begun [21]. Gallstones will have started to become apparent by 4 months [21]. Bile is not supersaturated consequent on TPN [69], but bile flow is impaired [70] and gallbladder emptying during both continuous and cyclic infusions is reduced [71]. A medium/long chain triglyceride mixture in a PN regimen may be more likely to cause biliary sludge than one of long chain triglycerides alone [67]. In children on PN, cholelithiasis may be associated with a massively dilated gallbladder [18].

Bile flow is impaired when PN is given [70]. Current evidence suggests that bile is not supersaturated as a consequence of PN [69], but that prolonged stasis may be the key pathogenetic mechanism for increased cholelithiasis. The evidence for the dominant role of stasis in this scenario comes from several sources. Gallbladder contractility measured by ultrasound is reduced in patients receiving parenteral feeding [71]. The cholesterol saturation index in bile in prairie dogs receiving PN is not increased but gallbladder stasis is noted [72].

Improved radiological imaging has lent itself to the investigation of gallbladder disease. Radionuclide imaging of the gallbladder revealed biliary tract abnormalities in 92% of patients who received PN [73]. Ultrasonographic measurements of gallbladder motility during use of PN showed that, while maximal gallbladder volume was similar in PN patients and controls, gallbladder emptying was significantly reduced in parenterally fed patients during both continuous and cyclic infusion [71].

The mechanism underlying impaired gallbladder contractility in patients receiving PN is unclear. In one animal model using cholesterol-fed ground squirrels, agents which bypassed receptors and their subsequent interactions with calcium channels in the sarcolemma can restore gallbladder contractility in gallstone disease [74]. This suggested that bile saturated with cholesterol causes excessive integration of cholesterol into the sarcolemma, thus changing its functional characteristics. The primary smooth muscle defect in this animal model would appear to involve the sarcolemmal membrane, rather than the intracellular signal transduction pathways or contractile apparatus [73].

The finding of biliary sludge and potential for gallstone formation during PN has also been documented during fasting after surgery. Ultrasound studies have provided evidence of the relationship between prolonged periods of fasting and gallbladder sludge formation in patients who have undergone gastrointestinal surgery [68].

Is gallbladder Stasis Alone Sufficient to Cause Gallbladder Disease in Patients Receiving PN?

In untreated coeliac disease, the gallbladder enlarges, contractility after a fatty meal is reduced and biliary sludge may occur [75, 76]. Reduced gallbladder contractility in response to a fatty meal has been noted in coeliac disease. This defect appears to correlate well with decreased cholecystokinin secretion [77]. Furthermore, gallbladder emptying improves after successful treatment with a gluten-free diet [77]. However, no increase in the prevalence of cholelithiasis has been found in patients with coeliac disease despite impaired gallbladder contractility. Thus, factors other than gallbladder stasis may be important in the development of gallstones but the lack of enteric stimulation of bile flow and impaired gallbladder contractility secondary to the absence of significant oral intake may be the primary factors in biliary sludge and gallstone development during PN use.

Type of Feed

In adults those receiving parenteral lipid were at greatest risk of stones [27]. In children on PN there was a higher prevalence of sludge on pure soya lipid. Predictors for sludge in these children were young age at PN, lack of enteral feed, and a motility disorder with stoma [78].

Surgery

Major abdominal (not involving the biliary system) [79], cardiac valve replacement surgery [80] and a period in an intensive care therapy [29] all predispose to gallstone development with an equal sex incidence. This is again likely to be due to bowel rest causing biliary stasis, biliary sludge and the formation of gallstones.

Many factors appear to influence development of gallstones in patients with inflammatory bowel disease who undergo surgery, including gender, episodes of fasting, TPN and the type of surgery involved. Particular operations such as ileal resection, which interfere with the enterohepatic bile salt cycle, are more likely to lead to gallstone formation. Major abdominal surgery itself (not involving the biliary system) also appears to accelerate gallstone development in some patients. Indeed, in one retrospective study of gallstone formation after major abdominal surgery, surgery and age were the only statistically significant independent predictors of gallstone development during follow-up [79].

The possible mechanisms responsible for gallstone formation in patients who have undergone major abdominal surgery outside the biliary tract. Lee et al. found that sludge preceded gallstone formation in six of 14 sludge-forming patients receiving TPN [51]. Gallbladder stasis and bowel rest were felt to be important factors in sludge development. Patients on intensive care units (who undergo periods of fasting) are predisposed to sludge development.

Harrison et al. found that patients who underwent valve replacement surgery for rheumatic heart disease had a gallstone prevalence of 39% compared to 12% in a matched control population [80]. No difference in the degree of haemolysis between the two groups was detected; undermining the suggestion that excess haemolysis might be the cause of increased cholelithiasis in the surgical group.

This finding has important practical and financial implications, and identification of patients at risk for development of gallstones postoperatively might encourage the use of prophylactic measures such as earlier enteral feeding or administration of cholecystokinin.

Rapid Weight Loss

Cholesterol gallstones are common (40%) in morbidly obese patients and this figure increases with a diet causing rapid weight loss or after weight reducing surgery [81]. 38% of patients undergoing gastric by-pass surgery developed gallstones and a further 12% developed gallbladder sludge [82] and these formed during the time of maximal weight loss. Reduced gallbladder motility is likely to be the most important factor but cholesterol saturation also increases [82]. A significant increase in the gallbladder volume occurred in obese patients taking a low-energy, low-fat diet after 10 days [83], and could be secondary to minimal cholecystokinin secretion or to excess secretion of pancreatic polypeptide or somatostatin (gallbladder wall relaxants).

The proposed factors involved in gallstone formation during weight loss include impaired gallbladder motility and modifications in biliary nucleation. Twenty-one obese patients were placed on a low-calorie, low-fat diet for weight

reduction purposes [83]. A significant increase in the gallbladder volume after 10 days ingestion of this diet was noted, and was attributed to poor gallbladder contractility secondary to minimal stimulation of cholecystokinin secretion or to excess secretion of gallbladder wall relaxants such as pancreatic polypeptide or somatostatin [84, 85].

Drug Treatments

The use of narcotics [86] and anti-cholinergics [87] both of which reduce gallbladder contractility, in patients receiving PN has led to an increase in gallbladder disease. Narcotics, by reducing bile flow through the sphincter of Oddi, encourage gallbladder stasis, and anti-cholinergics have been shown to antagonize the protective effect of sphincterotomy on gallstone formation—both lending strong support to the idea of gallbladder stasis playing the most important role in gallstone formation. Loperamide inhibits gallbladder contraction in healthy subjects at daily doses of 16 mg [88] and inhibits pancreatic and biliary secretions in patients with a short bowel at 6 mg daily [89].

Octreotide, a long-acting somatostatin analogue often used in the treatment of a high output jejunostomy, increases the risk of cholelithiasis [87]. It reduces post-prandial gallbladder contractility [90] secondary (more lithogenic) bile acids are formed by intestinal bacteria [91] and it inhibits cholecystokinin secretion.

Cholecystectomy and Sphincterotomy

As several risk factors have been identified for cholelithiasis in patients with a short bowel, namely ileal resection (especially if fewer than 120 cm of intestinal remnant is left), resection of the ileo-colonic junction, long-term PN and the presence of Crohn's disease itself, a role for prophylactic cholecystectomy in patients with a short bowel has been suggested [92]. In patients with a short bowel, cholelithiasis is usually symptomatic, often complicated by inflammation or bile duct stones, and is associated with a significant morbidity and mortality postoperatively.

The cumulative incidence for cholecystectomy in patients with Crohn's disease after an ileal resection was 0.5% at 1 year, 2.4% at 5 years, 4.6% at 10 years, and 10.3% after 20 years with a higher rate in women, and higher than in the general population [93]. Prophylactic cholecystectomy should be considered when an abdominal procedure is being done in patients with IF and gallstones [27]. The rationale for performing such an en-passent cholecystectomy is the markedly increased incidence of complications to gallstones in IF (76% in one study) [27]. Cholecystectomy is not without problems; however, as a postoperative bile leak may interfere with the healing of any new intestinal anastomosis. Longer-term, it may shorten gut transit time (mainly by accelerating colonic transit) and so increase dependency on PN. These sequelae which may be due to a change in bile acid composition (more diarrheogenic secondary bile acids) develop early and persist for at least 4 years [94]. Furthermore, some data suggest that patients who have a short bowel and a cholecystectomy may be more prone to liver fibrosis/cirrhosis [95].

Medical Prevention and Dissolution Therapies

There are many therapies that may prevent cholesterol gallstones (Table 2). It is more difficult for pigment stones. The studies/reports suggest that cholesterol gallstones can be prevented by giving statins, ezetimibe, w3 polyunsaturated fatty acids, liraglutide and many herbal, complementary or alternative medicines [1]. Dietary factors that may prevent the development of cholesterol gallstones include a vegetarian diet, polyunsaturated or monounsaturated fat, fiber, and caffeine. In the past direct contact dissolution of cholesterol stones was done by infusing methyltertbutylether via a cannula into the biliary tree. Experimentally calcium bilirubinate stones can be dissolved in a mixture of glycerol octanoate and EDTA [96], but no practical method of dissolving them have been used in human clinical trials.

The role of medical treatments for gallstones has diminished, but may on occasions, be considered an alternative to cholecystectomy in those patients who are not suitable for surgery. The main medical treatment for gallstones, used alone or in combination with extracorporeal shockwave lithotripsy, is an oral bile salt (originally chenodeoxycholic acid then subsequently ursodeoxycholic acid).

Changing Bile Composition

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) and chenodeoxycholic acid may, in addition to being used to help cholestatic IFALD, have roles in both prevention and dissolution of gallstones in patients with intestinal failure. Chenodeoxycholic acid was

Table 2 Prevention of gallstones and biliary sludge

Cholecystectomy and/or sphincterotomy	
Change bile composition	
• Directly	Ursodeoxycholic acid
• Indirectly	
– Change intestinal microflora	Antibiotics (Metronidazole)
– Increase gut transit	Prokinetics (Cisapride)
Prevent biliary stasis (promote gallbladder emptying)	
• Enteral feed	
• Cholecystokinin	
• Rapid amino acid infusions	
• NSAID's	
• Avoid octreotide	

used first but due to a dose-dependent increase in aminotransferases, an increase in serum low-density lipoprotein cholesterol and the development of bile salt-induced diarrhoea, it was superseded by ursodeoxycholic acid (urso stands for bear from which it is derived) and has been successfully used for patients to dissolve gallstones.

UDCA decreases biliary cholesterol saturation by 40–60% (i.e. makes cholesterol more soluble and less able to crystalize), by inhibition of cholesterol absorption in the intestine, reducing cholesterol secretion into bile and reducing the concentration of several crystallization-promoting factors (for example, amino-peptidase N, haptoglobin and some immunoglobulins) [97–99]. In addition UDCA decreases the toxicity of bile acids which can damage cell membranes and cause cholestasis [100].

UDCA is most effective in patients with good gallbladder function (and a patent cystic duct) who have few small non-radio-opaque cholesterol stones (<10–20 cm in size). UDCA has been used successfully to reduce the number of episodes of pancreatitis due to microscopic gallstones or biliary sludge [100]. The bile salt therapy may be required for more than 6 months. The problem of UDCA is that there is a high recurrence rate of gallstones of 30–50% at 5 years and 50–70% at 12 years, after successful treatment [101].

UDCA has not been studied in IF patients in whom there may be major problems with absorption.

Increase Gut Transit or Change Intestinal Microflora

Slow intestinal transit results in more primary bile acids being converted by bacteria to the more lithogenic secondary bile acids. Cisapride increases gastrointestinal transit rate (reversing any changes of octreotide treatment) and changes bile composition [91]. Thus it or another prokinetic drug could be useful in preventing gallstones in patients with intestinal failure due to small bowel dysfunction.

Metronidazole, by suppressing anaerobic intestinal organisms, reduced the rise in liver enzymes associated with parenteral nutrition in Crohn's disease [102]. This may be another simple way of reducing the chance of developing gallstones.

Prevent Biliary Stasis (Promote Gallbladder Emptying)

Oral Diet, Cholecystokinin, Rapid Amino Acid Infusions

As discussed cholestasis is an important contributor to the formation of gallstones and in part may be due to a lack of oral intake and thus reduced cholecystokinin which stimulates gallbladder contraction. cholecystokinin levels are low after a meal in patients with a short bowel and receiving PN [63]. Thus an oral diet and cholecystokinin injections could be a good preventative option in patients having PN with no or little oral intake. In prairie dogs, daily injections of cholecystokinin [30], or sphincterotomy [31], prevented gallstone formation. Data from human studies suggest that use of cholecystokinin in patients receiving TPN stimulates gallbladder emptying and prevents stasis and subsequent sludge formation [32, 72]. The prophylactic use of cholecystokinin in adult patients receiving total (no oral intake) PN, especially those with an ileal resection in whom the incidence of gallstone formation is increased may be beneficial. In children of whom 10% develop mostly asymptomatic gallstones while having total PN, cholecystokinin-octapeptide prophylaxis did not prevent the PN-associated gallstones forming. In addition, URDA did not dissolve gallstones, once identified [103].

The use of rapid infusion of amino acids [104–106] for example 125 mL of an aminoacid mixture (Synthamin 14 without electrolytes) over 5 min (2.1 g/min) produced a 64% reduction in gallbladder volume within 30 min [105]. A rapid infusion prevents the formation of biliary sludge [106].

Aspirin and Non-steroidal Anti-inflammatory Drugs

Studies involving the cholesterol-fed prairie dog showed that use of high-dose aspirin prevented gallstone recurrence after successful dissolution therapy. A decrease in mucin glycoprotein involved in nucleation was found and, as aspirin is an inhibitor of prostaglandin formation, it was suggested that secretion of mucin might be prostaglandin-mediated [107]. However, research in the same model showed that, at therapeutic doses, non-steroidal anti-inflammatory drugs (NSAIDs) had minimal effect on the production of mucin by the gallbladder [108].

NSAIDs may prevent gallstone formation by a prokinetic effect on the gallbladder. In a human study, subjects with gallstone disease given therapeutic doses of indomethacin had increased post-prandial gallbladder emptying [109]. This effect was not seen in healthy control subjects. The concentration of various eicosanoids in the gallbladder wall changes with bile cholesterol supersaturation and chronic inflammation and it may be that inhibitors of prostaglandin formation such as NSAIDs promote the production of prokinetic leukotrienes or prostaglandins in diseased but not in healthy gallbladders.

References

1. Swarne E, Srikanth MS, Shreyas A, Desai S, Mehdi S, Gangadharappa HV, Suman KKL. Recent advances, novel targets and treatments for cholelithiasis; a narrative review. Eur J Pharmacol. 2021;908:1–9.
2. Sakorafas GH, Milingos D, Peros G. Asymptomatic cholelithiasis: is cholecystectomy really needed? A critical reappraisal 15 years after the introduction of laparoscopic cholecystectomy. Dig Dis Sci. 2007;52(5):1313–25.

3. Lapidus A, Akerlund JE, Einarsson C. Gallbladder bile composition in patients with Crohn's disease. World J Gastroenterol. 2006;12(1):70–4.
4. Di Ciaula A, Wang DQ, Portincasa P. An update on the pathogenesis of cholesterol gallstone disease. Curr Opin Gastroenterol. 2018;34(2):71–80.
5. Shabanzadeh DM. Incidence of gallstone disease and complications. Curr Opin Dent. 2017;33:1–9.
6. Hill GL, Mair WSJ, Goligher JC. Gallstones after ileostomy and ileal resection. Gut. 1975;16:932–6.
7. Heaton KW, Read AE. Gallstones in patients with disorders of the terminal ileum and disturbed bile salt metabolism. Br Med J. 1969;3:494–6.
8. Fraquelli M, Losco A, Visentin S, Cesana BM, Pometta R, Colli A, Conte D. Gallstone disease and related risk factors in patients with Crohn's disease: an analysis of 330 consecutive cases. Arch Intern Med. 2001;161:2201–4.
9. Parente F, Pastore L, Bargiggia S, Cucino C, Greco S, Molteni M, Ardizzone S, Porro GB, Sampietro GM, Giorgi R, Moretti R, Gallus S. Incidence and risk factors for gallstones in patients with inflammatory bowel disease: a large case-control study. Hepatology. 2007;45(5):1267–74.
10. Kangas E, Lehmusto P, Matikainen M. Gallstones in Crohn's disease. Hepato-Gastroenterology. 1990;38:83–4.
11. Baker AL, Kaplan M, Norton AP, Patterson J. Gallstones in inflammatory bowel disease. Am J Dig Dis. 1974;19:109–12.
12. Hutchinson R, Tyrrell PNM, Kumar D, Dunn JA, Li JKW, Allan RN. Pathogenesis of gallstones in Crohn's disease: an alternative explanation. Gut. 1994;35:94–7.
13. Ha JH, Park YS, Seon CS, Son BK, Ahn SB, Jo YK, Kim SH, Jo YJ, Kim JH, Han JH, Jung YY, Chung SH. Increased risk of asymptomatic gallstones in patients with ulcerative colitis. Intest Res. 2015;13(2):122–7.
14. Mark-Christensen A, Brandsborg S, Laurberg S, Johansen N, Pachler JH, Thorlacius-Ussing O, Kjaer MD, Qvist N, Preisler L, Hillingsø J, Rosenberg J, Jepsen P. Increased risk of gallstone disease following colectomy for ulcerative colitis. Am J Gastroenterol. 2017;112(3):473–8.
15. Gao X, Zhang L, Wang S, Xiao Y, Song D, Zhou D, Wang X. Prevalence, risk factors, and complications of cholelithiasis in adults with short bowel syndrome: a longitudinal cohort study. Front Nutr. 2021;8:762240.
16. Nightingale JMD, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces the need for parenteral therapy, increases the incidence of renal stones but does not change the high prevalence of gallstones in patients with a short bowel. Gut. 1992;33:1493–7.
17. Peterson SR, Sheldon GF. Acute acalculous cholecystitis: a complication of hyperalimentation. Am J Surg. 1979;138:814–7.
18. Barth RA, Brasch RC, Filly RA. Abdominal pseudo-tumour in childhood: distended gallbladder with parenteral hyperalimentation. Am J Roentgenol. 1981;136:341–3.
19. Roslyn JJ, Pitt HA, Mann LL, Ament ME, Den Besten L. Gallbladder disease in patients on long-term parenteral nutrition. Gastroenterology. 1983;84:148–54.
20. Roslyn JJ, Berquist WE, Pitt HA, Mann LL, Kangarloo H, DenBesten L, Ament ME. Increased risk of gallstones in children on total parenteral nutrition. Paediatrics. 1983;71:784–9.
21. Messing B, Bories C, Kunstlinger F, Bernier J. Does total parenteral nutrition induce gallbladder sludge formation and lithiasis? Gastroenterology. 1983;84:1012–9.
22. Pitt HA, King W, Mann LL, Roslyn JJ, Berquist WE, Ament ME, DenBesten L. Increased risk of cholelithiasis with prolonged total parenteral nutrition. Am J Surg. 1983;145:106–12.
23. Roslyn JJ, Pitt HA, Mann L, Fonkalsrud EW, DenBesten L. Parenteral nutrition-induced gallbladder disease: a reason for early cholecystectomy. Am J Surg. 1984;148:58–63.
24. Manji N, Bistrian BR, Mascioli EA, Benotti PA, Blackburn GL. Gallstone diseae in patients with severe short bowel syndrome dependent on parenteral nutrition. J Parenter Enter Nutr. 1989;13:461–4.
25. Colomb V, Goulet O, Rambaud C, De Potter S, Sadoun E, Ben Hariz M, Jan D, Brousse N, Ricour C. Long-term parenteral nutrition in children: liver and gallbladder disease. Transplant Proc. 1982;24:1054–5.
26. Dray X, Joly F, Reijasse D, Attar A, Alves A, Panis Y, Valleur P, Messing B. Incidence, risk factors, and complications of cholelithiasis in patients with home parenteral nutrition. J Am Coll Surg. 2007;204(1):13–21.
27. Appleton ND, Lal S, Carlson GL, Shaw S, Stevens P, Peristerakis I, Soop M. Cholelithiasis and related morbidity in chronic intestinal failure: a longitudinal cohort study from a national specialized centre. J Gastrointest Surg. 2019;23(10):2002–6.
28. Murray FE, McNicholas M, Stack W, O'Donoghue DP. Impaired fatty-meal-stimulated gallbladder contractility in patients with Crohn's disease. Clin Sci. 1992;83:1–5.
29. Murray FE, Stinchcombe SJ, Hawkey CJ. Development of biliary sludge in patients on intensive care unit: results of a prospective ultrasonographic study. Gut. 1992;33:1123–5.
30. Roslyn JJ, DenBesten L, Pitt HA, Kuchenbecker S, Polarek JW. Effects of cholecystokinin on gallbladder stasis and cholesterol gallstone formation. J Surg Res. 1981;30:200–4.
31. Hutton SW, Sievert CE Jr, Vennes JA, Duane WC. Inhibition of gallstone formation by sphincterotomy in the prairie dog: reversal by atropine. Gastroenterology. 1982;82:1308–13.
32. Sitzmann JV, Pitt HA, Steinborn PA, Pasha ZR, Sanders RC. Cholecystokinin prevents parenteral nutrition induced biliary sludge in humans. Surg Gynecol Obstet. 1990;170:25–31.
33. Crawford JM, Möckel GM, Crawford AR, Hagen SJ, Hatch VC, Barnes S, Godleski JJ, Carey MC. Imaging biliary lipid secretion in the rat: ultrastructural evidence for vesiculation of the hepatocyte canalicular membrane. J Lipid Res. 1995;36:2147–63.
34. La Mont JT, Carey MC. Cholesterol gallstone formation. 2. Pathobiology and pathomechanics. Prog Liver Dis. 1992;10:165–91.
35. Igimi H, Carey MC. Cholesterol gallstone dissolution in bile: dissolution kinetics of crystalline cholesterol, with chenodeoxycholate, ursodeoxycholate and their glycine and taurine conjugates. J Lipid Res. 1981;22:254–63.
36. Admirand WH, Small DM. The physico-chemical basis of cholesterol gallstone formation in man. J Clin Invest. 1968;47:1043–52.
37. Isaakson B. On the dissolving power of lecithin and bile salts for cholesterol in human gallbladder bile. Acta Soc Med Ups. 1954;59:296–304.
38. Harvey PRC, Sömjen GJ, Gilat T, Gallinger S, Strasberg SM. Vesicular cholesterol in bile. Relationship to protein concentration and nucleation time. Biochim Biophys Acta. 1988;958:10–8.
39. Kibe A, Holzbach RT. Inhibition of cholesterol crystal formation by apolipoproteins in supersaturated model bile. Science. 1984;255:514–6.
40. Lee SP, La Mont JT, Carey MC. The role of gallbladder mucus hypersecretion in the evolution of cholesterol gallstones: studies in the prairie dog. J Clin Invest. 1981;67:1712–23.
41. Burnstein MJ, Ilson RG, Peturnka CN, Strasburg S. Evidence for a potent nucleating factor in the gallbladder of patients with gallstones. Gastroenterology. 1983;85:801–7.
42. Maki T, Matsuskiro T, Susuki N, Nakamutra N. The role of sulphated glycoprotein in gallstone formation. Surg Gynecol Obstet. 1974;132:497–502.
43. Pemsingh RS, MacPherson BR, Scott GW. Mucus hypersecretion in the gallbladder epithelium of ground squirrels fed a lithogenic diet for the induction of cholesterol gallstones. Hepatology. 1987;7:1267–71.

44. Shiffman ML, Shamburek RD, Schwartz CC, Sugerman HJ, Kellum JM, Moore EW. Gallbladder mucin, arachidonic acid, and bile lipids in patients who develop gallstones during weight reduction. Gastroenterology. 1993;105:1200–8.
45. Lee SP, Nicholls JF. Nature and composition of biliary sludge. Gastroenterology. 1986;90:677–86.
46. Konikoff FM, Chung DS, Donovan JM, Small DM, Carey MC. Filamentous, helical and tubular micro-structures during cholesterol crystallisation from bile. Evidence that biliary cholesterol does not nucleate classic monohydrate plates. J Clin Invest. 1992;90:1156–61.
47. Soloway RD, Trotman BW, Ostrow JD. Pigment gallstones. Gastroenterology. 1977;72:167–82.
48. Filly B, Allen B, Minton MJ, Bernhoft B, Way LW. In vitro investigation of the origin of echoes within biliary sludge. J Clin Ultrasound. 1980;8:193–200.
49. Lee SP. Pathogenesis of biliary sludge. Hepatology. 1990;12: 200–5.
50. Carey MC, Cahalane MJ. Whither biliary sludge? Gastroenterology. 1988;95:508–23.
51. Lee SP, Maher K, Nicholls JF. Origin and fate of biliary sludge. Gastroenterology. 1988;94:170–6.
52. Hill PA, Harris RD. Clinical importance and natural history of biliary sludge in outpatients. J Ultrasound Med. 2016;35(3):605–10.
53. Dowling RH, Bell GD, White J. Lithogenic bile in patients with ileal dysfunctions. Gut. 1972;13:415–20.
54. Pereira SP, Bain IM, Kumar D, Dowling RH. Bile composition in inflammatory bowel disease: ileal disease and colectomy, but not colitis, induce lithogenic bile. Aliment Pharmacol Ther. 2003;17:923–33.
55. Lapidus A, Einarsson K. Effects of ileal resection on biliary lipids and bile acid composition in patients with Crohn's disease. Gut. 1991;32:1488–91.
56. Pitt HA, Berquist WE, Mann LL, Fonkalsrud WE, Ament ME, Den Besten L. Parenteral nutrition induces calcium bilirubinate gallstones. Gastroenterology. 1983;84:1274.
57. Damiao AO, Sipahi AM, Vezozzo DP, Goncalves PL, Fukui P, Laudanna AA. Gallbladder hypokinesia in Crohn's disease. Digestion. 1997;58:458–63.
58. Vu MK, Gielkens HA, van Hogezand RA, van Oostayen JA, Lamers CB, Masclee AA. Gallbladder motility in Crohn disease: influence of disease localization and bowel resection. Scand J Gastroenterol. 2000;35(11):1157–62.
59. Dowling RH, Mack E, Small DM. Biliary lipid secretion and bile composition after acute and chronic interruption of the enterohepatic circulation in the rhesus monkey. J Clin Invest. 1971;50:1917–26.
60. Kelly TR, Klein RL, Woodford JW. Alterations in gallstone solubility following distal ileal resection. Arch Surg. 1972;105: 352–5.
61. Pitt HA, Lewinski MA, Muller EL, Porter-Fink V, DenBesten L. Ileal resection-induced gallstones: altered bilirubin or cholesterol metabolism? Surgery. 1984;96:154–62.
62. Brink MA, Slors JF, Keulemans YC, Mok KS, De Waart DR, Carey MC, Groen AK, Tytgat GN. Enterohepatic cycling of bilirubin: a putative mechanism for pigment gallstone formation in ileal Crohn's disease. Gastroenterology. 1999;116(6):1420–7.
63. Ling PR, Sheikh M, Boyce P, Keane-Ellison M, Thibault A, Burke P, Freedman S, Bistrian BR. Cholecystokinin (CCK) secretion in patients with severe short bowel syndrome (SSBS). Dig Dis Sci. 2001;46(4):859–64.
64. Ahonen A, Kyosola K, Penttila O. Enterochromaffin cells and macrophages in ulcerative colitis and irritable colon. Ann Clin Res. 1976;8:1–7.
65. Koch TR, Roddy DR, Carney JA, Go VLW. Peptide YY concentrations in normal ileum and colon and in idiopathic inflammatory bowel disease. Dig Dis Sci. 1988;33:1322–8.
66. Fagagnini S, Heinrich H, Rossel JB, Biedermann L, Frei P, Zeitz J, Spalinger M, Battegay E, Zimmerli L, Vavricka SR, Rogler G, Scharl M, Misselwitz B. Risk factors for gallstones and kidney stones in a cohort of patients with inflammatory bowel diseases. PLoS One. 2017;12(10):e0185193.
67. Rubin M, Halpern Z, Charach G, Dvir A, Antebi E, Gilat T, Lichtenberg D. Effect of lipid infusion on bile composition and lithogenicity in patients without cholesterol gallstones. Gut. 1992;33:1400–3.
68. Bolondi L, Gaiani S, Testa S, Labo G. Gallbladder sludge formation during prolonged fasting after gastrointestinal tract surgery. Gut. 1985;26:734–8.
69. Doty JE, Pitt HA, Porter-Fink V, Den Besten L. The effects of intravenous fat and total parenteral nutrition on biliary physiology. J Parenter Enter Nutr. 1984;8:265–8.
70. Lirussi F, Vaja S, Murphy GM, Dowling RH. Cholestasis of total parenteral nutrition: bile acid and bile lipid metabolism in parenterally nourished rats. Gastroenterology. 1989;96:493–502.
71. Cano N, Cicero F, Ranieri F, Martin J, Di Costanzo T. Ultrasonographic study of gallbladder motility during total parenteral nutrition. Gastroenterology. 1986;91:313–7.
72. Doty JE, Pitt HA, Porter-Fink V, Denbesten L. Cholecystokinin prophylaxis of parenteral nutrition-induced gallbladder disease. Ann Surg. 1985;201(1):76–80.
73. Shuman WP, Gibbs P, Rudd PG, Mack LA. PIPIDA scintigraphy for cholecystitis: false-positives in alcoholism and total parenteral nutrition. Am J Roentgenol. 1982;138:1–5.
74. Xu QW, Shaffer EA. The potential site of impaired gallbladder contractility in an animal model of cholesterol gallstone disease. Gastroenterology. 1996;110:251–7.
75. Delamarre J, Capron JP, Joly JP, Rémond A, Audebert M, Murat JL, Revert R, Trinez G. Atonie vésiculaire et maladie coeliaque de l'adulte. Etude radiographique et échographique de 15 cas [Gallbladder atony and celiac disease in adults. Radiographic and echographic study of 15 cases]. J Radiol. 1984;65(3): 133–6.
76. Marciani L, Coleman NS, Dunlop SP, Singh G, Marsden CA, Holmes GK, Spiller RC, Gowland PA. Gallbladder contraction, gastric emptying and antral motility: single visit assessment of upper GI function in untreated celiac disease using echo-planar MRI. J Magn Reson Imaging. 2005;22(5):634–8.
77. Maton PN, Selden AC, Fitzpatrick ML, Chadwick VS. Defective gallbladder emptying and cholecystokinin release in coeliac disease. Reversal by gluten-free diet. Gastroenterology. 1985;88:391–6.
78. Pichler J, Watson T, McHugh K, Hill S. Prevalence of gallstones compared in children with different intravenous lipids. J Pediatr Gastroenterol Nutr. 2015;61(2):253–9.
79. Little JM, Avramovic J. Gallstone formation after major abdominal surgery. Lancet. 1991;337:1135–7.
80. Harrison EC, Roschke EJ, Meyers HI, Edmiston WA, Chan LS, Tatter D, Lau FY. Cholelithiasis: a frequent complication of artificial heart valve replacement. Am Heart J. 1978;95:483–8.
81. Liddle RA, Goldstein RB, Saxton J. Gallstone formation during weight reduction dieting. Arch Intern Med. 1989;149: 1750–3.
82. Mok HY, Von Bergmann K, Crouse JR, Grundy SM. Biliary lipid metabolism in obesity: effects of bile acid feeding before and during weight reduction. Gastroenterology. 1979;76:556–67.
83. Marzio L, Capone F, Neri M, Mezzetti A, De Angelis C, Cuccurullo F. Gallbladder kinetics in obese patients. Effect of a regular meal and low-calorie meal. Dig Dis Sci. 1988;33:4–9.
84. Greenberg GR, McKloy RF, Adrian TE, Chadwick VS, Baron JH, Bloom SR. Inhibition of pancreas and gallbladder by pancreatic polypeptide. Lancet. 1978;2:1280–2.
85. Johansson C, Kollberg B, Efendic S, Uvnas-Wallensten K. Effects of graded doses of somatostatin on gallbladder emptying and

pancreatic enzyme output after oral glucose in man. Digestion. 1981;22:24–31.
86. Hutton SW, Sieverd CE Jr, Vennes JA, Duane WC. The effect of sphincterotomy on gallstone formation in the prairie dog. Gastroenterology. 1981;81:663–7.
87. Bigg-Wither GW, Ho KKY, Grunstein RR, Sullivan CE, Doust BD. Effects of long-term octreotide on gallstone formation and gallbladder function. Br Med J. 1992;304:1611–2.
88. Hopman WP, Rosenbusch G, Jansen JB, Lamers CB. Effect of increasing oral doses of loperamide on gallbladder motility in man. Br J Clin Pharmacol. 1990;29(1):55–60.
89. Remington M, Fleming CR, Malagelada JR. Inhibition of postprandial pancreatic and biliary secretion by loperamide in patients with short bowel syndrome. Gut. 1982;23(2):98–101.
90. van Liessum PA, Hopman WPM, Pieters GFFM, Jansen JBM, Smals AGH, Rosenbusch G, Kloppenborg PW, Lamers CB. Postprandial gallbladder motility during long-term treatment with the long-acting somatostatin analogue SMS 201-995 in acromegaly. J Clin Endocrinol Metab. 1989;69:557–62.
91. Hussaini SH, Pereira SP, Dowling RH, Wass JA. Slow intestinal transit and gallstone formation. Lancet. 1993;341:638.
92. Thompson JS. The role of prophylactic cholecystectomy in the short-bowel syndrome. Arch Surg. 1996;131:556–60.
93. Goet JC, Beelen EMJ, Biermann KE, Gijsbers AH, Schouten WR, van der Woude CJ, de Vries AC. Cholecystectomy risk in Crohn's disease patients after ileal resection: a long-term nationwide cohort study. J Gastrointest Surg. 2019;23(9):1840–7.
94. Fort JM, Azpiroz F, Casellas F, Andreu J, Malagelada JR. Bowel habit after cholecystectomy: physiological changes and clinical implications. Gastroenterology. 1996;111(3):617–22.
95. Thompson JS, Weseman RA, Rochling FA, Lyden E, Grant WJ, Vargas LM, Langnas AN, Mercer DF. Cholecystectomy and liver disease in short bowel syndrome. J Gastrointest Surg. 2016;20(2):322–7.
96. Leuschner U, Baumgärtel H. Chemical dissolution of common bile duct stones. Prog Clin Biol Res. 1984;152:193–225.
97. Portincasa P, van Erpecum KJ, Jansen A, Renooij W, Gadellaa M, vanBerge-Henegouwen GP. Behaviour of various cholesterol crystals in bile from gallstone patients. Hepatology. 1996;23:738–48.
98. van Erpecum KJ, Stolk MFJ, van den Broek AMWC, Renooij W, van de Heijning BJM, van Berge-Henegouwen GP. Bile concentration promotes nucleation of cholesterol monohydrate crystals by increasing the cholesterol concentration in the vesicles. Eur J Clin Investig. 1993;23:283–8.
99. Paumgartner G, Beuers U. Mechanisms of action and therapeutic efficacy of ursodeoxycholic acid in cholestatic liver disease. Clin Liver Dis. 2004;8(1):67–81. vi
100. Lazaridis KN, Gores GJ, Lindor KD. Ursodeoxycholic acid 'mechanisms of action and clinical use in hepatobiliary disorders'. J Hepatol. 2001;35:134–46.
101. Guarino MP, Cocca S, Altomare A, Emerenziani S, Cicala M. Ursodeoxycholic acid therapy in gallbladder disease, a story not yet completed. World J Gastroenterol. 2013;19(31):5029–34.
102. Capron JP, Gineston JL, Herve MA, Braillon A. Metronidazole in prevention of cholestasis associated with total parenteral nutrition. Lancet. 1983;1:446–7.
103. Tsai S, Strouse PJ, Drongowski RA, Islam S, Teitelbaum DH. Failure of cholecystokinin-octapeptide to prevent TPN-associated gallstone disease. J Pediatr Surg. 2005;40(1):263–7.
104. Nealon WH, Upp JR, Alexander RW, Gomez G, Townsend CR, Thompson JC. Intravenous amino acids stimulate human gallbladder emptying and hormone release. Am J Phys. 1990;259:G173–8.
105. Zoli G, Ballinger A, Healy J, O'Donnell LJD, Clark M, Farthing MJG. Promotion of gallbladder emptying by intravenous amino-acids. Lancet. 1993;341:1240–1.
106. Wu ZS, Yu L, Lin YJ, Jun ZJ, Min WS, Jun Y, Hua ZB. Rapid intravenous administration of amino acids prevents biliary sludge induced by total parenteral nutrition in humans. J Hepato-Biliary-Pancreat Surg. 2000;7(5):504–9.
107. Lee SP, Carey MC, LaMont JT. Aspirin prevention of cholesterol gallstone formation in prairie dogs. Science. 1981;211:1429–31.
108. O'Leary DP, La Morte WW, Scott TE, Booker ML, Stevenson J. Inhibition of prostaglandin synthesis fails to prevent gallbladder mucin hypersecretion in the cholesterol-fed prairie dog. Gastroenterology. 1991;101:812–20.
109. O'Donnell LJD, Wilson P, Guest P, Catnach SM, McLean A, Wickham JEA, Fairclough PD. Indomethacin and post-prandial gallbladder emptying. Lancet. 1992;339:269–71.

Nephrolithiasis and Nephrocalcinosis

Charles R. V. Tomson and Matthew Bultitude

Key Points

- Urate stones are common in patients with an ileostomy and are prevented/treated by making the urine alkaline.
- Calcium oxalate stones are common after an ileal resection/disease providing the colon is functional and in continuity. They can cause renal colic and/or end stage renal disease (ESRD) by causing nephrolithiasis and/or nephrocalcinosis which are both associated with inflammation.
- Calcium oxalate stones are prevented with a high fluid intake, low oxalate diet, calcium supplements (to bind oxalate in the gut), preventing hypomagnesaemia, acidosis (associated with low citrate) and pyridoxine deficiency. Cholestyramine and a reduced fat intake may be beneficial.
- Renal colic is common. Patients should have urine dipstick ± culture, serum creatinine, calcium and urate. A computerized tomography (CT) scan of the kidneys, ureters and bladder (CT KUB) is the recommended investigation due to high sensitivity and specificity.
- Septic obstructed kidney is a medical emergency and should prompt immediate drainage with ureteric stent or nephrostomy tube.
- For renal stones, treatment options are surveillance, shockwave lithotripsy, flexible ureteroscopy or percutaneous nephrolithotomy. Choice will depend on patient choice, surgical expertise, size and location of the stone.

Introduction

Kidney stone formation, nephrocalcinosis, and resultant chronic kidney disease are well-recognised complications of several forms of gut disease (Fig. 1). However, these are relatively rare, and late, complications of gut disease, so most physicians providing care for patients with gut disease lack experience in managing these complications. Conversely, gut disease contributes only a small fraction of the caseload managed by most nephrologists or urologists. There are no randomized controlled trials informing the management of these complications. Absence of evidence for the benefit of treatment is not the same of evidence of absence of benefit,

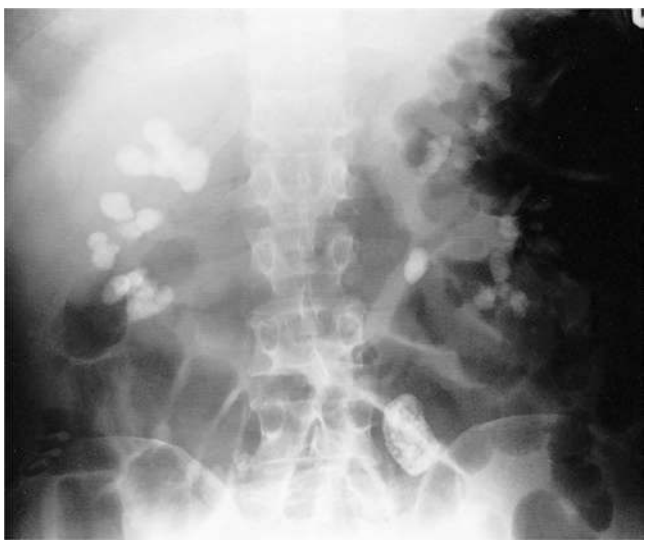

Fig. 1 Plain abdominal radiograph of a patient who had undergone extensive small bowel resection in 1985 as a result of spontaneous mesenteric thrombosis complicating the lupus anticoagulant syndrome. Stone formation was first reported in 1988, since when the patient had passed hundreds of calcium oxalate stones. Three months prior to this radiograph being taken he was admitted with acute renal failure, septicaemia and pyonephrosis as a result of obstruction by stones. Urinary oxalate was >1.0 mmol/day, but fell to 0.3 mmol/day on a synthetic oxalate-free diet

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however: patients developing these complications therefore require specialized management. Such treatment, albeit based on limited evidence, can undoubtedly be successful in changing the course of disease and preventing life-changing complications.

History and Epidemiology

The first reports suggesting an increased risk of kidney stones amongst patients with inflammatory bowel disease were published in the 1960s [1–10]. Both uric acid and calcium oxalate stones appeared to be more prevalent than expected. A landmark study in 1972 was the first to demonstrate hyperoxaluria in patients with ileal resection, bacterial overgrowth, sprue, and other conditions characterized by fat malabsorption [11]. It has subsequently become clear that patients with ileostomies are at increased risk particularly of uric acid stones; patients with malabsorption and an intact colon are at particularly high risk of calcium oxalate stones. The introduction of jejunoileal bypass for obesity was soon followed by recognition that this form of surgically induced intestinal disease was also associated with a significantly increased risk of stone disease [12–15].

Later reports have focused not only on kidney stone formation but also on biopsy-proven oxalate nephropathy causing progressive kidney failure amongst patients with Crohn's disease and other causes of enteric hyperoxaluria [14, 16–20].

The precise frequency of these complications is difficult to determine, as the risks of stone formation and oxalate nephropathy vary with the severity and type of the underlying gut disease and with length of follow-up. Amongst patients with Crohn's disease, urolithiasis is more common amongst patients who have undergone surgery compared to those undergoing medical management. Most early reports were single-centre case reports or series, with no denominator. Recent systematic literature reviews have summarized these reports [21–24], giving estimated life-time risks for urolithiasis of 9–18% in patients with inflammatory bowel disease: the risks are higher with increasing age, with Crohn's disease compared to ulcerative colitis [25], and with ileal resection, particularly of the distal ileum [25]. Colonic preservation is associated with an increased risk of stones [26]. Urolithiasis in children with inflammatory bowel disease is rare, but does occur [27, 28]. Patients with ileal pouch after total colectomy remain at risk [29], although there are no controlled comparisons of stone frequency with pouch compared to ileostomy. Amongst patients with ulcerative colitis, total colectomy is associated with markedly increased risk of stone disease [6, 10, 30].

Possibly the best prospectively collected information comes from the Swiss National Inflammatory Bowel Disease Cohort Study. Kidney stones were reported in 4.6% of patients with Crohn's disease and 3.0% of patients with Ulcerative Colitis, over a median disease duration of 12.8 and 11.2 years respectively. In multivariate analysis, male gender, higher disease activity, intestinal surgery, use of non-steroidal anti-inflammatory drugs and reduced physical activity were independent predictors of kidney stone disease. Similar risk factors were reported for gallstones; patients with gallstones had a relative risk of 4.87 (95% CI 2.8–8.0) for kidney stones [31].

No large-scale study of the epidemiology of kidney stones has identified the proportion of episodes that are attributable to intestinal disease. This proportion is probably very small, given the high and increasing frequency of kidney stone disease in the general population [32, 33].

Similarly, the proportion of incident end-stage kidney failure caused by complications of intestinal disease is also very small, although such cases do exist [19, 34]. The best attempt to quantify the risk comes from a national registry study in South Korea, in which 38,812 patients with inflammatory bowel disease were matched 3:1 with people from the general population. Over a mean follow-up period of 4.9 years, end-stage kidney disease (ESKD) was detected in 79 patients with inflammatory bowel disease (0.2%) compared to 0.1% of controls; this was driven by an increased risk of ESKD amongst patients with Crohn's disease (adjusted hazard ratio 6.33, 95% CI 2.75–14.56) with no increased risk in Ulcerative colitis (adjusted hazard ratio 2.01, 95% CI 0.9–4.51) [35].

Pathophysiology

The pathophysiology of kidney stone formation in general has been discussed in detail elsewhere [36, 37].

Calcium oxalate is highly insoluble, with a solubility of around 7 mg/L at 37 °C in simple solution. However, urine is an extremely complex solution, containing inhibitors and promoters of crystallization. For instance, citrate and pyrophosphate form soluble complexes with calcium, thus decreasing calcium availability; magnesium forms a soluble complex with oxalate; and Tamm-Horsfall glycoprotein and other glycosaminoglycans inhibit one or several phases of calcium oxalate stone formation. Even though normal urine is supersaturated with respect to calcium oxalate, calcium oxalate crystals do not normally form in free solution, but rather by deposition on existing surfaces, such as tubular casts, sodium urate or uric acid crystals, or cell debris [38].

Uric acid is a weak acid, with a pK of 5.75. Undissociated uric acid is highly insoluble, with a solubility limit of 100 mg/L, whereas urate salts are very much more soluble (e.g. 1200 mg/L of urate at pH 6.5). Urine pH is therefore the main determinant of uric acid solubility; the most important risk factors for uric acid stone formation are therefore high urine concentration and acid urine (Fig. 2). Total uric acid

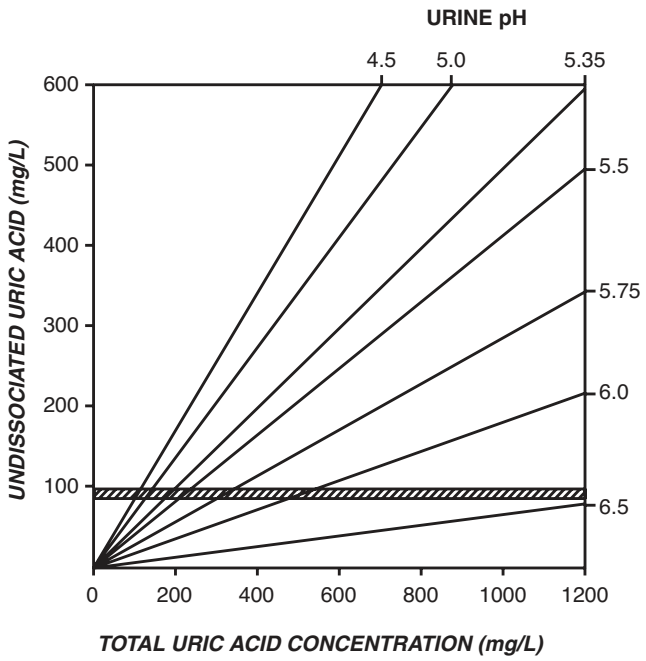

Fig. 2 Relationship between urine pH and solubility of uric acid. Redrawn with permission [100]

excretion is often normal in patients with uric acid stones, although increased production of uric acid as a result of increased purine catabolism can cause stone formation [39].

Patients with intestinal disease are at increased risk both of calcium oxalate stones and oxalate nephropathy, and of uric acid kidney stones. Although the two conditions share some risk factors, most importantly reduced urine volume and flow rate, calcium oxalate stones are largely caused by enteric hyperoxaluria, and uric acid stones by excessive urine acidity due to alkali loss in ileostomy effluent.

Influence of Dietary Calcium Intake on Oxalate Bioavailability

Epidemiological studies in men [40] and women [41] have shown that a high dietary calcium intake reduces the risk of developing renal stones. Other studies have also showed that variations in urinary calcium excretion are poorly, if at all predictive of stone recurrence, whereas the risk of recurrence appears to increase exponentially as urinary oxalate excretion increases [42]. The explanation for this paradoxical relationship between calcium intake and stone risk is twofold.

1. Studies *in vitro* and computerized iterative calculation of activity products show that the risk of calcium oxalate crystallization in urine is little affected by variations in urine total calcium concentration (as a result of the formation of soluble complexes which decreases calcium availability) but increases linearly with increasing oxalate concentration [43]. Thus, changes in urinary oxalate concentration are very much more important as a risk factor for stone formation than changes in urinary calcium concentration.
2. Oxalate is only absorbed from the gut in ionized form. Excess calcium in the gut lumen thus decreases oxalate bio-availability by the formation of insoluble calcium oxalate. Several studies have confirmed that, independent of other factors, urinary oxalate excretion decreases with increasing dietary calcium intake [43, 44], and, conversely, that dietary calcium restriction increases absorption of dietary oxalate, resulting in an increase in the probability of stone formation [45]. Similarly, administration of sodium cellulose phosphate (which decreases gut absorption of calcium) results in an increase in urinary oxalate excretion [46]. Increased intestinal absorption of calcium, as in vitamin D treatment and 'absorptive hypercalciuria' may also increase stone risk not so much because of the resulting increase in urinary calcium concentration but because of the resulting hyperabsorption of oxalate.

Enteric Hyperoxaluria

The major factor causing stone formation and kidney damage in gut disease is hyperoxaluria [47]. Enteric hyperoxaluria has now been reported in a wide range of conditions that alter oxalate bioavailability in the colon, including

- Ileal resection [11, 48]
- Jejuno-ileal bypass [18, 49, 50]
- Coeliac disease [51]
- High-dose oral phosphate supplementation [52]
- Intestinal lymphangiectasia [53]
- Roux-en-Y gastric bypass [19, 54, 55]
- Orlistat therapy [56, 57]
- Chronic pancreatitis [58]

It has been known since the 1970s that enteric hyperoxaluria is due to excessive absorption of dietary oxalate in the colon [48, 59–65]. Two major mechanisms account for this. Firstly, unabsorbed fatty acids form soaps with calcium in the gut lumen. This reduces the amount of calcium in the gut lumen that is available to bind to oxalate, thus increasing oxalate bioavailability. Secondly, unabsorbed bile acids increase colonic permeability to oxalate [66]. High-dose chenodeoxycholic acid for gallstone dissolution is associated with increased absorption of radiolabelled oxalate [67]. Absorption of oxalate after a test meal correlated so well with fat malabsorption that some investigators suggested that it should be used as a diagnostic test for steatorrhoea [68, 69] although this test did not prove reliable [70].

Figure 3 summarises current understanding of the pathogenesis of enteric hyperoxaluria, although the prominence given to the possible contribution of vitamin B6 deficiency to hyperoxaluria is, as discussed below, speculative at best.

Since the 1970s, our understanding of the mechanisms of oxalate transport in the colon has advanced considerably. It is now known that an active oxalate transporter, SLC26A6, is responsible for oxalate secretion into the gut lumen [71, 72]. Oxalate absorption has long been thought to be passive and paracellular [73] although more recently it has been suggested that SLC26A3 also mediates oxalate absorption [74]. Pro-inflammatory cytokines inhibit SLC26A6-mediated oxalate secretion, resulting in increased urinary oxalate excretion: this is one mechanism by which obesity increases the risk of calcium oxalate stones [75]. A case report in a patient with subclinical coeliac disease and oxalate nephropathy suggested reduced SLC26A6 expression as a contributor to hyperoxaluria [76]. SLC26A6 is also an inhibitor of the succinate transporter NaDC1, and reduced activity results in reduced urinary citrate and an increase in serum succinate—which may cause renin-dependent hypertension [77].

Pathogenesis of Oxalate Nephropathy

It was previously thought that hyperoxaluria caused kidney damage solely by causing obstructive nephropathy, resulting from tubular or ureteric obstruction by calcium oxalate kidney stones. While this may well play a role, it is now clear that calcium oxalate crystals cause parenchymal damage largely by activating an innate inflammatory pathway, the nucleotide-binding domain leucine-rich repeat inflammasome 3 (also called NALP3, NLRP3, or cyropyrin) [78–81]. In future, these findings might lead to new therapeutic options to prevent the progressive kidney failure that can complicate enteric hyperoxaluria.

Mechanisms of Stone Formation

Careful histopathological work has shown that the mechanism by which kidney stones form in patients with bypass surgery differs from that in 'idiopathic' kidney stone formers. Inner medullary collecting duct crystals, comprising calcium oxalate and hydroxyapatite, have been described in bypass patients but not in patients with idiopathic calcium oxalate stone disease [82]; whereas patients with ileostomies form interstitial hydroxyapatite deposits (known as Randall's plaques) and inner medullary collecting duct crystals made of hydroxyapatite and uric acid salts [83]. In patients with gut resection, deposits in the inner medullary collecting duct uniformly contain hydroxyapatite, with a minority also containing calcium oxalate, with abundant Randall's plaque [84].

Hypocitraturia

Citrate is the most important inhibitor of calcium oxalate crystallization in the urine; hypocitraturia is therefore a major risk factor for kidney stone formation [85, 86].

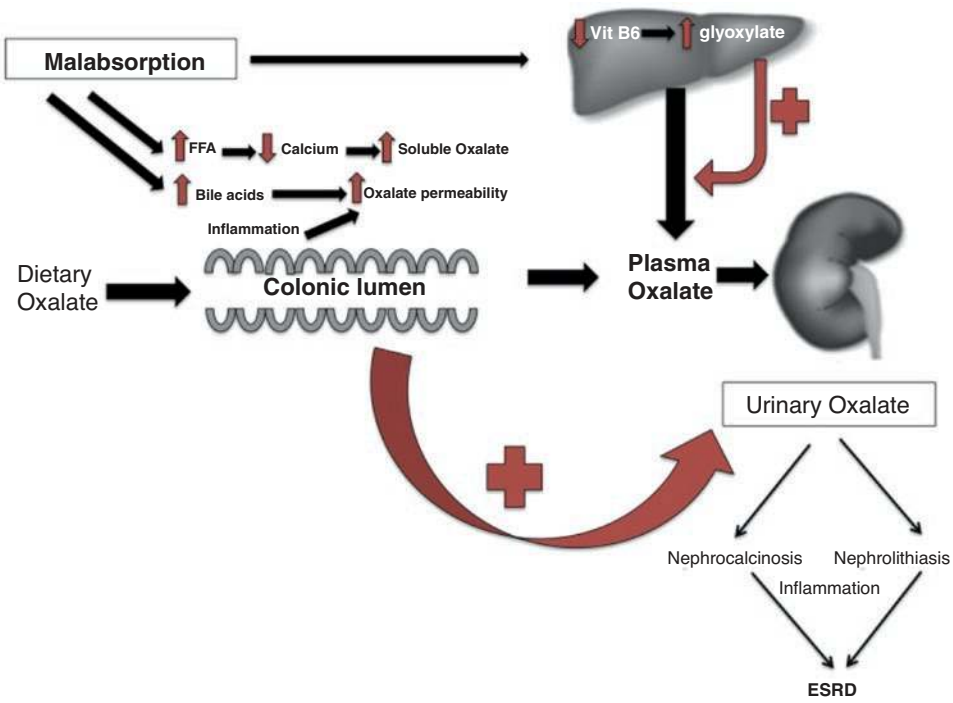

Fig. 3 Pathogenesis of enteric hyperoxaluria. From Nazzal et al. [34], with permission

Hypocitraturia is usually defined as urine citrate excretion <1.67 mmol/24 h; average daily excretion in healthy individuals is around 3.12 mmol/24 h [87]. Systemic acidosis is an important cause of hypocitraturia, but the amount of citrate filtered at the glomerulus is also a determinant. Hypocitraturia is common in patients with malabsorption and is due both to reduced filtered load and acidosis [88].

Low Urine pH

Highly acidic urine favours the formation of calcium oxalate and uric acid stones, and is common in patients with various forms of gastrointestinal disease, including those with ileostomy [47, 50, 89].

Low Urine Volume

Low urine volume results not only in increased concentration of stone components but also causes reduced flow rate, which increases the risk that crystals will agglomerate and adhere to the urothelium. Low urine volume is a common finding in many forms of gastrointestinal disease and results from excessive fluid loss in the gut [47, 50, 90].

Low Urine Magnesium

Along with citrate, magnesium is an important inhibitor of calcium oxalate crystal formation. Hypomagnesuria in gastrointestinal disease is caused by malabsorption of magnesium [50, 91], which can be exacerbated by long-term use of Proton Pump Inhibitors [92].

Effect of the Gut Microbiome

Our previous understanding, in which oxalate absorption was a passive process governed by oxalate intake and colonic 'permeability' to oxalate, has now been superseded as knowledge has grown. We now understand that the gut microbiome plays a crucial role in determining the amount of oxalate absorbed from the gut. Several organisms metabolise oxalate in the colon. In particular, the presence or absence of *Oxalobacter formigenes*, a normal anaerobic colonic commensal, helps to determine overall oxalate burden. This organism metabolises oxalate to carbon dioxide. Antibiotics can reduce both oxalate-degrading capacity and colonic carriage of the organism [93]. In the general population, exposure to antibiotics is associated with an increased risk of kidney stone formation [94, 95]. Absence of *Oxalobacter formigenes* in the gut microbiome is associated with higher urine oxalate excretion and an increased risk of recurrent stone formation in patients without gut disease [96]. In animal models, the organism promotes oxalate secretion into the colonic lumen [97]. However, numerous other gut organisms, including some species symbiotically linked to *Oxalobacter formigenes* but without a direct role in oxalate breakdown, can affect oxalate metabolism in the gut [98].

Vitamin Malabsorption

In health, most of the oxalate excreted in the urine comes from the liver, where oxalate is a metabolic end-product of amino-acid metabolism. Pyridoxine is a co-factor for alanine: glyoxylate aminotransferase, the enzyme that is defective in type 1 primary hyperoxaluria. Reduced enzyme activity results in accumulation of glyoxalate and subsequent overproduction of oxalate. High-dose pyridoxine can sometimes ameliorate hyperoxaluria in primary hyperoxaluria type 1, depending on genotype [99]. Pyridoxine deficiency caused by malabsorption could in theory contribute to hyperoxaluria in patients with intestinal disease [34], but this remains speculative: no study has demonstrated an association between pyridoxine status and endogenous oxalate production or urine oxalate excretion in patients with malabsorption, nor are there even case reports showing that pyridoxine supplementation reduces oxalate excretion in patients with enteric hyperoxaluria.

Uric Acid Kidney Stones Complicating Ileostomy

The major risk factor for the formation of uric acid stones is urine acidity (Fig. 2) [39, 100]. Urine uric acid concentration plays a lesser role. Although diet plays some part in determining urine acidity (ingestion of animal-derived protein being the major contributor to fixed acid excretion), the major cause of highly acidic urine is excessive gastrointestinal loss of bicarbonate—most commonly as the result of an ileostomy. This is combined with a chronic state of salt and water depletion causing reduced urine flow and increased urine concentration [4, 7, 90, 101]. These abnormalities are further exacerbated in patients with short gut.

Although less directly relevant in a chapter on intestinal failure, it is also noteworthy that obesity is strongly associated with an increased risk of uric acid stones, due to an ill-understood defect in urine buffering capacity that occurs in the presence of obesity and insulin resistance [102–104].

Dietary Sources of Oxalate

Restriction of dietary oxalate intake is clearly part of a logical approach to treatment of enteric hyperoxaluria. It should be obvious that advising patients to avoid a few very high oxalate foods (e.g. spinach, rhubarb, beetroot), that are infrequent components of most diets, is unlikely to have much effect on daily oxalate excretion: most dietary oxalate is ingested in commonly-used foods with moderate or high oxalate content: wheat bran is a good example.

Assessment of the oxalate content of food is complex, as oxalate content can vary within individual foods from cultivar to cultivar and from season to season, as can the proportion held as the calcium salt *versus* the soluble salts (predominantly potassium oxalate)—the soluble salts have much greater bioavailability. Boiling foods removes some soluble oxalate. Oxalate content also varies within foods—for instance, in whole grains oxalate is concentrated in the bran fraction, so refined flour contains less oxalate than unrefined flour, and bran products contain high amounts of oxalate. Preparation and cooking methods, and the calcium content of the food, further add to variability in bioavailability of dietary oxalate [105]. This variability probably explains the wide variation in publicly available sources of advice on dietary oxalate [106], and cannot easily be resolved (Table 1).

N.B. As discussed, both oxalate content and bioavailability are highly variable and can depend on the cultivar, the method of cultivation, the season of harvest, and the precise part of the plant used. Different sources give widely different values for oxalate content of the same foodstuff: this may relate to differences in assay method. Oxalate content may also change during processing. Some soluble oxalate (e.g. sodium oxalate) can be removed by cooking in water, but this will clearly depend on cooking time and volume of water. Bioavailability depends on what the food is ingested with: a large dollop of cream on a bowl of raspberries may well substantially reduce the amount of oxalate absorbed, as would milk taken with breakfast cereals derived from wheat bran. Many sources provide data on oxalate content of named brands, e.g. of breakfast cereals commonly sold in North America: these are of limited utility elsewhere. Oxalate content is often measured in mg/100 g, but can also be expressed per serving size: black pepper, for instance, has an oxalate content of >3000 mg/100 g, but the amounts used in cooking make this of very limited relevance.

Acute Oxalate Nephropathy

Acute oxalate nephropathy is increasingly recognized as a cause of acute kidney injury that can, if left untreated, progress to cause end-stage kidney failure. This syndrome is most

Table 1 High oxalate foods. Compiled from numerous sources, including: case reports of acute oxalate nephropathy (see text). United States Department of Agriculture Agriculture Handbook 8-11, 1984: https://www.ars.usda.gov/northeast-area/beltsville-md-bhnrc/beltsville-human-nutrition-research-center/nutrient-data-laboratory/docs/oxalic-acid-content-of-selected-vegetables/—the data from this table are also available sorted by oxalate content at http://www.petsnails.co.uk/documents/oxalates.html; a table previously published by the Oxalosis and Hyperoxaluria foundation, www.ohf.org but no longer available on their website; dietary advice from the University of Chicago, which provides detailed advice on food oxalate content, including how to translate this into practice http://kidneystones.uchicago.edu/how-to-eat-a-low-oxalate-diet/; data compiled by the Harvard TH Chan School of Public Health https://regepi.bwh.harvard.edu/health/Oxalate/files (this also provides advice on interpretation of the data, a table of low-oxalate alternatives to high-oxalate foods and other resources for dietitians); a website www.oxalate.org compiled by a patient from seven sources, not all of which remain available

Very high oxalate foods: to be avoided completely
Star fruit[a] (*Averrhoa carambola*)
Irumban pili[a] (*Averrhoa bilimbi)*
Rhubarb[a]
Peanuts[a]
Iced tea[a]
Chaga mushrooms[a]
Spinach[a]
Green ‘smoothies’ (depends on raw ingredients)[a]
Almonds
Amaranth seeds and leaves
Bamboo shoots
Beetroot and beet leaves
Black tea
Bran flakes
Brown rice and brown rice flour
Buckwheat groats, flour, and leaf
Bulghur wheat
Cassava
Chard
Chives
Cocoa powder
Corn grits
Cornmeal
Fava beans
Haricot beans (“Navy beans” in US parlance)
Millet
Miso soup
Okra
Parsley
Poppyseed
Potatoes, baked with skin
Purslane
Rice bran
Sesame seeds
Soya flour and other soy products
Sorrel
Tahini
Wheat bran
High oxalate foods
Nuts
Cashew nuts

(continued)

Table 1 (continued)

	Hazelnuts
	Peanut butter
	Pecan nuts
Vegetables and legumes	
	Beans—fava, red kidney, refried
	Carrots (raw)
	Celery (raw)
	Collard greens
	Okra
	Parsnip
	Mustard greens
	Potatoes—fried or chipped
	Swede (Rutabaga)
	Sweet potatoes—baked
	Tomato paste
	Turnip
	Yams
Breads, pasta, rice	
	French toast
	Lasagna
	Rice bran
	Spaghetti
Fruit and juice	
	Avocado
	Dates
	Grapefruit
	Kiwi fruit
	Orange
	Pineapple
	Raspberries
Breads, grains, and breakfast cereals	
	Bagels
	Bran flakes
	Cornmeal
	Couscous
	French toast
	Millet

[a] Implicated in case reports of acute oxalate nephropathy

commonly recognized after excessive ingestion of a dietary source of oxalate. Substances responsible include the following:

- Star fruit (Averrhoa carambola) [107–109]—ingestion can also cause chronic oxalate nephropathy [110]
- Irumban puli (Averrhoa bilimbi), used in a traditional remedy in Kerala [111]
- Rhubarb [112]
- Peanuts [113]
- Iced tea [114]
- Massive Ascorbic acid intake [115–117]
- Green smoothies [118, 119]
- Chaga mushrooms [120]

If dietary oxalate is excessive enough, this can occur without intestinal disease, but it is reasonable to assume that the presence of intestinal disease greatly increases the risk at any given level of oxalate intake, as demonstrated in a number of reports [121, 122]. These foods and food supplements should therefore be avoided in all patients at risk of enteric hyperoxaluria.

Dietetic Advice for Patients with Enteric Hyperoxaluria

Notwithstanding the variability in oxalate content and bioavailability discussed above, and the fact that studies of oxalate bioavailability have largely been performed in normal subjects rather than in patients with enteric hyperoxaluria, it remains reasonable to equip patients with advice on which foods to avoid entirely, which foods should be used with care, and which foods are likely to be 'safe' with respect to the risk of stone formation and oxalate nephropathy. Such advice should be given by a dietitian: ideally all services providing care for patients with enteric hyperoxaluria should have a dietitian who is knowledgeable in this area. Table 1 contains an initial guide to the oxalate content of food. A comprehensive list, compiled by a patient from a variety of sources, can be found at www.oxalate.org.

Investigation

Biochemistry

Patients with intestinal disease who develop symptomatic renal colic, are found to have asymptomatic kidney stones on imaging, or who develop unexplained acute or chronic kidney disease, should all be offered further investigation with a view to treatment. Biochemical evaluation should include the following

- Full biochemical profile (including eGFR, calcium, magnesium, bicarbonate, urate)
- Spot urine pH (ideally using a pH meter, as these are more accurate than urine dipsticks)
- 24 h urine for volume, creatinine, sodium, calcium, magnesium, citrate, and oxalate (all these analyses can be performed on a single 24 h urine collection: most laboratories recommend acidification of the sample to prevent *in vitro* changes, including 'in vitro oxalogenesis' from oxalate precursors)

The purpose of including 24 h urine creatinine is to allow assessment of the completeness of urine collection. This is particularly useful when comparing repeated 24 h urine collections over time: barring significant changes in muscle mass, creatinine excretion remains constant over time within

an individual. So if a given patient returns a 24 h urine collection containing around 10 mmol of creatinine on several measurements but then returns one containing only 5 mmol, it is safe to conclude that the latest collection is incomplete; similarly, if the latest collection contains 15 mmol, it is reasonable to conclude that the patient continued the collection for more than 24 h.

Amongst patients who cannot reliably collect a 24 h urine collection (children, for instance), the use of analyate: creatinine ratios is a reasonable 'second best' for assessment of urine chemistry. These ratios rely on the assumption that the excretion of both analytes remains constant over 24 h; and that an 'average' adult excretes around 10 mmol of creatinine per 24 h. An oxalate: creatinine ratio of 0.07 mmol/mmol, for instance, would suggest a 24 h urine oxalate of 0.07 × 10 = 0.7 mmol—significantly higher than the upper limit of normal of around 0.45 mmol/24 h. Creatinine and albumin excretion show little diurnal variation (hence the widespread use of albumin: creatinine ratios to quantitate albuminuria, for instance in diabetic kidney disease) but this is less true of urine calcium, magnesium, citrate, or oxalate, and 24 h creatinine excretion may be substantially less than 10mmol in many patients with intestinal disease—so these ratios should be interpreted with caution [123].

Because of differences in assay performance, the laboratory reference range should be used to interpret results. Normal adults 24 h oxalate excretion is typically <460 μmol/24 h; patients with enteric hyperoxaluria may excrete up to 1500 μmol/L, depending on the severity of the intestinal disease.

Measurement of plasma oxalate concentration (only performed in a few specialized laboratories) is not helpful in most patients, as plasma oxalate remains close to normal (e.g. <5 μmol/L) in patients with normal glomerular filtration rate even in the presence of enteric or primary hyperoxaluria. However, as GFR declines below 45 ml/min/1.73 m^2, plasma oxalate rises, even in the absence of increased oxalate load, often to concentrations of around 20–30 μmol/L. In parallel, 24 h oxalate excretion may fall (as calcium oxalate crystals are deposited in the body), so measurement of 24 h urine oxalate in a patient with advanced kidney failure may give a misleadingly 'normal' result [124]. In this situation, measurement of plasma oxalate may be helpful. Kidney failure of any cause will result in hyperoxalaemia; in patients receiving modern dialysis plasma oxalate concentrations are usually around 30 μmol/L [125, 126]. Concentrations significantly higher than this—e.g. >50 μmol/L—should prompt further investigation for primary or enteric hyperoxaluria. In less advanced chronic kidney disease, plasma oxalate concentration rises as GFR falls; at a given GFR, plasma oxalate is lower in patients with no disorder of oxalate metabolism, higher in patients with enteric hyperoxaluria, and higher still in patients with primary hyperoxaluria [127].

Differential Diagnosis

The primary hyperoxalurias (type 1, type 2, and type 3) are autosomal recessively inherited disorders of hepatic amino-acid metabolism that result in hyperoxaluria. Phenotype is variable in each type, but in general, type 1 has a more severe phenotype (earlier onset, higher oxalate excretion) than type 2, and type 3 is milder still; a subgroup of type 1 patients respond to high-dose pyridoxine [128]. Testing for known pathogenic mutations is now the best way to confirm a diagnosis.

Kidney Biopsy

Patients with suspected oxalate nephropathy may present with slowly progressive chronic kidney disease (CKD) or with an acute deterioration in kidney function, often on a background of stable or slowly progressive CKD. Urinalysis is often negative for blood and protein. A high index of clinical suspicion is required, as patients with CKD who have negative urinalysis are often assumed to have non-specific 'hypertensive nephrosclerosis'—a pattern of kidney damage for which there is no treatment other than optimization of cardiovascular risk factors. In a patient with intestinal disease likely to cause enteric hyperoxaluria, however, this assumption would be dangerous. Urine microscopy in patients with oxalate nephropathy can demonstrate calcium oxalate crystals, but the sensitivity and specificity of this finding is unknown. Kidney biopsy is the definitive test, and carries a low risk when undertaken by an experienced operator [129]; these risks can easily be justified by the possibility that the results will alter management in a patient with intestinal disease and unexplained chronic or acute kidney disease. Kidney biopsy is also indicated when mesalazine-induced nephropathy—another condition causing CKD with negative urinalysis and normal ultrasound appearances—is a possible differential diagnosis [23, 130].

Treatment

High Fluid Intake

The most rational, and certainly the safest, treatment to reduce the risk of stone formation in patients who have had an ileal resection or have ileal disease is to increase water intake, and thus to make the urine more dilute, reducing supersaturation with respect to calcium, oxalate and any other potential constituents of urinary tract stones. Ideally, water intake should also be increased at night, when decreased urine flow and increased urine concentration may increase the risk of stone formation, although fluid intake should also be increased at meal-times to compensate for

transient hyperoxaluria due to absorption of dietary oxalate. However, it is remarkably difficult to persuade patients with normal intestinal function to increase fluid intake to ensure a daily urine volume of >3 l. Drug therapy with the vasopressin antagonist Tolvaptan has been proposed [131, 132], but is extremely expensive.

In patients with short bowel and a retained colon, who may be even more reluctant to increase fluid intake, efforts should also be directed to minimizing gastrointestinal fluid losses, with drugs that reduce motility and/or secretions. In patients with an ileostomy or jejunostomy who have problems of renal stones, a glucose–electrolyte solution should be encouraged (chapter "Management of a High Output Stoma, Jejunotomy or Uncomplicated Enterocutaneous Fistula") or slow release sodium supplements (as chloride or bicarbonate). If receiving parenteral nutrition good hydration must be achieved and consideration given to reducing the acidity of the solution infused (if urate stones).

Treatment of Enteric Hyperoxaluria

The aim of treatment should be to prevent episodes of symptomatic kidney stone; to prevent obstructive nephropathy and resultant CKD from clinically silent obstructing kidney stones; and to prevent acute and chronic oxalate nephropathy. These risks vary from patient to patient, depending on the severity of the gut disease and on other variables including habitual diet and fluid intake. The extent to which patients will agree to additional treatment (including the drug treatments listed above, a high fluid intake, and significant dietary restrictions) will require shared decision-making based on the value placed on avoidance of long-term complications compared to the perceived burden of treatment—which, in the case of patients with intestinal failure, is likely to be in addition to an already significant burden (Table 2).

Ideally, all patients at risk of complications of enteric hyperoxaluria should achieve a high urine volume (e.g. >2.5 L per 24 h), urine oxalate excretion <300 μmol/24 h, urine citrate excretion >3.0 mmol/24 h. Hypercalciuria (e.g. urine calcium >6.5 mmol/24 h) should be avoided, but is seldom seen in patients with enteric disease.

Bile Acid Sequestrants

In the seminal paper describing enteric hyperoxaluria in 1972, Smith et al. reported that urinary oxalate excretion was normalized by Cholestyramine [11], but subsequent reports have cast doubt on the utility of bile acid sequestrants [67, 133] and this may well vary with the severity of bile salt malabsorption in the individual patient. Given that bile acid sequestrants can improve diarrhoea (and thus improve urine output) they remain a logical part of the treatment strategy for patients with enteric hyperoxaluria.

Table 2 Available measures to decrease risk of calcium oxalate stone formation in patients with a short small bowel in continuity with the colon. N.B. none of these therapies have been proven to prevent stone recurrence in trials: all recommendations are based on pathophysiological reasoning

1. Maintain a high flow of dilute urine by maximizing fluid absorption
2. Low oxalate diet
3. Calcium supplements with meals; consider sevelamer, lanthanum, aluminium as alternatives
4. Bile acid sequestrants, particularly if there are other indications
5. Citrate supplements (particularly if hypocitraturic)
6. Magnesium supplementation (but avoid diarrhoea)
7. Oral oxalate decarboxylase, if current trials prove successful
8. Biotherapy: oxalobacter formigenes

Restriction of Dietary Oxalate Intake

The early descriptions of enteric hyperoxaluria included convincing proof that a low-oxalate diet could normalize urine oxalate excretion, at least in the short term [59], but provision of a low oxalate diet for the purpose of this demonstration required a synthetic diet. Provision of such a diet can prove that hyperoxaluria is enteric in origin (Fig. 4). The extent to which dietary restriction of natural foods results in reduction of oxalate excretion has never been adequately tested. One short-term study in 9 patients with mild enteric hyperoxaluria after bariatric surgery suggested that a low oxalate (70–80 mg/day), moderate protein, normal calcium diet had negligible effect on urinary oxalate but did reduce calcium oxalate supersaturation by increasing urine volume, citrate and pH [134]. It is logical to advise patients with enteric hyperoxaluria to restrict intake of very high and high oxalate foods, but long-term studies are required.

Oxalate 'Binders' to Reduce Bio-availability of Dietary Oxalate

Calcium Salts

Although it may seem counter-intuitive to administer calcium salts to reduce the risk of formation of calcium oxalate stones, this is the treatment strategy for which there is the best evidence in enteric hyperoxaluria. There is extensive evidence in the general population that a low calcium diet is associated with a higher risk of kidney stone disease [40, 41, 135, 136], and good experimental evidence that absorption of oxalate from the diet is inversely related to dietary calcium [137, 138]. Amongst patients with idiopathic hypercalciuria, a randomized controlled trial showed a higher risk of recurrent stone formation with a low calcium diet [139]. In patients with enteric hyperoxaluria, short-term studies have

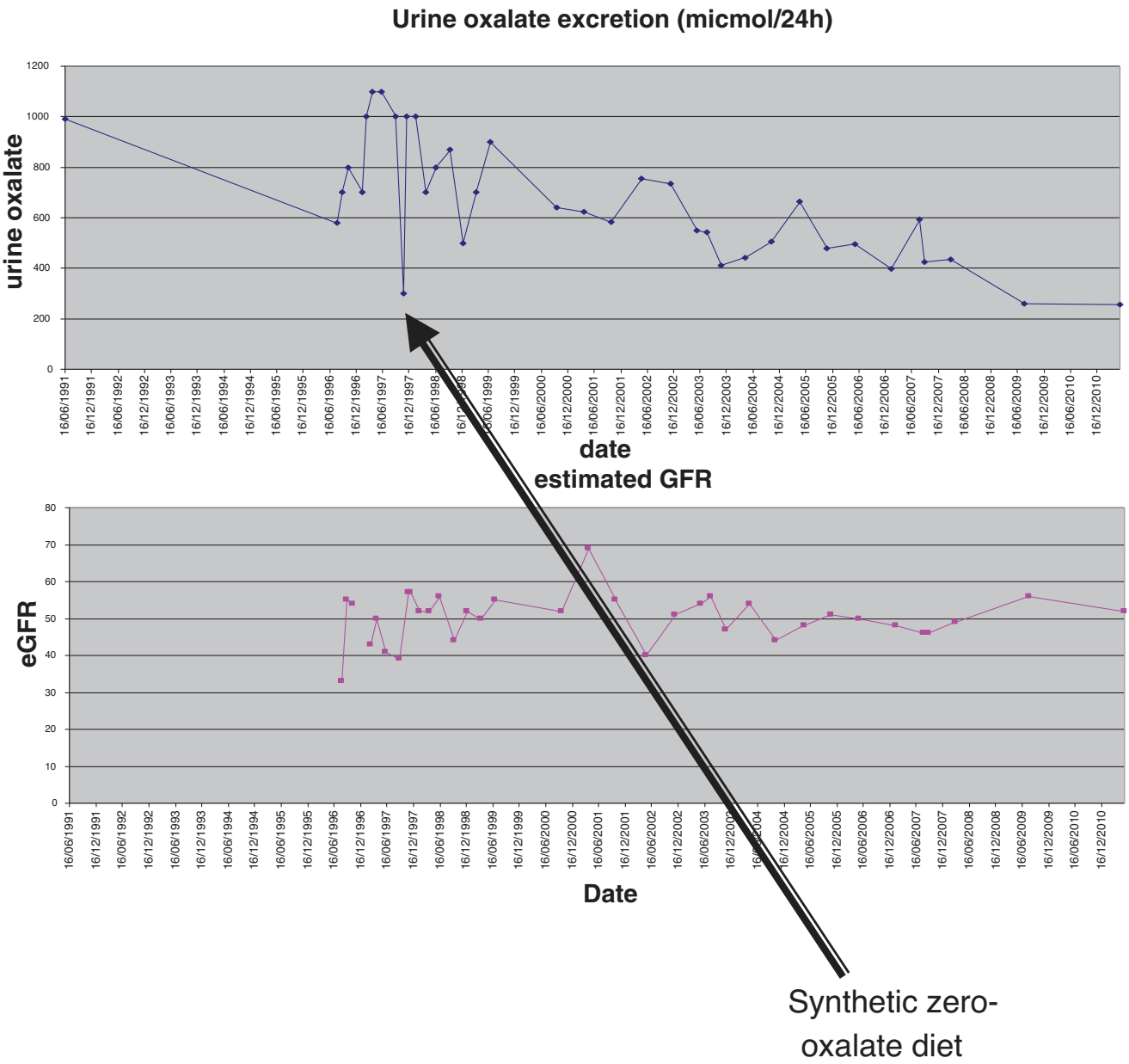

Fig. 4 Repeated measurements of urine oxalate in the patient whose radiograph is shown in Fig. 1, including measurements on a synthetic zero-oxalate diet

demonstrated a reduction in oxalate excretion with calcium supplements given with meals [67, 140–143]. The optimal dose probably varies between patients depending on the severity of the fatty acid malabsorption and on the calcium and oxalate content of the diet.

Aluminium Salts

Limited data suggest that aluminium hydroxide, administered with food, will reduce oxalate bioavailability [142, 144]. The use of aluminium salts to reduce phosphate absorption from the gut in patients with chronic kidney disease is now thought inadvisable because of the theoretical risk of aluminium intoxication (even though direct transfer of aluminium from dialysate water into the bloodstream is the dominant mechanism); the relative risk and benefit of using aluminium salts to reduce oxalate absorption in patients with enteric hyperoxaluria has never been studied.

Lanthanum Carbonate

Lanthanum carbonate is now widely used as phosphate binder for patients with chronic kidney disease, and has in vitro affinity for oxalate that exceeds that of calcium and aluminium [142]. Lanthanum reduces oxalate absorption in animal models [145], and although there are no published reports of its use in human enteric hyperoxaluria, it would be a logical drug to try if other treatments fail.

Sevelamer

Sevelamer, another drug licensed for treatment of hyperphosphataemia in chronic kidney disease, reduces urine oxalate excretion (although less effectively than calcium carbonate) in patients with chronic kidney disease [146] but was found to have disappointing effects in one small study of patients with enteric hyperoxaluria [147].

Magnesium

Magnesium is an inhibitor of calcium oxalate crystallization, so maintaining a high urine magnesium is likely to reduce the risk of stone formation. Magnesium also binds oxalate in the gut, reducing its bioavailability. Many patients with malabsorption are also hypomagnesaemic. Proton pump inhibitors can cause magnesium malabsorption [92] and should be avoided if possible. Magnesium supplements, given with meals to maximize the effect on oxalate bioavailability, should be given unless these prove to exacerbate diarrhoea.

Citrate Supplementation

Citrate supplementation has a proven role in reduction of stone recurrence rates amongst the general population of stone formers [148, 149]. Urine citrate excretion can be increased by dietary changes including drinking real lemonade [150] and increased intake of fruit and vegetables [87] but the effects of these dietary changes on oxalate excretion would need careful study in patients with enteric hyperoxaluria. Potassium calcium citrate supplementation has been shown to reduce the lithogenicity of urine in patients with enteric hyperoxaluria complicating bariatric surgery [151] but there are no long-term data on stone recurrence rate. Nevertheless, pharmacological treatment of hypocitraturia with citrate supplements is logical and usually well tolerated, and is an important therapeutic option amongst patients with enteric hyperoxaluria.

Thiazide-Type Diuretics

In the general population of stone-formers, treatment with thiazide-type diuretics, which decrease urine calcium excretion (and also probably preserve bone strength) has been shown to be effective in reducing stone recurrence rate [152]. However, their utility in patients with enteric hyperoxaluria, most of whom are hypocalciuric, is uncertain.

Biotherapy

The discovery (discussed above) that *Oxalobacter formigenes* regulates oxalate bioavailability in the colon by metabolizing luminal oxalate led to early studies in adults [153] and infants [154] with primary hyperoxaluria in which *Oxalobacter formigenes* was administed as frozen paste or enteric-coated capsules, resulting in time-limited reduction in urinary oxalate; however, faecal recovery of the organism dropped directly after cessation of administration of the biotherapy [153]. However, a small randomized controlled trial failed to show benefit, although this negative result could partly have been due to inaccurate 24 h urine collections [155]. Biotherapy with lactobacilli has also been studied, with positive preliminary results in patients with enteric hyperoxaluria [156] and after an oral load of oxalate [157] but negative results in stone-formers with mild hyperoxaluria and no gastrointestinal disease [158–160].

Enzyme Therapy

An attractive alternative to biotherapy is to deliver oxalate-degrading enzymes to the colon, where degradation of oxalate in the gut lumen will reduce the amount of oxalate available for absorption, and stimulate oxalate transport from the systemic circulation to the gut lumen [161]. A proof of principle study in human volunteers ingesting a high-oxalate, low-calcium diet demonstrated that oral capsules containing oxalate decarboxylase (Reloxaliase: Allena Pharmaceuticals) caused a significant reduction in urine oxalate, but did not fully correct the increase in oxalate excretion caused by the intervention diet [162]. At the time of writing, trials with this product are under way in patients with primary and enteric hyperoxaluria [163]. If it proves possible to prevent absorption of a dietary oxalate load by enzymatic digestion to CO_2 with a tolerable tablet burden, this treatment could revolutionise the treatment of enteric hyperoxaluria.

Prevention of Inflammation Caused by Crystalline Calcium Oxalate

In an animal model, N-acetyl cysteine ameliorated experimental oxalate nephropathy caused by star fruit ingestion [164]. The relevance of this finding for human oxalate nephropathy remains uncertain.

Reduction of Hepatic Synthesis of Oxalate

Although increased hepatic production of oxalate is not known to be a significant contributor to hyperoxaluria in intestinal disease, reduction of hepatic oxalate production would still be expected to ameliorate hyperoxaluria. Oxalate is produced in the liver from glyoxylate by the action of lactate dehydrogenase isoenzyme 5 (LDH5). The antiepileptic drug Stiripentol (used in a rare form of epilepsy, Dravet syn-

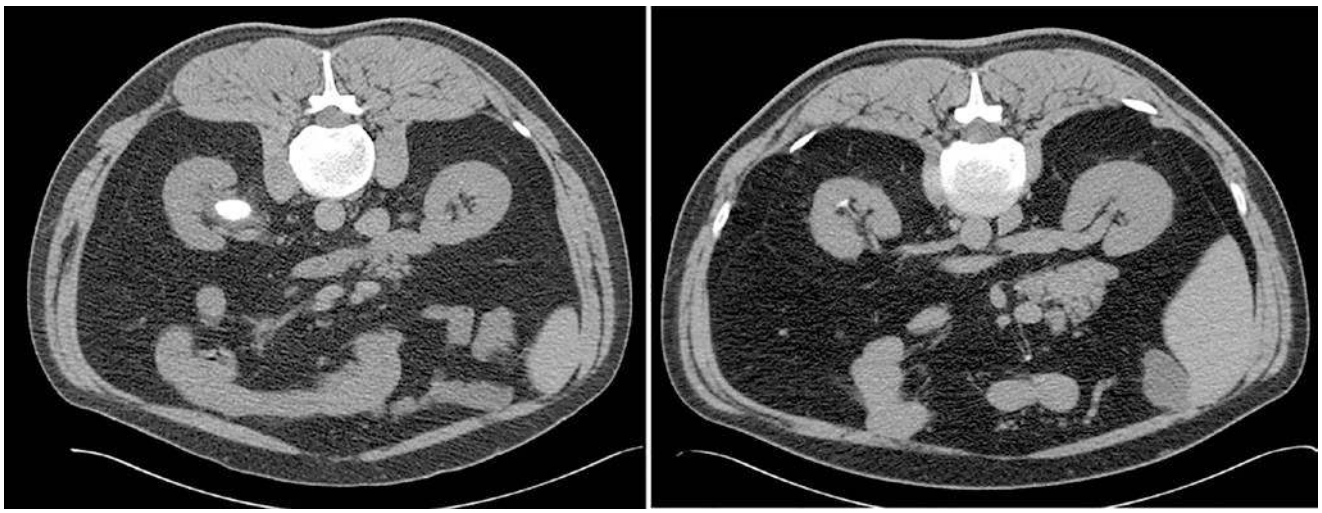

Fig. 5 Dissolution of a large uric acid kidney stone with potassium citrate in a patient with an ileostomy following urine alkalinisation

drome) inhibits neuronal LDH5, and has recently been shown to inhibit hepatic LDH5 as well, reducing hepatic oxalate production and alleviating experimental hyperoxaluria in experimental animals. Children with Dravet syndrome treated with Stiripentol had lower oxalate excretion than children with cystinuria, and Stiripentol caused a significant reduction in oxalate excretion in one child with primary hyperoxaluria [165].

Treatment of Kidney Failure: Dialysis and Kidney Transplantation

If oxalate nephropathy caused by enteric hyperoxaluria continues for long enough, end-stage kidney disease can result, necessitating renal replacement therapy with dialysis or kidney transplantation. As kidney function declines, oxalate load exceeds the capacity of the kidney to excrete oxalate, and plasma oxalate concentration rises, causing calcium oxalate supersaturation. When kidney failure complicates type 1 primary hyperoxaluria, kidney failure can result in a devastating syndrome of systemic oxalosis, caused by deposition of calcium oxalate in tissues including the eyes, blood vessels, heart and cardiac conducting system, peripheral nerves, and bones [126, 166]. Standard dialysis may be insufficient to prevent or reverse this syndrome. Patients with severe enteric hyperoxaluria are at risk of similar complications [167–169], although only a small number of such cases have been reported, probably because hyperoxaluria is usually less marked in enteric disease compared to type 1 primary hyperoxaluria. Kidney transplantation can be complicated by early oxalate nephropathy caused by mobilization of calcium oxalate deposits; for this reason, it is vital to ensure a high urine flow, high urine citrate, and to continue dialysis (to control hyperoxalaemia) until graft function is well established [170].

Treatment of Uric Acid Stones Complicating Ileostomy

Prevention of recurrent uric acid stones in patients with hypovolaemia and acid urine is highly rewarding. Regular alkali supplementation sufficient to achieve a urine pH of 7 or greater can result in complete dissolution of existing stones (Fig. 5) and prevents recurrent stone formation [171, 172]. Currently available alkalinizing agents are sodium bicarbonate (either in tablet form, or as baking powder, which can be dissolved in fruit juice to improve palatability) and potassium citrate (either in liquid, effervescent or tablet form: availability varies e.g. in the UK, tablets are not licensed for use, are available on an individual patient basis only and are prohibitively expensive). Some experts caution that sodium bicarbonate can increase calcium excretion, and thus increase the risk of calcium stones: this concern is probably misplaced, as sodium bicarbonate does not have the same effect on urine calcium excretion as sodium chloride [173]. Equipping patients with urine dipsticks and advice on how to titrate the dose of alkali to achieve a fasting urine pH of >7 can be an effective treatment strategy, depending on the activation and health literacy of the patient.

Surgical Aspects of Kidney Stones

Renal Colic

Renal colic is the term used to describe the pain experienced from obstruction of the ureter and should more correctly be termed ureteric colic. It can be one of the worst pains ever experienced and is caused by obstruction and spasm of the ureter. Pain classically starts suddenly and radiates to the flank, groin and testes or labia majora. It is an important teaching

point that although the pain is often assumed to be from stone (or stone passage), any acute obstruction of the ureter will cause the same symptoms so other causes are sloughed renal papilla or clot from a bleeding transitional cell carcinoma. All patients should have a urine dipstick (±urine culture) as well as blood tests for renal function, calcium and urate [174].

Non-contrast CT KUB (Fig. 6) is the recommended imaging of choice for patients presenting with renal colic [175] due to its high sensitivity and specificity and has almost completely replaced intravenous urogram (IVU) in most countries. Low dose protocols can be implemented to limit the radiation dose. Ultrasound is an alternative as an initial screening tool with the benefit of avoiding ionizing radiation although often patients will still require a CT in the situation of acute flank pain. It may be particularly useful in children and young adults [176] when an alternative diagnosis is more likely e.g. young female patients.

Patients usually require urgent pain relief. Non-steroidal anti-inflammatory medication (NSAID) should be offered first line [175, 176] along with intravenous paracetamol [176]. Opiates should be used as second line treatment for refractory pain. NSAID's have been shown in numerous trials to have better analgesic efficacy than opioids and avoid the side-effect profile of opiate medication [175]. There is no role for anti-spasmodic medication.

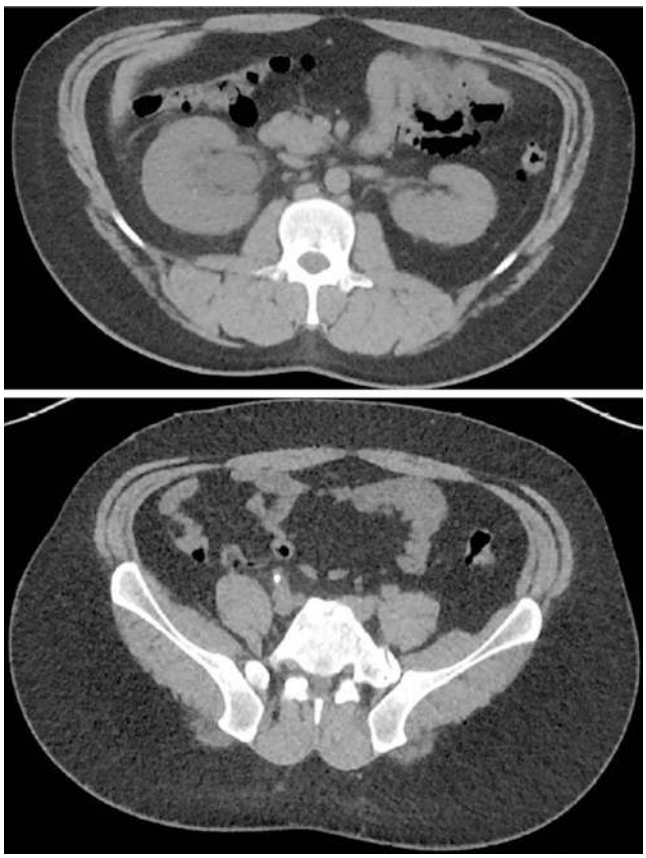

Fig. 6 Two axial slices of a CT scan of a patient with renal colic demonstrating hydronephrosis, mild perinephric stranding (top image) and a mid-ureteric stone (lower image). Ultrasound alone would have shown hydronephrosis but would not have seen the stone in that location

Management will depend on the clinical situation and will depend on numerous factors including presence of a normal contralateral kidney, renal function, evidence of infection/sepsis, size and location of the stone. Urgent surgical intervention is recommended in four situations: presence of an infected obstructed kidney, obstruction of a solitary kidney, bilateral obstruction or if there is uncontrolled pain [174]. An infected obstructed kidney is a surgical emergency as patients can become seriously unwell with sepsis and can be a cause of mortality. Patients should be treated with broad spectrum intravenous antibiotics, fluid resuscitation and urgent decompression of the kidney. This can be with either percutaneous nephrostomy or ureteric stent placement [177] and choice will depend on local preference and availability, stone characteristics and patient factors (obesity, coagulopathy, previous reconstruction etc.). Decompression should take place as soon as possible and treatment to the stone itself should not be attempted due to the risk of worsening the sepsis.

If the patient is well with normal renal function, no sepsis, normal contralateral kidney and controlled pain then often they can be managed conservatively and given chance to pass the stone spontaneously. Medical expulsive therapy (MET), mainly with alpha blockers, have been used to aid stone passage. However a number of high quality randomized trials have questioned the benefit of MET in recent years [178] although at the time of writing many guidelines continue to recommend the use of MET [175, 176] because of the cheap cost and favourable safety profile. The most benefit is likely for larger distal ureteric stones 5–10 mm in size [175]. Stones that fail to pass should be offered surgical treatment with either shockwave lithotripsy or ureteroscopy. Stones that are unlikely to pass e.g. large upper ureteric stones should be offered early intervention.

Stones in the Kidney

When stones form in the kidney they are often asymptomatic and are a common incidental finding on other imaging as it is estimated to be found in 8–10% of screened populations [179]. Thus it is important to realise that not all stones need treatment and small asymptomatic stones may be suitable for observation [175]. However patients with metabolic causes, such as those caused by intestinal disease, would be at higher risk of complications (stone growth, infection, colic) and should be carefully monitored if conservative treatment is chosen.

Stones in the kidney can cause a range of symptoms including discomfort, haematuria and infection. The presence of symptoms, stone growth, local obstruction, patient preference, social situation (e.g. a frequent traveler) would all be indications for intervention [176].

Fig. 7 A modern shockwave lithotripter

Stone Dissolution Therapy

Realistically only uric acid stones can be dissolved by medical management. The stone type maybe known from previous stone analyses or can be judged from radio-lucency (pure uric acid stones are not seen on plain KUB X-ray); stone density (Hounsfield Units of uric acid stones tend to be low) or surmised by body habitus (obesity), raised serum urate levels and/ or history of gout.

If there is a high suspicion of a uric acid stone then and there is no immediate need for surgery (e.g. obstruction) then attempt can be made to dissolve the stone by raising the pH of the urine with either sodium bicarbonate or potassium citrate. Regular pH monitoring should be undertaken to ensure that adequate levels (pH > 7) are reliably reached [175]. Regular imaging, often with ultrasound, should take place to track dissolution. Whilst sometimes disappointing, oral chemolysis can sometimes give spectacular results with dissolution of even complete staghorn stones.

Extracorporeal Shockwave Lithotripsy (ESWL)

ESWL (Fig. 7) was introduced in the early 1980s and revolutionised the treatment of urinary stones at the time [180]. Prior to this relatively few other options were available and open surgery was often required even for relatively small stones. The principal of the non-invasive treatment is that shockwaves are generated and targeted using either ultrasound or X-ray localization to the stone with the aim of fragmenting into smaller pieces which pass spontaneously. The first machines required general anaesthesia and hoisting into a water bath but modern machines typically require only oral analgesia or sedation with a thin water film as coupling

medium. The procedure is often performed by trained technicians/radiographers.

Unfortunately not all stones fragment with ESWL and making sensible choices improves stone-free rates. Consideration needs to be given to patient habitus as obesity makes targeting the stone more difficult with longer skin-to-stone distances and attenuation of the shockwaves. In addition large stone burdens significantly increases the risk of complications with ureteric fragments causing a steinstrasse (literally a stone-street of stone fragments in the ureter). Anatomy is important because success rates for stones in the lower pole of the kidney are lower as the fragments sit there are don't drain and lead to stone recurrence [175]. Thus assessment can be made of the angle and depth of the lower pole calyces [181]. Consensus guidelines suggest stones up to 2 cm can be offered ESWL in the renal pelvis, mid or upper pole and up to 1 cm in the lower pole [175]. Many urologists are likely to take into consideration other factors such as stone density and skin-to-stone distance. Certainly, if the stone does not respond in 2–3 treatments then alternative treatments should be offered. Complication rates are lower for ESWL compared with more invasive treatments and often patients will choose this as an initial treatment option.

Contraindications are bleeding diathesis, pregnancy, untreated urinary infection, distal obstruction, significant hypertension and proximity to abdominal aortic aneurysm [181]. Complications include haematuria, perinephric haematoma, renal colic. Previous concerns that it might cause development of diabetes have not been substantiated in large population based studies [182].

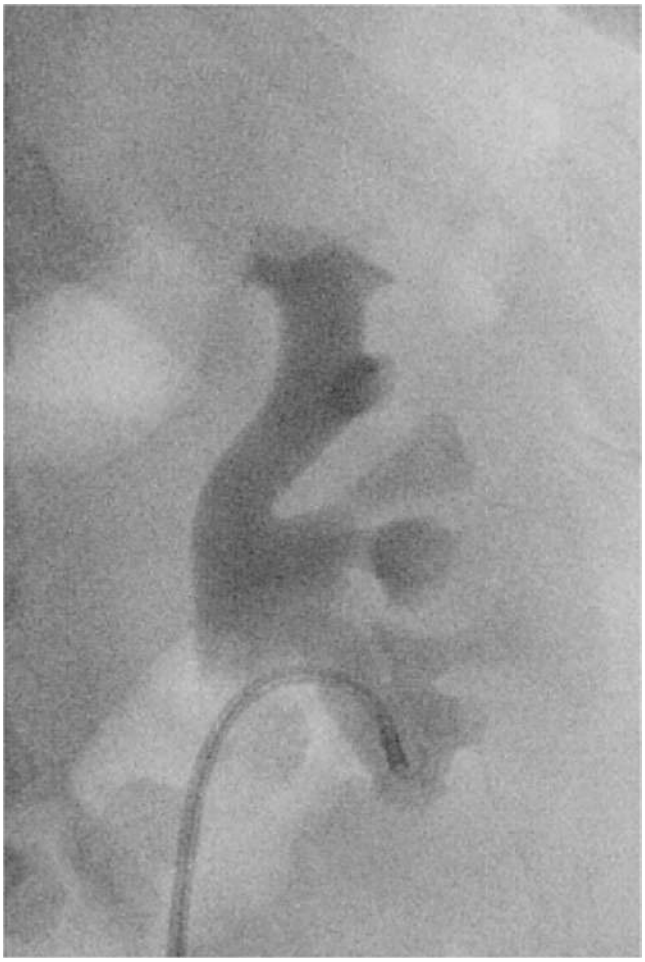

Fig. 8 An image intensifier image from the operating theatre with contrast opacifying the collecting system and a flexible ureteroscope (passed from the urethra and through the bladder) deflected into the lower pole

Uretero-renoscopy

Ureteroscopy can either be with a semi-rigid instrument—commonly called rigid ureteroscopy (rURS) or with a flexible fibre-optic instrument—flexible ureteroscopy (fURS) (Fig. 8), also known as retrograde intrarenal surgery (RIRS).

rURS is typically used to access stones in the lower, mid or upper ureter, while fURS is also used to access the upper ureter and the pelvi-calyceal system of the kidney. Advances in technology since the 1980s with smaller instruments and wider availability of wires, baskets and the holmium laser has made ureteroscopy a popular choice for all ureteric stones and renal stones up to 2 cm in size. Recent advances have seen the wider use of digital and disposable instruments.

Ureteroscopy requires general or spinal anaesthesia and is performed via the urethra. A guidewire is placed in the kidney and then followed with the ureteroscope. If small, a stone can be removed with a nitinol basket but usually it will be fragmented using the Holmium laser into dust and tiny fragments. Often a ureteric stent is left afterwards to ensure drainage of the kidney, allow oedema to settle and dilate the ureter to facilitate passage of the stone debris. Ureteric stents lead to a lot of the morbidity associated with ureteroscopy with 80% of people finding a reduction in quality of life [183].

Percutaneous Nephrolithotomy (PCNL)

The other major advance in the treatment of stone disease was PCNL with the first report in 1976 [184]. This became popularized in the 1980s around the world and is the mainstay of treatment for larger renal stones (Fig. 9a, b). Historically the procedure was performed in the prone position with ultrasound and fluoroscopy used to gain access to the kidney with a needle and guidewire. This tract was then dilated to 26–30 Fr to allow endoscopy, stone fragmentation and retrieval. Even the largest of staghorn stones can often be removed via a single tract.

More recently the supine position has become more popular and miniaturisation of instruments as small as 4.8Fr used for the procedure. Commonly mini-PCNL (11–20 Fr) is used for medium sized stones with larger tracts reserved for larger

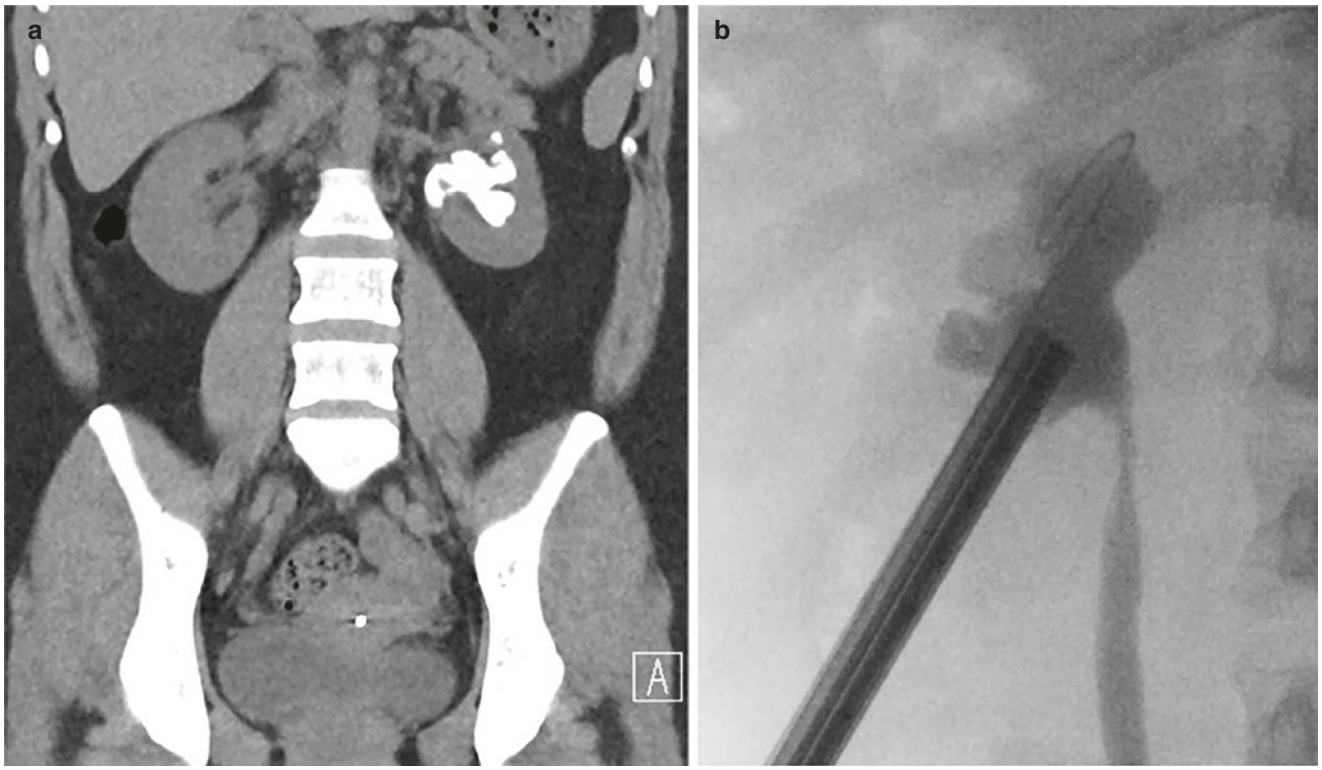

Fig. 9 (**a**) Complex staghorn stone of the left kidney. (**b**) Intraoperative Image intensifier image during PCNL showing the nephroscope (and guidewire). The stone has been cleared and contrast outlines the pelvicalyceal system

stone burdens [184]. Guidelines would suggest that stones >2 cm are best treated with PCNL [175], however miniaturisation has led to mini-PCNL taking on smaller stone burdens and a clear overlap in stone size indication with fURS. Patients are commonly left with a small bore nephrostomy afterwards with the benefit of avoiding an internal JJ stent. Ongoing trials are examining the best treatment modality for lower pole stones 1–2 cm in size.

One of the advantages of the supine position has been the advent of combining both fURS and PCNL simultaneously—endoscopic combined intra-renal surgery (ECIRS). This potentially offers the best of both worlds with the ability to retrieve large stone burdens via the PCNL tract, whilst access all the calyceal system with the fURS. Stones can potentially be moved to the PCNL surgeon—so called 'pass the parcel'.

PCNL is the most invasive of the procedures described in this chapter. Common risks include bleeding with risk of transfusion up to 7% [175] although this is commonly much lower. Other risks include fever, sepsis, injury to other organs (bowel, liver, spleen, pleura). A risk of 1:1000 of needing nephrectomy is often quoted if bleeding is uncontrolled. It is likely these risks are reduced with miniaturised techniques.

Choice of Treatment

When deciding on the choice of treatment consideration has to be given to size and location of the stone(s), anatomy of the kidney, stone type (if known), hardness of the stone (can be judged from previous surgery or by measuring the Hounsfield Units of the stone), patient preference and surgical experience. Careful patient counselling is required given the obvious differences between the treatments to ensure patient expectations are met whilst giving the best chance of stone clearance. For smaller renal stones <1 cm often ESWL will be offered 1st line with fURS as 2nd line treatment. For stones 1–2 cm, all 3 options are reasonable, and choice will depend on stone and anatomical characteristics as well as surgical opinion and patient choice. For stones >2 cm PCNL should be the 1st line treatment. Stone location and anatomy are important considerations e.g. a 15 mm stone in the lower pole of the kidney may be offered different treatment options to a 15 mm stone in the upper pole.

For patients with intestinal disease where recurrence risk is high then ensuring complete stone clearance is important and thus more invasive treatments may be considered, although this must be traded off against the high risk of needing repeat interventions in the future for recurrent stone formation. Ultimately careful review of these patients by a stone specialist taking into account patient choice is important to make the correct decisions.

Follow-up

Regardless of treatment choice, all patients with intestinal disease should have a thorough metabolic evaluation to mini-

mize risk of further stone formation. Follow-up for future stone formation should be undertaken. Usually this will be with periodic ultrasound and/or plain KUB X-ray (remembering uric acid stones are not seen on plain X-ray) although the timings of this will depend on the frequency of previous stones and anticipated risk going forwards.

References

1. Badenoch AW. Uric acid stone formation. Br J Urol. 1960;32:374–82.
2. Deren JJ, Porush JG, Levitt MF, Khilnani MT. Nephrolithiasis as a complication of ulcerative colitis and regional enteritis. Ann Intern Med. 1962;56:843–53.
3. Maratka Z, Nedbal J. Urolithiasis as a complication of the surgical treatment of ulcerative colitis. Gut. 1964;5:214–7.
4. Bennett RC, Jepson RP. Uric acid stone formation following ileostomy. Aust N Z J Surg. 1966;36(2):153–8.
5. Grossman MS, Nugent FW. Urolithiasis as a complication of chronic diarrheal disease. Am J Dig Dis. 1967;12(5):491–8.
6. Gelzayd EA, Breuer RI, Kirsner JB. Nephrolithiasis in inflammatory bowel disease. Am J Dig Dis. 1968;13(12):1027–34.
7. Clarke AM, McKenzie RG. Ileostomy and the risk of urinary uric acid stones. Lancet. 1969;2(7617):395–7.
8. Dowling RH, Rose GA, Sutor DJ. Hyperoxaluria and renal calculi in ileal disease. Lancet. 1971;1(7709):1103–6.
9. Ritchie JK. Ileostomy and excisional surgery for chronic inflammatory disease of the colon: a survey of one hospital region. Gut. 1971;12(7):528–40.
10. Bennett RC, Hughes ES. Urinary calculi and ulcerative colitis. Br Med J. 1972;2(5812):494–6.
11. Smith LH, Fromm H, Hofmann AF. Acquired hyperoxaluria, nephrolithiasis, and intestinal disease. Description of a syndrome. N Engl J Med. 1972;286(26):1371–5.
12. O'Leary JP, Thomas WC Jr, Woodward ER. Urinary tract stone after small bowel bypass for morbid obesity. Am J Surg. 1974;127(2):142–7.
13. Backman L, Bergstrom K, Hallberg D. Kidney stone–a complication caused by intestinal shunt in treatment of obesity. Lakartidningen. 1975;72(6):462–6.
14. Cryer PE, Garber AJ, Hoffsten P, Lucas B, Wise L. Renal failure after small intestinal bypass for obesity. Arch Intern Med. 1975;135(12):1610–2.
15. Gelbart DR, Brewer LL, Fajardo LF, Weinstein AB. Oxalosis and chronic renal failure after intestinal bypass. Arch Intern Med. 1977;137(2):239–43.
16. Drenick EJ, Stanley TM, Border WA, Zawada ET, Dornfeld LP, Upham T, et al. Renal damage with intestinal bypass. Ann Intern Med. 1978;89(5 Pt 1):594–9.
17. Mole DR, Tomson CR, Mortensen N, Winearls CG. Renal complications of jejuno-ileal bypass for obesity. QJM. 2001;94(2):69–77.
18. Nelson WK, Houghton SG, Milliner DS, Lieske JC, Sarr MG. Enteric hyperoxaluria, nephrolithiasis, and oxalate nephropathy: potentially serious and unappreciated complications of Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2005;1(5):481–5.
19. Nasr SH, D'Agati VD, Said SM, Stokes MB, Largoza MV, Radhakrishnan J, et al. Oxalate nephropathy complicating Roux-en-Y Gastric bypass: an underrecognized cause of irreversible renal failure. Clin J Am Soc Nephrol. 2008;3(6):1676–83.
20. Lumlertgul N, Siribamrungwong M, Jaber BL, Susantitaphong P. Secondary oxalate nephropathy: a systematic review. Kidney Int Rep. 2018;3(6):1363–72.
21. Gaspar SR, Mendonca T, Oliveira P, Oliveira T, Dias J, Lopes T. Urolithiasis and Crohn's disease. Urol Ann. 2016;8(3):297–304.
22. Gkentzis A, Kimuli M, Cartledge J, Traxer O, Biyani CS. Urolithiasis in inflammatory bowel disease and bariatric surgery. World J Nephrol. 2016;5(6):538–46.
23. Corica D, Romano C. Renal involvement in inflammatory bowel diseases. J Crohns Colitis. 2016;10(2):226–35.
24. Ambruzs JM, Larsen CP. Renal manifestations of inflammatory bowel disease. Rheum Dis Clin N Am. 2018;44(4):699–714.
25. Primas C, Novacek G, Schweiger K, Mayer A, Eser A, Papay P, et al. Renal insufficiency in IBD–prevalence and possible pathogenetic aspects. J Crohns Colitis. 2013;7(12):e630–4.
26. Nightingale JM, Lennard Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces need for parenteral therapy, increases incidence of renal stones, but does not change high prevalence of gall stones in patients with a short bowel. Gut. 1992;33(11):1493–7.
27. Torio M, Ishimura M, Ohga S, Doi T, Utsunomiya R, Ohkubo K, et al. Nephrolithiasis as an extra-intestinal presentation of pediatric inflammatory bowel disease unclassified. J Crohns Colitis. 2010;4(6):674–8.
28. Castro M, Papadatou B, Baldassare M, Balli F, Barabino A, Barbera C, et al. Inflammatory bowel disease in children and adolescents in Italy: data from the pediatric national IBD register (1996-2003). Inflamm Bowel Dis. 2008;14(9):1246–52.
29. Mukewar S, Hall P, Lashner BA, Lopez R, Kiran RP, Shen B. Risk factors for nephrolithiasis in patients with ileal pouches. J Crohns Colitis. 2013;7(1):70–8.
30. Bambach CP, Robertson WG, Peacock M, Hill GL. Effect of intestinal surgery on the risk of urinary stone formation. Gut. 1981;22(4):257–63.
31. Fagagnini S, Heinrich H, Rossel JB, Biedermann L, Frei P, Zeitz J, et al. Risk factors for gallstones and kidney stones in a cohort of patients with inflammatory bowel diseases. PLoS One. 2017;12(10):e0185193.
32. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol. 2010;12(2-3):e86–96.
33. Ziemba JB, Matlaga BR. Epidemiology and economics of nephrolithiasis. Investig Clin Urol. 2017;58(5):299–306.
34. Nazzal L, Puri S, Goldfarb DS. Enteric hyperoxaluria: an important cause of end-stage kidney disease. Nephrol Dial Transplant. 2016;31(3):375–82.
35. Park S, Chun J, Han KD, Soh H, Choi K, Kim JH, et al. Increased end-stage renal disease risk in patients with inflammatory bowel disease: a nationwide population-based study. World J Gastroenterol. 2018;24(42):4798–808.
36. Dawson CH, Tomson CR. Kidney stone disease: pathophysiology, investigation and medical treatment. Clin Med. 2012;12(5):467–71.
37. Sakhaee K, Maalouf NM, Sinnott B, Clinical review. Kidney stones 2012: pathogenesis, diagnosis, and management. J Clin Endocrinol Metab. 2012;97(6):1847–60.
38. Moe OW. Kidney stones: pathophysiology and medical management. Lancet. 2006;367(9507):333–44.
39. Asplin JR. Uric acid stones. Semin Nephrol. 1996;16(5):412–24.
40. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones [see comments]. N Engl J Med. 1993;328(12):833–8.
41. Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med. 1997;126(7):497–504.
42. Robertson WG, Peacock M. The cause of idiopathic calcium stone disease: hypercalciuria or hyperoxaluria? Nephron. 1980;26(3):105–10.
43. Smith LH. Diet and hyperoxaluria in the syndrome of idiopathic calcium oxalate urolithiasis. Am J Kidney Dis. 1991;17(4):370–5.

44. Lemann J Jr, Pleuss JA, Worcester EM, Hornick L, Schrab D, Hoffmann RG. Urinary oxalate excretion increases with body size and decreases with increasing dietary calcium intake among healthy adults. Kidney Int. 1996;49(1):200–8.
45. Messa P, Marangella M, Paganin L, Codardini M, Cruciatti A, Turrin D, et al. Different dietary calcium intake and relative supersaturation of calcium oxalate in the urine of patients forming renal stones. Clin Sci Colch. 1997;93(3):257–63.
46. Hayashi Y, Kaplan RA, Pak CY. Effect of sodium cellulose phosphate therapy on crystallization of calcium oxalate in urine. Metabolism. 1975;24(11):1273–8.
47. Parks JH, Worcester EM, O'Connor RC, Coe FL. Urine stone risk factors in nephrolithiasis patients with and without bowel disease. Kidney Int. 2003;63(1):255–65.
48. Stauffer JQ, Humphreys MH, Weir GJ. Acquired hyperoxaluria with regional enteritis after ileal resection. Role of dietary oxalate. Ann Intern Med. 1973;79(3):383–91.
49. Stauffer JQ. Hyperoxaluria and calcium oxalate nephrolithiasis after jejunoileal bypass. Am J Clin Nutr. 1977;30(1):64–71.
50. Obialo CI, Clayman RV, Matts JP, Fitch LL, Buchwald H, Gillis M, et al. Pathogenesis of nephrolithiasis post-partial ileal bypass surgery: case-control study. The POSCH Group. Kidney Int. 1991;39(6):1249–54.
51. Ciacci C, Spagnuolo G, Tortora R, Bucci C, Franzese D, Zingone F, et al. Urinary stone disease in adults with celiac disease: prevalence, incidence and urinary determinants. J Urol. 2008;180(3):974–9.
52. Reusz GS, Latta K, Hoyer PF, Byrd DJ, Ehrich JH, Brodehl J. Evidence suggesting hyperoxaluria as a cause of nephrocalcinosis in phosphate-treated hypophosphataemic rickets. Lancet. 1990;335(8700):1240–3.
53. Allen A, Clutterbuck E, Maidment G, Thompson E, Watts R, Pusey C. Enteric hyperoxaluria and renal failure associated with lymphangiectasia. Nephrol Dial Transplant. 1997;12(4):802–6.
54. Sinha MK, Collazo-Clavell ML, Rule A, Milliner DS, Nelson W, Sarr MG, et al. Hyperoxaluric nephrolithiasis is a complication of Roux-en-Y gastric bypass surgery. Kidney Int. 2007;72(1):100–7.
55. Lieske JC, Mehta RA, Milliner DS, Rule AD, Bergstralh EJ, Sarr MG. Kidney stones are common after bariatric surgery. Kidney Int. 2015;87(4):839–45.
56. Weir MA, Beyea MM, Gomes T, Juurlink DN, Mamdani M, Blake PG, et al. Orlistat and acute kidney injury: an analysis of 953 patients. Arch Intern Med. 2011;171(7):703–4.
57. Forryan J, Mishra V, Gibbons E. When the cause is not crystal clear. N Engl J Med. 2020;382(1):74–8.
58. Cartery C, Faguer S, Karras A, Cointault O, Buscail L, Modesto A, et al. Oxalate nephropathy associated with chronic pancreatitis. Clin J Am Soc Nephrol. 2011;6(8):1895–902.
59. Chadwick VS, Modha K, Dowling RH. Mechanism for hyperoxaluria in patients with ileal dysfunction. N Engl J Med. 1973;289(4):172–6.
60. Hofmann AF, Tacker MM, Fromm H, Thomas PJ, Smith LH. Acquired hyperoxaluria and intestinal disease. Evidence that bile acid glycine is not a precursor of oxalate. Mayo Clin Proc. 1973;48(1):35–42.
61. Earnest DL, Johnson G, Williams HE, Admirand WH. Hyperoxaluria in patients with ileal resection: an abnormality in dietary oxalate absorption. Gastroenterology. 1974;66(6):1114–22.
62. Saunders DR, Sillery J, McDonald GB. Regional differences in oxalate absorption by rat intestine: evidence for excessive absorption by the colon in steatorrhoea. Gut. 1975;16(7):543–8.
63. Dobbins JW, Binder HJ. Effect of bile salts and fatty acids on the colonic absorption of oxalate. Gastroenterology. 1976;70(6):1096–100.
64. Dobbins JW, Binder HJ. Importance of the colon in enteric hyperoxaluria. N Engl J Med. 1977;296(6):298–301.
65. Hylander E, Jarnum S, Jensen HJ, Thale M. Enteric hyperoxaluria: dependence on small intestinal resection, colectomy, and steatorrhoea in chronic inflammatory bowel disease. Scand J Gastroenterol. 1978;13(5):577–88.
66. Fairclough PD, Feest TG, Chadwick VS, Clark ML. Effect of sodium chenodeoxycholate on oxalate absorption from the excluded human colon–a mechanism for 'enteric' hyperoxaluria. Gut. 1977;18(3):240–4.
67. Caspary WF, Tonissen J, Lankisch PG. 'Enteral' hyperoxaluria. Effect of cholestyramine, calcium, neomycin, and bile acids on intestinal oxalate absorption in man. Acta Hepatogastroenterol. 1977;24(3):193–200.
68. Rampton DS, Kasidas GP, Rose GA, Sarner M. Oxalate loading test: a screening test for steatorrhoea. Gut. 1979;20(12):1089–94.
69. Rampton DS, McCullough AD, Sabbat JS, Salisbury JR, Flynn FV, Sarner M. Screening for steatorrhoea with an oxalate loading test. Br Med J. 1984;288(6428):1419.
70. Foster PN, Will EJ, Kelleher J, Losowsky MS. Oxalate-loading tests to screen for steatorrhoea: an appraisal. Clin Chim Acta. 1984;144(2-3):155–61.
71. Freel RW, Hatch M, Green M, Soleimani M. Ileal oxalate absorption and urinary oxalate excretion are enhanced in Slc26a6 null mice. Am J Physiol Gastrointest Liver Physiol. 2006;290(4):719–28.
72. Jiang Z, Asplin JR, Evan AP, Rajendran VM, Velazquez H, Nottoli TP, et al. Calcium oxalate urolithiasis in mice lacking anion transporter Slc26a6. Nat Genet. 2006;38(4):474–8.
73. Knauf F, Ko N, Jiang Z, Robertson WG, Van Itallie CM, Anderson JM, et al. Net intestinal transport of oxalate reflects passive absorption and SLC26A6-mediated secretion. J Am Soc Nephrol. 2011;22(12):2247–55.
74. Freel RW, Whittamore JM, Hatch M. Transcellular oxalate and Cl-absorption in mouse intestine is mediated by the DRA anion exchanger Slc26a3, and DRA deletion decreases urinary oxalate. Am J Physiol Gastrointest Liver Physiol. 2013;305(7):520–7.
75. Amin R, Asplin J, Jung D, Bashir M, Alshaikh A, Ratakonda S, et al. Reduced active transcellular intestinal oxalate secretion contributes to the pathogenesis of obesity-associated hyperoxaluria. Kidney Int. 2018;93(5):1098–107.
76. Capolongo G, Abul-Ezz S, Moe OW, Sakhaee K. Subclinical celiac disease and crystal-induced kidney disease following kidney transplant. Am J Kidney Dis. 2012;60(4):662–7.
77. Khamaysi A, Anbtawee-Jomaa S, Fremder M, Eini-Rider H, Shimshilashvili L, Aharon S, et al. Systemic succinate homeostasis and local succinate signaling affect blood pressure and modify risks for calcium oxalate lithogenesis. J Am Soc Nephrol. 2019;2019:030277.
78. Knauf F, Asplin JR, Granja I, Schmidt IM, Moeckel GW, David RJ, et al. NALP3-mediated inflammation is a principal cause of progressive renal failure in oxalate nephropathy. Kidney Int. 2013;84(5):895–901.
79. Kurts C. A crystal-clear mechanism of chronic kidney disease. Kidney Int. 2013;84(5):859–61.
80. Ermer T, Eckardt KU, Aronson PS, Knauf F. Oxalate, inflammasome, and progression of kidney disease. Curr Opin Nephrol Hypertens. 2016;25(4):363–71.
81. Mulay SR, Anders HJ. Crystal nephropathies: mechanisms of crystal-induced kidney injury. Nat Rev Nephrol. 2017;13(4):226–40.
82. Evan AP, Coe FL, Gillen D, Lingeman JE, Bledsoe S, Worcester EM. Renal intratubular crystals and hyaluronan staining occur in stone formers with bypass surgery but not with idiopathic calcium oxalate stones. Anat Rec. 2008;291(3):325–34.

83. Evan AP, Lingeman JE, Coe FL, Bledsoe SB, Sommer AJ, Williams JC Jr, et al. Intra-tubular deposits, urine and stone composition are divergent in patients with ileostomy. Kidney Int. 2009;76(10):1081–8.
84. Evan AP, Lingeman JE, Worcester EM, Bledsoe SB, Sommer AJ, Williams JC Jr, et al. Renal histopathology and crystal deposits in patients with small bowel resection and calcium oxalate stone disease. Kidney Int. 2010;78(3):310–7.
85. Goldberg H, Grass L, Vogl R, Rapoport A, Oreopoulos DG. Urine citrate and renal stone disease. CMAJ. 1989;141(3):217–21.
86. Hamm LL. Renal handling of citrate. Kidney Int. 1990;38(4):728–35.
87. Pachaly MA, Baena CP, Buiar AC, de Fraga FS, Carvalho M. Effects of non-pharmacological interventions on urinary citrate levels: a systematic review and meta-analysis. Nephrol Dial Transplant. 2016;31(8):1203–11.
88. Rudman D, Dedonis JL, Fountain MT, Chandler JB, Gerron GG, Fleming GA, et al. Hypocitraturia in patients with gastrointestinal malabsorption. N Engl J Med. 1980;303(12):657–61.
89. Ishii G, Nakajima K, Tanaka N, Hara H, Kato M, Ishii N. Clinical evaluation of urolithiasis in Crohn's disease. Int J Urol. 2009;16(5):477–80.
90. Kennedy HJ, Al-Dujaili EA, Edwards CR, Truelove SC. Water and electrolyte balance in subjects with a permanent ileostomy. Gut. 1983;24(8):702–5.
91. McConnell N, Campbell S, Gillanders I, Rolton H, Danesh B. Risk factors for developing renal stones in inflammatory bowel disease. BJU Int. 2002;89(9):835–41.
92. Perazella MA. Proton pump inhibitors and hypomagnesemia: a rare but serious complication. Kidney Int. 2013;83(4):553–6.
93. Duncan SH, Richardson AJ, Kaul P, Holmes RP, Allison MJ, Stewart CS. Oxalobacter formigenes and its potential role in human health. Appl Environ Microbiol. 2002;68(8):3841–7.
94. Tasian GE, Jemielita T, Goldfarb DS, Copelovitch L, Gerber JS, Wu Q, et al. Oral antibiotic exposure and kidney stone disease. J Am Soc Nephrol. 2018;29(6):1731–40.
95. Nazzal L, Blaser MJ. Does the receipt of antibiotics for common infectious diseases predispose to kidney stones? A cautionary note for all health care practitioners. J Am Soc Nephrol. 2018;29(6):1590–2.
96. Siener R, Bangen U, Sidhu H, Honow R, von Unruh G, Hesse A. The role of Oxalobacter formigenes colonization in calcium oxalate stone disease. Kidney Int. 2013;83(6):1144–9.
97. Hatch M, Cornelius J, Allison M, Sidhu H, Peck A, Freel RW. Oxalobacter sp. reduces urinary oxalate excretion by promoting enteric oxalate secretion. Kidney Int. 2006;69(4):691–8.
98. Miller AW, Choy D, Penniston KL, Lange D. Inhibition of urinary stone disease by a multi-species bacterial network ensures healthy oxalate homeostasis. Kidney Int. 2019;96(1):180–8.
99. Hoyer-Kuhn H, Kohbrok S, Volland R, Franklin J, Hero B, Beck BB, et al. Vitamin B6 in primary hyperoxaluria I: first prospective trial after 40 years of practice. Clin J Am Soc Nephrol. 2014;9(3):468–77.
100. Coe FL. Uric acid and calcium oxalate nephrolithiasis. Kidney Int. 1983;24(3):392–403.
101. Messaris E, Sehgal R, Deiling S, Koltun WA, Stewart D, McKenna K, et al. Dehydration is the most common indication for readmission after diverting ileostomy creation. Dis Colon Rectum. 2012;55(2):175–80.
102. Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY. Association of urinary pH with body weight in nephrolithiasis. Kidney Int. 2004;65(4):1422–5.
103. Maalouf NM, Cameron MA, Moe OW, Sakhaee K. Metabolic basis for low urine pH in type 2 diabetes. Clin J Am Soc Nephrol. 2010;5(7):1277–81.
104. Maalouf NM, Cameron MA, Moe OW, Adams-Huet B, Sakhaee K. Low urine pH: a novel feature of the metabolic syndrome. Clin J Am Soc Nephrol. 2007;2(5):883–8.
105. Massey LK. Food oxalate: factors affecting measurement, biological variation, and bioavailability. J Am Diet Assoc. 2007;107(7):1191–4; quiz 5-6.
106. Attalla K, De S, Monga M. Oxalate content of food: a tangled web. Urology. 2014;84(3):555–60.
107. Chen CL, Fang HC, Chou KJ, Wang JS, Chung HM. Acute oxalate nephropathy after ingestion of star fruit. Am J Kidney Dis. 2001;37(2):418–22.
108. Barman AK, Goel R, Sharma M, Mahanta PJ. Acute kidney injury associated with ingestion of star fruit: acute oxalate nephropathy. Indian J Nephrol. 2016;26(6):446–8.
109. Lee KG. Star fruit intoxication with acute kidney injury. Clin Med. 2012;12(5):494.
110. Abeysekera RA, Wijetunge S, Nanayakkara N, Wazil AW, Ratnatunga NV, Jayalath T, et al. Star fruit toxicity: a cause of both acute kidney injury and chronic kidney disease: a report of two cases. BMC Res Notes. 2015;8:796.
111. Bakul G, Unni VN, Seethaleksmy NV, Mathew A, Rajesh R, Kurien G, et al. Acute oxalate nephropathy due to 'Averrhoa bilimbi' fruit juice ingestion. Indian J Nephrol. 2013;23(4):297–300.
112. Albersmeyer M, Hilge R, Schrottle A, Weiss M, Sitter T, Vielhauer V. Acute kidney injury after ingestion of rhubarb: secondary oxalate nephropathy in a patient with type 1 diabetes. BMC Nephrol. 2012;13:141.
113. Park H, Eom M, Won Yang J, Geun Han B, Ok Choi S, Kim JS. Peanut-induced acute oxalate nephropathy with acute kidney injury. Kidney Res Clin Pract. 2014;33(2):109–11.
114. Syed F, Mena-Gutierrez A, Ghaffar U. A case of iced-tea nephropathy. N Engl J Med. 2015;372(14):1377–8.
115. Lawton JM, Conway LT, Crosson JT, Smith CL, Abraham PA. Acute oxalate nephropathy after massive ascorbic acid administration. Arch Intern Med. 1985;145(5):950–1.
116. Lamarche J, Nair R, Peguero A, Courville C. Vitamin C-induced oxalate nephropathy. Int J Nephrol. 2011;2011:146927.
117. Poulin LD, Riopel J, Castonguay V, Mac-Way F. Acute oxalate nephropathy induced by oral high-dose vitamin C alternative treatment. Clin Kidney J. 2014;7(2):218.
118. Makkapati S, D'Agati VD, Balsam L. "Green smoothie cleanse" causing acute oxalate nephropathy. Am J Kidney Dis. 2018;71(2):281–6.
119. Getting JE, Gregoire JR, Phul A, Kasten MJ. Oxalate nephropathy due to 'juicing': case report and review. Am J Med. 2013;126(9):768–72.
120. Kikuchi Y, Seta K, Ogawa Y, Takayama T, Nagata M, Taguchi T, et al. Chaga mushroom-induced oxalate nephropathy. Clin Nephrol. 2014;81(6):440–4.
121. Sunkara V, Pelkowski TD, Dreyfus D, Satoskar A. Acute kidney disease due to excessive vitamin c ingestion and remote Roux-en-Y gastric bypass surgery superimposed on CKD. Am J Kidney Dis. 2015;66(4):721–4.
122. Marques S, Santos S, Fremin K, Fogo AB. A case of oxalate nephropathy: when a single cause is not crystal clear. Am J Kidney Dis. 2017;70(5):722–4.
123. Clifford-Mobley O, Tims C, Rumsby G. The comparability of oxalate excretion and oxalate:creatinine ratio in the investigation of primary hyperoxaluria: review of data from a referral centre. Ann Clin Biochem. 2015;52(Pt 1):113–21.
124. Camici M, Balestri PL, Lupetti S, Colizzi V, Falcone G. Urinary excretion of oxalate in renal failure. Nephron. 1982;30(3):269–70.
125. Ermer T, Kopp C, Asplin JR, Granja I, Perazella MA, Reichel M, et al. Impact of regular or extended hemodialysis and hemodialfiltration on plasma oxalate concentrations in patients with end-stage renal disease. Kidney Int Rep. 2017;2(6):1050–8.

126. Tomson CR. The clinical significance of hyperoxalaemia. Int J Artif Organs. 1988;11(5):329–34.
127. Perinpam M, Enders FT, Mara KC, Vaughan LE, Mehta RA, Voskoboev N, et al. Plasma oxalate in relation to eGFR in patients with primary hyperoxaluria, enteric hyperoxaluria and urinary stone disease. Clin Biochem. 2017;50(18):1014–9.
128. Cochat P, Rumsby G. Primary hyperoxaluria. N Engl J Med. 2013;369(7):649–58.
129. Lees JS, McQuarrie EP, Mackinnon B. Renal biopsy: it is time for pragmatism and consensus. Clin Kidney J. 2018;11(5):605–9.
130. Oikonomou KA, Kapsoritakis AN, Stefanidis I, Potamianos SP. Drug-induced nephrotoxicity in inflammatory bowel disease. Nephron Clin Pract. 2011;119(2):89–94; discussion c6.
131. Cheungpasitporn W, Erickson SB, Rule AD, Enders F, Lieske JC. Short-term tolvaptan increases water intake and effectively decreases urinary calcium oxalate, calcium phosphate and uric acid supersaturations. J Urol. 2016;195(5):1476–81.
132. Letavernier E, Daudon M. Stones: tolvaptan might prevent kidney stone formation. Nat Rev Urol. 2016;13(3):130–1.
133. Nordenvall B, Backman L, Larsson L, Tiselius HG. Effects of calcium, aluminium, magnesium and cholestyramine on hyperoxaluria in patients with jejunoileal bypass. Acta Chir Scand. 1983;149(1):93–8.
134. Pang R, Linnes MP, O'Connor HM, Li X, Bergstralh E, Lieske JC. Controlled metabolic diet reduces calcium oxalate supersaturation but not oxalate excretion after bariatric surgery. Urology. 2012;80(2):250–4.
135. Lemann J Jr. Composition of the diet and calcium kidney stones. N Engl J Med. 1993;328(12):880–2.
136. Taylor EN, Curhan GC. Diet and fluid prescription in stone disease. Kidney Int. 2006;70(5):835–9.
137. Liebman M, Chai W. Effect of dietary calcium on urinary oxalate excretion after oxalate loads. Am J Clin Nutr. 1997;65(5):1453–9.
138. von Unruh GE, Voss S, Sauerbruch T, Hesse A. Dependence of oxalate absorption on the daily calcium intake. J Am Soc Nephrol. 2004;15(6):1567–73.
139. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med. 2002;346(2):77–84.
140. Barilla DE, Notz C, Kennedy D, Pak CY. Renal oxalate excretion following oral oxalate loads in patients with ileal disease and with renal and absorptive hypercalciurias. Effect of calcium and magnesium. Am J Med. 1978;64(4):579–85.
141. Hylander E, Jarnum S, Nielsen K. Calcium treatment of enteric hyperoxaluria after jejunoileal bypass for morbid obesity. Scand J Gastroenterol. 1980;15(3):349–52.
142. Earnest DL. Perspectives on incidence, etiology, and treatment of enteric hyperoxaluria. Am J Clin Nutr. 1977;30(1):72–5.
143. Lindsjo M, Fellstrom B, Ljunghall S, Wikstrom B, Danielson BG. Treatment of enteric hyperoxaluria with calcium-containing organic marine hydrocolloid. Lancet. 1989;2(8665):701–4.
144. Laker MF, Hofmann AF. Effective therapy of enteric hyperoxaluria: in vitro binding of oxalate by anion-exchange resins and aluminum hydroxide. J Pharm Sci. 1981;70(9):1065–7.
145. Robijn S, Vervaet BA, Hoppe B, D'Haese PC, Verhulst A. Lanthanum carbonate inhibits intestinal oxalate absorption and prevents nephrocalcinosis after oxalate loading in rats. J Urol. 2013;189(5):1960–6.
146. Caravaca F, Ruiz AB, Escola JM, Hernandez Gallego R, Cerezo I, Fernandez N, et al. Either calcium carbonate or sevelamer decreases urinary oxalate excretion in chronic renal failure patients. Nefrologia. 2007;27(4):466–71.
147. Lieske JC, Regnier C, Dillon JJ. Use of sevelamer hydrochloride as an oxalate binder. J Urol. 2008;179(4):1407–10.
148. Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CY. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. J Urol. 1993;150(6):1761–4.
149. Zuckerman JM, Assimos DG. Hypocitraturia: pathophysiology and medical management. Rev Urol. 2009;11(3):134–44.
150. Seltzer MA, Low RK, McDonald M, Shami GS, Stoller ML. Dietary manipulation with lemonade to treat hypocitraturic calcium nephrolithiasis. J Urol. 1996;156(3):907–9.
151. Sakhaee K, Griffith C, Pak CY. Biochemical control of bone loss and stone-forming propensity by potassium-calcium citrate after bariatric surgery. Surg Obes Relat Dis. 2012;8(1):67–72.
152. Moe OW, Pearle MS, Sakhaee K. Pharmacotherapy of urolithiasis: evidence from clinical trials. Kidney Int. 2011;79(4):385–92.
153. Hoppe B, Beck B, Gatter N, von Unruh G, Tischer A, Hesse A, et al. Oxalobacter formigenes: a potential tool for the treatment of primary hyperoxaluria type 1. Kidney Int. 2006;70(7):1305–11.
154. Hoppe B, Dittlich K, Fehrenbach H, Plum G, Beck BB. Reduction of plasma oxalate levels by oral application of Oxalobacter formigenes in 2 patients with infantile oxalosis. Am J Kidney Dis. 2011;58(3):453–5.
155. Hoppe B, Groothoff JW, Hulton SA, Cochat P, Niaudet P, Kemper MJ, et al. Efficacy and safety of Oxalobacter formigenes to reduce urinary oxalate in primary hyperoxaluria. Nephrol Dial Transplant. 2011;26(11):3609–15.
156. Lieske JC, Goldfarb DS, De Simone C, Regnier C. Use of a probiotic to decrease enteric hyperoxaluria. Kidney Int. 2005;68(3):1244–9.
157. Okombo J, Liebman M. Probiotic-induced reduction of gastrointestinal oxalate absorption in healthy subjects. Urol Res. 2010;38(3):169–78.
158. Lieske JC, Tremaine WJ, De Simone C, O'Connor HM, Li X, Bergstralh EJ, et al. Diet, but not oral probiotics, effectively reduces urinary oxalate excretion and calcium oxalate supersaturation. Kidney Int. 2010;78(11):1178–85.
159. Goldfarb DS, Modersitzki F, Asplin JR. A randomized, controlled trial of lactic acid bacteria for idiopathic hyperoxaluria. Clin J Am Soc Nephrol. 2007;2(4):745–9.
160. Borghi L, Nouvenne A, Meschi T. Probiotics and dietary manipulations in calcium oxalate nephrolithiasis: two sides of the same coin? Kidney Int. 2010;78(11):1063–5.
161. Grujic D, Salido EC, Shenoy BC, Langman CB, McGrath ME, Patel RJ, et al. Hyperoxaluria is reduced and nephrocalcinosis prevented with an oxalate-degrading enzyme in mice with hyperoxaluria. Am J Nephrol. 2009;29(2):86–93.
162. Langman CB, Grujic D, Pease RM, Easter L, Nezzer J, Margolin A, et al. A double-blind, placebo controlled, randomized phase 1 cross-over study with ALLN-177, an orally administered oxalate degrading enzyme. Am J Nephrol. 2016;44(2):150–8.
163. Nigwekar SU, Lingeman JE, Gyan P, Kausz A. Clinical characteristics and tolerability of ALLN-177 in Phase 2 studies of patients with secondary hyperoxaluria (abstract). J Am Soc Nephrol. 2017;28:1113.
164. Shimizu MH, Gois PH, Volpini RA, Canale D, Luchi WM, Froeder L, et al. N-acetylcysteine protects against star fruit-induced acute kidney injury. Ren Fail. 2017;39(1):193–202.
165. Le Dudal M, Huguet L, Perez J, Vandermeersch S, Bouderlique E, Tang E, et al. Stiripentol protects against calcium oxalate nephrolithiasis and ethylene glycol poisoning. J Clin Invest. 2019;129(6):2571–7.
166. Lorenz EC, Michet CJ, Milliner DS, Lieske JC. Update on oxalate crystal disease. Curr Rheumatol Rep. 2013;15(7):340.
167. Kiss D, Meier R, Gyr K, Wegmann W. Secondary oxalosis following small bowel resection with kidney insufficiency and oxalate vasculopathy. Schweiz Med Wochenschr. 1992;122(22):854–7.

168. Bernhardt WM, Schefold JC, Weichert W, Rudolph B, Frei U, Groneberg DA, et al. Amelioration of anemia after kidney transplantation in severe secondary oxalosis. Clin Nephrol. 2006;65(3):216–21.
169. Gregoriou S, Kalapothakou K, Kontochristopoulos G, Belyayeva H, Chatziolou E, Rigopoulos D. Subungual oxalate deposits in a patient with secondary hyperoxaluria. Acta Derm Venereol. 2011;91(2):195–6.
170. Roodnat JI, de Mik-van Egmond AME, Visser WJ, Berger SP, van der Meijden WAG, Knauf F, et al. A successful approach to kidney transplantation in patients with enteric (secondary) hyperoxaluria. Transplant Direct. 2017;3(12):e331.
171. Becker G. Caring for australians with renal I. The CARI guidelines. Kidney stones: uric acid stones. Nephrology. 2007;12(Suppl 1):S21–5.
172. Zisman AL. Effectiveness of treatment modalities on kidney stone recurrence. Clin J Am Soc Nephrol. 2017;12(10):1699–708.
173. Muldowney FP, Freaney R, Barnes E. Dietary chloride and urinary calcium in stone disease. QJM. 1994;87(8):501–9.
174. Bultitude M, Rees J. Management of renal colic. BMJ. 2012;345:e5499.
175. European Association of Urology Guidelines on Urolithiasis. 2021. https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urolithiasis-2021.pdf. Accessed April 2021.
176. Renal and ureteric stones: assessment and management. NICE Guidance [NG118]. 2019. https://www.nice.org.uk/guidance/ng118. Accessed April 2021.
177. Pearle MS, Pierce HL, Miller GL, Summa JA, Mutz JM, Petty BA, et al. Optimal method of urgent decompression of the collecting system for obstruction and infection due to ureteral calculi. J Urol. 1998;160(4):1260–4.
178. De Coninck V, Antonelli J, Chew B, Patterson JM, Skolarikos A, Bultitude M. Medical expulsive therapy for urinary stones: future trends and knowledge gaps. Eur Urol. 2019;76(5):658–66. https://doi.org/10.1016/j.eururo.2019.07.053.
179. Goldsmith ZG, Lipkin ME. When (and how) to surgically treat asymptomatic renal stones. Nat Rev Urol. 2012;9(6):315–20. https://doi.org/10.1038/nrurol.2012.43. PMID: 22450602.
180. Chaussy C, Schmiedt E, Jocham D, Brendel W, Forssman B, Walther V. First clinical experience with extracorporeally induced destruction of kidney stones by shock wave. J Urol. 1982;127:417–20.
181. Reynolds LF, Kroczak T, Pace KT. Indications and contraindications for shock wave lithotripsy and how to improve outcomes. Asian J Urol. 2018;5(4):256–63.
182. Ordon M, Welk B, Ghiculete D, Lee JY, Pace KT. Is extracorporeal shockwave lithotripsy a risk factor for the development of diabetes mellitus? A population-based study. BJU Int. 2019;123:1048–54.
183. Joshi HB, Stainthorpe A, MacDonagh RP, Keeley FX Jr, Timoney AG, Barry MJ. Indwelling ureteral stents: evaluation of symptoms, quality of life and utility. J Urol. 2003;169(3):1065–9; discussion 1069
184. Ghani KR, Andonian S, Bultitude M, Desai M, Giusti G, Okhunov Z, Preminger GM, de la Rosette J. Percutaneous nephrolithotomy: update, trends, and future directions. Eur Urol. 2016;70(2):382–96.

Bone and Joint Disease

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Key Points

1. A metabolic bone disease (MBD) characterized by osteopenia, osteoporosis or osteomalacia may affect 40–100% of patients on home parenteral nutrition (HPN) for chronic intestinal failure. Fifty percent will have osteopenia/osteomalacia when parenteral nutrition (PN) starts.
2. Osteopenia occurs in 13–57% and osteoporosis in 18–44% of patients receiving long-term HPN. It is more common in those who were young when starting PN and in those with a low body mass index (BMI). Many (35%) have bone pain.
3. The common reasons for bone mineral loss are general causes or underlying disease rather than intestinal failure (IF)/HPN. These include: older age/female, reduced physical activity, low sunlight exposure, smoking/alcohol, chronic inflammation and medication (e.g. corticosteroids, long-term anticoagulation).
4. Vitamin D deficiency is common in those not having daily PN with Vit D supplementation.
5. PN composition can affect the calcium loss in the urine. Excessive sodium should be avoided and the amino acid content kept to less than 2 g/kg/day. At least 7.5 mmol calcium and 30 mmol phosphorus daily promotes their net retention.
6. A Dual-energy-X-ray absorptiometry (DEXA) measurement is made from the lumbar spine representing trabecular bone, and at the femoral neck representing cortical bone. The result of DEXA is expressed as a number of standard deviations from mean bone mineral density. Two scores are given that relating to young adults (T-score) and that relating to age and sex-matched healthy subjects (Z-score). A T-score between −1 and −2.5 SD is osteopenia and lower than −2.5 SD is osteoporosis.
7. DEXA is recommended at yearly intervals. Biochemical measurements of serum concentrations and 24 h urinary excretion of minerals (calcium, phosphate and magnesium) are made every 4 months and the measurement of serum parathormone (PTH) and 25-hydroxivitamin D every year. Vitamin K is assessed indirectly every 4 months with the international normalised ratio (INR).
8. Treatment of osteopenia/osteoporosis includes life style changes (stop smoking, little alcohol, more exercise and some sunlight exposure). Adequate vit D, calcium and magnesium intake is ensured and if necessary biphosphate infusions are given (being aware of the rare complication of osteonecrosis of the jaw) or denosumab.
9. As there is a loss of the diurnal parathormone rhythm with nocturnal PN, daytime PN may be considered.
10. Chronic hypomagnesemia in patients with a short bowel may result in symptomatic chondrocalcinosis.

Introduction

The adult skeleton is composed by trabecular or cancellous bone and by cortical bone. The trabecular bone appears as filaments that form the internal structure of the bones and gives the bone its compressive strength. The cortical bone is located around the circumference of bone and consists of thick and densely packed layers of mineralized collagen. On an annual basis, about 4% of cortical bone and 28% of trabecular bone undergo to remodeling (or bone turnover), that is required to repair and reinforce bone to compensate for the mechanical stress placed on the skeleton. Remodeling consists of the balanced activity of skeletal destruction (or bone resorption) by osteoclasts and skeletal reconstruction (or bone formation) by osteoblasts. Skeletal remodeling is regulated by numerous factors, including parathyroid hormone (PTH), vitamin D, and serum calcium, magnesium, and phosphorus concentrations [1–3].

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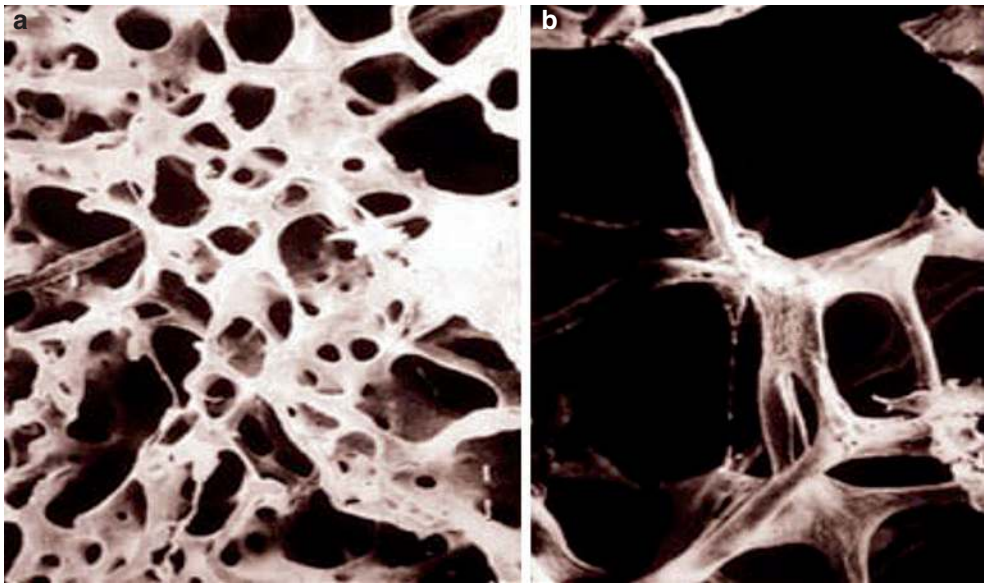

Fig. 1 Bone structure (**a**) normal, (**b**) osteoporosis

Table 1 Frequency of metabolic bone disease in patients receiving HPN according to dual-energy-X-ray absorptiometry (DEXA) assessment

Author, year	Patients (n.)	Osteopenia	Osteoporosis
Goodman WG, 2000	6	100%	
Pironi L, 2002	165	43%	41%
Raman M, 2006	25	37% (spine)	32% (spine)
		43% (femural hip)	21% (femural hip)
Raman M, 2007	69	18% (spine and femural hip)	46% (spine)
			13% (femural hip)
Ellegard L, 2013	78	44%	44%
Nygaard L, 2017	148	32%	57%

A metabolic bone disease (MBD) characterized by osteopenia, osteoporosis (Fig. 1) or osteomalacia may affect the 40–100% of patients on home parenteral nutrition (HPN) for chronic intestinal failure (CIF) [1, 4, 5] (Table 1).

Osteomalacia is characterized by defective mineralization and increased osteoid, which is the unmineralized bone matrix. Osteopenia is a state of low bone mass due to a decrease in bone mineralization that precedes the state of osteoporosis, characterized by a loss of bone mass due to an equal reduction in bone mineral and bone matrix [1–3].

The prevalence of MBD in patients with CIF was evaluated in a European multicentre survey [4] by dual-energy-X-ray absorptiometry (DEXA) at lumbar spine and femoral neck. This cross-sectional study showed that 43% of patients had osteopenia and 41% had osteoporosis. Associations between bone mineral density (BMD) and age at diagnosis of intestinal failure (lower BMD in younger patients), with body mass index (higher BMD with higher BMI) [6] and age at starting HPN (lower BMD in younger patients) [7] have been reported. Only the study by Raman et al. [8], reported a significant negative association between BMD and duration of HPN.

Actually, the real incidence of MBD during HPN is unknown. Indeed, a MBD frequently affect patients with intestinal insufficiency, who never underwent HPN [9] and a MBD is frequently present before the beginning of the HPN program [10]. Furthermore, as reported by longitudinal studies, long-term HPN is not necessarily associated with a worsening of bone health; in some cases an improvement on BMD may occur [7, 11–15].

Clinical Features

The main features of MBD in long term HPN may be asymptomatic osteopenia, bone pain localized mainly at spine and lower joints or bone fractures occurring with no or minimal trauma. The ESPEN prevalence study [4] showed that the lowest values of BMD were associated with bone pain in 35% of patients (mainly at spine, knee, hip, ankle, feet and hands) and with bone fractures in 10% (spine, rib and hip). Moreover, the patients' physical rehabilitation status may be negatively affected by MBD [16, 17].

Histology

The presence of either osteomalacia [13, 18–21] or osteoporosis [13, 19, 20, 22, 23] have been reported by histomorphometric studies. A low bone formation rate [2, 13, 18–22], as well as increased bone turnover [19, 23] or defective mineralization [18] were shown in most of the patients by the analysis of the dynamic histomorphometric indices.

HPN-associated MBD seems to be characterized by low bone turnover. The only one follow up observation performed by bone histology reported that most of the patients had a hyperkinetic bone turnover at the first assessment, evolving to a low bone formation rate 6–12 months later [18]. Data consistent with the early results by bone histomorphometry were reported by an observation using a bone formation marker serum osteocalcin (OC) (a hydroxyapatite-binding protein made by osteoblasts, odontoblasts, and hypertrophic chondrocytes which constitutes 15% of the non-collagenous bone matrix) and a bone resorption marker urinary pyridinium cross links; together they provide markers of bone turnover [24].

Pathogenesis

In patients on HPN, MBD is mainly due to general factors, like aging, postmenopausal status, alcohol and tobacco abuse, and to factors related to the patient's underlying disease (disease-associated MBD). However, accelerated bone loss has been reported during the HPN (HPN-associated MBD), raising the question of a specific role of HPN-related factors [11, 12, 25].

Disease-associated MBD has a multifactorial pathogenesis [1]. Some risk factors may be related to life-style changes, such as reduced physical activity and low sunlight exposure. Intestinal malabsorption of calcium, magnesium and vitamin D, calcium losses in the gut lumen, chronic inflammation and drugs, such as corticosteroids, immunosuppressive, loop diuretics, long-term anticoagulation with heparin or warfarin, are other disease-related factors. Chronic inflammation causes both increased bone resorption and decreased bone formation due to cytokines such as Tumour Necrosis Factor (TNF), Interluekin-1 (IL-1), Interleukin-6 (IL-6) and to Prostaglandin E2. In patients with a short bowel, the metabolic acidosis due to intestinal losses of bicarbonate or to D-lactic acidosis can activate the bone buffering systems may be directly affected by calcium and phosphorus resorption and can impair the metabolism of vitamin D.

There are several hypothesis about the HPN-related factors. In the seventies, aluminium overload due to aluminium contamination of the amino acid solutions deriving from caseine hydrolysis was demonstrated to be associated with high serum concentration and urinary excretion of aluminium, positive aluminium staining in bone, low serum concentrations of PTH and of 1,25 dihydroxyvitamin D and hypercalciuria, and an histologic feature of osteomalacia [21, 26, 27]. The reversal of this feature was observed by replacing casein hydrolysate with crystalline amino acid solutions, containing negligible quantities of aluminium [28]. Aluminium impairs bone mineralization by deposition at the mineralization zone of bone and by reduces the secretion of PTH, whose physiologic activity is to stimulate bone formation. The enzymatic conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the specific renal enzyme is also blocked by aluminium, thus directly inhibiting proliferation of osteoblasts [26]. Caseine hydrolysate solutions are no longer produced now-a-days, but other nutrient solutions, such as phosphate salts, calcium gluconate, vitamins and trace metals still may be contaminated with aluminium [26]. It may be possible to observe mild increase of serum aluminium concentrations, without an association with positive aluminium staining in bone histology [22].

Also vitamin D deficiency or toxicity may be related to MBD. Vitamin D increases intestinal absorption of calcium, phosphorus and magnesium, and enhances renal tubular calcium resorption. In bone, vitamin D induces osteoclast formation and bone resorption that indirectly promote bone mineralization via maintenance of extracellular calcium and phosphorus concentrations in a supersaturated state. Osteomalacia in adults and rickets in children are the consequences of vitamin D deficiency. Furthermore, the development of the giant osteoclast, as well as the regulation of the immune system, and of several cell functions, are significantly improved by vitamin D [29].

Most of adult patients on HPN (77–100%), who were receiving IV multivitamin supplementation including for each infusion day the recommended amount of 200 IU vitamin D3 (cholecalciferol), have been reported to have either vitamin D insufficiency or deficiency, diagnosed by serum concentration of 25-hydroxivitamin D <30 or <20 ng/mL, respectively [30, 31] (Table 2). When reading these results, however, it should be kept in mind the 25-hydroxivitamin D serum concentration behaviour as a negative inflammatory index. Therefore, the serum concentrations of inflammatory

Table 2 Vitamin D status in patients with intestinal failure or intestinal insufficiency, according to serum 25OH-vitamin D concentration (lower limit)

Author, year	Patients n.	Vit D insufficiency	Vit. D deficiency
Goodman WG, 2000	6, on HPN for CIF		100% (<50 nmol/L)
Compher C, 2007	8, on HPN for CIF		100% (<20 ng/mL)
Corey B, 2009	35, on HPN for CIF		77% (<30 ng/mL)
Thomson T, 2011	22, on HPN for CIF	27% (20–30 ng/mL)	68% (<20 ng/mL)
Kumar PR, 2012	15, on HPN for CIF	33% (27.5–75 nmol/L)	0 (≤27.5 nmol/L)
Ellegard L, 2013	106, on HPN for CIF		67% (<50 nmol/L)
Nygaard L, 2017	96, on HPN for CIF	28% (25–50 nmol/L)	14% (<25 nmol/L)
Nygaard L, 2017	71, intestinal insufficiency (no HPN)	31% (25–50 nmol/L)	17% (<25 nmol/L)

indices, such as C-reactive protein, should be considered when interpreting 25-hydroxivitamin D serum concentrations [32].

A higher risk of vitamin D deficiency was reported for those patients who did not receive daily administration of HPN [31]; moreover, during transition from HPN to enteral nutrition an increased risk has been observed [33]. High doses of oral vitamin D failed to achieve appropriate 25-hydroxivitamin D serum levels in patients with short bowel syndrome, either receiving HPN [34] or not [10].

According to a few studies from the same research group, the hypothesis of vitamin D-poisoning has been advanced. It seemed that the PTH secretion may be impaired by the daily intravenous infusion of 25-hydroxivitamin D amounts equal to the RDA for adult healthy people. Consequently, despite normal serum 25 hydroxyvitamin D concentrations, PTH physiologic effects like bone mineralization and 1,25-dihydroxyvitamin D synthesis might not occur. An increase of BMD together with the normalization of PTH and 1,25-dihydroxyvitamin D were observed after vitamin D withdrawal [25, 35]. These findings haven't been confirmed by any studies in the last decade.

Patients on HPN show frequently high urinary calcium excretion [13, 18, 19, 21–23]. The urinary excretion of electrolytes before (diurnal, 12 h) and during (nocturnal, 12 h) parenteral nutrition was measured by Boncompain-Gerard et al. [36] in 16 patients. Compared with diurnal urine, a significant increase in urine volume and excretion of urea, creatinine, sodium, magnesium, and phosphate but not potassium was observed in nocturnal urine. Referring to 24-h calciuria, 7 patients had normal values whereas 9 had hypercalciuria. Although the calcium supply was identical, only the hypercalciuric patients had diurnal hypercalciuria, whereas both had excessive nocturnal calciuria. In patients with normocalciuria BMD was slightly, although not significantly, higher, but in all patients, BMD had a significant correlation with calciuria. A positive correlation between renal calcium loss and the amount of infused amino acids, glucose, sodium and calcium with the parenteral nutrition solution has been shown by several cross-sectional studies [12]. Contrarily, other studies reported a negative correlation between urinary calcium and intravenous phosphate load, appearing to enhance calcium reabsorption by the renal tubules, independently of PTH actions [37–39]. Bone calcium reabsorption can be induced by metabolic acidosis, due to titratable acids produced by the metabolism of neutral and sulphur-containing amino acid [1, 12]. Finally, according to the study of Wood [40], cyclic infusion more than continuous infusions seem to be associated with a greater calciuria. Hypercalciuria during HPN may be related to both increased glomerular filtration rate (i.v. fluids, amino acids, calcium and sodium, metabolic acidosis) and decreased reabsorption by the renal tubules (excessive i.v. amino acids, glucose and calcium and low i.v. phosphate) [12]. According to some human studies [41] and an investigation on a nonhuman primate model, a reduction of renal calcium losses may occur during HPN adaptation [42].

It has also been hypothesized that the balance of the effect of PTH on bone between resorption and formation might be altered in the direction of resorption by parenteral nutrition [43]. According to Goodman et al. [20], the regularity of PTH secretion together with moderate but persistent elevations in serum PTH concentrations would be increased by long-term HPN. Consequently, the PTH-related peptide receptor expression might be lowered and the response to physiological blood concentrations of PTH in target tissues might be diminished. Bone formation and turnover and the renal calcium resorption would be both reduced.

HPN-associated MBD might also be related to deficiency or toxicity of micronutrients known to interfere with bone metabolism [1, 19, 23]. In patients with SBS receiving HPN a positive correlation between serum fluoride concentrations and lumbar BMD, but no correlation with femoral neck BMD, have been observed [44]. This data reflect the action of this electrolyte on trabecular bone formation, increasing cancellous bone density, but having no effect on cortical bone density. However, as some studies describe, the risk of fluoride toxicity must also be considered: actually an increased risk for bone fractures has been associated with high amounts of fluoride in drinking water. Other factors involved in bone formation are osteocalcin, matrix Gla protein (a small vitamin K-dependent protein, that is the most powerful natural occurring known inhibitor of calcification in humans), and protein S, which is also a vitamin K-dependent protein. HPN patients supplemented with vitamin K seemed to have a trend toward a better hip BMD compared with patients without supplementation, as described by Aljarallah et al. [45]. There are no studies investigating the role of boron, silicon and copper deficiency in MBD as well as the potential toxicity from other micronutrients, like vitamin A, cadmium, strontium and vanadium, in patients on HPN [46].

Finally, according to a limited number of human studies and a large number of animal investigations, low BMD during HPN administration is the result of a chronic inflammatory condition characterized by increased circulating concentrations of pro-inflammatory cytokines, such as TNF-αand IL-6, which stimulate osteoclast activity. Both the lack of significant small intestinal mass (as in short bowel syndrome) or the absence of small intestine stimulation (as in dysmotility syndromes), as well as the components within the PN solution, like lipid emulsions rich in omega-6, may lead to this chronic inflammation. Another suggestion is that the immune system interacts with the catheter as a foreign body, leading to inflammation [47].

Table 3 Instrumental and biochemical parameters for the diagnosis and follow up of metabolic bone disease in patients on home parenteral nutrition for chronic intestinal failure due to benign disease (frequency of assessment)

• Bone mineral density by dual-energy-X-ray absorptiometry (DEXA) (at starting HPN, then yearly)
• Serum and urinary Ca, Mg and P (every 4 months; additional measurement according to the clinical feature)
• Serum 25-hydroxyvitamin D, PTH and markers of bone turnover (yearly; additional measurement according to the clinical feature)
• Serum 1,25-dihydroxyvitamin D (in case of suspected vitamin D toxicity)
• Serum aluminium and other micronutrients (according to the clinical suspicion)
• Bone biopsy (with/without) double tetracycline labelling (if doubtful diagnosis between osteomalacia and osteoporosis)

Diagnosis and Follow Up (Table 3)

The guidelines for CIF of the European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) (ESPEN) [48] recommend that for routine purposes both diagnosis and monitoring of MBD is based on a combination of bone densitometry scanning (Dual-Energy X-ray Absorptiometry, DEXA) and biochemistry. DEXA is used for the definition of the degree of MBD at starting HPN and its evolution during the treatment, whereas biochemical parameters are important for the assessment of bone turnover and the investigation of the potential pathogenetic mechanism (Table 1). DEXA assessment is usually made at lumbar spine, representing trabecular bone, and/or at hip, with femoral neck, representing cortical bone. The result of DEXA is expressed as a number of standard deviations from mean BMD value of young adult reference mean (T-score) and of age and sex-matched healthy subjects (Z-score). The severity of MBD as osteopenia or osteoporosis has been defined by the WHO Study Group [49] on the basis of the T-score value. The relative risk of any fracture has been estimated to be 1.4–1.6 for every decrease in BMD of 1 SD below the BMD Z-score [2]. Also in HPN patients the predictive value of the BMD for the assessment of fracture risk has been suggested [4]. DEXA measures BMD independently of the presence of osteomalacia or osteoporosis; bone histology is mandatory when a differential diagnosis is needed. For BMD monitoring, DEXA is recommended at yearly interval and biochemical assessment, serum concentrations and 24 h urinary excretion of minerals (Ca, P, Mg) every 4 months and the measurement of serum PTH and 25-hydroxivitamin D every year.

Prevention and Treatment (Table 4)

The potential pathogenetic mechanisms determine the prevention and treatment of MBD. The ESPEN guidelines [48] recommend that general risk factors for developing osteoporosis be promptly addressed, as well as factors with a possible negative impact on bone health, i.e. chronic inflammation, infections, drugs and other relevant factors related to the underlying disease, in all patients on long-term HPN.

Table 4 Prevention and treatment of metabolic bone disease in patients on home parenteral nutrition for chronic intestinal failure due to benign disease

General and life-style recommendations
• Regular low impact physical exercise program
• Regular and adequate sunlight exposure (UVB radiation from a tanning bed or other UVB emitting device might be considered)
• Maintain protein-calorie nutritional status
• Diet rich in dairy food (depending on the underlying intestinal functions)
• Avoid cigarette smoking and limit alcohol intake
• Estrogen replacement therapy in perimenopausal and postmenopausal period (depending on the underlying risk for vein thrombosis)
Correction of the underlying disease-related factors
• Treatment of chronic inflammation
• Limitation of bone damaging drugs
• Prevention and treatment of metabolic acidosis
• Oral calcium supplementation (500–1000 mg bid)
• Oral magnesium supplementation (Mg oxide 12–24 mmol/day)
Parenteral nutrition-related factors
• Fluids: as required to maintain fluid balance
• Infusion rate: slowing the infusion rate may decrease hypercalciuria
• Sodium: as required for maintain Na balance; excess urinary Na may induce hypercalciuria
• Minerals (Ca, P, Mg): as required of maintain balance; Ca/P ratio to be adjusted to precent hypercalciuria as well as formation of calcium-phosphate crystals in the admixture
• Acetate: as required to maintain normal serum bicarbonate
Amino acids: balance between requirement for protein synthesis and to avoid amino acid induced hypercalciuria
• Vitamin D: daily iv with multivitamin vials, 220 IU of cholecalciferol or 200 IU of ergocalcipherol; PN infusion <7 day/week: add oral or im vitamin D supplementation as required
• Vit K supplementation: as required to maintain normal prothrombin time
• Aluminium contamination of the PN admixture: <25 μg/L
Drug therapy (published protocols)
• Biphosphonates: clodronate, 1500 mg iv every 3 months; pamidronate, 30–60 mg im/monthly or 90 mg iv every 3–6 months
• Denosumanb: 60 mg sc/yearly

Research and treatment of the general and underlying disease related factors is absolutely important. HPN associated MBD can be prevented by the optimisation of the parenteral solution. Aluminium contamination should be less than 25 μg/L [26]. The amounts of minerals should aim to maintain the normal serum concentrations and 24-h urinary excretions. The Ca/P ratio in the solution should be always carefully observed, although, the optimal ratio cannot always be achieved due to problems of stability in the solution. It has been observed that supplying at least 15 mEq calcium and 30 mmol phosphorus on a daily basis can promote retention of these elements [37]. Berkelhammer et al.

[39], reported a positive calcium balance giving 12 mEq of calcium and 45 mmol of phosphate; according to other studies the phosphate amount should be 33–42 mmol [38]. Thus, to achieve a positive calcium balance it seems to be required a Ca/P ratio ranging from 1 mEq of calcium to 1 or 2 mmol of phosphate. However, chronic excess of phosphorus can lead to bone loss as a result of secondary hyperparathyroidism. Amino acids and sodium should not be added in amounts greater than losses [12]. The recommended intravenous vitamin D for adults is 200 IU/day [1]. In some patients, hypercalciuria may be reduced by slowing the infusion rate [12].

The ESPEN guidelines recommend as the primary step for treatment of metabolic bone disease to optimize the program for parenteral nutrition with the required supplements of vitamin D, calcium and phosphate. Further, medical treatment may be useful to increase bone mineral density and lower fracture risk. Recently, the American Society for Parenteral and Enteral Nutrition (ASPEN) has expressed concern as to whether the daily dose of 200 IU/day in the current PN products is adequate to maintain normal serum concentrations of 25-hydroxivitamin D in most patients requiring long-term PN [50]. Oral or intramuscular vitamin D supplementation, as well as exposure to sunlight or UVB emitting device could be required [29, 51]. Bisphosphonates provided intravenously at regular intervals (Clodronate, Pamidronate, or Zolindronic acid), may support bone mineral health in patients with osteopenia.

An ESPEN survey on the current practice of MBD management in patients on HPN for CIF reported that zolidronate, alendronate pamidronate and clodronate were the most common used [52]. So far, there are only one randomised controlled study and a few prospective observations about the use of biphosphonates in patients on HPN. The study of Haderslev et al. [53] showed that intravenous clodronate could decrease the urinary excretion of markers of bone resorption and maintain BMD at lumbar spine in patients on HPN after 12 months, but has no significant effect in increasing BMD. Improvement of BMD at both spine and hip has been observed with the use of intravenous pamidronate [8, 54]. The case-report reported normalized BMD after 18 months in a patient on HPN for short bowel syndrome with osteoporosis, treated with the subcutaneous administration of the recombinant PTH, teriparatide [55]. Another case report suggests that BMD may be also improved by growth hormone used to treat short bowel syndrome [56]. A recent study reported an improvement of BMD assessed by DEXA in patients on long-term HPN, after 12 months of treatment with denosumab, a fully human monoclonal antibody that inhibits bone resorption by neutralizing receptor activator of NF-κB ligand (RANKL) (a mediator for osteoclast formation and function) [57].

Joint Diseases and Enterophatic Arthritis

Two case reports described patients with chronic hypomagnesemia induced by SBS who developed symptomatic chondrocalcinosis due to deposition of calcium pyrophosphate dihydrate (CPPD) crystals in hyaline and fibrous cartilage [58, 59]. Magnesium deficiency in SBS is the consequences of intestinal malabsorption, increased renal losses and inadequate supplementation. Malabsorption is due to the loss of bowel absorptive area, especially ileum and proximal colon, to low 1,25-hydroxy-vitamin D levels leading to abnormal jejunal Mg absorption and to Mg bounding by fatty acids derived from both high dietary fat intake (long-chain triglycerides) and bacterial fermentation of malabsorbed carbohydrates. In patients with dehydration, increased renal losses of Mg result from hyperaldosteronism. Oral supplementation of Mg may cause intestinal motility and diarrhoea, which can further compromise adequate Mg absorption.

Magnesium is a cofactor for alkaline phosphatases, an enzyme playing a key role in converting inorganic pyrophosphates to orthophosphate. Moreover, Mg increases the solubility of CPPD crystals in vitro. Thus, hypomagnesemia could facilitate intra-articular elevation of extracellular inorganic pyrophosphate and/or reduced saturation product of CPPD, thus favouring crystal nucleation of CPPD. The clinical presentation of chondrocalcinosis is characterized by acute or chronic arthritis (attacks of pseudogout, typically in knees and ankles). The diagnosis relies on radiological finding of thin linear calcification of the cartilage. CPPD crystals can be identified by polarizing light microscopy. The prevalence of CPPD increases with age (10–15% for people in the 6 and 7 decades of age), whereas in younger individuals several disease can cause CPPD deposition disease, such as hemochromatosis, hyperparathyroidism, hyperparathyroidism, hypomagnesemia or hypophosphatemia [60]. The treatment of CPPD in SBS patients consists in the correction of Mg deficiency by parenteral supplementation of Mg associated with correction of vitamin D deficiency, administration of opioids to slow bowel transit, and colchicine as a long-term therapy instead of steroids, when required [59].

The underlying disease of patients with CIF may complicate with enteropathic arthritis or enteroarthritis (EA). In 8–36% of patients who underwent intestinal bypass surgery for obesity, polyarthralgia and sometimes arthritis has been reported to occur weeks or years following surgery, as a postoperative complication of this technique. Arthritis affected knee, wrist, ankle, shoulder and finger joints [61].

Inflammatory bowel disease (IBD) represents a good model for the pathological events that may predispose to the development of EA. EA may be diagnosed before, simultaneously or after the diagnosis of IBD, with a prevalence ranging between 17% and 39%. The main clinical features

are peripheral arthritis (women, 25–45 years old, asymmetric mono-oligoarthritis mostly in lower limbs, episodic and recurrent, frequent exacerbations) and axial arthritis (men, strongly association with HLA B27, early onset, and independent from IBD) [62]. The pathogenesis of EA has not been completely clarified; current hypotheses provide a possible relationship between inflammation of the gut mucosa and arthritis, supposing an aberrant migration of intestinal lymphocytes in genetically predisposed subjects. Other potential risk factors for EA are active bowel disease, family history of IBD and cigarette smoking. Other gastrointestinal diseases potentially developing EA are Whipple's disease and celiac disease [62]. Currently, "gold standard" criteria are not yet available. The diagnosis of EA is generally established on the basis of medical history and physical examination, according to the European Spondyloarthropathy Study Group (ESSG) criteria. In established disease, these clinical criteria have a sensitivity of 86% and a specificity of 87% and can be applicable without radiological examination and laboratory testing [62]. The treatment of EA requires different pharmacological therapies for both intestinal and joint disease. Corticosteroids are recommended for patients with mild exacerbations; cyclic intra-articular injections of steroids might have also beneficial effects. Sulfasalazine and 5-aminosalicylic acid can reduce mild peripheral arthritis, particularly in patients with ulcerative colitis, but have no effect on the evolution of joint damage; conversely, methotrexate, azathioprine, cyclosporine, and leflunomide can lead to a reduction of joint symptoms as well as laboratory parameters of disease activity [63]. The anti-TNFα, especially infliximab and adalimumab, are widely used to treat EA for their efficacy on both axial and peripheral symptoms of EA, especially in patients with Crohn's disease; Etanercept, instead, seems to be effective only to control joint symptoms but not the intestinal ones. Other non-pharmacological therapies for the treatment of EA might be probiotics, rest and physiokinesitherapy [64].

References

1. Seidner DL. Parenteral nutrition-associated metabolic bone disease. JPEN J Parenter Enteral Nutr. 2002;26(5 Suppl):S37–42.
2. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet. 2002;359(9321):1929–36.
3. Ferrone M, Geraci M. A review of the relationship between parenteral nutrition and metabolic bone disease. Nutr Clin Pract. 2007;22(3):329–39.
4. Pironi L, Labate AM, Pertkiewicz M, Przedlacki J, Tjellesen L, Staun M, De Francesco A, Gallenca P, Guglielmi FW, Van Gossum A, Orlandoni P, Contaldo F, Moreno Villares JM. Prevalence of bone disease in patients on home parenteral nutrition. Clin Nutr. 2002;21(4):289–96.
5. Staun M, Pironi L, Bozzetti F, Baxter J, Forbes A, Joly F, Jeppesen P, Moreno J, Hébuterne X, Pertkiewicz M, Mühlebach S, Shenkin A, Van Gossum A. ESPEN guidelines on parenteral nutrition: home parenteral nutrition (HPN) in adult patients. Clin Nutr. 2009;28(4):467–79.
6. Cohen-Solal M, Baudoin C, Joly F, Vahedi K, D'Aoust L, De Vernejoul MC, Messing B. Osteoporosis in patients on long-term home parenteral nutrition: a longitudinal study. J Bone Miner Res. 2003;18(11):1989–94.
7. Pironi L, Tjellesen L, De Francesco A, Pertkiewicz M, Morselli Labate AM, Staun M, Przedlacki J, Lezo A, Orlandoni P, Pasanisi F. ESPEN-home artificial nutrition working group. Bone mineral density in patients on home parenteral nutrition: a follow-up study. Clin Nutr. 2004;23(6):1288–302.
8. Raman M, Aghdassi E, Baun M, Yeung M, Fairholm L, Saqui O, Allard JP. Metabolic bone disease in patients receiving home parenteral nutrition: a Canadian study and review. JPEN J Parenter Enteral Nutr. 2006;30(6):492–6.
9. Nygaard L, Skallerup A, Olesen SS, Køhler M, Vinter-Jensen L, Kruse C, Vestergaard P, Rasmussen HH. Osteoporosis in patients with intestinal insufficiency and intestinal failure: prevalence and clinical risk factors. Clin Nutr. 2018;37(5):1654–60.
10. Haderslev KV, Jeppesen PB, Sorensen HA, Mortensen PB, Staun M. Vitamin D status and measurements of markers of bone metabolism in patients with small intestinal resection. Gut. 2003;52(5):653–8.
11. Foldes J, Rimon B, Muggia-Sullam M, Gimmon Z, Leitcher I, Steinberg R, Menczel J, Freund HR. Progressive bone loss during long-term home total parenteral nutrition. JPEN J Parenter Enteral Nutr. 1990;14(2):139–42.
12. Klein GL, Coburn JW. Parenteral nutrition: effect on bone and mineral homeostasis. Annu Rev Nutr. 1991;11:93–119.
13. Saitta JC, Ott SM, Sherrard DJ, Walden CE, Lipkin EW. Metabolic bone disease in adults receiving long-term parenteral nutrition: longitudinal study with regional densitometry and bone biopsy. JPEN J Parenter Enteral Nutr. 1993;17(3):214–9.
14. Cohen-Solal M, de Vernejoul MC. [Bone remodeling]. Therapie. 2003;58(5):391–3. Review.
15. Haderslev KV, Tjellesen L, Haderslev PH, Staun M. Assessment of the longitudinal changes in bone mineral density in patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2004;28(5):289–94.
16. Van Gossum A, Vahedi K, Abdel-Malik, Staun M, Pertkiewicz M, Shaffer J, Hebuterne X, Beau P, Guedon C, Schmit A, Tjellesen L, Messing B, Forbes A, ESPEN-HAN Working Group. Clinical, social and rehabilitation status of long-term home parenteral nutrition patients: results of a European multicentre survey. Clin Nutr. 2001;20(3):205–10.
17. Pironi L, Paganelli F, Labate AM, Merli C, Guidetti C, Spinucci G, Miglioli M. Safety and efficacy of home parenteral nutrition for chronic intestinal failure: a 16-year experience at a single Centre. Dig Liver Dis. 2003;35(5):314–24.
18. Shike M, Harrison JE, Sturtridge WC. Metabolic bone disease in patients receiving long-term total parenteral nutrition. Ann Intern Med. 1980;92(3):343–50.
19. Lipkin EW, Ott SM, Klein GL. Heterogeneity of bone histology in parenteral nutrition patients. Am J Clin Nutr. 1987;46(4):673–80.
20. Goodman WG, Misra S, Veldhuis JD, Portale AA, Wang HJ, Ament ME, Salusky IB. Altered diurnal regulation of blood ionized calcium and serum parathyroid hormone concentrations during parenteral nutrition. Am J Clin Nutr. 2000;71(2):560–8.
21. Klein GL, Targoff CM, Ament ME, Sherrard DJ, Bluestone R, Young JH, Norman AW, Coburn JW, et al. Bone disease associated with total parenteral nutrition. Lancet. 1980;2(8203):1041–4.
22. de Vernejoul MC, Messing B, Modrowski D, Bielakoff J, Buisine A, Miravet L. Multifactorial low remodelling bone disease during cyclic total parenteral nutrition. J Clin Endocrinol Metab. 1985;60(1):109–13.

23. Shike M, Shils ME, Heller A, Alcock N, Vigorita V, Brockman R, Holick MF, Lane J, Flombaum C. Bone disease in prolonged parenteral nutrition: osteopenia without mineralization defect. Am J Clin Nutr. 1986;44(1):89–98.
24. Pironi L, Zolezzi C, Ruggeri E, Paganelli F, Pizzoferrato A, Miglioli M. Bone turnover in short-term and long-term home parenteral nutrition for benign disease. Nutrition. 2000;16(4):272–7.
25. Verhage AH, Cheong WK, Allard JP, Jeejeebhoy KN. Increase in lumbar spine bone mineral content in patients on long-term parenteral nutrition without vitamin D supplementation. JPEN J Parenter Enteral Nutr. 1995;19(6):431–6.
26. Klein GL. Aluminum in parenteral solutions revisited-again. Am J Clin Nutr. 1995;61(3):449–56.
27. Ott SM, Maloney NA, Klein GL, Alfrey CA, Ament ME, Coburn JW, Sherrard DJ. Bone disease associated with total parenteral nutrition. Ann Intern Med. 1983;98(6):910–4.
28. Vargas JH, Klein GL, Ament ME, Ott SM, Sherrard DJ, Horst RL, Berquist WE, Alfrey AC, Slatopolsky E, Coburn JW. Metabolic bone disease of total parenteral nutrition: course after changing from casein to amino acids in parenteral solution with reduced aluminium content. Am J Clin Nutr. 1988;48(4):1070–8.
29. DeLuca HF. Vitamin D and the parenteral nutrition patient. Gastroenterology. 2009;137(5 Suppl):S79–91.
30. Compher C, Pazianas M, Benedict S, Brown JC, Kinosian BP, Hise M. Systemic inflammatory mediators and bone homeostasis in intestinal failure. JPEN J Parenter Enteral Nutr. 2007;31(2):142–7.
31. Thomson P, Duerksen DR. Vitamin D deficiency in patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2011;35(4):499–504. https://doi.org/10.1177/0148607110381269. Epub 2011 May 3.
32. Waldron JL, Ashby HL, Cornes MP, Bechervaise J, Razavi C, Thomas OL, Chugh S, Deshpande S, Ford C, Gama R. Vitamin D: a negative acute phase reactant. Clin Pathol. 2013;66:620–2.
33. Yang CJ, Duro D, Zurakowski D, Lee M, Jaksic T, Duggan C. High prevalence of multiple micronutrient deficiencies in children with intestinal failure: a longitudinal study. J Pediatr. 2011;159(1):39–44.
34. Kumar PR, Fenton TR, Shaheen AA, Raman M. Prevalence of vitamin D deficiency and response to oral vitamin D supplementation in patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2012;36(4):463–9.
35. Shike M, Sturtridge WC, Tam CS, Harrison JE, Jones G, Murray TM, Husdan H, Whitwell J, Wilson DR, Jeejeebhoy KN. A possible role of vitamin D in genesis of parenteral-nutrition-induced metabolic bone disease. Ann Intern Med. 1981;95(5):560–8.
36. Boncompain-Gérard M, Robert D, Fouque D, Hadj-Aïssa A. Renal function and urinary excretion of electrolytes in patients receiving cyclic parenteral nutrition. JPEN J Parenter Enteral Nutr. 2000;24(4):234–9.
37. Sloan GM, White DE, Murray MS, Brennan F. Calcium and phosphorus metabolism during total parenteral nutrition. Ann Surg. 1983;197(1):1–6.
38. Wood RJ, Sitrin MD, Cusson GJ, Rosenberg IH. Reduction of total parenteral nutrition-induced urinary calcium loss by increasing the phosphorus in the total parenteral nutrition prescription. JPEN J Parenter Enteral Nutr. 1986;10(2):188–90.
39. Berkelhammer C, Wood RJ, Sitrin M. Inorganic phosphorus reduces hypercalciuria during total parenteral nutrition by enhancing renal tubular calcium absorption. JPEN J Parenter Enteral Nutr. 1998;22(3):142–6.
40. Wood RJ, Bengoa JM, Sitrin MD, Rosenberg IH. Calciuretic effect of cyclic versus continuous total parenteral nutrition. Am J Clin Nutr. 1985;41(3):614–9.
41. Lipkin EW, Ott SM, Chesnut CH III, Chait A. Mineral loss in parenteral nutrition patients. Am J Clin Nutr. 1988;47(3):515–23.
42. Lipkin EW. A longitudinal study of calcium regulation in a non-human primate model of parenteral nutrition. Am J Clin Nutr. 1998;67(2):246–54.
43. Jeejeebhoy KN. Metabolic bone disease and total parenteral nutrition: a progress report. Am J Clin Nutr. 1998;67(2):186–7.
44. Boulétreau PH, Bost M, Fontanges E, Lauverjat M, Gutknecht C, Ecochard R, Delmas PD, Chambrier C. Fluoride exposure and bone status in patients with chronic intestinal failure who are receiving home parenteral nutrition. Am J Clin Nutr. 2006;83(6):1429–37.
45. Aljarallah B, Fernandes G, Jeejeebhoy KN, Gramlich LM, Whittaker JS, Armstrong D, Duerksen DR, Allard JP. The Canadian home total parenteral nutrition (HTPN) registry: vitamin K supplementation and bone mineral density. JPEN J Parenter Enteral Nutr. 2012;36(4):415–20.
46. Nielsen FH. Micronutrients in parenteral nutrition: boron, silicon, and fluoride. Gastroenterology. 2009;137(5 Suppl):S55–60.
47. Hise M, Compher C, Brown J. Inflammatory mediators and home parenteral nutrition. Nutr Clin Pract. 2008;23(1):42–8.
48. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, Joly F, Kelly D, Lal S, Staun M, Szczepanek K, Van Gossum A, Wanten G, Schneider SM, Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35(2):247–307.
49. WHO. Assessment of osteoporotic fracture risk and its role in screening for post-menopausal osteoporosis. WHO Technical Report Series. Geneva: WHO; 1994.
50. Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, Kochevar M, Shenkin A, Valentine CJ. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. Nutr Clin Pract. 2012;27(4):440–91.
51. Koutkia P, Lu Z, Chen TC, Holick MF. Treatment of vitamin D deficiency due to Crohn's disease with tanning bed ultraviolet B radiation. Gastroenterology. 2001;121(6):1485–8.
52. Pironi L, Cuerda C, Baxter J, Joly F, Szczepanek K, Gillanders L, Wanten G, Staun M. Survey on current practice of managing metabolic bone disease in patients on long-term home parenteral nutrition for benign chronic intestinal failure. Clin Nutr. 2014;33:S209.
53. Haderslev KV, Tjellesen L, Sorensen HA, Staun M. Effect of cyclical intravenous clodronate therapy on bone mineral density and markers of bone turnover in patients receiving home parenteral nutrition. Am J Clin Nutr. 2002;76(2):482–8.
54. D'Aoust L, Baudoin C, Joly F, Vahedi K, Cohen-Solal M, Messing B. Osteoporosis in patients under long term home parenteral nutrition: results of iv biphosphonate treatment. Clin Nutr. 2002;21(Suppl 1):51.
55. Pazianas M, Compher C, Schiavone-Gatto P, Kinosian BP. Intestinal failure-associated metabolic bone diseases and response to teriparatide. Nutr Clin Pract. 2006;21(6):605–9.
56. Tangpricha V, Luo M, Fernández-Estívariz C, Gu LH, Bazargan N, Klapproth JM, Sitaraman SV, Galloway JR, Leader LM, Ziegler TR. Growth hormone favourably affects bone turnover and bone mineral density in patients with short bowel syndrome undergoing intestinal rehabilitation. JPEN J Parenter Enteral Nutr. 2006;30(6):480–6.
57. Szczepanek K, Pedziwiatr M, Klek S. Denosumab improves bone mineral density in patients with intestinal failure receiving home parenteral nutrition: results from a randomized, controlled clinical trial. JPEN J Parenter Enteral Nutr. 2018;42(3):652–7.
58. Richette P, Ayoub G, Bardin T, Bouvet S, Orcel P, Badran AM. Hypomagnesemia and chondrocalcinosis in short bowel syndrome. J Rheumatol. 2005;32:2434–6.
59. Hahn M, Raithel M, Hagel A, Biermann T, Manger B. Chronic calcium pyrophosphate crystal inflammatory arthritis induced

by extreme hypomagnesemia in short bowel syndrome. BMC Gastroenterol. 2012;12:129.
60. Announ N, Guerne PA. [Diagnosis and treatment of calcium pyrophosphate crystal-induced arthropathy]. Z Rheumatol. 2007,66:573–574. , 576–578.
61. Rudwaleit M, Baeten D. Ankylosing spondylitis and bowel disease. Best Pract Res Clin Rheumatol. 2006;20:451–71.
62. Peluso R, Di Minno MN, Iervolino S, Manguso F, Tramontano G, Ambrosino P, Esposito C, Scalera A, Castiglione F, Scarpa R. Enteropathic spondyloarthritis: from diagnosis to treatment. Clin Dev Immunol. 2013;2013:631408.
63. Peluso R, Atteno M, Iervolino S, Bruner V, Caso F, Costa L, Raimondo M, Lofrano M, Manguso F, Scarpa R. Methotrexate in the treatment of peripheral arthritis in ulcerative colitis. Reumatismo. 2009;61(1):15–20.
64. Neumanand MG. Inflammatory bowel disease: role of diet, microbiota, life style. Transl Res. 2012;160(1):29–44.

Intestinal Adaptation

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Key Points

1. Intestinal adaptation involves behavioural (hyperphagia), structural (morphological or anatomical) and functional changes.
2. Due to the practical and ethical challenges in conducting clinical studies following massive small bowel resection current understanding of the adaptive response has mainly been derived from animal models. Animal studies usually involve a jejunal resection and rarely a jejunostomy, whereas in man an ileal ± colon resection is more common.
3. Patients with a jejunostomy show no jejunal structural or functional adaptation over time.
4. Patients with a jejunum in continuity with a colon usually undergo a functional adaptive response that may continue to occur for 2–3 years. There may be a degree of structural adaptation. The colon also adapts both structurally and functionally.
5. The mediators for adaptive changes include nutrition, intestinal secretions (especially pancreaticobiliary), gastrointestinal hormones and peptide growth factors (e.g. growth hormone, (GH), Insulin like growth factor-1 (IGF-1), glucagon-like peptide-2 (GLP-2), epidermal growth factor (EGF), peptide YY) and the gut microbiome.
6. Pharmacological approaches may be used to promote adaptation by enhancing intestinal growth and/or function; these include fibre (pectin), glutamine, short chain fatty acids (SCFAs), long-chain fatty acids (LCFAs), GH, glutamine, EGF, GLP-1 and 2 analogues and aminoguanidine.
7. Surgical approaches to resolve mechanical barriers and enhance gut function are aimed at optimising the gut environment and facilitate the adaptative response.

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Introduction

Intestinal adaptation is a physiological response following intestinal resection aimed at restoring the digestive and absorptive capacity of the remaining bowel to meet metabolic and growth requirements. Following intestinal resection, a number of mechanisms also contribute to malabsorption; such as gastric acid hypersecretion, impaired motility with rapid transit of intestinal content, bacterial overgrowth and excess water secretion when presented with an osmotic load [1]. The severity of malabsorption is influenced by the primary indication for intestinal resection, the residual length and segment of the remnant intestine [2]. For example, resection of the peptide YY producing distal ileum and proximal colon compromises the inhibitory function known as the "ileal and colonic brakes" that would normally delay gastric emptying, slow small intestine transit time and influence early satiety [3–6].

In an effort to compensate for the malabsorption due to the loss of intestinal length; altered diet a) and slowing of intestinal transit in occurs. The stomach and colon contribute to absorptive function that normally would be performed

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by the small intestine [7]. The remaining small intestine undergoes adaptation changes to recover absorptive and functional capacity. Intestinal adaptation involves a broad range of changes, including changes in behaviour (hyperphagia), morphologic (structural and ultrastructural) and functional changes in the residual bowel [8]. Evolving knowledge of the molecular mechanisms involved in regulating the adaptive response provides the opportunity to identify targets and novel therapies to stimulate and enhance the adaptive response.

Due to the practical and ethical challenges in conducting clinical studies following massive small bowel resection, current understanding of the physiology of the adaptive response has mainly been derived from animal models. Studies in rodent models have been used extensively for studies describing intestinal adaptation whereas the large animal models, such as the porcine model are considered to more accurately reflect human gastrointestinal physiology and nutrition. Differences in the age and maturation stage at time of resection may impact elements of the adaptive response and studies from neonatal and growing animals may more accurately reflect the response in infants and children.

Hyperphagia

An early clinical feature of adaptation is an increase in food intake (hyperphagia) that occurs in compensation for the macronutrient malabsorption. Hyperphagia is reported in 70% of adult SBS patients and is defined as an oral intake >1.5 times their resting energy requirements. Hyperphagia may indirectly contribute to the morphological and functional adaptation of the remnant bowel through the provision of luminal nutrients. The development of hyperphagia in SBS patients, particularly after colonic continuity is re-established (by re-anastomosis), is considered a good prognostic indicator. The mechanism controlling hyperphagia is not well understood. In rodents jejuno-colonic anastomosis has been associated with elevated levels of serum ghrelin and peptide YY [9]. Ghrelin promotes appetite while PYY suppresses it. In addition, the hypothalamic mRNA levels of orexigenic Neuropeptide Y (NPY) and Agouti-related peptide (AgRP) were noted to be markedly elevated following jejuno-colonic anastomosis in rodents, suggesting that the gut-brain axis is involved in intestinal adaptation. Similar serum changes of serum ghrelin and peptide YY were confirmed in humans with a jejuno-colonic anastomosis; and there was also a failure to suppress post-prandial ghrelin secretion [9].

Historically, weight loss to reduce nutritional requirement was hypothesized to be a compensatory mechanism following massive intestinal resection. With the widespread availability of parenteral nutrition support in patients with intestinal failure, weight loss post-surgical resection is no longer considered an acceptable clinical outcome.

Morphologic Adaptation

Stassoff is credited as being the first person to report small bowel 'hypertrophy' and increased absorption in the remaining small intestine of dogs after a large resection of small intestine [10]. After a predominantly jejunal resection in animals (some ileum and colon left intact), there is structural adaptation with dilatation and elongation of the remaining intestine (compensatory hypertrophy), and the villi become longer, crypts deepen and the cell number over a given length of villus increases (epithelial hyperplasia) [11–14], but the size of the enterocytes do not change. These changes are much more marked in an ileal compared to a jejunal remnant [12, 13].

The morphologic features of the adaptive response involve all layers of the bowel wall, including muscular hypertrophy (increased bowel diameter and thickness, increase in length), mucosal hyperplasia (increased cell proliferation resulting in deepening crypts and lengthening of the villi) and angiogenesis (new blood vessel development) (Fig. 1) [15]. There is also an increase in cellular DNA, RNA and protein content [16]. Early crypt proliferation is regulated by IFRD1 (Tis7) which is a transcriptional co-regulator that alters the transcription of target genes (including *cyclin D1* and hedgehog signalling pathway genes including *Gli1, Hhip, Gli2*) through interaction with the mSin3B complex and histone deacetylases [16, 17]. In Tis7−/− mice undergoing mid-small bowel resection, crypt cell proliferation was reduced at 72 h and this was associated with inhibition in the expression of the target genes [17]. Inhibition of expression of hedgehog signalling commences soon after resection and is maintained for up to 2 weeks following 50% small bowel resection in mice [18].

Morphologic adaptation commences 24–48 h after resection in mice with colon in continuity and is characterized by a rapid expansion of putative enterocyte stem cells at 48–72 h that continues for up to 7 days before returning to baseline by 6 weeks [19]. Concurrent with the expansion of the putative stem cell population in the crypts, gut epithelial secretory cells, including goblet cell and Paneth cell proliferation, continue for up to 28 days post-resection [20, 21]. Interestingly, the rate of enterocyte apoptosis is modestly increased and thought to maintain the crypt-villus axis in the presence of an increased enterocyte proliferation [22]. The colon also undergoes morphological and functional adaptation following small intestinal resection. In a mouse model of 60% jejunal ileal resection, colonic adaptation was observed with a twofold increase in colonic mass and crypt depth. These changes were observed despite the absence of enteral nutrition, indicating non-nutritive factors influence colonic adaptation [23]. In the piglet model, early and late features of the

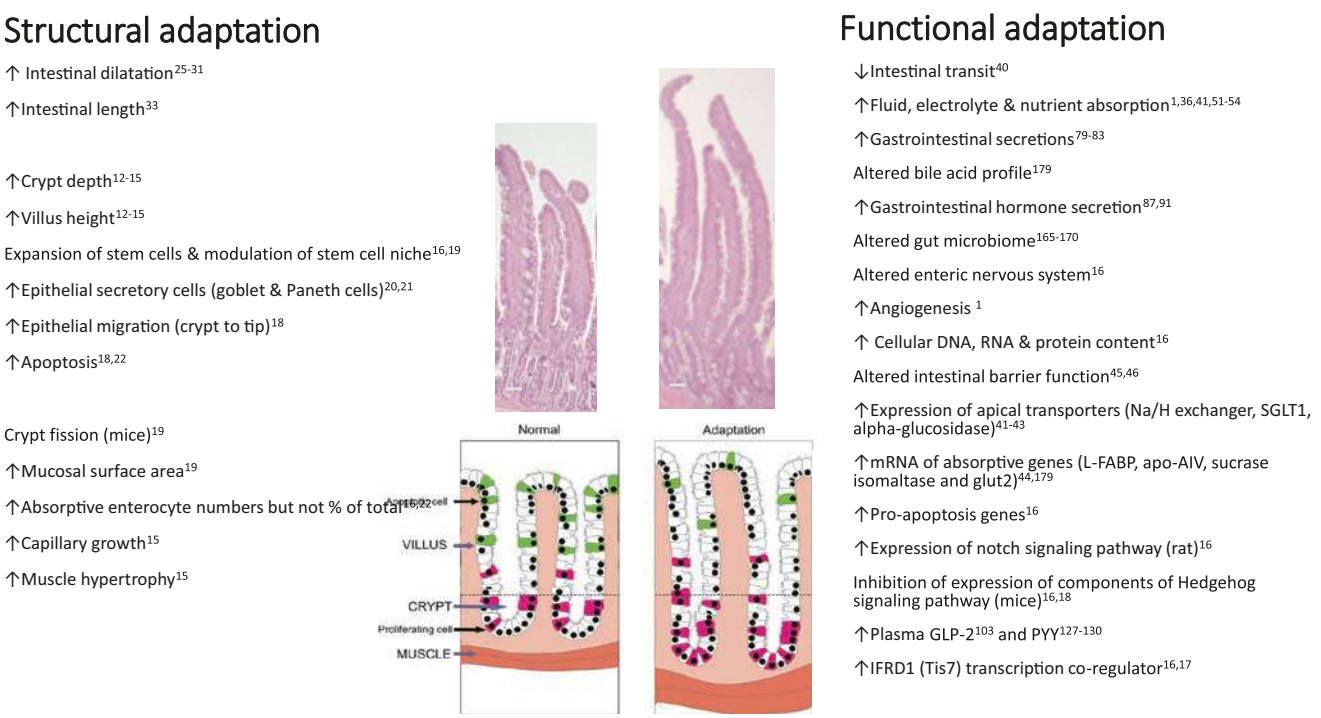

Fig. 1 Features of the adaptive response

adaptive response in the colon were reported, with early changes of increase enterocyte numbers and late changes of increase cell proliferation. Goblet cell and enteroendocrine cell numbers were continuously elevated at all time points of adaptation. Increased nutrient complexity enhanced colonic adaptation in this model [24].

In humans, various case reports have described dilatation of the stomach, duodenum, jejunum, ileum and colon after a massive small bowel resection [25–31]. However, there is a risk that some reports may reflect bowel dilatation proximal to an anastomotic stricture and not morphological adaptation. An increase in bowel length was reported in one case [25]; whereas another case report, with a carefully documented set of observations described over the 5 years from the original resection, demonstrated no change in residual bowel length [32]. This patient had a mesenteric infarction requiring resection leaving 105 cm of small intestine (95 cm jejunum and 10 cm terminal ileum) and a functioning colon remaining in situ. She subsequently had four caesarean sections over 5 years; on each occasion bowel length and diameter was measured [32]. There is also limited clinical data on the microscopic features of adaptation following resection, with the majority of data derived from paediatric studies. In 33 premature infants who underwent small intestinal resection for necrotising enterocolitis (NEC), there was a 32% and 22% increase in villus and crypt depth respectively from baseline, recorded at the time of small bowel stoma closure at a mean 74 days (range 61–90 days) after primary resection [33]. The change in villus height (in mainly ileum) correlated with length of small bowel resected. Similar observations have been observed in adults with enterocyte hyperplasia of 70–75% increase in villus height 2 years after jejuno-ileal bypass surgery in comparison to controls [34].

Colonic adaptation following small bowel resection in humans is poorly documented. Joly et al. studied the colon of 12 adult hyperphagic patients with jejuno-colonic SBS [35]. In patients with SBS compared to controls, the crypt depth and the number of cells per crypt were 35% and 22% higher respectively, resulting in increased absorptive surface [35]. There was no change to the apoptosis/proliferation ratio per crypt. This is the first convincing human study of colonic adaptation in SBS.

Patients with Jejunum–Colonic Anastomosis or Jejunostomy

In small and large animal models, adaptation in the duodenum and jejunum proximal to the site of a large small bowel resection has been observed, supporting a possible role for circulating growth factors in the adaptative response [1]. However, there is little data from human studies to suggest there is significant morphological adaptation in the jejunum of patients with residual jejunum anastomosed to a functioning colon. Two reports of jejunal biopsies from four patients with jejunum anastomosed to colon showed epithelial hyperplasia [36, 37], and a larger study of ten patients showed, not hyperplasia, but atrophy in most patients [38]. There is a lack of data on the impact of a proximal jejunal end-stoma on the adaptive response in animal models due to the practical challenges. No structural features of adaptation have been

observed in biopsies from the distal duodenal mucosa in patients with an established jejunostomy [39].

Functional Adaptation

The remaining intestine may also undergo adaptive changes to increase absorptive capacity of fluid, electrolyte and nutrients. A key measure of functional adaptation is an increase in the absorption of macro- and/or micro-nutrients over a given length of bowel that occurs over time or when compared with normal subjects. Functional adaptation may occur as a result of structural changes (such as an increase in enterocytes or enteroendocrine cells), a slowing of transit time or a range of intracellular events (e.g. increased transport and/or enzyme activity) (Fig. 1) [40]. However these changes are site specific and there is no clinical evidence that remaining jejunum acquires any of the specialized transport functions of the ileum (e.g. vitamin B_{12} or bile salt absorption).

The expression of over 60 proteins have been reported to change in response to massive small bowel resection in a piglet model [41]. Animal studies have demonstrated an increase expression of transporter proteins including the apical sodium glucose cotransporter (SGLT 1), NA+/H+ exchanger and Na+/K+ adenosine triphosphatases [41–43]. Fatty acid transporters L-FABP, FABP-6 and I-FABP are up regulated as early as 2 weeks post resection and gradually increase over 6 weeks in parallel with the increase in total villus area [44]. Serum bile acids and serum triglycerides were observed to increase with the changes in FABP. The upregulation of L-FABP, a known determinant of bile acid metabolism in the liver is speculated to be hepatoprotective against parenteral nutrition-associated liver disease. The increase in transporter function is consequent to both villus cell hyperplasia (e.g.: SGLT1) and functional adaptation on a per cell basis (e.g. enterocytes express increased digestive enzymes and transporters). The overall net result of these changes is to increase the digestive and absorptive capacity of the residual intestine [1, 41]. The translocation of luminal bacteria to mesenteric lymph nodes, blood, liver and spleen in animal resection models have been linked to abnormalities in intestinal barrier permeability [45]. Increased paracellular permeability occurring after small bowel resection has been linked to increased activation of toll-like receptor-4 in a mouse model [46].

Data describing the features of functional adaptation in humans is sparse and inconclusive. Glucose absorption in adults post-resection has been reported to be increased but these studies could not differentiate between increased absorptive capacity as a result of enterocyte proliferation, versus enhanced functional protein expression, or a combination of both. Whereas results of dipeptide and tripeptide transporters PepT1 expression in the human colon have been conflicting [35, 47]. Suffice to say, studies of intestinal adaptation in humans are limited for practical and ethical reasons, including the fact that massive intestinal resection is uncommon, patients are often critically ill and may have a variety of primary aetiologies resulting in the need for resection. Functional adaptation has been observed in children and adults post-resection if the ileum and/or colon are retained, as evidenced by achievement of intestinal autonomy in parenteral nutrition dependent patients, sometimes several years following resection [2, 48–51].

Patients with Jejunum–Colonic Anastomosis, Ileostomy or Jejunostomy

There is limited evidence for structural (morphological) adaptation in patients with a jejunostomy; however, there is evidence for functional adaptation in patients with jejunum anastomosed to a functioning colon and in patients with an ileostomy. In patients with jejunum in continuity with a functioning colon there is a small reduction in faecal weight in the 3 months following a small bowel resection [14]. There is also increased jejunal absorption of macronutrients, water, sodium, glucose and calcium with time [36, 51–54], associated with an increased chance of the patient being able to stop parenteral nutrition [51, 54, 55]. Patients who have an ileostomy following a colectomy (usually for ulcerative colitis) have a reduction in stomal output over the first 4 months after surgery [56–58]. This is not the case, however, when there has also been an ileal resection. In a study of patients who had an 'ileostomy' after an ileal resection, Hill et al. showed, that there was no decrease in ileostomy water, sodium and potassium losses over the period from 11 days to 6 months after the resection [58]. Nightingale et al. demonstrated no change in the nutritional or fluid requirements of patients with a jejunostomy from 6 to 24 months after their last resection [59]. Thus there is no clinical or experimental evidence for functional adaptation in jejunostomy patients.

Timing of Adaptive Changes

In animal models, features of the adaptive response are observed within hours following a surgical resection. In the rat, there is an increase in mucosal DNA synthesis within 24–36 h after a bowel resection. Villus epithelial hyperplasia, probably occurring as a result of increased crypt cell production rather than villus tip cell loss, is evident at 1–2 weeks and maximal at 1 month [13].

In 1959, Pullan described three clinical phases ("Extensive Mucosal Disease: Coeliac Disease and Eosinophilic Enteritis" chapter) after massive small bowel resection in patients with the colon remaining intact. Following the large fluid losses that occurs (phase 1), in phase 2 the emphasis shifts from fluid balance to nutritional support, and over the

next 12–24 months as diarrhoea improves, the amount of nutritional support can be reduced or even stopped. It is during this phase that most adaptation occurs. In phase 3 there is no further clinical improvement and no major adaptive changes occur [60].

While major adaptive changes are clinically evident within a few weeks in those with a retained colon, the full clinical benefits may take years to be complete. For example, intestinal calcium absorption may continue to increase for more than 2 years after the resection [54]. If parenteral nutrition is still required 2 years after a bowel resection, the chances of subsequently being able to wean from parenteral nutrition without additional intervention is limited (~6% of patients) [55]. Data from adults on home parenteral support suggests that no further changes in parenteral nutrition requirements occur after 3 years following resection [1]. Of 57 patients who have bowel continuity restored after a small bowel resection due to mesenteric infarction, 20 (35%) patients were successful weaned from PN within 1 year, 29 (50%) patients weaned within 2 years and 44 (77%) patients with 5 years suggesting that adaptation can continue to occur for up to 5 years in a favourable intestinal environment [51]. There is no reliable measure to determine who will successfully adapt or when maximum adaptation has occurred, although predictions can be made based on a range of clinical factors including age, underlying disease, the length and section of bowel remaining and other co-morbidities. There is currently no accurate biomarker to monitor the adaptative response. Plasma citrulline has been proposed as a useful clinical marker to assess changes in enterocyte cell mass. However the accuracy of plasma citrulline to monitor the progress of the clinical adaptive response remains controversial [61, 62].

Mediators of Intestinal Adaptation

The mediators of intestinal adaptation are multiple and contribute individually to overall intestinal adaptation. These include delivery of intraluminal nutrients, anatomic factors and gastrointestinal resections (Table 1). More recently, research and clinical advances have focussed predominantly on identifying trophic factors that successfully induce rapid adaptation and eventual enteral autonomy (Table 1).

Intraluminal Nutrients

The presence of food within the intestinal lumen ('luminal nutrition') is the most potent stimulus for intestinal epithelial cell proliferation [63]. In the absence of luminal nutrients mucosal atrophy and a decrease in digestive enzyme and transport function is observed. The mechanism whereby food induces adaptation is not entirely known, however, increased dietary complexity and some nutrients, including

Table 1 Factors influencing intestinal adaptation in humans

Factor	Structural adaptation	Functional adaptation
Patient related factors [1, 2, 6–8, 15]		
Age [33, 50]	Potential for >increase in length in young	
Underlying disease mechanism	↓with ongoing inflammation	↓with ongoing inflammation
Co-morbidities	↓with chronic pathology	↓chronic pathology
	↓with multisystem disease and/or specific drugs	↓with multisystem disease and/or specific drugs
Factors related to remaining intestine [1, 12, 13, 15]		
Site of resection/ segment remaining	Maximum adaptation requires presence of ileum	
Extent of resection	~100 cm of SI or 60 cm SI with residual colon needed to wean from PN	
Stoma present		
Jejunostomy [36–39, 50]	Nil significant	Nil significant
ICV absent [1]	↑risk of bacterial overgrowth	Loss of inhibition on gastric emptying and SI transit
Colon present [56–58]	↑crypt depth, ↑cells per crypt, ↑surface area	
Integrity of remaining intestine	↓with ongoing inflammation and disease	↓with ongoing inflammation and disease
Dysmotility [17, 25–31, 174–177]	Dilatation, ↑risk of bacterial overgrowth	
Nutritional factors [63–78]		
Composition (e.g. diet complexity, protein, short chain fatty acids, pectin, glutamine, long chain triglycerides)	Stimulation of intestinal growth	Stimulation of intestinal function
		Modification of intestinal transit
Nutritional status	Support mucosal integrity and repair	Maintain mucosal barrier function
Gastrointestinal secretions [79–84]		
Pancreatic [79, 80]	↑volume of secretions	
Biliary [98, 99, 173]	↑volume of secretions	Alteration in bile acid profile
Hormones and peptide growth factors		

(continued)

Table 1 (continued)

Factor	Structural adaptation	Functional adaptation
Growth hormone [131, 132]	Conflicting data	↑absorptive capacity (PN weaning)
IGF-1 [119–126]		?downstream effector of GLP-2
GLP-2 [85–106]	↑crypt cell proliferation, ↑villus height, ↑surface area	↑absorptive capacity (↓fluid and PN requirement)
		↑absorptive capacity
		↑Tolerance of enteral nutrition
Epidermal growth factor [110–116]		No change in intestinal permeability
Peptide YY [127–130]		↓gastric emptying, SI transit
		↓stimulated intestinal secretion
Gut microbiome		Production of short chain fatty acids
Dysbiosis [166–171]	?enterocyte turnover	Impairment of T-cell proliferation
		?alternation in enteric nervous system function and gut motility
		Microbial-derived metabolites potentially impact a range of functions

PN parenteral nutrition, *SI* small intestine

glutamine, pectin, short chain fatty acid (SCFA) and long chain fatty acids, have a specific trophic effect [64].

Glutamine, a non-essential α-amino acid has been studied extensively with mixed results [65]. Glutamine is the major substrate for mitochondrial in enterocytes with the majority of absorbed glutamine metabolized by the intestine. Glutamine has many functions in the intestine including modulating tight junction expression and inhibition of apoptosis [65–67]. Nevertheless, there is sparse evidence of glutamine supplementation improving adaptation, with lower enterocyte protein and DNA levels observed in participants treated with glutamine when compared to controls [68, 69].

Fats, especially long chain triglyceride, appear to promote intestinal adaptation [70, 71]. Whether polyunsaturated or saturated long chain fat is of greater benefit remain to be convincingly established. Studies of rats fed high polyunsaturated fatty acid showed greater increase in DNA, protein and mucosal weight [72]. While, two other studies of high saturated fat diet showed increase in the transport of glucose, increase villus height and crypt depth [73, 74]. Similarly, intravenous short chain fatty acids (SCFA) have been shown to enhance intestinal adaptation in rats [75, 76]. The tolerability of high fat diet in humans to allow for intestinal adaptation is limited by steatorrhea, especially in those with the colon in continuity. While the data for pectin derived SCFA did not achieve statistical significance for increased fluid absorption in the colon.

Colostrum, which is rich in growth factors (including EGF) and antibacterial peptides, enhanced adaptation in a piglet short bowel syndrome model but in a randomized cross-over study in nine children with short bowel syndrome was not associated with improved intestinal function [77, 78].

Intestinal Secretions

In addition to providing nutrition to the intestinal mucosa, feeding into the gut stimulates pancreatic secretions, stimulates factors essential for bile acid transport and gastrointestinal hormone secretion (i.e. glucagon like pepetide-2 (GLP-2)) and plays a key role in the intestinal adaptive response. In animal models of biliopancreatic bypass, the mucosa of the bypassed limb maintained normal morphology despite exposure only to bilio-pancreatic secretions [79]. The intensity of the adaptation in the bilio-pancreatic limb is markedly less in comparison to animals subjected to massive small bowel resection alone [80]. Sequential experiments introducing bile with or without pancreatic secretions highlighted the compounding effect of pancreatic secretions to intestinal adaptation [81]. Bile delivered to the ileum increased the adaptive hyperplasia of the ileum, regardless of pancreatic secretions. The addition of pancreatic secretions further augmented the adaptation process in the distal small bowel. Bile salt dependent lipase (BSDL) in pancreatic secretions has been identified to have proadaptive activities likely mediated by the Wnt signalling pathway in the enterocytes [82]. The presence of nutrients in the colon may be important in promoting small intestinal adaptation. A colonic infusion of glucose in rats caused jejunal adaptation as measured by an increase in the crypt cell production rate, mucosal wet weight, DNA and protein content per unit length of small intestine [83]. Based on this observation the authors postulated that plasma enteroglucagon is a colonic derived growth factor that stimulates small bowel growth [83]. The reduction of colonic carbohydrate fermentation induced by administration of metronidazole in rats was associated with decreased small intestinal adaptation [84].

Glucagon-Like Peptide-2

Glucagon-like peptide-2 GLP-2) is a 33 amino acid proglucagon derived peptide released by the enteroendocrine L cells located predominantly in the ileum and proximal colon

[85]. GLP-2 is released in response to stimulation by luminal nutrients such as glucose, fatty acids and dietary fibre [86]. The half-life of GLP2 is approximately 7 min before it is cleaved to the inactive GLP-2(3-33) by DPP-IV [87, 88]. The DPP-IV resistant GLP-2 analogue, Teduglutide has greater bioactivity because of the longer circulating half-life [89]. GLP-2 is also cleared by glomerular filtration [90].

The intestinotrophic effects of GLP-2 are both morphologic and functional. Administration of GLP-2 or its analogues induces crypt cell proliferation, villus hypertrophy and inhibits enterocyte apoptosis resulting in an increase of absorptive surface in both the small and large intestine of animals [91–94]. The functional gains following the administration of GLP-2 include increase glucose transport via activation of the SGLT-1 and GLUT-2 transporters, increase expression of numerous brush border digestive enzymes and facilitates the intestinal absorption of lipids and secretion of chylomicrons [92, 95]. In addition to the intestinal structural and functional changes, GLP-2 decreases gastric emptying and proximal gut motility, decreases intestinal permeability with enhanced tight junction protein expression and has local intestinal anti-inflammatory effects that are mediated via vasoactive intestinal polypeptide [96, 97]. GLP-2 treatment is associated with alterations in the hepatic expression of genes involved in bile acid synthesis at a transcriptional level, including an up regulation of Farnesoid X receptor (FXR), cytochrome P450, family 7, subfamily A, polypeptide 1 (CYP7A1), multidrug resistance-associated proteins 2 (MRP2) and MRP3 [98]. The differences in bile acid profile observed with GLP-2 treatment may explain the improvement of parenteral nutrition-associated cholestasis reported following treatment with GLP-2 [98, 99].

The intestinotrophic effects of GLP-2 are mediated via the Glucagon-like peptide-2 receptor (GLP-2R) mainly localized to the intestine, with limited expression in the central nervous system. The highest expression of GLP2R is in the jejunal, with expression in enteroendocrine cells, enteric neurons, subepithelial myofibroblasts, vagal afferents and colonic submucosal glia [100, 101]. The expression of GLP-2R in different cell compartments of the intestinal suggests that GLP-2 may act indirectly via multiple mediators [102].

In preclinical models, elevated GLP-2 levels were associated with adaptation, while immunoneutralization diminished morphological adaptation in rats with proximal intestinal resection [103, 104]. Conversely, the adaptive potential in distal intestinal resection is diminished in comparison to proximal resection, possibly due to removal of the ileum and a significant proportion of the intestinal L cell mass in the ileum [105]. While, chronic administration of exogenous GLP-2 in rats with proximal intestinal resection demonstrated increases in growth, digestive, and absorptive capacity and barrier function of the remnant intestine [106].

In adults and children, the exogenous administration of long acting GLP-2 (teduglutide) has been found to improve measures of intestinal growth and function. Twenty-four weeks of treatment with teduglutide resulted in a reduction (≥20%) in PN requirements in 63% of adults who had required 3 days or more per week of PN compared with 30% who received placebo ($p < 0.01$) [107]. Improvement was associated with an increase in small bowel villus height and total surface area in responders. Twelve months after cessation of teduglutide, 15 of 37 (40%) of patients required an increase in PN volume, 15 of 37 patients (40%) maintained the same PN volume and 7 patients had a further reduction in PN volume, including 3 patients who ceased PN (8%). In the post-hoc analysis of the phase 3 study of teduglutide in patients with short bowel syndrome, the greatest benefit on parenteral volume and nutrition was observed in patients with higher baseline requirements, including patients with a jejunostomy or ileostomy [108].

The early experiences with teduglutide treatment in children with short bowel syndrome associated intestinal failure have been encouraging [109]. Following 12 weeks of teduglutide administration in children, 3 of 15 subjects (20%) who received 0.05 mg/kg/day and 1 subject of 14 subjects (7%) who received 0.025 mg/kg/day developed independence from parenteral nutrition although 4 weeks after discontinuation of teduglutide 2 of the 4 subjects had resumed PN. At a dose of 0.05 mg/kg/day for 12 weeks, PN volume reduced a median of −1.3 L/week (−11.0, 1.0), and PN energy content of −17 (−45, 53) kcal/kg/day, while enteral energy intake increased by a median of 7 (−1, 63) kcal/kg/day. With more prolonged therapy with teduglutide, changes in PN volume observed at 12 weeks were maintained through to a total of 24 weeks treatment [109]. It remains unclear whether teduglutide has a role in augmenting early intestinal adaptation immediately following massive intestinal resection.

Epidermal Growth Factor

The epidermal growth factor (ECF) family of peptides include EGF, transforming growth factor-alpha (TGF-α), heparin binding growth factor (HB-EGF), neuregulin and neuregulin-2. The major sites of EGF synthesis are the salivary glands and kidney [110]. The normal small intestinal epithelium does not synthesize EGF except in duodenal Brunner's gland in response to injury. The main EGF receptor (EGFR) is present on the majority of epithelial and stromal cells, with EGFR expressed on the basolateral surface of enterocytes [110]. Activation of EGFR results in numerous downstream cellular signals involved in enterocyte proliferation and apoptosis, while selective inhibition of EFGR abrogates the adaptive response after massive intestinal resection [111, 112].

EGF therapy has been shown to promote morphological and functional intestinal adaptation in rodent models of SBS [113, 114]. Enteral EGF administration in the rat intestinal resection model increases villus height, crypt depth, attenuates enterocyte apoptosis and decrease permeability to macromolecules. In unresected piglets, EGF administration stimulated weight gain and reversed the weaning induced loss of glucose cotransporter SGLT1 [115]. EGF downstream signalling is important for the trophic effects of GLP-2 in the intestine. The collective information from experimental models of mutated EGFR mice, GLP-2R knockout or EFGR receptor inhibitors indicate EGF signalling is required for the trophic effects of GLP-2, although the exact mechanism remains to be fully elucidated [101, 116]. Interestingly, the combined administration of EGF and GLP-2 to neonatal piglets with short bowel syndrome resulted not only in the known trophic effects of the hormones, but also lengthening of the bowel, particularly in the absence of the ileum [117].

There is limited experience of EGF therapy in humans. In a study of 5 paediatric patients, enteral administration of EGF for 6 weeks resulted in improved both carbohydrate absorption and enteral energy intake but not weight gain [118].

Insulin-Like Growth Factor-I

Insulin like growth factor-1 (IGF-I) is secreted by many cells in the body, including the gastrointestinal tract. The circulating IGF-1 is predominantly synthesized by the liver and its secretion is regulated by growth hormone (GH), insulin and protein/caloric intake [119]. Unlike GLP-2, circulating IGF-I concentration doesn't increase following massive intestinal resection. The adaptive growth effects of IGF-I are thought to be pleiotropic as a result of its paracrine/autocrine and endocrine effects on the different compartments of the intestinal tract [120–123]. In transgenic mice with IGF-I over-expression in the myofibroblasts, a 50% increase in intestinal length was reported post-resection suggests that IGF-1 plays a role in intestinal lengthening post-resection [122]. Following exogenous administration of IGF-I an increase in intestinal wet weight, villus height and crypt depth in the jejunum and intestinal lengthening is observed [124].

It is suggested that IGF-I is a downstream effector of GLP-2 in the intestine based on data from IGF-I knock-out mice and IGF-I receptor null animals [125, 126]. In the IGF-I knock out mice, administration of GLP-2 failed to increase intestinal weight, morphometry or enterocyte proliferation [125]. Similarly, IGF-I receptor null mice did not exhibit increase crypt-cell proliferation following chronic exposure to GLP-2 [126].

Peptide YY

Peptide YY, like GLP-2, is produced by the L cells of the ileum and colon; it slows gastric emptying and small bowel transit and may be responsible for the 'ileal' and 'colonic' brakes [127]. At physiological doses in man, peptide YY increases small bowel transit time and reduces stimulated intestinal secretion [128]. Peptide YY serum levels are high in patients with a retained colon and low in patients with a jejunostomy, thus it may be responsible for part of the functional adaptation that occurs in patients with a retained colon [3]. It is unlikely to be responsible for any structural changes as it does not induce gut growth in rats fed only with parenteral nutrition [129, 130].

Growth Hormone

Growth hormone (GH) is a polypeptide produced by the somatotroph cells of the anterior pituitary gland. GH secretion from the pituitary is under neural control from the hypothalamus via growth hormone releasing hormone (GHRH), somatostatin and ghrelin [131]. Negative feedback on GH secretion is exerted by IGF-1 and by GH levels. IGF-1 inhibits GH secretion by influencing GHRH and somatostatin production in the hypothalamus. GH acts via the GH receptor (GHR) in its target cells and stimulates IGF-1 production locally. In the intestine, GHR is localized throughout the intestinal epithelium, lamina propria, muscularis mucosa, submucosa and muscularis propria, indicating the potential for GH therapy within the intestine [132].

Results from preclinical animal experiments of GH therapy following massive intestinal resection have been conflicting. Early data from GH deficient and hypophysectomy rats demonstrated impaired intestinal adaptation while GH supplementation normalised this process [133–135]. Data from a number of animal models of GH supplementation in short bowel have demonstrated trophic effects, including an increase in jejunal-ileal length, villus height, ileal cell proliferation and ileal villus height [136–138]. Conversely, other studies did not demonstrate GH-induced morphologic adaptation in rats [139, 140]. Although the evidence to support structural adaptation following GH treatment is conflicting, GH has been shown to increase the functional capacity of the residual intestine. The administration of GH in animal models resulted in significant increases of brush border transport of glutamine and leucine, increase glucose transport across ileal mucosa, and stimulated sucrase and maltase activity in the small intestine [141, 142].

The clinical experience of GH supplementation with or without glutamine in human intestinal failure is probably of historical interest especially in the current era of alternate intestinotrophic therapeutic options. Initial data from non-randomized controlled studies were encouraging with a

modest reduction in PN requirement in a third of patients with about 50% of subjects eventually weaning from PN [143–146]. However, randomized controlled double blind cross-over studies of GH therapy with or without glutamine supplementation, albeit with small sample sizes, demonstrable no improvement in absorptive capacity of the residual intestine [147–150].

Other Potential Mediators of Intestinal Adaptation

Keratinocyte growth factor (KGF), also known as FGF7, is a potent mitogen and exerts its effects via the FGF receptor 2 which is expressed by various types of epithelial cells, including the intestinal epithelium [151]. KGF expression is strongly upregulated following acute and chronic injury. In animal models of massive intestinal resection, KGF administration augmented small intestinal growth, including mucosal thickening, villus length and modestly increased both small intestinal and colonic crypt depth [152]. KGF administration also improves the functional indices of adaptation such as basic ionic transport, alanine and glucose absorption [153, 154].

Other potential trophic mediators that have been studied include vasoactive intestinal peptide (VIP), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF) and oral insulin [155–158]. Both VIP and VEGF have been identified to be downstream mediators of GLP-2 function, therefore upstream GLP-2 administration possibly provides adequate stimulation of both VIP and VEGF pathways for intestinal adaptation [155, 156]. Oral insulin has been studied in a small human trial involving ten paediatric subjects [159]. Although two infants were weaned of PN, the role of oral insulin remains uncertain complicated by the significant degradation of insulin in the stomach.

There is limited data of R-spondin1 in short bowel syndrome. However, it is a peptide of interest because of its potent and specific proliferative effects on intestinal crypt cells mediated via the wnt signalling pathway [160]. In vivo experiments using exogenous administered R-spondin1 lead to expansion of many intestinal parameters including small intestinal diameter, weight, crypt density and intestinal stem cell numbers [161]. In rats with induced colitis, exogenous R-spondin1 administration ameliorated the intestinal inflammation while preserving the mucosa integrity in both small and large bowel by stimulating epithelial cell mitosis [162].

Aminoguanidine

Within the epithelial cell, ornithine is converted by ornithine decarboxylase to polyamines (putrescine, spermidine and spermine) which are responsible for inducing epithelial hyperplasia [163]. The concentration of polyamines in jejunostomy fluid increases with refeeding [164]. It is postulated that this occurs in response to the presence of nutrients, increased mucosal blood flow, a neural or a humoral response [164]. Aminoguanidine, which inhibits diamine oxidase and reduces polyamine breakdown, has been used successfully in animals to induce epithelial hyperplasia and increased nutrient absorption [165].

Intestinal Microbiome

The gut microbiome contributes a wide range of metabolic and biochemical activities that support the host to digest, absorb, metabolise and excrete nutrients. Following massive intestinal resection, the intestinal microbiome changes in response to the new luminal environment [166]. Independent of the surgery, multiple factors contribute to the change in the microbiome including stress response, use of antibiotics, fasting and exposure of the intestinal lumen to oxygen. Experimental models have shown intestinal resection reduces the diversity of the microbiome in the remnant bowel, specifically a predominance of gram-positive *Firmicutes* phyla and a decrease of *Bacteroides* [167, 168]. Gnotobiotic animal models have smaller intestinal crypts, lower proliferation index but taller villi post intestinal resection [169, 170]. Following the introduction of microbes into gnotobiotic mice, there was an increase in both crypt depth and enterocyte proliferation. Microbiota induced inflammation was associated with significantly deeper crypts, taller villi and proliferation index in interleukin-10 deficient mice, while genes involved with adaptive and innate immunity were up-regulated following intestinal resection in zebrafish [169, 171]. These observations suggest a possible synergistic effect between the immune system, microbiota and intestinal adaptation.

Metabolites generated from the breakdown of luminal nutrients by intestinal bacteria play an important role in intestinal adaptation. Short chain fatty acid (SCFA), the most studied metabolite of commensal colonic bacteria fermentation has been shown to improve adaptation in the small and large bowel, enhance intestinal barrier function and modulate energy salvage [75, 76, 172]. Specifically, butyrate appears to be the main SCFA responsible for the increase structural and functional changes in the early adaptation [173].

Intestinal Maladaptation

The goal of intestinal adaptation following massive intestinal loss is the eventual return of enteral homeostasis. Clinically this is reflected in the successful transition from the state of

intestinal failure necessitating parenteral nutrition support, to enteral insufficiency and subsequently enteral autonomy. As described above, the process of adaptation involves a complex series of structural, functional and molecular responses. However, there may be unexpected consequences of the adaptive process. Segments of dilated intestine tend to have poorer motility [174]. The severity of the dysmotility is variable ranging from mild to functional obstruction; and is frequently proportional to the length, extent and site of the dilated loop of intestine [175]. Generally marked dilatation of a proximal bowel loop presents with feeding intolerance and vomiting; whereas, a distal distended bowel segment often is associated with lower gastrointestinal symptoms such as diarrhoea. While stasis of intestinal content promotes the likelihood of small intestinal bacteria overgrowth or dysbiosis with its antecedent complications of worsening diarrhoea, D-lactic acidosis and increase risk of bacteria translocation [176–178]. Intestinal microbiome dysbiosis results in significant bile acid dysmetabolism which may contribute to the observed disturbance in FXR-mediated pathways in the gut and liver. It is postulated that this may play an important role in the development of Intestinal Failure-Associated Liver Disease [179]. It remains unclear whether short bowel syndrome with its associated adaptive response and complications is an independent risk factor for the development of gastrointestinal malignancy.

References

1. Tappenden KA. Intestinal adaptation following resection. JPEN J Parenter Enteral Nutr. 2014;38(1 Suppl):23S–31S.
2. Jeppesen PB. Spectrum of short bowel syndrome in adults: intestinal insufficiency to intestinal failure. JPEN J Parenter Enteral Nutr. 2014;38(1 Suppl):8S–13S.
3. Nightingale JM, Kamm MA, van der Sijp JR, Ghatei MA, Bloom SR, Lennard-Jones JE. Gastrointestinal hormones in short bowel syndrome. Peptide YY may be the 'colonic brake' to gastric emptying. Gut. 1996;39(2):267–72.
4. Pironi L, Stanghellini V, Miglioli M, Corinaldesi R, De Giorgio R, Ruggeri E, Tosetti C, Poggioli G, Morselli Labate AM, Monetti N, et al. Fat-induced ileal brake in humans: a dose-dependent phenomenon correlated to the plasma levels of peptide YY. Gastroenterology. 1993;105(3):733–9.
5. Van Citters GW, Lin HC. Ileal brake: neuropeptidergic control of intestinal transit. Curr Gastroenterol Rep. 2006;8(5):367–73.
6. van Avesaat M, Troost FJ, Ripken D, Hendriks HF, Masclee AA. Ileal brake activation: macronutrient-specific effects on eating behaviour? Int J Obes (Lond). 2015;39(2):235–43.
7. Williamson RCN, Chir M. Intestinal adaptation. N Engl J Med. 1978;298:1393–402. 1444–1450.
8. Goodlad R, Nightingale J, Playford R. Intestinal adaptation. In: Nightingale JMD, editor. Intestinal failure. Cambridge: Greenwich Medical Media Limited; 2001. P 243-260141-152.
9. Gillard L, Billiauws L, Stan-Iuga B, Ribeiro-Parenti L, Jarry AC, Cavin JB, Cluzeaud F, Mayeur C, Thomas M, Freund JN, Lacorte JM, Le Gall M, Bado A, Joly F, Le Beyec J. Enhanced ghrelin levels and hypothalamic orexigenic AgRP and NPY neuropeptide expression in models of jejuno-colonic short bowel syndrome. Sci Rep. 2016;21(6):28345.
10. Stassoff B. Experimentelle Untersuchungen uber die Kompensatorischen Vorgange bei Darmresektionen. Beitr Klin Chir. 1914;89:527–86.
11. Flint JM. The effect of extensive resections of the small intestine. Bull Johns Hopkins Hosp. 1912;23:127–44.
12. Nygaard K. Resection of the small intestine in rats. III. Morphological changes in the intestinal tract. Acta Chir Scand. 1967;133:233–348.
13. Dowling RH, Booth CC. Structural and functional changes following small intestinal resection in the rat. Clin Sci. 1967;32:139–49.
14. Weser E, Hernandez MH. Studies of small bowel adaptation after intestinal resection in the rat. Gastroenterology. 1971;60:69–75.
15. Tappenden KA. Pathophysiology of short bowel syndrome: considerations of resected and residual anatomy. JPEN J Parenter Enteral Nutr. 2014;38(1 Suppl):14S–22S.
16. Rubin DC, Levin MS. Mechanisms of intestinal adaptation. Best Pract Res Clin Gastroenterol. 2016;30:237–48.
17. Yu C, Jiang S, Coughlin CC, Wang Y, Swietlicki EA, Wang L, Vietir I, Huber LA, Cikes D, Coleman T, Xie Y, Semenkovich CF, Davidson NO, Levin MS, Rubin DC. Deletion of Tis7 protects mice from high-fat diet-induced weight gain and blunts the intestinal adaptive response postresection. J Nutr. 2010;140(11):1907–14.
18. Tang Y, Swietlicki EA, Jiang S, Buhman KK, Davidson NO, Burkly LC, Levin MS, Rubin DC. Increased apoptosis and accelerated epithelial migration following inhibition of hedgehog signaling in adaptive small bowel postresection. Am J Physiol Gastrointest Liver Physiol. 2006;290:G1280–8.
19. Dekaney CM, Fong JJ, Rigby RJ, Lund PK, Henning SJ, Helmrath MA. Expansion of intestinal stem cells associated with long-term adaptation following ileocecal resection in mice. Am J Physiol Gastrointest Liver Physiol. 2007;293(5):G1013–22.
20. Jarboe MD, Juno RJ, Stehr W, Bernal NP, Profitt S, Erwin CR, Warner BW. Epidermal growth factor receptor signaling regulates goblet cell production after small bowel resection. J Pediatr Surg. 2005;40(1):92–7.
21. Helmrath MA, Fong JJ, Dekaney CM, Henning SJ. Rapid expansion of intestinal secretory lineages following a massive small bowel resection in mice. Am J Physiol Gastrointest Liver Physiol. 2007;292(1):G215–22.
22. Helmrath MA, Erwin CR, Shin CE, Warner BW. Enterocyte apoptosis is increased following small bowel resection. J Gastrointest Surg. 1998;2(1):44–9.
23. Gillingham MB, Dahly EM, Carey HV, Clark MD, Kritsch KR, Ney DM. Differential jejunal and colonic adaptation due to resection and IGF-I in parenterally fed rats. Am J Physiol Gastrointest Liver Physiol. 2000;278(5):G700–9.
24. Healey KL, Bines JE, Thomas SL, Wilson G, Taylor RG, Sourial M, Pereira-Fantini PM. Morphological and functional changes in the colon after massive small bowel resection. J Pediatr Surg. 2010;45(8):1581–90.
25. McClenahan JE, Fisher B. Physiologic effect of massive small intestinal resection and colectomy. Am J Surg. 1950;79:684–8.
26. Martin JR, Patee CJ, Gardener C, Marien B. Massive resection of the small intestine. Can Med Assoc J. 1953;69:429–33.
27. Trafford HS. The outlook after massive resection of small intestine, with a report of two cases. Br J Surg. 1956;44:10–3.
28. Clayton BE, Cotton DA. A study of malabsorption after resection of the entire jejunum and proximal half of the ileum. Gut. 1961;2:18–22.
29. Meyer HW. Sixteen-year survival following extensive resection of small and large intestine for thrombosis of the superior mesenteric artery. Surgery. 1961;51:755–9.

30. Kinney JM, Goldwyn RM, Barr JS Jr, Moore FD. Loss of the entire jejunum and ileum, and the ascending colon: management of a patient. JAMA. 1962;179:529–32.
31. Anderson CM. Long-term survival with six inches of small intestine. Br Med J. 1965;1:419–22.
32. Butler DB. Compensatory mechanisms following massive small bowel resection for intestinal volvulus. Surg Gynecol Obstet. 1959;109:479–81.
33. McDuffie LA, Bucher BT, Erwin CR, Wakeman D, White FV, Warner BW. Intestinal adaptation after small bowel resection in human infants. J Pediatr Surg. 2011;46(6):1045–51.
34. Doldi SB. Intestinal adaptation following jejuno-ileal bypass. Clin Nutr. 1991;10(3):138–45.
35. Joly F, Mayeur C, Messing B, Lavergne-Slove A, Cazals-Hatem D, Noordine ML, Cherbuy C, Duée PH, Thomas M. Morphological adaptation with preserved proliferation/transporter content in the colon of patients with short bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2009;297(1):G116–23.
36. Porus RL. Epithelial hyperplasia following massive small bowel resection in man. Gastroenterology. 1965;48:753–9.
37. Weinstein LD, Shoemaker CP, Hersh T, Wright HK. Enhanced intestinal absorption after small bowel resection in man. Arch Surg. 1969;99:560–2.
38. De Francesco A, Malfi G, Delsedime L, et al. Histological findings regarding jejunal mucosa in short bowel syndrome. Transplant Proc. 1994;26:1455–6.
39. O'Keefe SJD, Haymond MW, Bennet WM, Oswald B, Nelson DK, Shorter RG. Long-acting somatostatin analogue therapy and protein metabolism in patients with jejunostomies. Gastroenterology. 1994;107:379–88.
40. Bury KD. Carbohydrate digestion and absorption after massive resection of the small intestine. Surg Gynecol Obstet. 1972;135:177–87.
41. Sigalet DL, Martin GR. Mechanisms underlying intestinal adaptation after massive intestinal resection in the rat. J Pediatr Surg. 1998;33(6):889–92.
42. Hines OJ, Bilchik AJ, McFadden DW, Skotzko MJ, Whang EE, Zinner MJ, Ashley SW. Up-regulation of Na+, K+ adenosine triphosphatase after massive intestinal resection. Surgery. 1994;116(2):401–7; discussion 408.
43. Hines OJ, Bilchik AJ, Zinner MJ, Skotzko MJ, Moser AJ, McFadden DW, Ashley SW. Adaptation of the Na+/glucose cotransporter following intestinal resection. J Surg Res. 1994;57(1):22–7.
44. Stephens AN, Pereira-Fantini PM, Wilson G, Taylor RG, Rainczuk A, Meehan KL, Sourial M, Fuller PJ, Stanton PG, Robertson DM, Bines JE. Proteomic analysis of the intestinal adaptation response reveals altered expression of fatty acid binding proteins following massive small bowel resection. J Proteome Res. 2010;9(3):1437–49.
45. Ghosh SS, Wang J, Yannie PJ, Ghosh S. Intestinal barrier dysfunction, LPS translocation, and disease development. J Endocr Soc. 2020;4(2):1–15.
46. Courtney CM, Onufer EJ, McDonald KG, Steinberger AE, Sescleifer AM, Seiler KM, Tecos ME, Newberry RD, Warner BW. Small bowel resection increases paracellular gut barrier permeability via alterations of tight junction complexes mediated by intestinal TLR4. J Surg Res. 2021;258:73–81.
47. Ziegler TR, Fernández-Estívariz C, Gu LH, Bazargan N, Umeakunne K, Wallace TM, Diaz EE, Rosado KE, Pascal RR, Galloway JR, Wilcox JN, Leader LM. Distribution of the H+/peptide transporter PepT1 in human intestine: up-regulated expression in the colonic mucosa of patients with short-bowel syndrome. Am J Clin Nutr. 2002;75(5):922–30.
48. Messing B, Crenn P, Beau P, Boutron MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition-dependency of adult patients with nonmalignant short bowel. Transplant Proc. 1998;30(6):25–48.
49. Squires RH, Duggan C, Teitelbaum DH, Wales PW, Balint J, Venick R, Rhee S, Sudan D, Mercer D, Martinez JA, Carter BA, Soden J, Horslen S, Rudolph JA, Kocoshis S, Superina R, Lawlor S, Haller T, Kurs-Lasky M, Belle SH, Pediatric Intestinal Failure Consortium. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. J Pediatr. 2012;161(4):723–8.e2.
50. Khan FA, Squires RH, Litman HJ, Balint J, Carter BA, Fisher JG, Horslen SP, Jaksic T, Kocoshis S, Martinez JA, Mercer D, Rhee S, Rudolph JA, Soden J, Sudan D, Superina RA, Teitelbaum DH, Venick R, Wales PW, Duggan C, Pediatric Intestinal Failure Consortium. Predictors of enteral autonomy in children with intestinal failure: a multicenter cohort study. J Pediatr. 2015;167(1):29–34.e1.
51. Adaba F, Rajendran A, Patel A, Cheung YK, Grant K, Vaizey CJ, Gabe SM, Warusavitarne J, Nightingale JM. Mesenteric infarction: clinical outcomes after restoration of bowel continuity. Ann Surg. 2015;262:1059–64.
52. Althausen TL, Doig RK, Uyeyama K, Weiden S. Digestion and absorption after massive resection of the small intestine. II. Recovery of the absorptive function as shown by intestinal absorption tests in two patients and a consideration of compensatory mechanisms. Gastroenterology. 1950;16:126–34.
53. Dowling RH, Booth CC. Functional compensation after small bowel resection in man: demonstration by direct measurement. Lancet. 1966;ii:146–7.
54. Gouttebel MC, Saint Aubert B, Colette C, Astre C, Monnier LH, Joyeux H. Intestinal adaptation in patients with short bowel syndrome. Measurement by calcium absorption. Dig Dis Sci. 1989;34:709–15.
55. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud J-C, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology. 1999;117:1043–50.
56. LeVeen HH, Lyons A, Becker E. Physiologic adaptation to ileostomy. Am J Surg. 1962;103:35–41.
57. Wright HK, Cleveland JC, Tilson MD, Herskovic T. Morphology and absorptive capacity of the ileum after ileostomy in man. Am J Surg. 1969;117:242–5.
58. Hill GL, Mair WSJ, Goligher JC. Impairment of 'ileostomy adaptation' in patients after ileal resection. Gut. 1974;15:982–7.
59. Nightingale JMD, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces the need for parenteral therapy, increases the incidence of renal stones but does not change the high prevalence of gallstones in patients with a short bowel. Gut. 1992;33:1493–7.
60. Pullan JM. Massive intestinal resection. Proc R Soc Med. 1959;52:31–7.
61. Nightingale JMD, Woodward J, Small bowel/Nutrition Committee of BSG. Guidelines for the management of patients with a short bowel. Gut. 2006;55(Suppl IV):iv1–12.
62. Lansing M, Turner JM, Wizzard P, Lavallee CM, Lim DW, Muto M, Nation PN, Pencharz PB, Ball RO, Wales PW. Plasma citrulline in not a biomarker for intestinal adaptation in short bowel syndrome, studied in piglets: a model for human neonates. Pediatr Surg Int. 2019;35:657–63.
63. Levine GM, Deren JD, Yezdimir E. Small bowel resection: oral intake is the stimulus for hyperplasia. Dig Dis. 1976;21:542–6.
64. Bines JE, Taylor RG, Justice F, Paris MC, Sourial M, Nagy E, Emselle S, Catto-Smith AG, Fuller PJ. Influence of diet complexity on intestinal adaptation following massive small bowel resection in a preclinical model. J Gastroenterol Hepatol. 2002;17(11):1170–9.

65. Kim MH, Kim H. The roles of glutamine in the intestine and its implication in intestinal diseases. Int J Mol Sci. 2017;18(5):pii: E1051.
66. Wang B, Wu Z, Ji Y, Sun K, Dai Z, Wu G. L-glutamine enhances tight junction integrity by activating CaMK kinase 2-AMP-activated protein kinase signaling in intestinal porcine epithelial cells. J Nutr. 2016;146(3):501–8.
67. Liu N, Ma X, Luo X, Zhang Y, He Y, Dai Z, Yang Y, Wu G, Wu Z. l-glutamine attenuates apoptosis in porcine enterocytes by regulating glutathione-related redox homeostasis. J Nutr. 2018;148(4):526–34.
68. Neves Jde S, Aguilar-Nascimento JE, Gomes-da-Silva MH, Cavalcanti RN, Bicudo AS, Nascimento M, Nochi RJ Jr. Glutamine alone or combined with short-chain fatty acids fails to enhance gut adaptation after massive enterectomy in rats. Acta Cir Bras. 2006;21(Suppl 4):2–7.
69. Vanderhoof JA, Blackwood DJ, Mohammadpour H, Park JH. Effects of oral supplementation of glutamine on small intestinal mucosal mass following resection. J Am Coll Nutr. 1992;11(2):223–7.
70. Sukhotnik I, Mor-Vaknin N, Drongowski RA, Miselevich I, Coran AG, Harmon CM. Effect of dietary fat on early morphological intestinal adaptation in a rat with short bowel syndrome. Pediatr Surg Int. 2004;20(6):419–24.
71. Chen WJ, Yang CL, Lai HS, Chen KM. Effects of lipids on intestinal adaptation following 60% resection in rats. J Surg Res. 1995;58(3):253–9.
72. Kollman KA, Lien EL, Vanderhoof JA. Dietary lipids influence intestinal adaptation after massive bowel resection. J Pediatr Gastroenterol Nutr. 1999;28(1):41–5.
73. Keelan M, Cheeseman CI, Clandinin MT, Thomson AB. Intestinal morphology and transport after ileal resection in rat is modified by dietary fatty acids. Clin Invest Med. 1996;19(2):63–70.
74. Sukhotnik I, Hayari L, Bashenko Y, Chemodanov E, Mogilner J, Shamir R, Bar Yosef F, Shaoul R, Coran AG. Dietary palmitic acid modulates intestinal re-growth after massive small bowel resection in a rat. Pediatr Surg Int. 2008;24(12):1313–21.
75. Tappenden KA, Thomson AB, Wild GE, McBurney MI. Short-chain fatty acid-supplemented total parenteral nutrition enhances functional adaptation to intestinal resection in rats. Gastroenterology. 1997;112(3):792–802.
76. Koruda MJ, Rolandelli RH, Settle RG, Zimmaro DM, Rombeau JL. Effect of parenteral nutrition supplemented with short-chain fatty acids on adaptation to massive small bowel resection. Gastroenterology. 1988;95(3):715–20.
77. Nagy ES, Paris MC, Taylor RG, Fuller PJ, Sourial M, Justice F, Bines JE. Colostrum protein concentrate enhances intestinal adaptation after massive small bowel resection in juvenile pigs. J Pediatr Gastroenterol Nutr. 2004;39(5):487–92.
78. Aunsholt L, Jeppensen PB, Lund P, Sangild PT, Ifaoui IBR, Qvist N, Husby S. Bovine colostrum to children with short bowel syndrome: a randomized, double-blind, crossover pilot study. JPEN. 2014;38(1):99–106.
79. Evrard S, Aprahamian M, Hoeltzel A, Vasilescu M, Marescaux J, Damgé C. Trophic and enzymatic adaptation of the intestine to biliopancreatic bypass in the rat. Int J Obes Relat Metab Disord. 1993;17(9):541–7.
80. Martínez Moreno JM, Reyes-Ortiz A, Lage Sánchez JM, Sánchez-Gallegos P, Garcia-Caballero M. Timeline of intestinal adaptation after malabsortive surgery: effect of luminal nutrients, biliopancreatic secretion, and glutamine supplementation. Obes Surg. 2017;27(12):3133–41.
81. Terpstra OT, Dahl EP, Shellito PC, Malt RA. Predominant role of bile in modulation of early postresectional enteric hyperplasia. Arch Surg. 1981;116(6):800–2.
82. Yang Y, Zheng T, Zhou J, Song H, Cai W, Qian L. Bile salt dependent lipase promotes intestinal adaptation in rats with massive small bowel resection. Biosci Rep. 2018;38(3):BSR20180077.
83. Miazza BM. Hyperenteroglucagonaemia and small intestinal mucosal growth after colonic perfusion of glucose in rats. Gut. 1985;26:518–24.
84. Aghdassi E, Plapler H, Kurian R, et al. Colonic fermentation and nutritional recovery in rats with massive small bowel resection. Gastroenterology. 1994;107:637–42.
85. Amato A, Baldassano S, Mulè F. GLP2: an underestimated signal for improving glycaemic control and insulin sensitivity. J Endocrinol. 2016;229(2):R57–66.
86. Brubaker PL. The glucagon-like peptides: pleiotropic regulators of nutrient homeostasis. Ann N Y Acad Sci. 2006;1070:10–26.
87. Hartmann B, Johnsen AH, Orskov C, Adelhorst K, Thim L, Holst JJ. Structure, measurement, and secretion of human glucagon-like peptide-2. Peptides. 2000;21(1):73–80.
88. Hartmann B, Harr MB, Jeppesen PB, Wojdemann M, Deacon CF, Mortensen PB, Holst JJ. In vivo and in vitro degradation of glucagon-like peptide-2 in humans. J Clin Endocrinol Metab. 2000;85(8):2884–8.
89. Baldassano S, Amato A. GLP-2: what do we know? What are we going to discover? Regul Pept. 2014;194–195:6–10.
90. Tavares W, Drucker DJ, Brubaker PL. Enzymatic- and renal-dependent catabolism of the intestinotropic hormone glucagon-like peptide-2 in rats. Am J Physiol Endocrinol Metab. 2000;278(1):E134–9.
91. Drucker DJ, Erlich P, Asa SL, Brubaker PL. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. Proc Natl Acad Sci U S A. 1996;93(15):7911–6.
92. Brubaker PL, Izzo A, Hill M, Drucker DJ. Intestinal function in mice with small bowel growth induced by glucagon-like peptide-2. Am J Physiol. 1997;272(6 Pt 1):E1050–8.
93. Tsai CH, Hill M, Asa SL, Brubaker PL, Drucker DJ. Intestinal growth-promoting properties of glucagon-like peptide-2 in mice. Am J Physiol. 1997;273(1 Pt 1):E77–84.
94. Burrin DG, Stoll B, Jiang R, Petersen Y, Elnif J, Buddington RK, Schmidt M, Holst JJ, Hartmann B, Sangild PT. GLP-2 stimulates intestinal growth in premature TPN-fed pigs by suppressing proteolysis and apoptosis. Am J Physiol Gastrointest Liver Physiol. 2000;279(6):G1249–56.
95. Cheeseman CI. Upregulation of SGLT-1 transport activity in rat jejunum induced by GLP-2 infusion in vivo. Am J Physiol. 1997;273(6):R1965–71.
96. Nagell CF, Wettergren A, Pedersen JF, Mortensen D, Holst JJ. Glucagon-like peptide-2 inhibits antral emptying in man, but is not as potent as glucagon-like peptide-1. Scand J Gastroenterol. 2004;39(4):353–8.
97. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A, Lambert DM, Muccioli GG, Delzenne NM. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut. 2009;58(8):1091–103.
98. Lim DW, Wales PW, Mi S, Yap JY, Curtis JM, Mager DR, Mazurak VC, Wizzard PR, Sigalet DL, Turner JM. Glucagon-like peptide-2 alters bile acid metabolism in parenteral nutrition--associated liver disease. JPEN J Parenter Enteral Nutr. 2016;40(1):22–35.
99. Lim DW, Wales PW, Josephson JK, Nation PN, Wizzard PR, Sergi CM, Field CJ, Sigalet DL, Turner JM. Glucagon-like peptide 2 improves cholestasis in parenteral nutrition--associated liver disease. JPEN J Parenter Enteral Nutr. 2016;40(1):14–21.
100. Munroe DG, Gupta AK, Kooshesh F, Vyas TB, Rizkalla G, Wang H, Demchyshyn L, Yang ZJ, Kamboj RK, Chen H, McCallum K, Sumner-Smith M, Drucker DJ, Crivici A. Prototypic G protein-coupled receptor for the intestinotrophic factor glucagon-like peptide 2. Proc Natl Acad Sci U S A. 1999;96(4):1569–73.

101. Yusta B, Huang L, Munroe D, Wolff G, Fantaske R, Sharma S, Demchyshyn L, Asa SL, Drucker DJ. Enteroendocrine localization of GLP-2 receptor expression in humans and rodents. Gastroenterology. 2000;119(3):744–55.
102. Dubé PE, Brubaker PL. Frontiers in glucagon-like peptide-2: multiple actions, multiple mediators. Am J Physiol Endocrinol Metab. 2007;293(2):E460–5.
103. Martin GR, Wallace LE, Hartmann B, Holst JJ, Demchyshyn L, Toney K, Sigalet DL. Nutrient-stimulated GLP-2 release and crypt cell proliferation in experimental short bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2005;288(3):G431–8.
104. Perez A, Duxbury M, Rocha FG, Ramsanahie AP, Farivar RS, Varnholt H, Ito H, Wong H, Rounds J, Zinner MJ, Whang EE, Ashley SW. Glucagon-like peptide 2 is an endogenous mediator of postresection intestinal adaptation. JPEN J Parenter Enteral Nutr. 2005;29(2):97–101.
105. Koopmann MC, Liu X, Boehler CJ, Murali SG, Holst JJ, Ney DM. Colonic GLP-2 is not sufficient to promote jejunal adaptation in a PN-dependent rat model of human short bowel syndrome. JPEN J Parenter Enteral Nutr. 2009;33(6):629–38; discussion 638–9.
106. Martin GR, Wallace LE, Sigalet DL. Glucagon-like peptide-2 induces intestinal adaptation in parenterally fed rats with short bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2004;286(6):G964–72.
107. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011;60(7):902–14.
108. Jeppesen PB, Gabe SM, Seidner DL, Lee HM, Olivier C. Factors associated with response to teduglutide in patients with short-bowel syndrome and intestinal failure. Gastroenterology. 2018;154(4):874–85.
109. Carter BA, Cohran VC, Cole CR, Corkins MR, Dimmitt RA, Duggan C, Hill S, Horslen S, Lim JD, Mercer DF, Merritt RJ, Nichol PF, Sigurdsson L, Teitelbaum DH, Thompson J, Vanderpool C, Vaughan JF, Li B, Youssef NN, Venick RS, Kocoshis SA. Outcomes from a 12-week, open-label, multicenter clinical trial of teduglutide in pediatric short bowel syndrome. J Pediatr. 2017;181:102–111.e5.
110. Barnard JA, Beauchamp RD, Russell WE, Dubois RN, Coffey RJ. Epidermal growth factor-related peptides and their relevance to gastrointestinal pathophysiology. Gastroenterology. 1995;108(2):564–80.
111. Shin CE, Falcone RA Jr, Duane KR, Erwin CR, Warner BW. The distribution of endogenous epidermal growth factor after small bowel resection suggests increased intestinal utilization during adaptation. J Pediatr Surg. 1999;34(1):22–6.
112. O'Brien DP, Nelson LA, Williams JL, Kemp CJ, Erwin CR, Warner BW. Selective inhibition of the epidermal growth factor receptor impairs intestinal adaptation after small bowel resection. J Surg Res. 2002;105(1):25–30.
113. Shin CE, Helmrath MA, Falcone RA Jr, Fox JW, Duane KR, Erwin CR, Warner BW. Epidermal growth factor augments adaptation following small bowel resection: optimal dosage, route, and timing of administration. J Surg Res. 1998;77(1):11–6.
114. Sham J, Martin G, Meddings JB, Sigalet DL. Epidermal growth factor improves nutritional outcome in a rat model of short bowel syndrome. J Pediatr Surg. 2002;37(5):765–9.
115. Bedford A, Chen T, Huynh E, Zhu C, Medeiros S, Wey D, de Lange C, Li J. Epidermal growth factor containing culture supernatant enhances intestine development of early-weaned pigs in vivo: potential mechanisms involved. J Biotechnol. 2015;196-197:9–19.
116. Bahrami J, Yusta B, Drucker DJ. ErbB activity links the glucagon-like peptide-2 receptor to refeeding-induced adaptation in the murine small bowel. Gastroenterology. 2010;138(7):2447–56.
117. Lim DW, Levesque CL, Vine DF, Muto M, Koepke JR, Nation PN, Wizzard PR, Li J, Bigam DL, Brubaker PL, Turner JM, Wales PW. Synergy of glucagon-like peptide-2 and epidermal growth factor coadministration on intestinal adaptation in neonatal piglets with short bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2017;312(4):G390–404.
118. Sigalet DL, Martin GR, Butzner JD, Buret A, Meddings JB. A pilot study of the use of epidermal growth factor in pediatric short bowel syndrome. J Pediatr Surg. 2005;40(5):763–8.
119. Kuemmerle JF. Insulin-like growth factors in the gastrointestinal tract and liver. Endocrinol Metab Clin North Am. 2012;41(2):409–23.
120. Powell DW, Mifflin RC, Valentich JD, Crowe SE, Saada JI, West AB. Myofibroblasts. II. Intestinal subepithelial myofibroblasts. Am J Physiol. 1999;277(2):C183–201.
121. Powell DW, Mifflin RC, Valentich JD, Crowe SE, Saada JI, West AB, Myofibroblasts I. Paracrine cells important in health and disease. Am J Physiol. 1999;277(1):C1–9.
122. Knott AW, Juno RJ, Jarboe MD, Profitt SA, Erwin CR, Smith EP, Fagin JA, Warner BW. Smooth muscle overexpression of IGF-I induces a novel adaptive response to small bowel resection. Am J Physiol Gastrointest Liver Physiol. 2004;287(3):G562–70.
123. Dubé PE, Forse CL, Bahrami J, Brubaker PL. The essential role of insulin-like growth factor-1 in the intestinal tropic effects of glucagon-like peptide-2 in mice. Gastroenterology. 2006;131(2):589–605. Erratum in: Gastroenterology. 2007 Mar;132(3):1208.
124. Peterson CA, Ney DM, Hinton PS, Carey HV. Beneficial effects of insulin-like growth factor I on epithelial structure and function in parenterally fed rat jejunum. Gastroenterology. 1996;111(6):1501–8.
125. Rowland KJ, Trivedi S, Lee D, Wan K, Kulkarni RN, Holzenberger M, Brubaker PL. Loss of glucagon-like peptide-2-induced proliferation following intestinal epithelial insulin-like growth factor-1-receptor deletion. Gastroenterology. 2011;141(6):2166–75.
126. Dong CX, Zhao W, Solomon C, Rowland KJ, Ackerley C, Robine S, Holzenberger M, Gonska T, Brubaker PL. The intestinal epithelial insulin-like growth factor-1 receptor links glucagon-like peptide-2 action to gut barrier function. Endocrinology. 2014;155(2):370–9.
127. Nightingale JMD, Kamm MA, van der Sijp JRM, et al. Disturbed gastric emptying in the short bowel syndrome. Evidence for a 'colonic brake'. Gut. 1993;34:1171–6.
128. Playford RJ, Domin J, Beacham J, Parmar KB, Tatemoto K, Bloom SR, Calam J. Preliminary report: role of peptide YY in defence against diarrhoea. Lancet. 1990;335:1555–7.
129. Savage AP, Gornacz GE, Adrian TE, Ghatei MA, Goodlad RA, Wright NA, Bloom SR. Is raised plasma peptide YY after intestinal resection in the rat responsible for the trophic response? Gut. 1985;26:1353–8.
130. Goodlad RA, Ghatei MA, Dornin J, Bloom SR, Wright NA. Is peptide YY trophic to the intestinal epithelium of parenterally fed rats? Digestion. 1990;46:177–81.
131. Kato Y, Murakami Y, Sohmiya M, Nishiki M. Regulation of human growth hormone secretion and its disorders. Intern Med. 2002;41(1):7–13.
132. Delehaye-Zervas MC, Mertani H, Martini JF, Nihoul-Feketé C, Morel G, Postel-Vinay MC. Expression of the growth hormone receptor gene in human digestive tissue. J Clin Endocrinol Metab. 1994;78(6):1473–80.
133. Taylor B, Murphy GM, Dowling RH. Pituitary hormones and the small bowel: effect of hypophysectomy on intestinal adaptation to small bowel resection in the rat. Eur J Clin Invest. 1979;9(2 Pt 1):115–27.
134. Durant M, Gargosky SE, Dahlstrom KA, Hellman BH Jr, Castillo RO. Regulation of postnatal intestinal maturation by growth hor-

mone: studies in rats with isolated growth hormone deficiency. Pediatr Res. 1996;40(1):88–93.
135. Tei TM, Kissmeyer-Nielsen P, Christensen H, Flyvbjerg A. Growth hormone treatment increases transmural colonic growth in GH-deficient dwarf rats. Growth Horm IGF Res. 2000;10(2):85–92.
136. Gu Y, Wu ZH, Xie JX, Jin DY, Zhuo HC. Effects of growth hormone (rhGH) and glutamine supplemented parenteral nutrition on intestinal adaptation in short bowel rats. Clin Nutr. 2001;20(2):159–66.
137. Zhou X, Li YX, Li N, Li JS. Glutamine enhances the gut-trophic effect of growth hormone in rat after massive small bowel resection. J Surg Res. 2001;99(1):47–52.
138. Benhamou PH, Canarelli JP, Richard S, Cordonnier C, Postel JP, Grenier E, Leke A, Dupont C. Human recombinant growth hormone increases small bowel lengthening after massive small bowel resection in piglets. J Pediatr Surg. 1997;32(9):1332–6.
139. Vanderhoof JA, Kollman KA, Griffin S, Adrian TE. Growth hormone and glutamine do not stimulate intestinal adaptation following massive small bowel resection in the rat. J Pediatr Gastroenterol Nutr. 1997;25(3):327–31.
140. Waitzberg DL, Cukier C, Mucerino DR, Logulo AF, Torrinhas RS, de Castro I. Small bowel adaptation with growth hormone and glutamine after massive resection of rat's small bowel. Nutr Hosp. 1999;14(2):81–90. Review.
141. Durant M, Gargosky S, Dahlstrom K, Fang R, Hellman B Jr, Castillo R. The role of growth hormone in adaptation to massive small intestinal resection in rats. Pediatr Res. 2001;49(2):189–96.
142. Park JH, Vanderhoof JA. Growth hormone did not enhance mucosal hyperplasia after small-bowel resection. Scand J Gastroenterol. 1996;31(4):349–54.
143. Byrne TA, Persinger RL, Young LS, Ziegler TR, Wilmore DW. A new treatment for patients with short-bowel syndrome. Growth hormone, glutamine, and a modified diet. Ann Surg. 1995;222(3):243–54; discussion 254–5.
144. Byrne TA, Morrissey TB, Nattakom TV, Ziegler TR, Wilmore DW. Growth hormone, glutamine, and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. JPEN J Parenter Enteral Nutr. 1995;19(4):296–302.
145. Weiming Z, Ning L, Jieshou L. Effect of recombinant human growth hormone and enteral nutrition on short bowel syndrome. JPEN J Parenter Enteral Nutr. 2004;28(6):377–81.
146. de Agustin JC, Vázquez JJ, Rodríguez-Arnao D, Canals MJ, Soler J, Alvarez E. Severe short-bowel syndrome in children. Clinical experience. Eur J Pediatr Surg. 1999;9(4):236–41.
147. Scolapio JS, Camilleri M, Fleming CR, Oenning LV, Burton DD, Sebo TJ, Batts KP, Kelly DG. Effect of growth hormone, glutamine, and diet on adaptation in short-bowel syndrome: a randomized, controlled study. Gastroenterology. 1997;113(4):1074–81.
148. Scolapio JS. Effect of growth hormone, glutamine, and diet on body composition in short bowel syndrome: a randomized, controlled study. JPEN J Parenter Enteral Nutr. 1999;23(6):309–12; discussion 312–3.
149. Ellegård L, Bosaeus I, Nordgren S, Bengtsson BA. Low-dose recombinant human growth hormone increases body weight and lean body mass in patients with short bowel syndrome. Ann Surg. 1997;225(1):88–96.
150. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study. Gastroenterology. 2003;124(2):293–302.
151. Danilenko DM. Preclinical and early clinical development of keratinocyte growth factor, an epithelial-specific tissue growth factor. Toxicol Pathol. 1999;27(1):64–71.
152. Johnson WF, DiPalma CR, Ziegler TR, Scully S, Farrell CL. Keratinocyte growth factor enhances early gut adaptation in a rat model of short bowel syndrome. Vet Surg. 2000;29(1):17–27.
153. Washizawa N, Gu LH, Gu L, Openo KP, Jones DP, Ziegler TR. Comparative effects of glucagon-like peptide-2 (GLP-2), growth hormone (GH), and keratinocyte growth factor (KGF) on markers of gut adaptation after massive small bowel resection in rats. JPEN J Parenter Enteral Nutr. 2004;28(6):399–409.
154. Yang H, Wildhaber BE, Teitelbaum DH. 2003 Harry M. Vars Research Award. Keratinocyte growth factor improves epithelial function after massive small bowel resection. JPEN J Parenter Enteral Nutr. 2003;27(3):198–206; discussion 206–7.
155. de Heuvel E, Wallace L, Sharkey KA, Sigalet DL. Glucagon-like peptide 2 induces vasoactive intestinal polypeptide expression in enteric neurons via phophatidylinositol 3-kinase-γ signaling. Am J Physiol Endocrinol Metab. 2012;303(8):E994–1005.
156. Lei NY, Ma G, Zupekan T, Stark R, Puder M, Dunn JC. Controlled release of vascular endothelial growth factor enhances intestinal adaptation in rats with extensive small intestinal resection. Surgery. 2011;150(2):186–90.
157. Kato Y, Yu D, Schwartz MZ. Enhancement of intestinal adaptation by hepatocyte growth factor. J Pediatr Surg. 1998;33(2):235–9.
158. Ben Lulu S, Coran AG, Shehadeh N, Shamir R, Mogilner JG, Sukhotnik I. Oral insulin stimulates intestinal epithelial cell turnover following massive small bowel resection in a rat and a cell culture model. Pediatr Surg Int. 2012;28(2):179–87.
159. Shamir R, Kolacek S, Koletzko S, Tavori I, Bader D, Litmanovitz I, Flidel-Rimon O, Marks KA, Sukhotnik I, Shehadeh N. Oral insulin supplementation in paediatric short bowel disease: a pilot observational study. J Pediatr Gastroenterol Nutr. 2009;49(1):108–11.
160. Mah AT, Yan KS, Kuo CJ. Wnt pathway regulation of intestinal stem cells. J Physiol. 2016;594(17):4837–47.
161. Kim KA, Kakitani M, Zhao J, Oshima T, Tang T, Binnerts M, Liu Y, Boyle B, Park E, Emtage P, Funk WD, Tomizuka K. Mitogenic influence of human R-spondin1 on the intestinal epithelium. Science. 2005;309(5738):1256–9.
162. Zhao J, de Vera J, Narushima S, Beck EX, Palencia S, Shinkawa P, Kim KA, Liu Y, Levy MD, Berg DJ, Abo A, Funk WD. R-spondin1, a novel intestinotrophic mitogen, ameliorates experimental colitis in mice. Gastroenterology. 2007;132(4):1331–43.
163. Luk GD, Baylin SB. Polyamines and intestinal growth – increased polyamine biosynthesis after jejunectomy. Am J Physiol. 1983;245:G656–60.
164. Thompson JS, Laughlin K. Relationship of jejunostomy and urine polyamine content to refeeding and intestinal structure and function. J Parenter Enteral Nutr. 1989;13:13–7.
165. Rokkas T, Vaja S, Murphy GM, Dowling RH. Aminoguanidine blocks intestinal diamine oxidase (DAO) activity and enhances the intestinal adaptive response to resection in the rat. Digestion. 1990;46(Suppl 2):447–57.
166. Marchix J, Goddard G, Helmrath MA. Host-gut microbiota crosstalk in intestinal adaptation. Cell Mol Gastroenterol Hepatol. 2018;6(2):149–62.
167. Devine AA, Gonzalez A, Speck KE, Knight R, Helmrath M, Lund PK, Azcarate-Peril MA. Impact of ileocecal resection and concomitant antibiotics on the microbiome of the murine jejunum and colon. PLoS One. 2013;8(8):e73140.
168. Lapthorne S, Pereira-Fantini PM, Fouhy F, Wilson G, Thomas SL, Dellios NL, Scurr M, O'Sullivan O, Ross RP, Stanton C, Fitzgerald GF, Cotter PD, Bines JE. Gut microbial diversity is reduced and is associated with colonic inflammation in a piglet model of short bowel syndrome. Gut Microbes. 2013;4(3):212–21.
169. Speck KE, Garrison AP, Rigby RJ, von Allmen DC, Lund PK, Helmrath MA. Inflammation enhances resection-induced intestinal adaptive growth in IL-10 null mice. J Surg Res. 2011;168(1):62–9.

170. Willing BP, Van Kessel AG. Enterocyte proliferation and apoptosis in the caudal small intestine is influenced by the composition of colonizing commensal bacteria in the neonatal gnotobiotic pig. J Anim Sci. 2007;85(12):3256–66.
171. Schall KA, Holoyda KA, Isani M, Schlieve C, Salisbury T, Khuu T, Debelius JW, Moats RA, Pollack HA, Lien CL, Fowler K, Hou X, Knight R, Grikscheit TC. Intestinal adaptation in proximal and distal segments: two epithelial responses diverge after intestinal separation. Surgery. 2017;161(4):1016–27.
172. Koruda MJ, Rolandelli RH, Settle RG, Saul SH, Rombeau JL, Harry M, Vars award. The effect of a pectin-supplemented elemental diet on intestinal adaptation to massive small bowel resection. JPEN J Parenter Enteral Nutr. 1986;10(4):343–50.
173. Bartholome AL, Albin DM, Baker DH, Holst JJ, Tappenden KA. Supplementation of total parenteral nutrition with butyrate acutely increases structural aspects of intestinal adaptation after an 80% jejunoileal resection in neonatal piglets. JPEN J Parenter Enteral Nutr. 2004;28(4):210–22; discussion 222-3.
174. Bianchi A, Morabito A. The dilated bowel: a liability and an asset. Semin Pediatr Surg. 2009;18(4):249–57.
175. Pakarinen MP. Autologous intestinal reconstruction surgery as part of comprehensive management of intestinal failure. Pediatr Surg Int. 2015;31(5):453–64.
176. Kaufman SS, Loseke CA, Lupo JV, Young RJ, Murray ND, Pinch LW, Vanderhoof JA. Influence of bacterial overgrowth and intestinal inflammation on duration of parenteral nutrition in children with short bowel syndrome. J Pediatr. 1997;131(3):356–61.
177. Mayeur C, Gillard L, Le Beyec J, Bado A, Joly F, Thomas M. Extensive intestinal resection triggers behavioral adaptation, intestinal remodeling and microbiota transition in short bowel syndrome. Microorganisms. 2016;4(1):16.
178. Cole CR, Ziegler TR. Small bowel bacterial overgrowth: a negative factor in gut adaptation in pediatric SBS. Curr Gastroenterol Rep. 2007;9(6):456–62.
179. Periera-Fantini PM, Lapthrone S, Joyce SA, Dellios NL, Wilson G, Fouhy F, Thomas SL, Scurr M, Hill C, Gahan CGM, Cotter PD, Fuller PJ, Hardikar W, Bines JE. Altered FXR signalling is associated with bile acid dysmetabolism in short bowel syndrome-associated liver disease. J Hepatol. 2014;61(5):1115–25.

Part V

Assessment and Treatment of Intestinal Failure

Assessment of Nutritional and Fluid Status

Kirstine Farrer and Sorrel Burden

Key Points

1. Traditionally nutritional screening is done using a measurement of body mass index, percentage weight loss and the likelihood of being able to eat/drink.
2. A nutritional assessment additionally includes measurements of body composition and a review of the dietary intake.
3. In many countries "subjective global assessment" is used and it includes weight change, dietary input, gastrointestinal symptoms, underlying disease, functional capacity and physical examination.
4. The Global Leadership Initiative on Malnutrition (GLIM) is being increasingly used and incorporates five criteria for malnutrition 3 are phenotypic criteria (non-volitional weight loss; low body mass index; and reduced muscle mass) and 2 etiological ones (reduced food intake/assimilation and inflammation/disease burden). The diagnosis of malnutrition is based upon the presence of at least one phenotypic criterion and one etiologic criterion.
5. Body composition can be measured in the clinical environment with anthropometric measurements such as mid upper arm circumference (MUAC), triceps skin fold thickness (TSF), and mid arm muscle circumference (MAMC). Muscle function may be assessed using hand grip strength (hand-held dynamometer).
6. More detailed assessments of body composition are available including: dual-energy X-ray absorptiometry, bioelectrical impedance analysis, and computer tomography or air displacement plethysmography. These techniques are usually only performed in a research setting.
7. Underhydration is detected by a rapid weight loss, thirst, fall in postural systolic blood pressure, low urine output, and a rise in serum urea and creatinine.
8. Overhydration is commonly due to excessive amounts of intravenous saline being given and causes rapid weight gain, pitting oedema of the extremities, ascites, pleural effusions and a raised jugular venous pressure. It many take 10 or more days to excrete the saline load.

Introduction

Nutritional health is maintained by a state of equilibrium in which nutrient intake and an individual's requirements balance. Protein-energy malnutrition occurs when net nutrient intake (nutrient intake corrected for abnormally large faecal or urinary losses) is less than requirements. Protein-energy malnutrition leads to a succession of metabolic abnormalities, physiological changes, reduced organ and tissue function, and loss of fat mass and skeletal muscle mass. Concurrent stresses such as trauma, sepsis, inflammation and burns will accelerate loss of tissue mass and function [1–3]. Nutritional screening aims to quickly detect patients who may be or be at risk of becoming malnourished. A nutritional assessment is a more detailed evaluation of intake, body function/losses and needs. It is performed beside an assessment of hydration.

The assessment of hydration is of immediate importance and a nutrition support team may spend more time in managing hydration issues than managing the nutritional support. This is because sick patients including those who have, sepsis or inflammation or refeeding, often retain salt and water while patients with stoma or fistulae or drains may lose much fluid. A patient's hydration is assessed by observing weight changes, fluid balance, postural systolic blood pressure, skin/

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mucus membrane turgor, central venous pressure and biochemical measures.

This chapter will briefly address nutritional screening then will concentrate on methods of doing a nutritional assessment before summarizing how subjective global assessment (SGA) [4] and Global Leadership Initiative on Malnutrition (GLIM) [5] are performed. It completes with hydration assessment and some of the abnormalities encountered.

Nutritional Screening

There are a number of screening tools that incorporate these criteria including the UK Malnutrition Universal Screening Tool ('MUST') [6] (Fig. 1). The Mini Nutritional Assessment (MNA) includes more information than 'MUST' and is often used in older adults. In addition to percentage weight loss and BMI the short form includes food intake, mobility, neuropsychological status and a measurement of calf circumference [7].

Nutritional Assessment

Nutritional assessment involves a more detailed careful evaluation of a patient's nutritional status and is a broader topic. It is important for two reasons. Firstly for it to be of clinical importance the ideal method should be able to predict whether the individual would have an associated morbidity and mortality risk in the absence of nutritional support. Unfortunately, disease and nutrition interact so that disease may cause secondary protein-energy malnutrition, or pre-existing protein-energy malnutrition may adversely influence the underlying disease. Secondly the measurement of nutritional status is essential for determining the provision of nutritional interventions and subsequent monitoring of interventions administered [8]. Assessment of nutritional status is required to determine requirements for nutritional support and accurately assess energy and protein requirements if predictive formulas are being employed [8, 9]. Monitoring the provision and adequacy of nutritional support treatment plans is also reliant on being able to assess changes in nutritional status and body composition.

Nutritional assessment methods encompass a variety of different types of measurements looking to determine very different aspects of the human physical form. These include anthropometric measurements, body composition measurements, biomarkers and measurements of functionality. Anthropometry is the measurements of the human body and forms in integral part of assessment of nutritional status in clinical practice. Anthropometric measurements include measurement of whole body weight, height, body mass index, trunk measurements including: waist and hip circumferences; sagittal abdominal diameter; limb measurements (mid-upper arm and calf circumferences) and skinfold thickness [10]. Body composition measurements aim to assess individual components of the human body including fat, muscle, bone and water content. Body composition measurements that are available include bioelectrical impedance, ultra sound, computed tomography, magnetic resonance imaging, air displacement plethysmography, isotope dilution, dual-energy X-ray absorptiometry and whole body counting/neutron activation.

Biomarkers in nutritional assessment aim to identify indicators of nutritional status and can be assessed by any biological specimen that is derived from dietary intake or metabolism [11], including measuring serum, plasma or urine levels. Functional measurements aim to determine muscle strength as a potential indicator of body muscle status or function [12]. There are also a number of questionnaires available to determine overall assessment derived from a combination of measurements, visual observations and points about disease type and severity [13]. Finally, there are numerous nutritional screening tools available some of which have been validated.

Anthropometric Measurements

Body Mass Index and Percentage Weight Loss

Body weight is a simple measure of total body components and although is useful for identifying changes, within individuals, is of limited use without interpreting in conjunction with height and age. Weight is usually used to calculate body mass index (BMI) or Quetelet index and is BMI is calculated as weight in kilograms divided by height in meters squared [14] (Appendix 1). A BMI indicating an individual is underweight is <18.5 kg/m^2 and a normal BMI within a healthy range is 18.5–24.99 kg/m^2 [14]. A BMI indicating undernutrition has been shown to correlate with an increase in all-cause mortality [15]. However, measurements of body weight in patients in hospital cannot be seen in isolation without considering fluid balance and hydration status. Both dehydration and over hydration are well recognised consequences of illness particularly in the critically ill, postoperative period, liver disease, cancer and renal failure, which can lead to oedema and ascites [16].

Unintentional weight loss greater than 10% is a good prognosticator of clinical outcome [17, 18] (Appendix 2) However, it may be difficult to determine true weight loss. However, weight loss is often subject to memory recall and this has been shown to vary considerable in relation to the length of time weight history is required, gender, age and also BMI [19, 20]. Furthermore, the nutritional significance of changes in body weight can again be confounded by changes in hydration status, particularly an increase in extra cellular fluid.

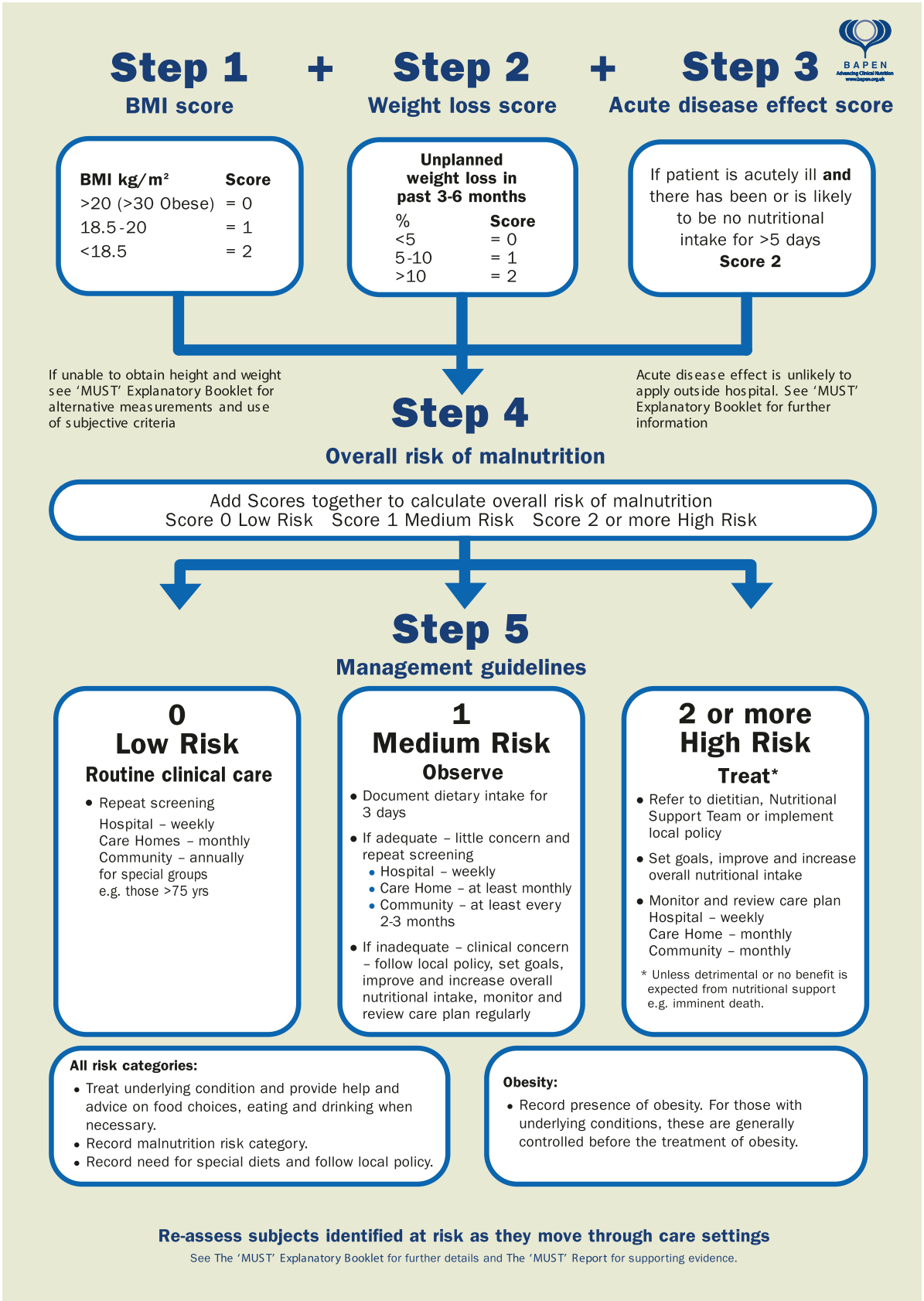


Fig. 1 Malnutrition Universal Screening Tool 'MUST'. (Reproduced with the kind permission of BAPEN (British Association for Parenteral and Enteral Nutrition). For further information on 'MUST' see www.bapen.org.uk')

Mid-arm Muscle Circumference

Triceps and subscapular skinfold thickness provide an index of body fat and have been described in detail [21, 22]. Mid-arm muscle circumference (MAMC) provides a measure of muscle mass and can be calculated from skinfold thickness and mid upper arm circumference (MUAC) (Appendix 3). MUAC has been used to identify chronic energy deficit and has been found to be of prognostic value in relation to mortality in patients who are in hospital [23, 24].

The reliability of skinfold thickness is debated and there has been some debate about the reproducibility of these measurements. The measurements have been shown to be more reliable in thinner people where there is less fat to measure and more reproducible when the same observer performs sequential measurements [25]. Experienced practitioners can achieve a high rate of reproducibility and more so then those observers who are less experienced, although there is measurement error in reproducibility between people [26].

There are references ranges that can be used for skin fold thickness, MUAC and mid arm muscle circumference based on population distributions (Appendix 4). Values less than the fifth percentile have been used to classify individuals as undernourished, although due to changes over time within populations, older reference values have been questioned [27, 28].

The most commonly used standards for triceps skinfold thickness and mid-arm muscle circumference are those reported by Jelliffe [29], which are based on measurements of European male military personnel and low-income American women, and those reported by Frisancho [30] which are based on measurements of white males and females participating in the 1971–1974 United States Health and Nutrition Survey. The use of these standards to identify protein-energy malnutrition in many patients is problematic because of the restricted database and the absence of correction factors for age, hydration status and physical activity on anthropometric parameters. Several studies have demonstrated that 20–30% of healthy control subjects would be considered undernourished based on these standards [28, 31] and that there is poor correlation between the Jellife and Frisancho standards in classifying patients [28]. Although attempts have been made to create standards for diseases such as renal dialysis patients [32] the validity of standards have been questioned and interpretation of data may be limited by inter-rater variability [33].

Body Composition

Assessment of nutritional status based on body composition involves detecting the loss (or gain) of body components relative to previous measurements and relating these values to standard reference ranges bases on healthy populations or data derived from specific populations. The former is affected by the reproducibility and error in the measurements, while the latter is dependent upon the relevance of the reference data or standards available.

Body composition measurements have been divided into a five-level model to provide a structural framework [34]. The five levels include atomic, molecular, cellular, tissues-organs and whole body. Each of these levels measure difference components to determine body composition that can include fat mass: fat free mass; total body water; body cell mass; bone mineral; skeletal muscle or total body protein [34]. The most frequently used measurements of body composition use the 2-compartmental model which measures fat mass and fat free mass [35]. It is important to note that some models measure a component of fat free mass then calculate fat free mass and then secondarily derive fat mass (e.g. bioelectrical impedance) whereas the other techniques measure fat mass then subsequently calculate fat free mass (e.g. ultra sound) [35]. This is important when evaluating the precision of measurement and the potential for the degree of error incurred during the measurement.

In healthy weight stable subjects there are relatively constant relationships between these components which are correlated with each other.

Isotope Dilution

Total body water, measured by, is usually the largest molecular level component. Water maintains a relatively stable relationship to fat-free body mass and thus measured water isotope dilution volumes allow prediction of fat-free body mass and fat (i.e. body weight minus fat-free body mass). The relationship between total body water and other body composition components may change with disease and this should be considered when interpreting data from hospitalised or chronically ill patients. The usual approach is to measure a dilution volume using one of three isotopes, tritium, deuterium, or ^{18}O-labelled water. This first step allows estimation of a dilution volume of one of the three isotopes. In the second step it is assumed that the proportion of fat-free body mass as water is constant at 0.732. This allows calculation of fat-free body mass and fat [36].

Dual-Energy X-Ray Absorptiometry

Dual-energy X-ray absorptiometry (DEXA) is a method developed originally for the measurement of bone density and mass. Systems today also quantify soft tissue composition, and it is possible to measure total and regional fat, bone mineral and bone mineral-free lean components with DEXA. The method is based on the attenuation characteristics of tissues exposed to X-rays at two peak energies. Mathematical algorithms allow calculation of the separate components using various physical and bio logical models. Software can be used to measure regions separately if desired. A typical whole body scan takes approximately

30 min and exposes the subject to ~1 mrem radiation. This method provides an accurate and practical means of measuring bone mineral mass and offers the opportunity to study appendicular muscle mass.

Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) is a method of estimating body fluid volumes by measuring the resistance to a high frequency, low amplitude alternating electric current (50 kHz at 500–800 mA). The amount of resistance measured (R) is inversely proportional to the volume of electrolytic fluid in the body, and to a lesser extent on the proportions of this volume. A regression equation is then developed based between a reference measurement of fat-free body mass (i.e. isotope dilution) and the measured R, height and other variables. Recent research in this area has focused on separate measurements of extra- and intracellular water. In healthy adults it is possible to predict total body water within 2–3 L however; these prediction may not be reliable in individuals with medical conditions that effect fluid balance including renal and cardiac disease. So caution needs to be taken where fluid shifts are a likely occurrence in disease states [37].

In a cohort of patients with intestinal failure BIA had good agreement with air displacement plethysmography (ADP) as a criterion measure when measuring body composition [38], which is in accordance with previous data measuring percentage fat in 41 healthy participants using ADP and BIA where good agreement was shown [39]. Phase angle derived from BIA has been shown to be predictive of mortality and hospital length of stay in people with intestinal failure on home parenteral nutrition [40].

Computed Tomography and Magnetic Resonance Imaging

These methods measure components at the tissue-system level of body composition, including skeletal muscle, adipose tissue, visceral organs and brain. Computed tomography (CT) systems measure X-ray attenuation as the source and detector rotate in a perpendicular plane around the subject. Magnetic resonance imaging (MRI) systems measure nuclear relaxation times from nuclei of atoms with a magnetic moment that are aligned within a powerful magnetic field.

The use of CT and MRI imaging is becoming more popular in research and clinical practice internationally. The development of computer software packages that allows body composition to be determined from CT and MRI images is now readily available. These software packages have been reviewed and been found to be highly correlated for the measurement of cross sectional muscle area [41]. The level of the third lumbar vertebra (L3) is often used as a reference point and this has been found to correlate well with whole body composition [42]. Fat and muscle mass areas can be calculated from CT images described by Prado et al. [43], including the quantification of muscle within a Hounsfield unit (HU) range of −30 to +150, and fat within −190 to −30.

The value obtained for muscle mass area (cm^2) is linearly related to whole-body muscle mass [42], and can be standardised according to height by dividing muscle area by $height^2$ to provide a skeletal muscle index, which can be compared to cut off values for the identification of low muscle mass [43, 44]. Low muscle mass derived from CT images was found not to correlate with survival in a cohort of patients on home parenteral nutrition with intestinal failure [45].

Magnetic resonance imaging can be used to assess body composition and is useful as it does not expose individuals to radiation. MRI images for whole body assessment with a full set of images to evaluate full body composition can take about 30 min. However, there is validation work enabling the use of a single slice at lumbar vertebra 4 and 5 to assess skeletal muscle mass and adipose tissue [46].

Air Displacement Plethysmography

This is four compartmental method of measuring body composition. Participants are asked to wear swim wear and a cap over their hair. All jewellery is removed as well as glasses. Participant weight is taken on the Air displacement plethysmography (ADP) scales before they enter the capsule. Participant is asked to sit in the ADP chamber, remain relaxed and breathe normally. The door is closed and the participant is asked to remain as still as possible during a 30–50 s period, whilst the machine takes a reading. The measurement is taken twice unless the machine instructs a third measure to be taken. Body fat mass and fat free mass is calculated by the ADP machine software (BODPOD). The BODPOD uses the principles of whole body densitometry to determine body composition.

This method of assessment was offered to patients receiving home parenteral nutrition with short bowel syndrome, although in a research environment the uptake was very low [38]. It was suggested that this was due to the requirement to wear swimwear which was possibly due to individual's being self-conscious about body image due to the presences of a stoma [47]. In addition, in this study the BODPOD was located at a different location so travel may have been a factor in the low uptake for this measurement [38].

Ultrasound

Ultra sound is a fairly fast noninvasive method of assessing body composition in clinical practice and research, it is relatively inexpensive and also portable device are available. It does not subject people to any radiation so suitable for sequential measurements. Ultra sound uses high frequency sound waves that travel in the form of cyclical waves greater than 20 KHz [48]. A transducer produces pulses of ultrasounds that are transmitted through the skin and when the

beam comes into contact with a tissue interface of either skin, fat, muscle or bone an echo is sent back though the transducer [48]. These echoes are then processed by the transducer and turned into signals. It is these signals that are represented by waves. To perform an ultrasound scan the transducer is moved over the skin where gel has been applied and for a single site measurement this movement is approximately 5 cm. However, whole thigh or calf can be scanned depending on what is required. The image is then read on a screen using software. Some packages have been designed for the purpose of measuring fat, muscle and bone and reliability and validity data are available for the A Mode ultrasound [49, 50].

Ultra sound has been compared to air displacement plethysmography (ADP) in a small number of patients with intestinal failure and showed for fat free mass measured by ultrasound in comparison to ADP there was a moderate intraclass correlation (ICC) (ICC 0.659, 95% confidence interval −0.27 to 0.92), although this was poor for fat mass (ICC −0.005, 95% CI −0.73 to 0.65) [38].

Clinical Assessment of Nutritional Status

The clinical assessment of nutritional status involves a focused history and physical examination in conjunction with selected measurements of body composition or laboratory tests. Laboratory tests can identify specific nutrient deficiencies and body composition measurements can assess the incidence of sarcopenia, myopenia or sarcopenic obesity. A full nutritional assessment can also potentially identify those who are at risk of becoming malnourished or developing future nutritional abnormalities.

History

The nutritional history should evaluate the following questions:

1. Has there been a recent change in body weight, particularly in the last 3 months and was the change intentional or unintentional?
2. Is dietary intake adequate? An assessment of habitual eating and current dietary intake should be assessed by a dietitian in relation to overall nutritional adequacy and specific micronutrient intakes. An assessment of nutrient supplements being taken needs to be undertaken and their contribution to nutrient intake including both macro and micronutrient intakes. A diary documenting food intake may be useful when the history is inconclusive and this can be in the form of a paper diary or one of a number of digital applications that are available to use on SMART phones or tablets [51].
3. What reasons are given for the change in dietary intake? Has appetite changed? Is there a disturbance in taste, smell, or the ability to chew or swallow food? Has there been a change in mental status or increased depression? Has there been a change in the ability to prepare meals? Are there gastrointestinal symptoms, such as early satiety, post-prandial pain, nausea, or vomiting? Is the patient taking medications that affect food intake?
4. Is there evidence of malabsorption? Does the patient have gastrointestinal disease? Has there been a change in bowel habits?
5. Are there symptoms of specific nutrient deficiencies including macro-minerals (e.g. sodium, potassium, calcium or magnesium), micronutrients and water?

Physical Examination

The physical examination corroborates and adds to the findings obtained by history:

Anthropometric Assessment

Current body weight should be compared with previously recorded weights, if available (Appendix 1). Weight for height should be compared with reference values for BMI (Appendix 2). A search for evidence demonstrating depletion of body fat and muscle masses should be made. A general loss of adipose tissue can be judged by clearly defined bony, muscular and venous outlines, and loose skinfolds. The presence of hollow cheeks, buttocks and perianal area suggests body fat loss. An examination of the temporalis, deltoids, and quadriceps muscles should be made to search for muscle wasting.

Fluid Status

An evaluation for dehydration (hypotension, tachycardia, postural changes, mucosal xerosis, dry skin, and swollen tongue) and excess body fluid (oedema, ascites) should be made (see below).

Evaluation for Specific Nutrient Deficiencies

Rapidly proliferating tissues, such as oral mucosa, hair, skin, and bone marrow are often more sensitive to nutrient deficiencies than are tissues that turn over more slowly.

Laboratory Tests

The results of the history and physical examination may lead to a suspicion of specific nutrient deficiencies, which can be further corroborated by appropriate diagnostic laboratory tests.

Functional Assessment

Hand Grip Strength

Handgrip strength is a measure of muscle function or strength and is used in research and clinical practice. Handgrip measure has been seen to be valid in hospitalised patients and reliable when undertaken in the sitting or supine position [52]. Handgrip strength has been shown to correlate with outcome in hospitalised patients, surgery and cardiovascular disease [53, 54].

Biomarkers: Serum Proteins

There is no laboratory test that is both sensitive to and specific for protein energy malnutrition. Historically albumin and pre albumin have been used as markers of nutritional status and to identify energy and protein malnutrition. However it has since been recognised that hepatic proteins are not good markers of nutritional status, but measurements of disease even though there is evidence of correlation between mortality, morbidity and recovery from disease. During a critical illness, factors that alter serum albumin and prealbumin may include the following: the acute-phrase response; hydration (intravascular volume) status; disease state; clinical condition; leakage of albumin from intravascular to extravascular spaces; and severe zinc deficiency. Evidence has demonstrated that serum levels of these proteins do not change in relation to the intake of protein. They should not be used in clinical environments to assess disease related malnutrition but are useful as a tool to indicate severity of disease [8, 55]. It is imperative that the dietitian interprets hepatic protein levels in the context of overall health and lifestyle [8, 56].

Subjective Global Assessment

World-wide the Patient-Generated Subjective Global Assessment (PG-SGA) is often used. It is a clinical method for evaluating nutritional status, termed subjective global assessment (SGA), encompasses historical, symptomatic and physical parameters [4, 13, 57]. This approach defines undernourished patients as those who are at increased risk for medical complications and who will presumably benefit from nutritional therapy. The basis of this assessment is to determine whether nutrient assimilation has been restricted because of decreased food intake, or malabsorption, whether any effects of protein-energy malnutrition on organ function and body composition have occurred, and whether the individual's disease process influences nutrient requirements. The specific features of the history and physical examination used in the SGA are listed in Tables 1, 2, 3, and 4.

The history used in the SGA focuses on five areas. The percentage of body weight lost in the previous 6 months is characterized as mild (<5%), moderate (5–10%), and severe (>10%). The pattern of loss is also important and it is possible for a patient to have significant weight loss but still be considered well-nourished if body weight (without oedema or ascites) recently increased. For example, a patient who has had a 10% body weight loss but regained 3% of that

Table 1 Features of subjective global assessment

History		
1. Weight change and height		
Current:	Height	_____ cm
	Weight	_____ kg
Overall loss in past 6 months:		_____ kg
		_____ %
Change in past 2 weeks (use + or −):		_____ kg
		_____ %
2. Dietary intake change (relative to usual intake)		
No change		
Change:	Duration ____ days	
Type:	Suboptimal solid diet	
	Hypocaloric liquids	
	Starvation	
Supplement: (circle)		
	Nil	
	Vitamins	
	Minerals	
3. Gastrointestinal symptoms that persisted for >2 weeks		
None		
Nausea		
Vomiting		
Diarrhoea		
Pain:	At rest	
	On eating	
4. Functional capacity		
No dysfunction		
Dysfunction:	Duration____ days	
	Type:	Working sub-optimally
		Ambulatory but not working
		Bedridden
5. Disease and its relation to nutritional requirements		
Primary diagnosis: _____		
Metabolic demand (stress):		
	No stress	
	Moderate stress	
	High stress (burns, sepsis, severe trauma)	
Physical status (for each trait specify: 0 = normal, 1 = mild deficit, 2 = established deficit)		
Loss of subcutaneous fat		
Muscle wasting		
Oedema		
Ascites		
Mucosal lesions		
Cutaneous and hair changes		
SGA Grade _____		
A: well nourished; B: moderate or suspected protein-energy malnutrition; C: severe protein-energy malnutrition		

weight over the past month, would be considered well-nourished. Dietary intake is classified as normal or abnormal as judged by a change in intake and whether the current diet is nutritionally adequate. The presence of persistent gastrointestinal symptoms, such as anorexia, nausea, vomiting, diarrhoea and abdominal pain, which have occurred almost daily for at least 2 weeks, is recorded. The patient's functional capacity is defined as bedridden, suboptimally active, or full capacity. The last feature of the history concerns the metabolic demands of the patient's underlying disease state. Examples of high-stress illnesses are burns, major trauma and severe inflammation, such as acute colitis. Moderate-stress diseases might be a mild infection or limited malignant tumour.

The features of the physical examination are noted as normal, mild, moderate, or severe alterations. The loss of subcutaneous fat measured in the triceps region and the mid-axillary line at the level of the lower ribs. These measurements are not precise, but are merely a subjective impression of the degree of subcutaneous tissue loss. The second feature is muscle wasting in the temporal areas and in the deltoids and quadriceps, as determined by loss of bulk and tone detectable by palpation. A neurological deficit will interfere with this assessment. The presence of oedema in the ankle and sacral regions and the presence of ascites are noted. Co-existing disease such as renal or congestive failure will modify the weight placed on the finding of oedema. Mucosal and cutaneous lesions are recorded, as are colour and appearance of the patient's hair.

The findings of the history and physical examination are used to categorize patients as being well-nourished (category A), having moderate or suspected protein-energy malnutrition (category B), or having severe protein-energy malnutrition (category C) (Table 5).

The rank is assigned on the basis of subjective weighting. Equivocal information is given less weight than definitive data. Fluid shifts related to onset or treatment of oedema or ascites must be considered when interpreting changes in body weight. In general, a patient who has experienced weight loss and muscle wasting but is currently eating well and is gaining weight is classified as well nourished. A patient who has experienced moderate weight loss, continued compromised food intake, continued weight loss, progressive functional impairment, and has a 'moderate-stress' illness is classified as moderately undernourished. An individual, who has experienced severe weight loss, continues to have poor nutrient intake, progressive functional impairment and muscle wasting is classified as severely undernourished independent of disease stress. Baker et al. [57] and Detsky et al. [4] found that the use of SGA in evaluating hospitalised patients gives reproducible results and there was more than 80% agreement when two blinded observers assessed the same patient.

Table 2 Subjective global assessment—clinical observations of loss of subcutaneous fat stores

Physical examination	Normal	Mild/moderate	Severe
Under eyes	Slightly bulging area	Somewhat hollow look, slightly dark circles	Hollow look, depression, dark circles
Triceps	Large space between fingers	Some depth to fat tissue, but not ample. Loose skin	Very little space between fingers or fingers touch
Ribs, lower back, side of body trunk	Chest is full, ribs are not visible, slight to no protrusion of the iliac crest	Ribs obvious and indentations are not marked. Crest somewhat prominent	Indentation between ribs very obvious, iliac crest very prominent

Table 3 Subjective global assessment: clinical observations of loss of muscle mass

Physical examination	Normal	Mild/moderate	Severe
Temple	Well defined muscle	Slight depression	Hollowing depression
Clavicle	Not visible in males, may be visible but not prominent in females	Some protrusion; may not be all the way along	Protruding/prominent bone
Shoulder	Rounded	Not square in appearance, acromion process may protrude slightly not all areas	Square appearance, bones prominent
Scapula/ribs	Bones not prominent no significant depressions	Mild depressions or bone may show slightly not all areas	Bones prominent significant depression medially
Quadriceps	Well defined	Depression/atrophy medially	Prominent knee. Severe depression medially
Interosseous muscle between thumb and forefinger (back of the hand)	Muscle protrudes could be flat in females	Slightly depressed	Flat or depressed areas

Table 4 Subjective global assessment—clinical observations of fluid retention

Physical examination	Normal	Mild/moderate	Severe
Oedema	None	Pitting oedema of extremities/pitting to knees, possible sacral oedema if bedridden	Pitting beyond knees, sacral oedema if bedridden may also have generalised oedema
Ascites	Absent	Present (may only be present on imaging)	Present (may only be present on imaging)

Table 5 Subjective global assessment—categories

Category A	Well-nourished no decrease in food/nutrient intake; <5% weight loss; no/minimal symptoms affecting food intake; no deficit in function; no deficit in fat or muscle mass OR an individual with criteria for SGA, B or C but with recent adequate food intake; non-fluid weight gain; significant recent improvement in symptoms allowing adequate oral intake; significant recent improvement in function; and chronic deficit in fat and muscle mass but with recent clinical improvement in function.
Category B	Mildly/moderately malnourished definite decrease in food/nutrient intake; 5–10% weight loss without stabilization or gain; mild/some symptoms affecting food intake; moderate functional deficit or recent deterioration; mild/moderate loss of fat and/or muscle mass OR an individual meeting criteria for SGA C but with improvement (but not adequate) of oral intake, recent stabilisation of weight, decrease in symptoms affecting oral intake, and stabilisation of functional status.
Category C	Severely malnourished severe deficit in food/nutrient intake; >10% weight loss which is on-going; significant symptoms affecting food/nutrient intake; severe functional deficit OR recent significant deterioration obvious signs of fat and/or muscle loss. Cachexia—If there is an underlying predisposing disorder (e.g. malignancy) and there is evidence of reduced muscle and fat and no or limited improvement with optimal nutrient intake, this is consistent with cachexia sarcopenia—If there is an underlying disorder (e.g. aging) and there is evidence of reduced muscle and strength and no or limited improvement with optimal nutrient intake

Illustrative Cases

Case 1

A 55-year-old woman was admitted to the hospital for elective resection of a colon carcinoma. Her weight was 65 kg, height 1.65 m and BMI 23.9 kg/m^2. She had lost 10% of her initial weight over a 6 month period before admission. However, she recently gained weight after therapy with nutritional supplement drinks providing an additional 600 kcal + 25 g protein per day and these have subsequently been stopped as her dietary intake is classified as 'normal'. She has no adverse gastrointestinal symptoms or pain. Current weight 68 kg (BMI 25 kg/m^2). She continued to work as a teacher and is active. On physical examination, there was no loss of subcutaneous fat stores; her ribs are not visible and there is no protrusion of the iliac crest. There are no signs of muscle wastage; her shoulders are rounded and the temple shows no signs of depression. She is classified as SGA—'A', 'well nourished'.

Case 2

A 40-year-old man with an acute exacerbation of Crohn's disease had lost 10% of his body weight within the previous 2 weeks. His weight is 65 kg, height 1.83 m, BMI 19.4 kg/m^2 and he was drinking liquids to avoid gastrointestinal discomfort associated with ingesting solid food (vomiting, nausea and diarrhea). He was ambulatory, but he was not going to work. On physical examination, he had slight loss of subcutaneous tissue manifested by a reduced buccal fat pad (on the facial cheek), his ribs are obvious and iliac crest somewhat prominent and loose skinfolds over the arms. His acromion process protrudes slightly and his interosseous muscle on the back of his hand is slightly depressed. He is classified as SGA 'B'—'moderate or suspected protein energy malnutrition'.

Case 3

A 67-year-old man with oesophageal cancer had minimal food intake for almost 3 months. His weight was 55 kg, height 1.77 m and BMI 17.6 kg/m^2. He has lost 15% of his body weight during the previous 4 months and is continuing to lose weight—1 kg per week. He was able to move around the house but had marked muscle weakness and fatigue and did not walk outdoors. Hi oral intake is restricted to fluids 1.5 L/day (soup, ice-cream and milk). On physical examination, he lacked subcutaneous fat tissue, had hollow temples, dark circles under his eyes, deltoid wasting, square shoulders, prominent knees, and mild pitting oedema. He is SGA 'C'—severe protein energy malnutrition.

Global Leadership Initiative on Malnutrition (GLIM)

In 2016 the global consensus for diagnosing malnutrition in adult patients was launched; commonly known as the Global Leadership Initiative on Malnutrition (GLIM) [5]. Nutritional screening is the first line of nutritional assessment and is now informed by the Global Leadership Initiative on Malnutrition (GLIM) where appropriate criteria are specified for phenotypes and aetiological criteria (Table 6). A **global team of experts agreed on five criteria for malnutrition which include non-volitional weight loss; low body mass index;**

Table 6 Thresholds for severity grading of malnutrition (both need one phenotypic criteria) [5]

	Weight loss		BMI[a]	
	In last 6 months	Beyond 6 months	kg/m^2	Muscle mass
Stage 1				
Moderate malnutrition	5–10%	10–20%	<20–22[a,b]	Mild/ moderate deficit
Stage 2				
Severe malnutrition	>10%	>20%	<18.5 <20 if aged 70 years or over	Severe deficit
Aetiological criteria				
Reduced food intake or assimilation				
• 50% of ER >1 week, or any reduction for >2 weeks, or any chronic GI condition that adversely impacts food assimilation or absorption				
Inflammation				
• Acute disease/injury or chronic disease-related				

[a] 20 in less than 70 years old and 22 if more than 70 years old
[b] Lower BMI in Asian population <18.5–20

and reduced muscle mass as phenotypic criteria, and reduced food intake/assimilation and inflammation/disease burden as etiologic criteria. It was proposed that the diagnosis of malnutrition be based upon the presence of at least one phenotypic criterion and one etiologic criterion.

Conclusions About Nutritional Assessment

Protein-energy malnutrition results in a continuum which starts when an individual fails to eat sufficient oral diet to meet their nutritional requirements. There are numerous methods to assess nutritional status and body composition and some methods are suited to research and others to clinical practice. Measurements can now be used to start identifying malnutrition, sarcopenia, sarcopenic obesity and myopenia. However, there is also the need to assess risk of those individuals who are likely to become malnourished in the future, because prevention is better than cure.

The identification of risk of malnutrition and malnutrition should follow with the appropriate intervention being made available to correct macro and micro nutrient deficiencies. Appropriate assessment and monitoring of disease related malnutrition allows the correct intervention to be administered with the ultimate aim of effecting change in an individual's disease trajectory, whilst influencing overall mortality, morbidity and patient reported outcome measures. There is a vast literature on the reliability and validity of measurements of body composition and nutritional status covering multiple measurement techniques. It is the skill in application of these techniques in different settings that facilitates appropriate assessment and monitoring of individuals and ensuring the monitoring is the role of a dietitian/registered nutritionist.

Assessment of Fluid Status

Water and salt are critically important constituents of the body, and disturbances of salt and water have quicker and more profound effects on health than nutrients. Body water comprises 73% of the lean body mass but 54% of body weight because fat does not contain water. Consequently, obese persons have less water in relation to body weight. Of total body water, 40% is the volume in which chloride is distributed and is extracellular; 60% resides in cells and is called the intracellular water in which body potassium and magnesium is distributed. The assessment of fluid status depends upon recognizing that body fluids are composed of isotonic saline and free water. The changes in the normal saline content alters the volume of the extracellular fluid and leaves the electrolyte concentration unchanged, while changes in free water alter the osmolarity and change plasma sodium concentration.

Clinically the hydration status is assessed by:

1. History of conditions which can cause deficits or overload.
2. History of symptoms suggestive of abnormal fluid status.
3. Physical examination.
4. Biochemical tests.

Underhydrated (Hypovolaemic, Extracellular Fluid Depletion)

This is common especially when there are large losses such as diarrhoea, large stomal/intestinal fistula output and/or vomiting. When the changes are mild with less than 10%

reduction of extracellular fluid volume (ECF), the patients may have very few complaints except for rapid weight loss. When there is a greater reduction of ECF then there are symptoms of marked weight loss, dizziness and palpitations on changing from a recumbent to an erect posture, weakness, thirst and fainting. On examination there is postural tachycardia and fall in systolic blood pressure on changing posture. In normal individuals or those with <7% volume depletion the pulse will rise by 10 beats/min, the systolic pressure will fall by 5–10 mm and the diastolic will rise by 5–10 mm when the posture is changed from a recumbent to an erect state. With greater loss of the ECF the pulse rises by 20 beats/min and the postural change in systolic pressure will be 20 mm or more without a similar compensatory rise in the diastolic pressure. Weight loss always occurs, with severe depletion (>15%) the jugular venous wave is not seen even when the patient is lying flat. The changes in blood pressure may be missed unless the blood pressure is taken only after waiting for 10 min after change of position. The clinical features of ECF volume depletion are summarized in Table 7 and the electrolyte changes in Table 8.

On biochemical testing the plasma sodium concentration is normal unless the patient has been drinking water to quench thirst, in which case the plasma sodium may fall below the normal range (hyponatraemia). When patients have a short bowel, losses of fluid from a jejunostomy, which is isotonic will cause serious volume contraction but leave the plasma sodium, potassium, chloride and bicarbonate concentrations normal. Losses from other sites can change the plasma electrolyte picture as indicated in Table 8. In addition renal urine electrolytes will show a marked reduction in sodium concentration <10 mmol/L.

Table 7 History and clinical features of hypovolaemia/ECF depletion

History	Symptoms	Physical signs
Losses of fluid: vomiting and diarrhea	Weakness, thirst, dizziness, postural	Weight loss
Renal disease with diuresis	Symptoms	Dry mucous membranes
Diuretic therapy		Reduced skin turgor
		Reduced central venous pressure
		Postural changes in pulse >10 beats/min and a fall in systolic pressure >15 mm

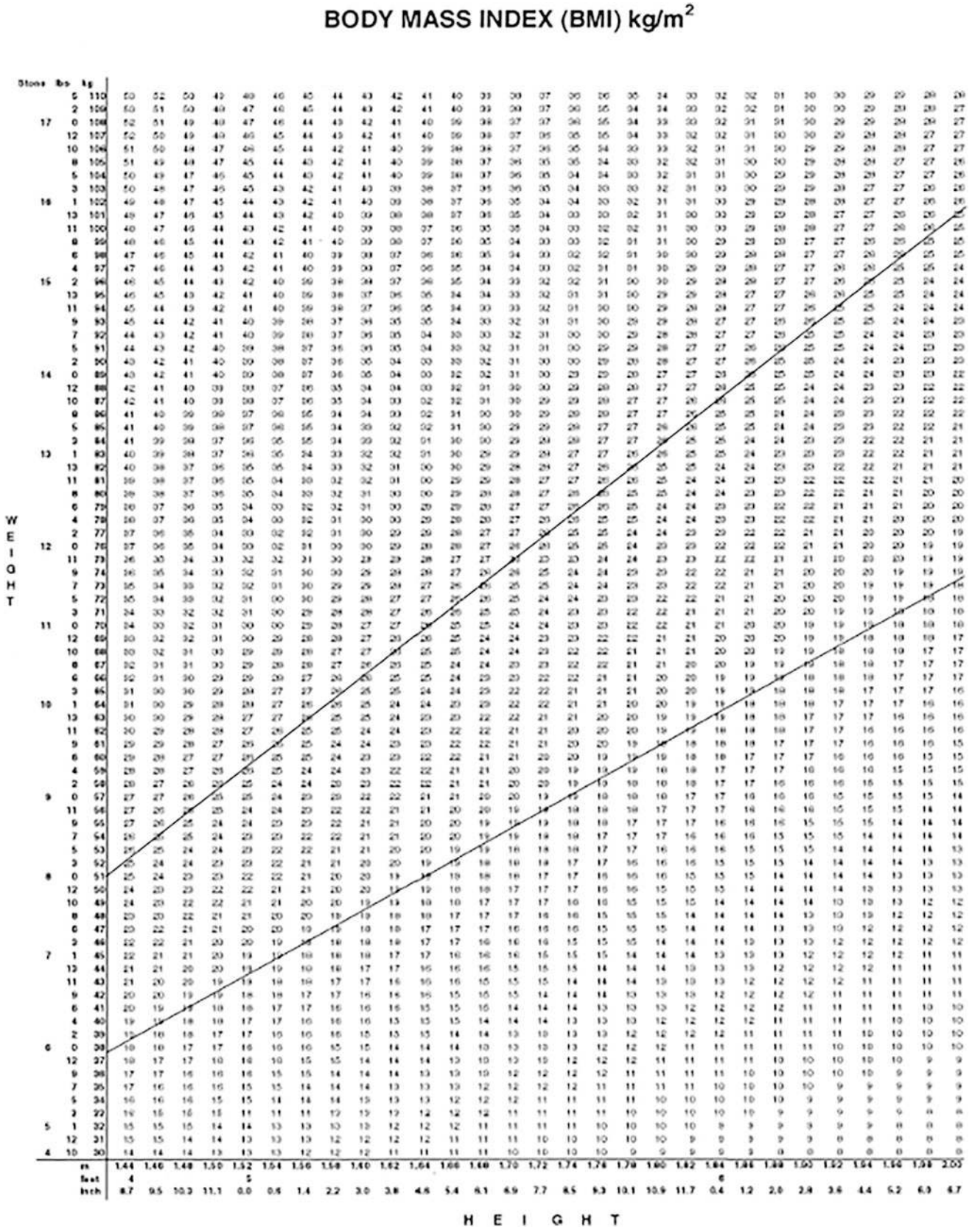
Table 8 Changes in plasma electrolytes with conditions resulting in loss of ECF

Clinical condition	Sodium	Potassium	Chloride	Bicarbonate
Vomiting	Normal	Low	Low	High
Jejunostomy losses	Normal	Normal	Normal	Normal
Pancreatic fistula	Normal	Normal	High	Low
Ileostomy	Normal	Normal or low	Normal or high	Normal or low
Diarrhoea	Normal	Low	High	Low

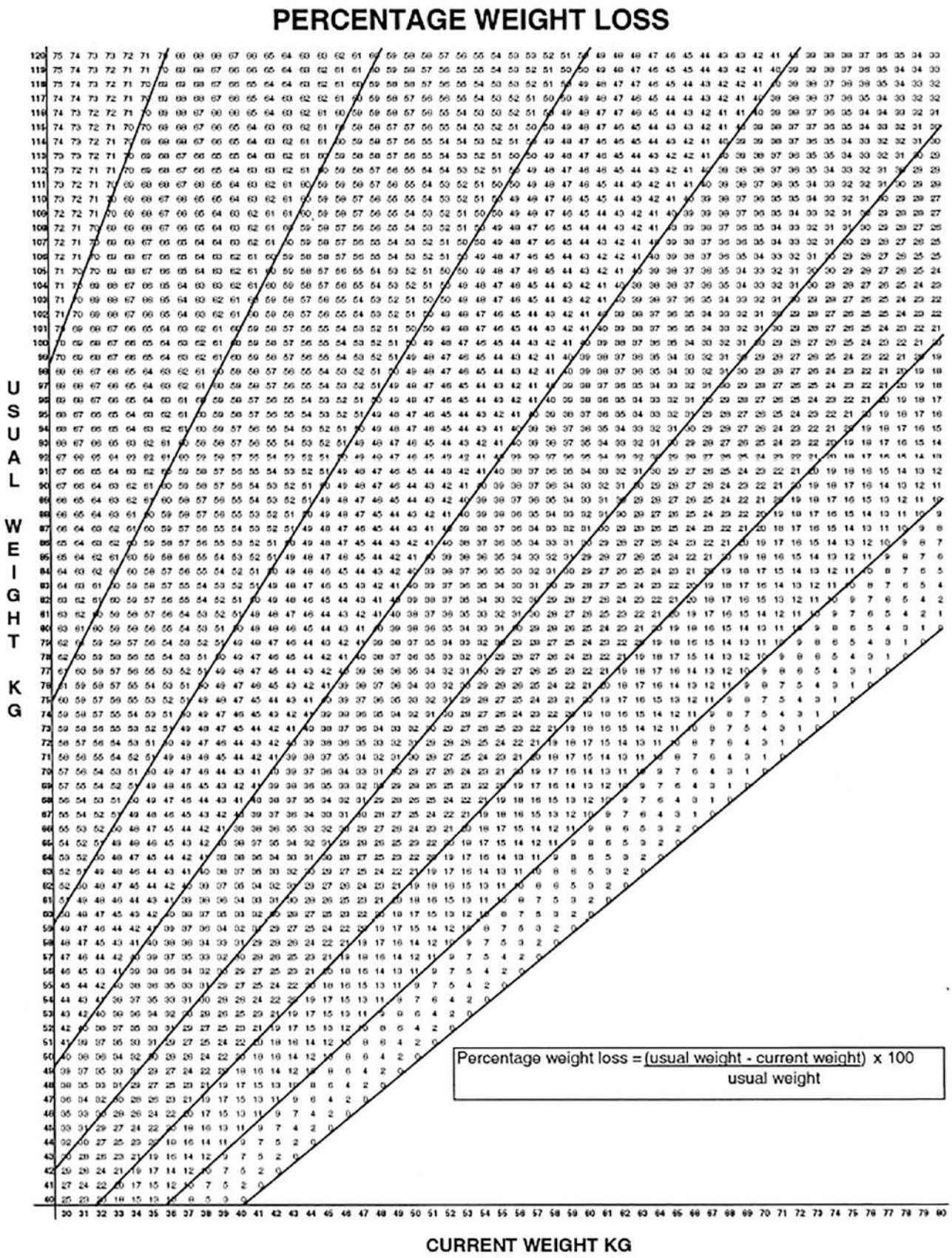
Overhydrated (Hypervolaemic, Increased Extracellular Fluid)

This commonly occurs when excessive saline is given intravenously (e.g. after vigorous resuscitation with sodium-containing fluids or in the perioperative period). Two liters of 0.9% saline given to healthy volunteers reduced the albumin by about 10 g/L and it took 2 weeks to return completely to normal [58]. Thus humans have poor mechanisms for excreting a sodium load. Saline overload causes rapid weight gain, swelling of the extremities and abdomen, and breathlessness. On examination there may be one or more of the following: acute weight gain, pitting oedema (pretibial or if bed bound of thighs or sacral area), ascites, raised jugular venous pressure and pleural effusions. In this condition the plasma electrolytes will be normal unless the patient has received diuretics and continues to drink water or receive fluids without sodium (e.g. isotonic glucose). These patients need saline intake restricting, or very occasionally are given intravenous albumin with or without a loop diuretic.

Appendix 1


BODY MASS INDEX (BMI) kg/m²
Stone lbs kg
WEIGHT
m
feet
inch
HEIGHT

Appendix 2


PERCENTAGE WEIGHT LOSS
USUAL WEIGHT KG
CURRENT WEIGHT KG
Percentage weight loss = (usual weight - current weight) x 100
usual weight

Appendix 3 MID-ARM MUSCLE CIRCUMFERENCE (MAMC)

	50	49	49	48	47	47	46	46	45	44	44	43	42	42	41	41
	49	48	48	47	46	46	45	45	44	43	43	42	41	41	40	40
	48	47	47	46	45	45	44	44	43	42	42	41	40	40	39	39
	47	46	46	45	44	44	43	43	42	41	41	40	39	39	38	38
	46	45	45	44	43	43	42	42	41	40	40	39	38	38	37	37
	45	44	44	43	42	42	41	41	40	39	39	38	37	37	36	36
M	**44**	43	43	42	41	41	40	40	39	38	38	37	36	36	35	35
I	**43**	42	42	41	40	40	39	39	38	37	37	36	35	35	34	34
D	**42**	41	41	40	39	39	38	38	37	36	36	35	34	34	33	33
A	**41**	40	40	39	38	38	37	37	36	35	35	34	33	33	32	32
R	**40**	39	39	38	37	37	36	36	35	34	34	33	32	32	31	31
M	**39**	38	38	37	36	36	35	35	34	33	33	32	31	31	30	30
	38	37	37	36	35	35	34	34	33	32	32	31	30	30	29	29
	37	36	36	35	34	34	33	33	32	31	31	30	29	29	28	28
	36	35	35	34	33	33	32	32	31	30	30	29	28	28	27	27
C	**35**	34	34	33	32	32	31	31	30	29	29	28	27	27	26	26
I	**34**	33	33	32	31	31	30	30	29	28	28	27	26	26	25	25
R	**33**	32	32	31	30	30	29	29	28	27	27	26	25	25	24	24
C	**32**	31	31	30	29	29	28	28	27	26	26	25	24	24	23	23
U	**31**	30	30	29	28	28	27	27	26	25	25	24	23	23	22	22
M	**30**	29	29	28	27	27	26	26	25	24	24	23	22	22	21	21
F	**29**	28	28	27	26	26	25	25	24	23	23	22	21	21	20	20
E	**28**	27	27	26	25	25	24	24	23	22	22	21	20	20	19	19
R	**27**	26	26	25	24	24	23	23	22	21	21	20	19	19	18	18
E	**26**	25	25	24	23	23	22	22	21	20	20	19	18	18	17	17
N	**25**	24	24	23	22	22	21	21	20	19	19	18	17	17	16	16
C	**24**	23	23	22	21	21	20	20	19	18	18	17	16	16	15	15
E	**23**	22	22	21	20	20	19	19	18	17	17	16	15	15	14	14
	22	21	21	20	19	19	18	18	17	16	16	15	14	14	13	13
	21	20	20	19	18	18	17	17	16	15	15	14	13	13	12	12
	20	19	19	18	17	17	16	16	15	14	14	13	12	12	11	11
C	**19**	18	18	17	16	16	15	15	14	13	13	12	11	11	10	10
M	**18**	17	17	16	15	15	14	14	13	12	12	11	10	10	9	9
	17	16	16	15	14	14	13	13	12	11	11	10	9	9	8	8
	16	15	15	14	13	13	12	12	11	10	10	9	8	8	7	7
	15	14	14	13	12	12	11	11	10	9	9	8	7	7	6	6
	14	13	13	12	11	11	10	10	9	8	8	7	6	6	5	5
	13	12	12	11	10	10	9	9	8	7	7	6	5	5	4	4
	12	11	11	10	9	9	8	8	7	6	6	5	4	4	3	3
	11	10	10	9	8	8	7	7	6	5	5	4	3	3	2	2
	10	9	9	8	7	7	6	6	5	4	4	3	2	2	1	1
		0.2	**0.4**	**0.6**	**0.8**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0**	**2.2**	**2.4**	**2.6**	**2.8**	**3.0**
				TRICEPS SKIN FOLD THICKNESS CM												

$$\text{MAMC} = \text{Mid} - \text{arm circumference} - \left(3.14 \times \text{Triceps skin fold thickness}\right)$$

The mid-arm circumference and triceps skin fold measurement are made mid-way between the tip of the acromion (shoulder tip) and the olecranon process (elbow) on the relaxed extended left (non-dominant) arm

Appendix 4 MID-ARM MUSCLE CIRCUMFERENCE (CM) PERCENTILES

				cm			
		Men				**Women**	
	5th	10th	15th		5th	10th	15th
Age (years)							
20–29	22	23	24		18	19	19
30–39	22	23	23		18	19	19
40–49	23	23	24		19	19	20
50–59	22	23	23		19	19	19
60–69	22	23	23		19	19	20
70–79	21	22	23		18	19	19
80–89	20	21	22		17	18	18
>90	20	20	21		17	17	18
All ages	22	22	23		18	19	19

This 'normal range' of mid-arm muscle circumference (MAMC) has been chosen as it includes a large age range [59]. A MAMC of less than 19 cm in women and less than 21 cm in men of all ages, would detect most patients found to be undernourished by a loss of 10% body weight or a body mass index of less than 19.0 kg/m^2 [60].

The MAMC is useful for monitoring the progress of nutritional support especially in patients who cannot be weighed, have fluid retention or are obese

References

1. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. International Consensus Guideline Committee. Adult starvation and disease related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. J Parenter Enter Nutr. 2010;34:156–9. Clin Nutr 2010;29:151–3.
2. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017;36:49–64.
3. Soeters PB, Reijven PL, van Bokhorst-de van der Schueren MA, Schols JM, Halfens RJ, Meijers JM, et al. A rational approach to nutritional assessment. Clin Nutr. 2008;27:706–16.
4. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? J Parenter Enter Nutr. 1987;11(1):8–13.
5. Jenson GL, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. JPEN J Parenter Enteral Nutr. 2019;43(1):32–40.
6. Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). J Gerontol A Biol Sci Med Sci. 2001;56(6):M366–72.
7. Elia M. The 'MUST' report. Nutritional screening for adults: a multidisciplinary responsibility. Development and use of the 'Malnutrition Universal Screening Tool' (MUST) for adults British Association for Parenteral and Enteral Nutrition (BAPEN); 2003.
8. Parenteral and Enteral Nutrition Group of the British Dietetic Association. A pocket guide to clinical nutrition. 5th ed. Birmingham, UK; 2018.
9. Henry CJ. Basal metabolic rate studies in humans: measurement and development of new equations. Public Health Nutr. 2005;8(7a):1133–52.
10. Madden AM, Smith S. Body composition and morphological assessment of nutritional status in adults: a review of anthropometric variables. J Hum Nutr Diet. 2016;29(1):7–25.
11. Potischman N, Freudenheim JL. Biomarkers of nutritional exposure and nutritional status: an overview. J Nutr. 2003;133(3):873S–4S.
12. Russell MK. Functional assessment of nutrition status. Nutr Clin Pract. 2015;30(2):211–8.
13. Detsky AS, Baker JP, Mendelson RA, Wolman SL, Wesson DE, Jeejeebhoy KN. Evaluating the accuracy of nutritional assessment techniques applied to hospitalized patients: methodology and comparisons. JPEN J Parenter Enteral Nutr. 1984;8(2):153–9.
14. World Health Organization. Obesity: preventing and managing the global epidemic report of a WHO consultation. World Health Organisation technical report series, vol. 894. Geneva: WHO; 2000. p. i–xii, 1–253.
15. Roh L, Braun J, Chiolero A, Bopp M, Rohrmann S, Faeh D, et al. Mortality risk associated with underweight: a census-linked cohort of 31,578 individuals with up to 32 years of follow-up. BMC Public Health. 2014;14:371.
16. Leach RM, Brotherton A, Stroud M, Thompson R. Nutrition and fluid balance must be taken seriously. BMJ. 2013;346:f801.
17. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med. 1980;69(4):491–7.
18. Langius JAE, Bakker S, Rietveld DHF, Kruizenga HM, Langendijk JA, Weijs PJM, et al. Critical weight loss is a major prognostic indicator for disease-specific survival in patients with head and neck cancer receiving radiotherapy. Br J Cancer. 2013;109:1093–9.
19. Perry GS, Byers TE, Mokdad AH, Serdula MK, Williamson DF. The validity of self-reports of past body weights by U.S. adults. Epidemiology. 1995;6(1):61–6.
20. Klipstein-Grobusch K, Kroke A, Boeing H. Reproducibility of self-reported past body weight. Eur J Clin Nutr. 1998;52(7):525–8.
21. Stewart AD, Sutton L. Body composition in sport exercise and health. New York: Routledge; 2012.
22. Frisancho AR. Anthropometric standards: an interactive nutritional reference of body size and body composition for children and adults. 2nd ed. Ann Arbor: University of Michigan Press; 2008.
23. James WPT, Mascie-Taylor CGN, Norgan NG, Bistrian BR, Shetty PS, Ferro-Luzzi A. The value of arm circumference measurements in assessing chronic energy deficiency in third world adults. Eur J Clin Nutr. 1994;48:883–94.
24. Powell-Tuck J, Hennessy EM. A comparison of mid upper arm circumference, body mass index and weight loss as indices of undernutrition in acutely hospitalized patients. Clin Nutr. 2003;22(3):307–12.
25. Krishan K, Kanchan T. Measurement error in anthropometric studies and its significance in forensic casework. Ann Med Health Sci Res. 2016;6(1):62–3.
26. Ulijaszek SJ, Kerr DA. Anthropometric measurement error and the assessment of nutritional status. Br J Nutr. 1999;82(3):165–77.
27. Bishop CW, Bowen PE, Ritchey SJ. Norms for nutritional assessment of American adults by upper arm anthropometry. Am J Clin Nutr. 1981;34(11):2530–9.
28. Thuluvath PJ, Triger DR. How valid are our reference standards of nutrition? Nutrition. 1995;11(6):731–3.
29. Jelliffe DB, World Health Organization. The assessment of the nutritional status of the community (with special reference to field surveys in developing regions of the world). Derrick B. Jelliffe; prepared in consultation with twenty-five specialists in various countries. Geneva: World Health Organization. 1966. http://www.who.int/iris/handle/10665/41780.
30. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr. 1981;34(11):2540–5.
31. Harries AD, Jones LA, Heatley RV, Rhodes J. Malnutrition in inflammatory bowel disease: an anthropometric study. Hum Nutr Clin Nutr. 1982;36(4):307–13.

32. Nelson EE, Hong CD, Pesce AL, Peterson DW, Singh S, Pollak VE. Anthropometric norms for the dialysis population. Am J Kidney Dis. 1990;16(1):32–7.
33. Gray GE, Gray LK. Anthropometric measurements and their interpretation: principles, practices, and problems. J Am Diet Assoc. 1980;77(5):534–9.
34. Wang ZM, Pierson JRN, Heymsfield SB. The five-level model: a new approach to organizing body-composition research. Am J Clin Nutr. 1992;56(1):19–28.
35. Lee SY, Gallagher D. Assessment methods in human body composition. Curr Opin Clin Nutr Metab Care. 2008;11(5):566–72.
36. Heymsfield SBLT, Wang Z. Human body composition. 2nd ed. Champaign, IL: Human Kinetics; 2005.
37. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis--part I: review of principles and methods. Clin Nutr. 2004;23(5):1226–43.
38. Jones DJ, Lal S, Gittins M, Strauss BJG, Burden ST. Practical measurement of body composition using bioelectrical impedance, air displacement plethysmography and ultrasound in stable outpatients with short bowel syndrome receiving home parenteral nutrition: comparison of agreement between the methods. J Hum Nutr Diet. 2019;32(3):288–94.
39. Hillier SE, Beck L, Petropoulou A, Clegg ME. A comparison of body composition measurement techniques. J Hum Nutr Diet. 2014;27(6):626–31.
40. Køhler M, Olesen SS, Rasmussen HH. Body composition predicts clinical outcome in patients with intestinal failure on long-term home parenteral nutrition. Clin Nutr ESPEN. 2018;28:193–200.
41. van Vugt JLA, Levolger S, Gharbharan A, Koek M, Niessen WJ, Burger JWA, et al. A comparative study of software programmes for cross-sectional skeletal muscle and adipose tissue measurements on abdominal computed tomography scans of rectal cancer patients. J Cachexia Sarcopenia Muscle. 2017;8(2):285–97.
42. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985). 2004;97(6):2333–8.
43. Prado CM, Liefers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629–35.
44. Martin L, Hopkins J, Malietzis G, Jenkins JT, Sawyer MB, Brisebois R, et al. Assessment of computed tomography (CT)-defined muscle and adipose tissue features in relation to short-term outcomes after elective surgery for colorectal cancer: a multicenter approach. Ann Surg Oncol. 2018;25(9):2669–80.
45. Oke SM, Rye B, Bottle RA, Malietzis GA, Willsmore JD, Gabe SM, et al. Survival & sarcopenia as defined by CT in patients with intestinal failure on HPN. Clin Nutr. 2018;37:S23.
46. Ross R. Advances in the application of imaging methods in applied and clinical physiology. Acta Diabetol. 2003;40(Suppl 1):S45–50.
47. Aktas D, Baykara ZG. Body image perceptions of persons with a stoma and their partners: a descriptive, cross-sectional study. Ostomy Wound Manage. 2015;61(5):26–40.
48. Wagner DR. Ultrasound as a tool to assess body fat. J Obes. 2013;2013:280713.
49. Smith-Ryan AE, Fultz SN, Melvin MN, Wingfield HL, Woessner MN. Reproducibility and validity of A-mode ultrasound for body composition measurement and classification in overweight and obese men and women. PLOS One. 2014;9(3):e91750.
50. Smith-Ryan AE, Blue MNM, Trexler ET, Hirsch KR. Utility of ultrasound for body fat assessment: validity and reliability compared to a multicompartment criterion. Clin Physiol Funct Imaging. 2018;38(2):220–6.
51. Chen J, Lieffers J, Bauman A, Hanning R, Allman-Farinelli M. The use of smartphone health apps and other mobile health (mHealth) technologies in dietetic practice: a three country study. J Hum Nutr Diet. 2017;30(4):439–52.
52. Savino E, Martini E, Lauretani F, Pioli G, Zagatti AM, Frondini C, et al. Handgrip strength predicts persistent walking recovery after hip fracture surgery. Am J Med. 2013;126(12):1068–75.e1.
53. Bohannon RW, Peolsson A, Massy-Westropp N, Desrosiers J, Bear-Lehman J. Reference values for adult grip strength measured with a Jamar dynamometer: a descriptive meta-analysis. Physiotherapy. 2006;92(1):11–5.
54. Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A Jr, Orlandini A, et al. Prognostic value of grip strength: findings from the prospective urban rural epidemiology (PURE) study. Lancet. 2015;386(9990):266–73.
55. Marcason W. Should albumin and prealbumin be used as indicators for malnutrition? J Acad Nutr Diet. 2017;117(7):1144.
56. Shenkin A. Serum prealbumin: is it a marker of nutritional status or of risk of malnutrition? Clin Chem. 2006;52(12):2177–9.
57. Baker JP, Detsky AS, Wesson DE, Wolman SL, Stewart S, Whitewell J, et al. Nutritional assessment: a comparison of clinical judgement and objective measurements. N Engl J Med. 1982;306(16):969–72.
58. Lobo DN, Stanga Z, Simpson JA, Anderson JA, Rowlands BJ, Allison SP. Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. Clin Sci (Lond). 2001;101(2):173–9.
59. Symreng T. Arm anthropometry in a large reference population and in surgical patients. Clin Nutr. 1982;1:211–9.
60. Nightingale JMD, Walsh N, Bullock ME, Wicks AC. Comparison of three simple methods for the detection of malnutrition. J R Soc Med. 1996;89:144–8.

Radiology in Intestinal Failure

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Key Points

1. The radiologist is a key member of the intestinal failure multidisciplinary team and helps with both diagnostic and therapeutic procedures.
2. The choice of radiological technique depends upon the availability of equipment, the expertise of the local radiology department, and whether the patient is acutely unwell or stable with chronic problems.
3. A plain abdominal radiograph is useful in the acute setting to diagnose obstruction, ileus, perforation and the extent/severity of colitis, and can be helpful in monitoring progress.
4. Computerised tomography (CT) is usually the best choice in an acute setting where it is easily accessible, quick to perform, can be relatively easier to interpret and allows an extra-intestinal assessment including the state of the abdominal wall.
5. Magnetic resonance enterography (MRE) produces high quality images of the small bowel, but it can be challenging to obtain high quality images in all patients. Patient movement, bowel peristalsis or inability to maintain a breath hold can result in sub-optimal non-diagnostic images, so careful patient selection is needed.
6. Ultrasound (US) is user dependent, but with appropriate expertise, US scans can provide greater resolution and information than is possible with other imaging modalities, particularly in thin patients or when the probe can be placed close to the pathology.
7. Intra-abdominal sepsis is usually detectable by CT, but a multi-modality approach may be needed. Drainage can be achieved by CT or US guidance, depending upon which provides the best accessibility or visibility of the collection.
8. Diagnosis of obstruction or ischaemia can be challenging. If there is a strong clinical suspicion of either and the initial radiology report doesn't match the clinical concern, urgent review by a specialist Gastro-intestinal radiologist maximises the chance of making a correct diagnosis.
9. A barium follow through (BFT) alone or in combination with a CT scan will usually give the information required (length and quality of bowel) for mapping bowel before reconstructive surgery.
10. Contrast fluoroscopy (with bowel distension) is good to determine the patency, length and quality of out of circuit bowel prior to distal feeding or reconstructive surgery.
11. Mapping a fistula tract is dependent on its location, accessibility and complexity, and upon the general state of the patient. A CT and /or BFT can provide an accurate overview, with fluoroscopy (fistulogram) or focussed MRI adding more detail.
12. Expert review of all current and previous imaging, including those obtained in other institutions, may provide an understanding of complex anatomy not discernible on a single examination or modality, and can guide further imaging.

Introduction

Diagnostic imaging and interventional radiology is used frequently in managing patients with IF. The radiologist should be regarded as part of the multidisciplinary team caring for the patients with IF. They are able to help define the initial diagnosis of perforations, sepsis, ischaemia and obstruction/ileus. Small bowel obstruction can easily be misdiagnosed as ileus, and similarly reversible bowel ischaemia can be missed as signs can be non-specific. Using a variety of modalities they can accurately map the remaining bowel (length and quality) and abdominal wall before reconstructive surgery.

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An increasing number of therapeutic procedures, from draining sepsis to inserting enteral and parenteral feeding lines, require radiology input and a dynamic and collaborative interface with the radiology department will facilitate best clinical practice. This chapter covers the imaging modalities, the radiological assessment of relevant conditions, and techniques for bowel and fistula mapping.

Imaging Modalities

Plain Films: Conventional and Digital Radiography (CR & DR)

Radiography is the oldest imaging modality, and its persistence in spite of the many advances in medical imaging is testament to its extensive utility. Its most common role lies in the assessment of the acutely unwell patient, with particular advantages including ease of access (such as the potential for portable films for the unstable patient) and a relatively low radiation dose (usually <0.5 mSV). Plain films can often be more readily interpreted than other modalities, allowing rapid identification or exclusion of major pathology.

Abdominal radiographs (AXRs) are most commonly requested for emergency presentations such as suspected bowel obstruction, though may also demonstrate other pathologies such as colitis and perforation leading to pneumoperitoneum. They are used in the diagnosis of small bowel ileus (either post-operative or related to other systemic processes), and pseudo-obstruction. Serial AXRs are useful and accurate for monitoring colonic disease and dilatation in ulcerative colitis.

AXR following water-soluble contrast (e.g. oral Gastrografin®) can be used in prognostication of acute small bowel obstruction, helping to predict which patients can be managed conservatively. Our institution utilises 100 mL of contrast diluted with an equal volume of water with films taken at 4 and if necessary 24 h post-ingestion. Post operatively, some centres may also administer water-soluble contrast orally for its potential therapeutic effect (to stimulate bowel peristalsis), as well as for its use as a diagnostic aid.

The position of enteral support devices such as nasogastric (NGT) and nasojejunal (NJT) tubes as well as central venous catheters (peripherally inserted and internal jugular) can be readily assessed with radiography. An improperly sited NGT may be ineffective at decompressing the stomach and represent a risk of aspiration.

Chest radiographs are used to identify complications related to acute IF, such as pneumonias (aspiration or nosocomial), or an erect film when a perforated viscus is suspected.

Fluoroscopy

Until recently fluoroscopy relied on the fluoroscopic properties of crystalline media, converting x-rays to collectible light to form a visible image. Modern digital fluoroscopy units now use digital flat panel detectors that convert the transmitted x-rays directly into electrical current allowing higher resolution images and potentially lower radiation doses. Fluoroscopy has the distinct advantage over most other modalities of allowing the operator to provide functional assessment by acquiring dynamic ('cine') images.

Fluoroscopy utilising either barium based or iodinated (water-soluble) contrast remains a useful tool in the IF patient. Water soluble contrast can safely be administered via any route, including vascular or where there is risk of entering the peritoneal cavity, whereas barium is generally only safe to administer into the lumen of the GI tract.

Barium is generally preferred when opacifying the GI tract, as it provides more detail and does not become so diluted in the distal bowel, which can minimise the interpretation difficulties due to overlapping bowel segments [1]. In addition the greater density and other properties of barium may increase the sensitivity in identifying a fistula. Barium should be avoided where acute, non-mature enteric fistulae are suspected, and generally should not be given within 3 months of acute fistulation. Water soluble contrast may be useful in these circumstances and when there is a risk of acute perforation or if surgery may be performed soon after the study. This is because barium can precipitate peritonitis if it enters the peritoneal cavity either at the time of the radiology examination or through inadvertent spillage during surgery if residual barium remains in the bowel.

Barium Follow Through

After a period of fasting (between 4–12 h), to ensure the small intestine is empty, a barium follow through (BFT) involves ingestion of barium suspension (typically 300–600 mls of 50% w/v BaSO4). In addition, some centres use aerogenic powder (30 min before the examination) but this is only necessary if mucosal detail is required. Ingestion of oral barium is followed by imaging every 10–15 min until the barium has passed through the ileocaecal valve into the colon.

Whilst historically BFT studies have been the mainstay for evaluation of the small bowel, expertise is reducing in many parts of the world, particularly where CT or MR enterography (CTE or MRE) are readily available. Nonetheless, the examination still has significant utility in particular circumstances, and can provide greater assessment of mucosa and fold pattern for example (Fig. 1), not easily appreciable on other tests. Increased fold density, and subtle global or segmental fold thickening as seen in vascular insufficiency or low protein states, can be important signs or indicators of underlying pathology or disease response.

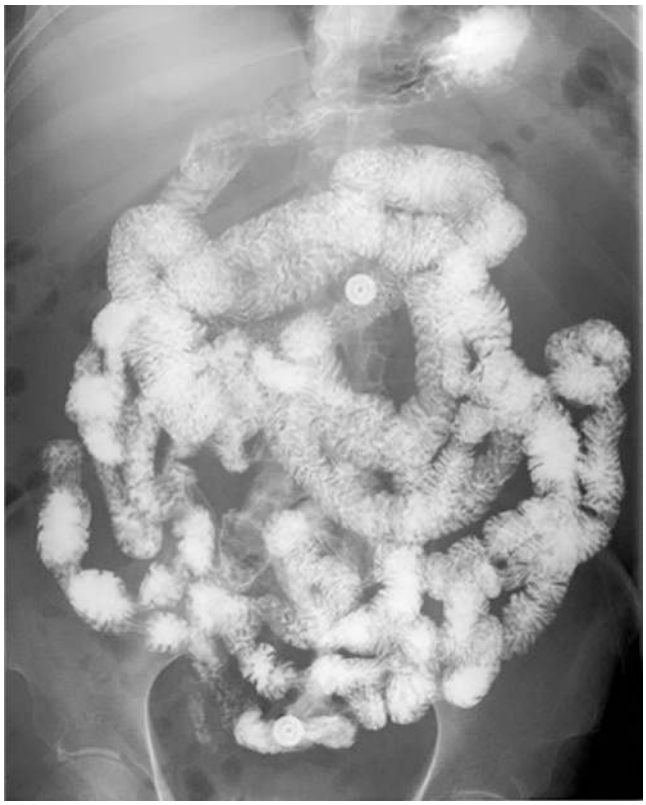

Fig. 1 Barium follow through which demonstrates the alteration in fold pattern seen in some conditions such as idiopathic sprue, coeliac and other malabsorptive states

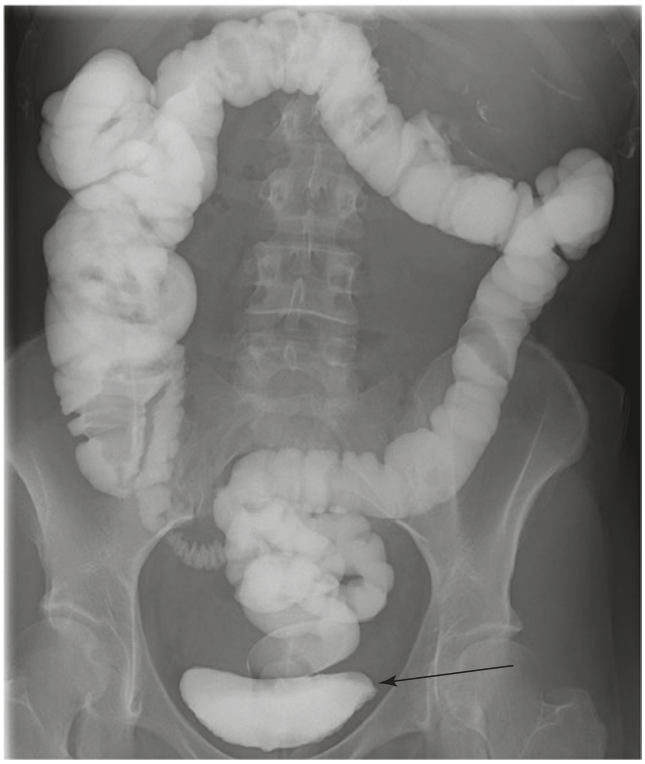

Fig. 2 Water soluble contrast enema. The rectum and colon are filled with contrast and there is reflux into the terminal ileum. Note the contrast in the bladder (arrow) and renal collecting systems due to iv contrast given earlier for a CT

Cine images and serial evaluation over the course of several (usually 2–4) hours can demonstrate evidence of evolving or intermittent obstruction (most commonly due to adhesions) or dysmotility which can be difficult to differentiate on static modalities such as CT and MRI (although newer MRI techniques described later which are still evolving may allow similar dynamic evaluation).

Contrast is generally given orally to assess the 'in circuit' bowel, but can be instilled via the afferent orifice of a defunctioning loop or an end stoma as well as via the efferent stoma orifice to assess the downstream 'out-of-circuit' bowel ('loopogram'). A combination of these techniques can help determine residual lengths of in situ bowel when planning further surgery (either for stoma formation or restoring continuity), to identify and localise the origin of fistulae (entero-enteric and entero-colic), evaluate strictures, and determine suitability for distal limb feeding in patients with short bowel.

Fistulography

A contrast fistulogram may be obtained by cannulating the cutaneous opening of a suspected entero-cutaneous fistula and contrast injected in order to demonstrate its communication to bowel. This examination and other techniques to evaluate fistula are also described later in the chapter.

Contrast Enemas

Water soluble contrast enema studies, are performed by retrograde administration of approximately 500 ml of dilute contrast into the rectum (Fig. 2) or an ileal pouch. They are used to assess the integrity of anastomoses, length and diameter of a stricture and identify any fistula related to a number of causes such as complications of prior pelvic surgery, as well as neoplastic or inflammatory disease.

Other Procedures

Fluoroscopy may be used in siting enteral support devices (nasojejunal tubes and radiologically inserted gastrostomies), insertion of and assessment of vascular devices (peripherally inserted or central venous catheters for total parenteral nutrition), and in placement of trans-jugular intrahepatic portosystemic shunt (TIPSS) for portal hypertension.

Computed Tomography

Modern (spiral) multi-detector computed tomography (CT) utilises an x-ray source and sensor array directly opposite it mounted on a gantry. Through software it effectively creates

a three-dimensional volume of data as it rotates around the patient. It is now widely accessible and has become the most frequently utilised cross sectional examination in most radiology departments. This is in part due to its widespread availability, but also its excellent diagnostic utility and it offers advantages for both patient (often more convenient compared to an MRI) and radiologist (greater consistency of obtaining a high quality scan) compared to other imaging options. Intravenous iodinated contrast is routinely used and further augments the versatility of CT, allowing better differentiation between structures and clear visualisation of vasculature.

Though CT of the abdomen and pelvis carries a relatively high radiation dose (5–10 mSv), the short scanning time (less than 10 s in modern scanners) and out-of-hours access available in most acute hospitals, make it the superior modality for the acutely unwell patient compared to MRI, where diagnostic images are reliant on patients' ability to remain still and follow breathing instructions.

Contrast enhanced CT (CECT) utilises intravenous contrast, which can be optimised with specific contrast phases, mainly by using unenhanced, arterial (at 30 s), and portal venous (at 70 s) phases, the choice of phases being determined by which structures are being investigated. The widespread use of CECT increases the ability to identify ischaemia, arguably at earlier stages, which in turn may improve prognosis, [2] and this in addition to a range of other benefits likely justifies the increased use.

Studies may be further augmented by use of very dilute water-soluble or barium oral contrast media, which acts as a 'positive' contrast. A dilution of 1 part contrast to 10 parts water is effective for most cases (see Table 1 below). Dilution of oral contrast is required to optimise the density for CT, as undiluted contrast used for other x-ray examinations results in "streak" artefact, significantly compromising the image quality. Therefore CT should generally be avoided soon after enteric gastrografin® administration due to residual relatively undiluted contrast. Such a situation may arise when a CT is requested for example following an abdominal radiograph, taken 4 h after oral intake of gastrografin, which demonstrates features of small bowel obstruction (SBO). In these circumstances, a delay in CT scanning should be considered if feasible, to allow either absorption or dilution of the luminal contrast to avoid excess artefact.

Due to the risks of barium entering the peritoneum in enteric perforation, water soluble contrast is used in most CT examinations, particularly in acute settings, and barium is generally reserved for specific indications such as allergy or other contraindication to water soluble contrast. In recent years, routine use of any oral contrast is reducing, in part due to the increased logistical complexity and delay required before scanning, and additional cost and therefore it is usually reserved for answering a specific question or concern in more complex patients. Indications for positive oral contrast in IF include: better delineation of bowel anatomy in the complex surgical abdomen, to aid differentiation of bowel from adjacent collections, or to demonstrate points of fistulation and anastomotic compromise/leak.

Table 1 Water soluble luminal contrast in CT

Indication	Protocol[a]	Considerations
Small bowel	250–1000 ml over 45–60 min and scan after 45–60 min	More than 500 ml is usually impractical in small bowel obstruction and a more realistic volume of 250–500 ml helps reduce risk of patient vomiting
Large bowel	1000 ml over 60 min and scan after 2–4 h	If scan is for a distal colonic/rectal anastomosis, rectal contrast may be more successful
Rectum	Depends on height of anastomosis, but ~100–300 ml injected via Foley catheter in the rectum Catheter balloon: generally avoid inflating if recent anastomosis	Consider need for a pre-contrast scan to define anastomosis level

Considerations:
Enteric tubes should be clamped
Timings may need to be increased in suspected obstruction or shortened in patients with short bowel
[a]Contrast dilution: 1:10 is sufficient for most cases in CT, e.g. 50 ml contrast in 500 ml of water

Though most commonly given orally or via a nasogastric tube, luminal contrast may alternatively be administered via a stoma, rectally via a catheter, or even through a suspected entero-cutaneous fistula. It is naturally important to consider the patient's anatomy and what route of contrast will feasibly reach the area of concern, particularly relevant in patients with defunctioned bowel.

CT-fistulography may be performed in cases where an external opening is present and prolonged fluoroscopic fistulography is not practical, or when greater anatomical detail and relationships to adjacent structures is required, though it lacks the benefit of dynamic cine imaging. The fistula is cannulated and dilute contrast injected (1:10) with the volume used informed by previous imaging and surgical history, though this can be difficult to predict. A single CT can be immediately acquired, usually with intravenous contrast [3].

CT-Enterography

CT-Enterography (CTE) is a specific modification to the standard CT technique to allow detailed assessment of the small bowel. The protocol involves oral administration of 1.5–2 L of a contrast agent such as dilute mannitol solution (or a similar alternative) to act as a neutral or low-density luminal contrast (so appears the same as water) and provide small bowel distention. This is followed by intravenous con-

trast timed in the enteric phase, which is obtained by scanning at 50 s post-intravenous contrast administration, the timing of which maximises mucosal enhancement [4].

The administration of oral contrast is usually started around 45 min prior to CT, following a 4–12 h fast. Immediately prior to the scan, an intravenous injection of an anti-spasmodic agent (most commonly Hyoscine butylbromide (Buscopan®)) is given to reduce small intestine muscular tension. Relatively rapid image acquisition and the use of antispasmodics reduce motion artefacts caused by respiratory and gastrointestinal peristalsis respectively. CT has the advantage of providing volumetric data, allowing multiplanar imaging reconstruction and the ability to use image analysis software (for example vascular and bowel luminal software) which can allow 3D virtual reconstruction. CTE provides the additional benefits over radiography of a combined luminal assessment and evaluation of extramural structures and other organs.

Specific indications include assessment of strictures, inflammatory bowel disease, fistulae, small bowel and mesenteric root tumours, and obstruction related to above mentioned conditions or other causes including adhesional disease. The necessity for the patient to ingest a large volume of fluid generally limits the use of CTE to well outpatients.

Magnetic Resonance Imaging

An advantage of magnetic resonance imaging (MRI), compared to the imaging options described above, is the lack of ionising radiation. MR scanners employ very powerful magnets and receiving coils to create the images. The strength of these magnets is measured in units of Tesla (T). In theory, the more powerful the magnet, the better or quicker the images can be obtained. Most MR scanners in clinical use currently have a 1.5T magnet. The most powerful MRI magnets available for routine clinical indications are 3T. Unfortunately they can have greater problems with artefacts and more practical limitations than 1.5T scanners, including increased risks of localised heating causing tissue damage. As manufacturers find solutions to overcome these problems, increasingly 3T scanners are becoming more widely available in hospitals, leading to the potential for significant improvements in the quality of MR imaging.

When high quality MR scans are obtained, they can provide excellent anatomical detail, in addition to assessments of disease activity (Fig. 3). Newer functional MR techniques can evaluate other parameters such as motility (described in more detail later).

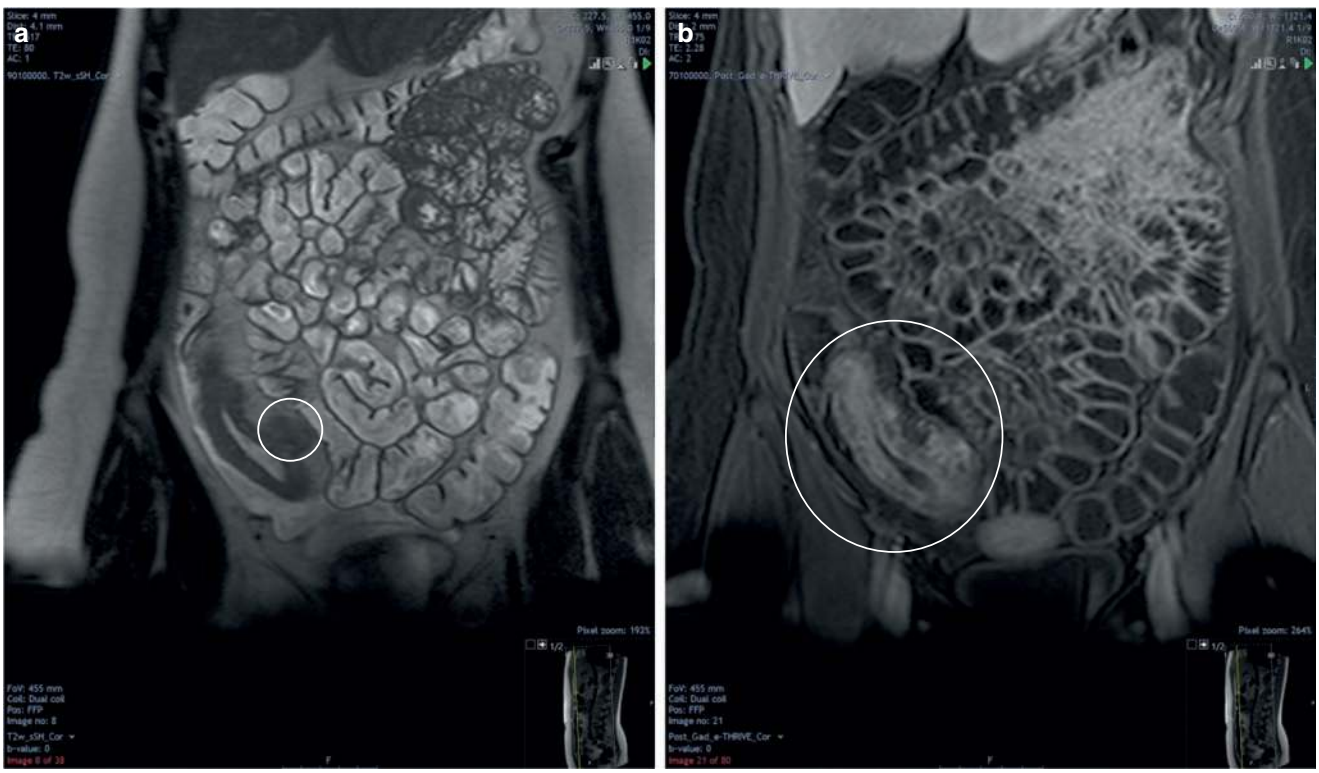

Fig. 3 MRE (**a**) Coronal T2 sequence showing Terminal Ileum mural thickening, with fat hypertrophy causing loop separation and penetrating disease demonstrated by adjacent mesenteric abscess (circled) and on the (**b**) coronal T1 post contrast image, there is mural stratification of the thickened TI (circled)

MR Enterography

MR Enterography (MRE) shares some elements of patient preparation with CTE, including the requirement for the patient to drink up to 1.5 L of oral solution, after a period of at least 4 h of fasting. There are a number of oral solutions available [5], but the most commonly used in the UK are mannitol or Lactulose based solutions. The choice of oral solution will generally be determined by local preference. Most oral contrast has an increased osmolality compared to water, which reduces absorption in the small bowel, but as a direct consequence, this often leads to the commonest side effect which is diarrhoea. MRE also requires intravenous injection of an anti-spasmodic agent (Hyoscine butylbromide (Buscopan®)) to reduce small intestine muscular contraction, and to reduce motion artefacts caused by gastrointestinal peristalsis. Any movement is a significant problem during many MR sequences, and therefore any bowel, respiratory or patient motion can markedly degrade the images.

Most MRE protocols generally utilise a gadolinium based intravenous contrast agent, which can be an advantage in those patients who have an allergy to iodine based agents required for CT.

Most radiology departments have access to MR scanners, but availability in some centres may be more limited compared to CT or other modalities. The time taken to acquire an MR scan is longer compared to CT, which can be a factor in determining how quickly or easily an MR scan can be arranged, particularly in the acute setting. MR enterography usually requires the patient to be in the scanner room for up to 45 min (compared to 10 min scanner room time for many CT scans), or longer if additional sequences are utilised. This relatively long scan time is also one of the reasons MRI is usually a more expensive scan than other imaging modalities.

To avoid respiratory motion artefact, the patient is asked to hold their breath for up to 20 s during most MRE sequences, whilst the images are acquired. Most MRE protocols will include around 8–10 breath hold sequences. If a patient is unwell, claustrophobic or finds it difficult holding their breath (particularly in older or younger patients), undergoing an MRE can be quite challenging or even unpleasant. As a result, achieving high quality MRE examinations consistently is difficult as it requires full compliance. It is therefore helpful for clinicians to be aware of these issues when discussing imaging requests with their radiologist to decide when MR is the most appropriate imaging option.

Ultrasound

Ultrasound (US) is made up of mechanical waves that can transmit through different materials like fluids, soft tissues and solids. Medical ultrasound machines generate and receive ultrasound waves with a frequency ranging between 2 and 20 MHz. Changing the frequency of ultrasound waves will alter the penetration and resolution of the images. The higher the frequency, the better the resolution is, however the depth of penetration decreases. Utilising the highest frequency probes (15–20 MHz), sub-millimetre resolution can be achieved, but the structures being evaluated must be within 3–4 cm of the probe to obtain this resolution. It is therefore easy to understand why US can be optimal when scanning thin patients, and conversely may be of limited value in patients with high BMI or where the probe can't be placed close to the site of the pathology. Views may also be limited if there is gas between the probe and the area to be visualised (e.g. in bowel or in enteric perforation causing free gas). In addition, the quality of images can be poor in patients who are tender, preventing the operator from pressing the probe deeper into the abdomen, which is often required to optimise resolution. US scanning may also be hindered by overlying dressings, stoma bags and subcutaneous oedema, though communication between referring clinicians and radiologists and good patient preparation can help optimise studies.

US of the bowel can provide real time evaluation of features such as motility, and correlation with areas of patient tenderness can allow accurate localisation of pathology. Most centres don't require patients to drink any oral solution, or cannulation for intravenous agents, which means that typically US is less intimidating for children than an MRE. As a consequence, many centres now advocate the use of US as a first line or as a complementary test to MRE [6], for younger children in particular. However, it should be borne in mind that US is very operator dependant, and so unsurprisingly its use is dependent on the availability of appropriately skilled operators (radiologists, sonographers or other clinicians).

Common indications for Imaging in Intestinal Failure

Sepsis

Radiology plays an essential role in the localisation of sepsis, particularly given that patients may present atypically due to their impaired immunity and failure to thrive may be the only manifestation [7].

Contrast-enhanced CT is a highly sensitive test and has the benefits of being quick to perform and well tolerated except in the most unstable patients. Positive oral contrast can be crucial in problem solving in the complex abdomen, and particularly in helping to differentiate bowel from intra-abdominal collections.

Radiation dose from studies should be minimised, but this must be balanced against the benefits of identifying and then

potentially draining infected collections, given the high mortality rates associated with sepsis [3, 7].

Ultrasound can provide greater anatomical detail for evaluation of the biliary system than CT and is superior in differentiating cholecystitis from physiological gallbladder oedema. Its portability also means it is useful in assessing patients who are too unstable to attend for CT.

Fluoroscopy's dynamic aspect can be helpful in identifying suspected fistulae which may be driving sepsis, particularly those that are more subtle and less apparent on static cross-sectional studies [3, 7].

MRI generally has a more limited role in the acutely unwell IF patient, when clinical questions can usually be answered with other modalities, and is therefore generally confined to problem solving following other imaging. Pelvic sepsis is one exception where MRI can be superior to CT, as the relative lack of respiratory motion that makes abdominal MR imaging difficult, can allow for detailed analysis of pelvic structures. Optimal MRI scans of the main pelvic cavity require meticulous attention to detail and close co-operation between clinician, radiologist and radiographer to utilise the full potential of modern MRI scanners. In these circumstances, pelvic MRI can be successful in identifying the source of sepsis, when other techniques have failed.

Once the underlying site of sepsis has been detected, imaging can be used for planning further management. Percutaneous radiological drainage (either under CT or US) may provide a safer alternative to surgery and allows antimicrobial rationalisation following culturing of aspirate.

Collections, often rim enhancing on CT scans, are common in the early days after surgical intervention especially in undernourished patients, due to a reactive and exudative process in the peritoneum. The presence of an enhancing rim alone is not sufficient to define an infected collection, and its shape is equally important, looking for imaging features to indicate whether it is under tension and becoming spherical and deforming, or if it conforms to the peritoneal recesses. Clinical assessment is critical, and in the post-operative period collections should only be drained if symptomatic with swinging fevers or localising pain or persistently elevated/rising inflammatory markers. If there is an enteric leak driving the collections then in most circumstances a fistula will develop along the drainage track. Consideration should therefore be given to the location of the drain with respect to an amenable site for placing a stoma bag later. Small inter-loop collections should generally be left to evolve, unless they are amenable to trans-gastric or other safe drainage option.

Small Bowel Obstruction

Small bowel obstruction (SBO) is a common condition occurring when normal transit of bowel contents is prevented by mechanical or functional causes [8]. In the UK it accounts for nearly half of all laparotomies performed, with an associated 30-day mortality rate of 7% [9]. Effective treatment depends on a rapid and accurate diagnosis, requiring a comprehensive approach with imaging often playing a pivotal role.

Definitions of SBO [10]:

1. Complete/high grade obstruction: no fluid or gas passes beyond the site of obstruction
2. Partial/low grade obstruction: some fluid or gas is able to pass beyond site of obstruction
3. Closed loop obstruction: a segment of bowel that is obstructed at two points along its length and is at risk of ischaemia
4. Strangulated obstruction: indicates that blood flow has been compromised.

The causes of SBO can be divided into three main categories:

1. Intrinsic: inflammatory disease, neoplastic, vascular, haematoma, intussusception
2. Extrinsic: adhesions, hernia, haematoma, endometriosis
3. Intraluminal: gallstones, bezoars, foreign bodies

Traditional teaching states that three main aetiologies account for most causes of mechanical SBO: adhesions, hernias and neoplasia [10]. Adhesions are the most common cause of obstruction, and account for 50–80% of SBO cases [8, 11, 12]. Whilst hernias remain common in developing countries, Crohn's disease has now replaced hernias in Western society as one of the most common causes of SBO [8, 12].

Identification of Obstruction

As well as confirming a diagnosis of SBO, imaging can be used to determine its site and cause, and identify any associated complications [10].

Plain film radiography is advocated as the initial examination due to widespread availability and low cost, although it has a reported accuracy ranging from 50 to 60% [12]. A more recent study reported sensitivities of around 80% [13]. However, in a setting of IF where surgery is not imminent, and removing diagnostic uncertainty may change management, then cross-sectional imaging is warranted. Multi-detector computed tomography (CT) has become the mainstay of imaging where available, with a sensitivity of 82–100% [8]. Ultrasound is often unhelpful due to intraluminal bowel gas obscuring the view of deeper structures, rendering the images non-diagnostic.

Plain Abdominal Radiograph Findings

The hallmark of SBO is the presence of dilated bowel loops (>3 cm) proximal to the obstruction. There are a range of other findings in radiographs for SBO, including a 'string of beads' sign, secondary to slow resorption of intraluminal air, with residual small bubbles trapped between the valvulae conniventes [14]. However, aside from inguinal hernias and gallstone ileus, the cause of SBO is rarely seen on a radiograph, and hence further cross-sectional imaging is usually obtained.

CT Technique and Findings

CT is the preferred investigation for SBO, given its speed and sensitivity. It has a greater ability to determine the site of the transition point, its cause and exclude a closed loop obstruction. The transition point is the point of abrupt calibre change (Fig. 4). If a clear transition point is identified, then the cause can almost always be determined or inferred.

Traditionally, positive oral contrast was administered in patients suspected of having SBO. An advantage to this approach includes a prognostic element, based on the observation that if the contrast passes distally into the decompressed bowel, then high grade SBO is excluded. However, many centres now scan without oral contrast, because (a) nauseated patients may vomit potentially leading to aspiration; (b) in SBO the retained intraluminal fluid serves as an excellent neutral contrast agent, without the need for additional positive oral contrast; (c) its omission eliminates the need for a delay in the examination [10]. Similarly, CTE, which requires ingestion of a large volume (usually at least 1 L) of oral contrast, is therefore not usually performed in an acute setting.

Intravenous contrast is administered, and the patient scanned in the portal venous phase (60–70 s delay) which provides optimal assessment of most abdominal and pelvic structures and also achieves good enhancement of the bowel wall.

The diagnosis of SBO on CT is determined by the presence of dilated small bowel loops (>3 cm diameter) proximal to a transition point, with normal calibre or collapsed loops distally. The colon is often decompressed, depending on the degree of SBO.

The 'small bowel faeces' sign is the presence of particulate material with gas bubbles in the small bowel, similar to the appearance of stool in the colon. This is presumed to be secondary to delayed transit, with increased fluid absorption and accumulation of undigested food as a result of obstruction or stasis [15, 16]. Whilst studies disagree about whether its presence correlates to the degree of obstruction, it serves as a useful aid in finding the transition point [17].

The many causes of SBO have differing appearances; some of the most common causes are outlined below:

Adhesions

Adhesions are bands of fibrous tissue which connects surfaces or organs within the peritoneal cavity that are normally

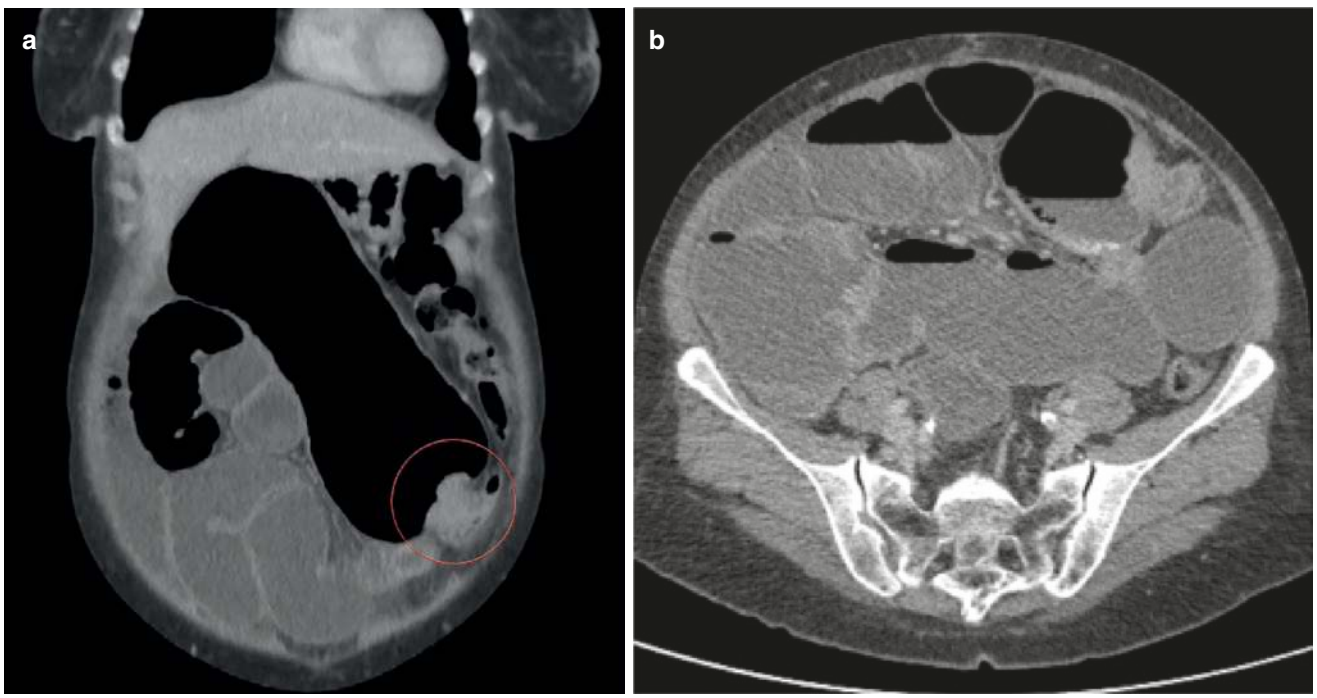

Fig. 4 Coronal (**a**) and axial (**b**) CT shows large bowel obstruction due to transverse colon cancer associated with a clear transition point (arrow) and collapsed colon distal to this

separated [18]. Almost all are secondary to surgery, with a minority caused by peritonitis. The adhesion itself is usually not visible on CT and as such, typically is a diagnosis of exclusion; its presence is inferred when there is an abrupt transition point or sharp angulation of bowel loops, in the absence of an alternative identifiable structural cause [10]. On a BFT, absence of movement of the bowel with respiration or on extrinsic compression increases the level of confidence for adhesions but this assessment is limited by large body habitus and presence of fistula or stoma. Similar observations can also be made with MRI on cine sequences or on US, but again both of these modalities may be challenging in large or unwell patients.

Whilst BFT and CT remain the key examinations for identification of adhesions in clinical practice, a review of multiple studies has shown that both transabdominal ultrasound and dynamic MRI can achieve a diagnostic accuracy between 76% and 92%. Ultrasound can identify adhesions by assessing movement of small bowel, small bowel morphology and visceral glide. Dynamic MRI on the other hand can be assessed during breathing or straining to assess visceral slide. However, one large limitation of most of these studies is a lack of blinding, as surgeons were made aware of findings prior to intraoperative correlation [19].

Crohn's Disease

When SBO occurs due to the acute presentation of Crohn's, this is characterised by stenosis of the bowel lumen, usually secondary to the transmural inflammation. Affected segments may demonstrate wall thickening and hyperenhancement (Fig. 3), associated with mesenteric hypertrophy, vascular engorgement and lymphadenopathy [20]. Classically, the adjacent fat appears clean homogeneous and black in contrast to the oedematous fat stranding seen in other inflammatory conditions. SBO may also manifest in chronic disease, seen on imaging as stenotic strictures but without evidence of active inflammation.

Hernias

Hernias are classified by the anatomic location of the defect through which the bowel protrudes [8]. They are broadly classified as either internal or external, with external being the most common. Common hernia sites include the inguinal canal, the femoral canal and the anterior abdominal wall. The hallmark of SBO secondary to a hernia is the presence of dilated bowel loops with a transition point at the entrance in to the hernia sac and decompressed bowel exiting from the sac [10].

Complicated SBO: Closed Loop Obstruction

A closed loop obstruction is a segment of bowel that becomes obstructed at two points along its length, essentially leading to its isolation from the remainder of the bowel. Commonly, it is caused by a single adhesive band, but internal hernias or iatrogenic defects in the mesentery are also recognised causes [10].

CT findings of closed loop obstruction depend on the orientation of the loop relative to the plane of imaging. Fluid-filled dilated loops with a U-shaped or C-shaped configuration (in longitudinal section) and a corresponding radial distribution (in an orthogonal plane) [21] can be best identified by using multi-planar reformatting for image review. Fusiform tapering at the site of obstruction ("beak" sign) may be present [21]. A "whirl" sign, representing rotated intestinal vessels surrounded by mesenteric soft tissue, fat and bowel loops has also been described [21, 22]. Strangulation occurs in 10% of patients with closed loop obstruction, leading to ischaemia [23] and the earliest sign of this is oedema and associated effects in the affected segmental mesentery together with venous engorgement/dilatation.

Post-operative Ileus

Post-operative ileus (POI) is the impairment or arrest of gastrointestinal motility following surgery. Despite its reported incidence rate of 10–30% for abdominal surgery [24–29] with resultant increase in morbidity and length of stay, there remains no internationally accepted standard definition of POI, nor any consistent distinction between the 'normal' physiological period of dysmotility and the prolonged pathological entity [30, 31].

Whilst clinical presentation of mechanical obstruction and POI are similar in early stages, key differences in radiological findings may sway the diagnosis. A reported feature on abdominal radiographs is gaseous distension of both the small bowel and colon. However, this finding is not reliable, as the colon is difficult to visualise when it is fluid-filled, or if the patient has had a colectomy [32]. CT is more definitive, usually demonstrating dilated bowel loops similar to SBO, but without an abrupt transition point, often gradually tapering to normal calibre distally.

In cases of prolonged ileus, there should be a low threshold for considering alternative underlying pathologies such as anastomotic leak, perforation or collection – all of which can be seen on CT.

Gut Ischaemia

Ischaemia can increase the morbidity and mortality associated with SBO. The physical examination and laboratory findings are not specific and imaging findings can support a diagnosis of ischaemia in the correct clinical context. Accuracy of CT varies amongst studies, with a reported 83–100% sensitivity and 61–93% specificity [33–35].

CT technique for ischaemia remains a contested issue, with some centres advocating for 'triple phase' approach (unenhanced, arterial and portal venous), stating that (a) the unenhanced study allows for a point of reference when determining bowel enhancement and (b) unenhanced increased

bowel wall density reflects haemorrhagic transmural necrosis [36]. However, others argue that unenhanced CT is not required for diagnosis of ischaemia, with its low sensitivity [37]. Most centres opt for a dual phase approach, with an arterial phase to assess the arterial vasculature and portal venous phases to assess bowel wall enhancement and mesenteric/portal venous system.

CT Findings: Arterial vs Venous Ischaemia

The appearances of bowel ischaemia on CT include: bowel wall thickening (>3 mm); mesenteric oedema and/or fluid in the mesentery or peritoneal space; decreased bowel wall enhancement; pneumatosis (intramural gas) with or without associated gas in the mesenteric/portal veins [10]. Pneumatosis is a late sign and is suggestive of infarction. The vasculature should be carefully scrutinised, with accompanying knowledge of the arterial supply and venous drainage of the bowel.

Arterial

Arterial thromboembolism can be seen as a filling defect within or occlusion of the supplying artery, best visualised on the arterial phase. There may be extensive background atherosclerotic disease. Bowel enhancement is absent or decreased due to cessation of arterial supply, with bowel wall thickening rarely occurring unless reperfusion occurs [38]. Perhaps most useful, is the identification of a difference in bowel enhancement within a segment of bowel, compared to adjacent proximal and distal bowel, and may be matched by reduction or absent enhancement of the supplying arterial vessels. The bowel wall may become thinner as ischaemia progresses, leading to pneumatosis as infarction develops (Fig. 5) [39]. Mesenteric inflammatory stranding and ascites are rare but can occur with infarction and perforation [39].

Venous

Venous occlusions accounts for 5–10% of bowel ischaemia [39]. Impairment of the venous drainage increases the hydrostatic pressure, leading to extravasation of fluid into the bowel wall and mesentery [39]. Thrombus in the mesenteric venous system is usually visible [40]. Bowel wall thickening, fat stranding and ascites are commonly present [38].

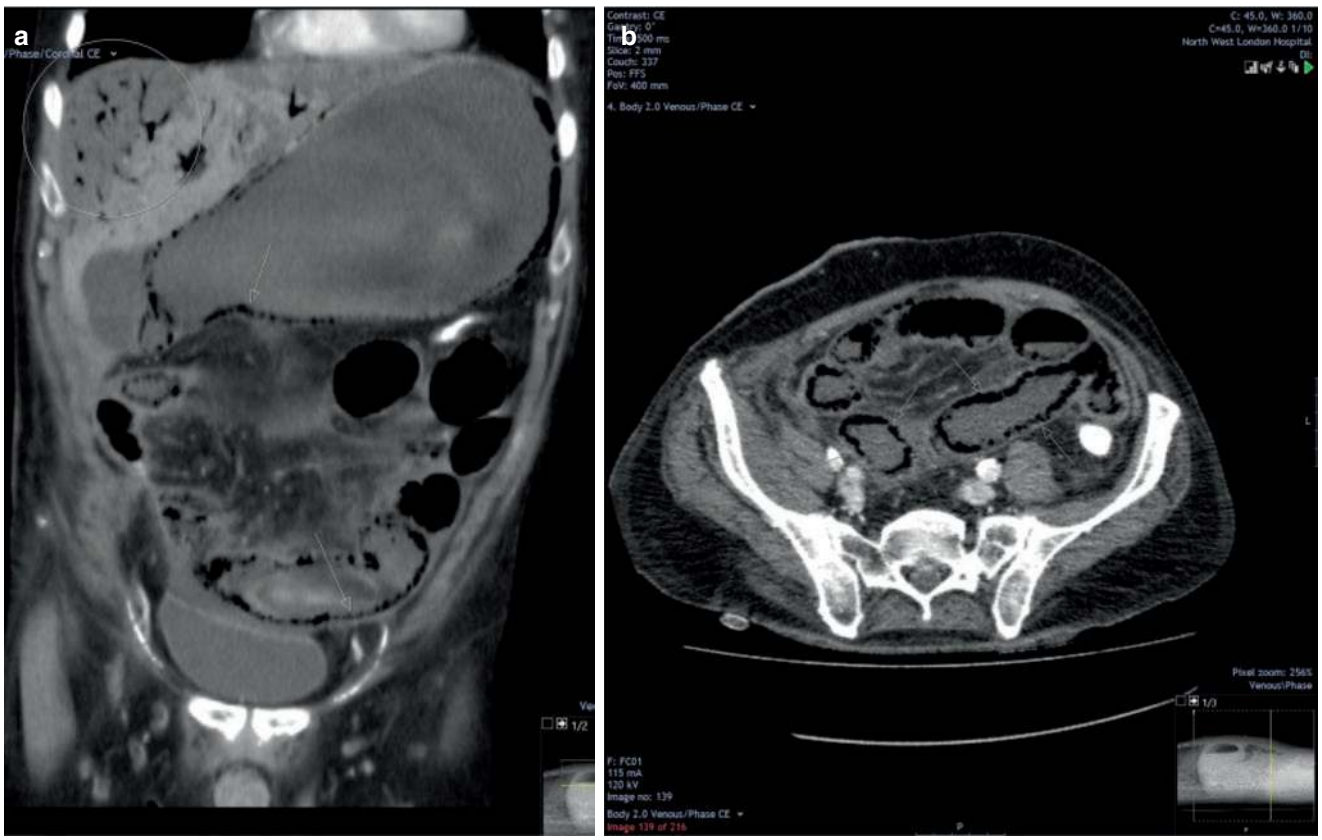

Fig. 5 CT demonstrates extensive pneumatosis indicating bowel infarction. On the coronal image (**a**), there is gas in the wall of the stomach (upper arrow), and in the small bowel (lower arrow). In addition there is portal venous gas associated with liver infarction (circle). Axial CT (**b**) there is gas in the wall of most the visible small bowel (arrows)

Management

Whilst historically management of acute mesenteric ischaemia has focussed on a surgical approach, with restoration of blood flow and resection of necrotic bowel, endovascular treatment (EVT) is now playing an important role [38]. A variety of techniques including catheter directed thrombolysis, embolectomy and stenting can be employed to treat acute thrombotic superior mesenteric artery occlusion [41]. Anticoagulation or low molecular weight heparin is recommended as first line treatment for venous thrombosis, EVT can be considered in certain scenarios if patients deteriorate despite medical treatment [42].

In summary, there are a wide range of CT findings which may or may not be present depending on the stage of ischaemia, and sometimes these changes may be reversible, exacerbating the challenge in making a timely diagnosis, and explaining why there is such a wide range of diagnostic accuracy for identification of ischaemia by CT. Clinicians as well as radiologists must be mindful of the difficulty in excluding bowel ischaemia even with good quality imaging. Clinicians and radiologists should have a low threshold to seek early specialist GI radiology review, as perhaps the most efficient route to addressing any diagnostic uncertainty, if there is a discrepancy between the initial imaging report and clinical suspicion of ischaemia.

Assessing Length of Small Bowel

An accurate understanding of the length of small intestine remaining is particularly important in patients requiring repeated small intestine resection, which may result in short bowel syndrome (SBS) [43]. The morbidity and mortality of SBS is directly related to remaining small intestine length [44], with the degree of malabsorption being influenced by the length of remnant small intestine as well as the status of the patient, their colon, underlying disease process and other absorptive organs [45–48]. Remnant small intestine length is an important indicator for management decisions including autologous small intestine lengthening procedures [49–51], and can be an important factor in assessing likelihood of patients surviving without parenteral nutrition [52]. Therefore, accurate measurement of the remnant small intestinal length is important for clinical prognostication and treatment planning.

Intra-operative

Intra-operative measurement of small intestinal length by an experienced gastrointestinal surgeon, which involves measuring along the anti-mesenteric border (without stretching the bowel) from the ligament of Treitz to the end of the small intestine using known lengths of suture material and a ruler, is regarded as the gold standard [53]. However it is usually only an appropriate option when surgery is indicated for some other reason and length assessment is carried out by a surgeon familiar with the technique. Whilst knowledge of intestinal length is crucial for future decisions, direct measurement may not be available due to: surgery being performed in an emergency situation, variation in surgical expertise, a hostile abdominal environment, or simply an inability to review detailed patient records. Therefore, measurement of small intestinal length by non-invasive radiographic examination is a common route for developing patient specific management plans.

Barium Follow Through

Two studies have demonstrated a correlation between bowel length assessment measured by BFT and clinical prognosis [50, 51]. It is a relatively cheap and widely available study but is limited by 2D imaging, wherein collapsed or superimposed/overlapping bowel segments and loops may result in underestimation of the length when remnant bowel length is over 150 cm. Moreover, patients in the post-operative context can frequently suffer from adhesions and sometimes related to this, pelvic bowel loop aggregation, both of which may further reduce accuracy if overlapping loops can't be separated. Application of an opisometer can improve the accuracy of BFT length assessment [54]. Overall the BFT-surgical measurement correlation was found to be moderate (r^2 values <0.75) [1, 55], including in studies of SBS patients [54].

In our institution, BFT compares favourably with intra-operative measurements of bowel length, particularly with residual lengths of less than 150 cm, and may allow a more accurate assessment of length, compared to CTE or MRE.

One of the limitations of BFT is that it is only able to measure in circuit bowel length. In order to accurately assess length of the out of circuit bowel, a further examination is often required, such as a distal loopogram, with barium or water soluble contrast introduced per catheter, to the afferent limb or fistula, to access the out of circuit bowel.

CT Enterography

The use of CTE had a statistically significant correlation with surgical measurement and outperformed BFT with regards surgical measurement correlation, in a small study of SBS patients [54].

MR Enterography

Measurements of small intestine length are performed on a range of rapid image-acquisition techniques, usually utilising assessments on a range of sequences obtained as each can have a different advantage or drawback for measurement of length (Fig. 6). On some studies, MRE has been shown to more accurately correlate with surgical measurement than CTE [54, 56] but may be very operator dependent.

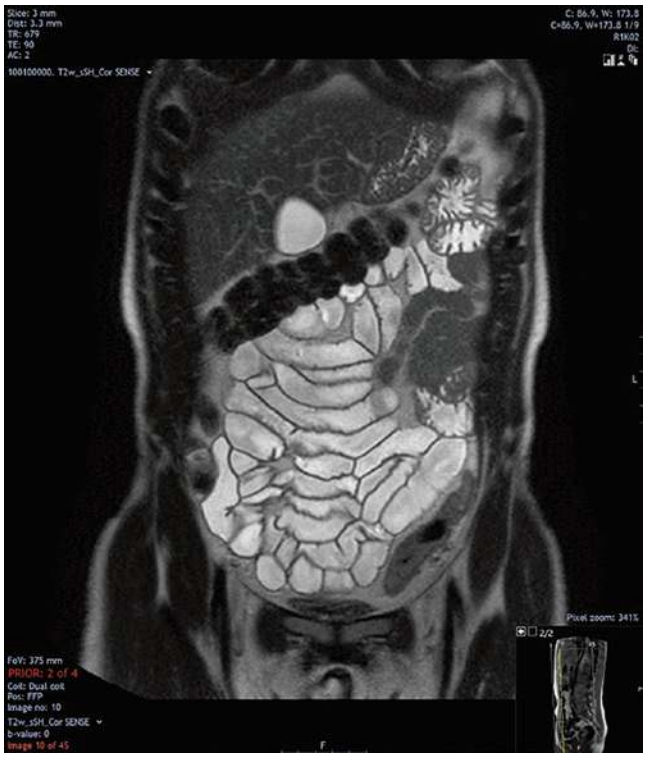

Fig. 6 This is a single coronal image from a T2 sequence of a normal MRE. The majority of the small bowel is well distended, and the quality allows a good assessment of bowel length, when following the course of the small bowel on all of the images in this sequence

Novel Techniques

Preliminary studies have evaluated the use of software aided manual [56] and algorithm based automated [57] methods of small intestine measure on MRE images. Although the latter has so far only been conducted in mice studies, the results are promising and in the future may provide a useful adjunct to improve accuracy of non-invasive methods [57].

The measuring tools available on all PACs software allow accurate measurement of bowel length with all of the modalities described above. However, despite the ability of CT and MR to view the bowel in multiple planes, the course of the bowel may weave in and out of the standard planes, necessitating a very time consuming process of measuring multiple short segments, by repeatedly changing planes to follow all the twists and turns of the entire small bowel. In practical terms, whichever technique is utilised, time is required to meticulously navigate the course of the bowel, either while acquiring the images (BFT) or when analysing them on PACs. A BFT is still readily available in many centres and can be inexpensive, but may be limited by 2D imaging, adhesions, aggregation, pelvic pooling and overlapping bowel loops, and potentially requires more radiologist time to perform the exam. However if good quality images are obtained, paradoxically, the time required to measure bowel length is often less when compared to CT or MR. CTE has been shown on some studies to be superior to BFT and to strongly correlate with surgical measurement. In our institution, CT is gradually becoming the most common technique utilised for assessment of length, in part because many of the patients will have had a CT at their base hospital prior to being referred to our unit.

In general the longer the remaining length of bowel, the longer it will take to complete this process, and the harder it may be to get an accurate measurement of the length. In addition, in patients who have multiple collapsed or adhesed segments, measurement may be difficult or of limited value on a single examination. However, many of these patients will have had at least 2 or more scans at different times, typically associated with acute admissions. In such patients, an accurate measurement may only be obtained by analysis of multiple different examinations at different times, assuming segments that are poorly visible on one exam, are better visualised and hence more easily measured on a different exam obtained at a different time.

Assessment of Quality of Small Bowel

The quality of small bowel and the disease affecting it are important determinants of its ability to carry out its functions of absorption and motility, which are linked to morbidity even when bowel length is maintained [3].

Fluoroscopic examination with luminal contrast is an effective technique for short bowel segments (<150 cm) [58] and contrast can be introduced via multiple routes including orally, via stoma or fistula or per rectum. As a dynamic study it allows a more targeted examination than other modalities, and is particularly helpful in assessment of the distal out of circuit bowel where there has been a defunctioning stoma created, or an enterocutaneous fistula (ECF). There is a significant benefit in watching and controlling luminal distension and in the assessment of fistulae tracts in real time.

Often, studies using a variety of modalities and instillation routes may be required to assess bowel segments independently to overcome issues such as under-distended or overlapping loops, maximise accuracy and provide as much detail as possible to optimise management decisions.

Cross sectional (CT/MRI) imaging has the added benefit of global intestinal and extra-intestinal assessment; mural and mesenteric pathologies can be occult at luminal imaging such as fluoroscopy or capsule endoscopy but may be apparent on CT which is now the mainstay of imaging assessment in most centres due its sensitivity and ubiquity. CT is performed individually or adjunctive to fluoroscopy, for cases

with complex post-surgical anatomy. Water soluble oral contrast is often used with CT to delineate fistulation, sinuses or to demonstrate collections where these are suspected. CTE protocol with bowel distension (as described earlier) is often the optimal technique for assessment of mucosa, wall thickness and bowel lumen calibre, particularly if strictures are suspected [59].

It is important to be aware of the normal cross sectional appearances and parameters of small bowel: fold patterns varies between jejunum, possessing feathery thin closely spaced folds (valvulae conniventes), and ileum which demonstrates a lesser density of folds. On CTE normal small bowel wall thickness should be less than 3 mm when the lumen is distended [60]. Intravenous contrast enhancement is assessed at multiple phases timed following high flow bolus administration of contrast; bowel mucosal enhancement is optimally assessed in the enteric phase (50 s following contrast injection) [61, 62] but can also be adequately assessed on portal venous phase imaging (70 s) [63], whilst arterial phase (30 s) is useful for assessment of vascular compromise.

Features of acute inflammation include: mural hyper-enhancement, bowel wall thickening and stratification (with mural hyper-enhancement being the most sensitive CT imaging sign of active inflammation in the setting of Crohn's disease [61]. Mural stratification describes the laminated appearance to the bowel wall, the appearance occurring due to the presence of mucosal hyper-enhancement with submucosal thickening and hypo-attenuation due to oedema/inflammatory infiltration. Intramural fat can be a normal finding in the ileocaecal valve but can be a sign of chronic inflammation elsewhere [60].

Inflammatory changes in Crohn's disease are frequently on the mesenteric aspect of the bowel and can be penetrating, with a spectrum ranging from ulceration to fistula, appearing as hyper-enhancing transmural/extra-mural tracts within the mesentery. Mesenteric hypertrophy produces a characteristic expansion of the mesenteric fat easily identified on CT with a clean and sharp appearance of fat creating a striking contrast to the increased size and prominence of the mesenteric vascular arcades and producing a classical comb sign in an affected hyperaemic bowel segment. Beyond the acute stages, chronic intestinal inflammation and deposition of extracellular matrix protein are contributory factors to small bowel fibrosis; on imaging this is suggested by the presence of wall thickening in the absence of mural oedema or hyper-enhancement, upstream dilatation and delayed enhancement [64].

Many of the features described above can also be seen on MRE (Fig. 3). Cine MRI is an evolving technique described further in the next section, may in the near future may be a more widely available adjunct to MRE in providing a non-invasive and non-ionising assessment of gut motility [65]. Diffusion weighted imaging, a technique already widely used in other systems notably neuro-imaging, provides an alternative to intravenous contrast for functional evaluation which is particularly valuable in patients with renal impairment, when unenhanced CT would be of limited use. MRE has a high sensitivity and specificity for assessing disease activity in Crohn's disease [58, 60] and when it includes "cine" sequences, can be particularly useful in assessing and demonstrating strictures and complex adhesions.

Mapping Distal Bowel for Distal Feeding and Pre-operative Assessment

With the improvement in clinical nutrition, critical care medicine and minimally invasive bowel sparing surgery, there has been great progress in the management of enterocutaneous fistulae. However, high output fistulae pose a clinical challenge with associated malnutrition and organ dysfunction due to high volume loss of water and electrolytes [66]. This is particularly significant in the setting of patients with a short bowel or small intestine dysfunction, where the absorptive capacity of the remnant gut is reduced.

The conditions for utilisation of enteric nutrition are intestinal continuity and a minimum length of 75 cm of bowel [67]. In these patients imaging assessment with a combination of CT and fluoroscopy, is often used to map the distal bowel and assess integrity prior to feeding; including measurement of the length of the distal bowel, the continuity or otherwise of the remaining segments, as well as the mural and luminal status.

Fluoroscopy can be in the form of a loopogram where a stoma allows access to distal bowel or fistulogram if a fistula is present which may be a suitable entry point for distal feeding. The calibre of the distal bowel is assessed and, in particular, strictures and obstruction should be excluded as these may prohibit distal feeding (Fig. 7) or surgical anastomosis for restoring continuity. The orientation, fold pattern and lumen calibre of the excluded distal bowel may appear abnormal on the imaging assessment however it is worth noting that the imaging appearances may also underestimate structural and functional changes of bypassed segment related to altered blood flow, motility, hormones, secretions and mucosal surface area.

Fistuloclysis involves insertion of a balloon Foley catheter into the fistula and advancement of the catheter under fluoroscopic guidance to a depth of 5 cm into the distal intestinal lumen followed by insufflation of the balloon catheter. The proximal intestine lumen is intubated with a double pipe to collect intestinal fluid [67].

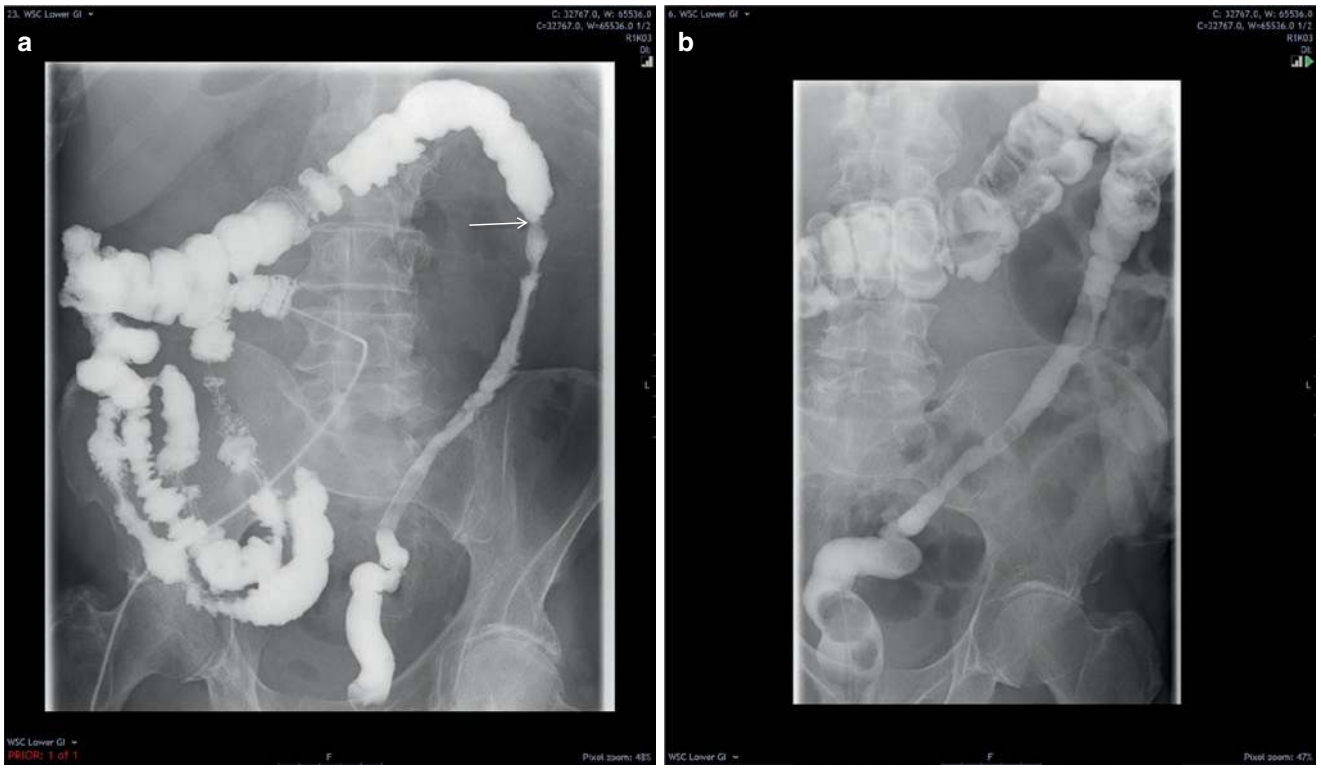

Fig. 7 (**a**) Distal loopogram to assess colon pre distal feeding, shows narrowing of the descending colon (arrow) with a clear transition from normal to reduced calibre. (**b**) A water soluble contrast enema, in the same patient after a period of distal feeding shows increased calibre of the descending colon

Motility Assessments

Dynamic small bowel imaging, which allows assessment of motility, is an evolving area of research, and includes various techniques which increasingly are being used in routine MRI small bowel protocols. Small single centre studies have shown that motility assessment protocols not only increases lesion detection rate compared with conventional MR enterography, [68] but that motility also is altered in distant macroscopically non-affected segments with active Crohn's disease (CD) [69]. Active inflammation, penetrating disease and a fixed stricture are associated with decreased small bowel motility [70]. Terminal ileum motility correlated with histology findings for active and chronic CD but did not allow differentiation between active and chronic disease, [71] and during flares, small bowel motility correlated with blood markers including calprotectin and CRP [72]. The length of inflammatory segments and wall thickening on the other hand did not correlate with the frequency of contractions [73].

Several studies have investigated the quantification of small bowel motility. One study has shown that quantification of small bowel motility is repeatable and sensitive to changes in response to drug therapy [74].

Fistula Tract Mapping

Fistulography

A fistulogram has been considered the best way of mapping a fistula tract when there is an external opening. Contrast is injected through the external opening and images are acquired using fluoroscopy [75]. One key limitation is the limitation in visualisation of adjacent or extramural pathology [76]. When an external opening cannot be identified, other contrast techniques described below and elsewhere can be carried out per stoma or per rectum to identify the luminal origin of the ECF.

Barium/Water Soluble Contrast Follow-Through

A small bowel follow through (SBFT) study can help to delineate the fistula tract when fistulography is inconclusive and to assess the bowel both proximal and distal to any fistula. Utilising barium rather than water soluble contrast may increase the sensitivity for detection of tracts. However, SBFT may fail to locate the tract if contrast passes through quickly or if the tract is small or occluded. As a consequence of this and the inability to evaluate occluded or incompletely patent fistula, SBFT may have a lower accuracy than CT and MRI [77].

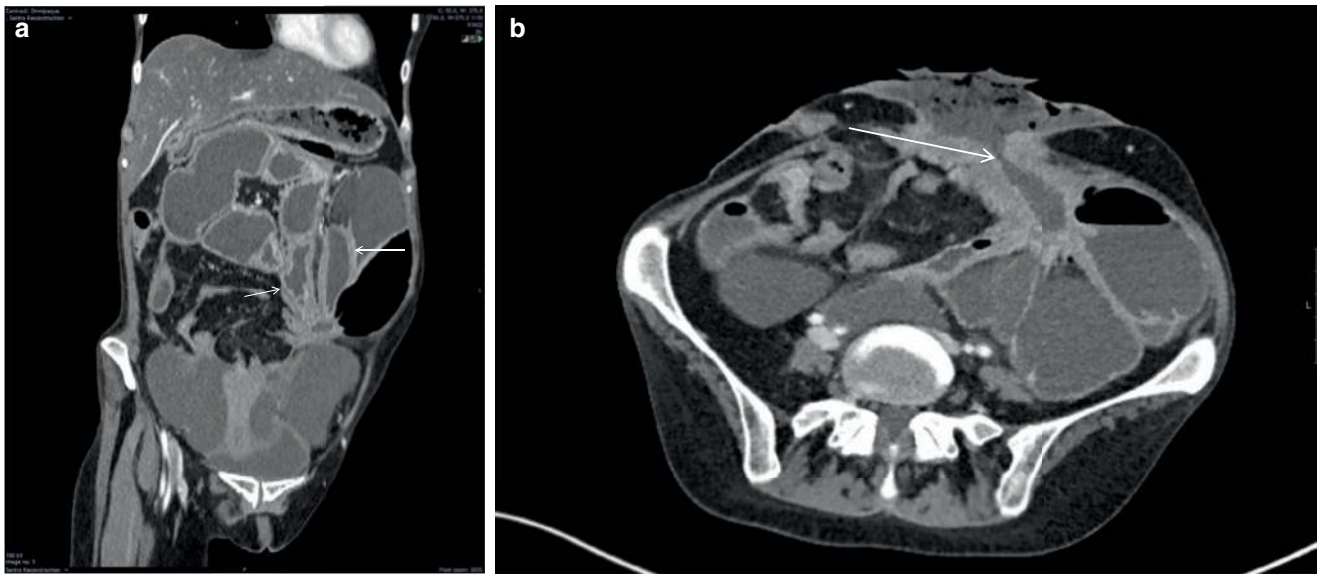

Fig. 8 (**a**) Coronal CT showing multiple loops converging towards a EC fistula. The increased mucosal enhancement and wall thickness indicates active disease (arrows). The whole of the EC fistula is fully appreciated on the axial CT (**b**) which shows the EC tract reaching the external opening (arrowed)

CT

CT allows high spatial resolution images of the fistula tract and its relationship to adjacent structures (Fig. 8). Positive oral contrast can help to better identify bowel loops especially in cases where patients lack intra-abdominal fat. Furthermore, if contrast opacifies the tract, it not only makes identification of a fistula tract easier, it also confirms patency. Another option is carrying out CT fistulography with injection of dilute contrast material through the external opening prior to CT. Care should be taken to ensure that very dilute contrast is used as the concentration required for per-oral or per fistula techniques on fluoroscopy are too high for use in CT where considerable artefacts will be generated. The typical appearance of an ECF is a tubular structure extending from a bowel loop anteriorly towards the peritoneum, crossing subcutaneous tissues towards the skin. Loops of bowel can become adherent to the anterior abdominal wall converging towards the fistula tract.

MRI

MRI has an established role in perianal and other pelvic fistulating disease, but can also be used in the assessment of cutaneous fistulae throughout the abdomen and pelvis. Use of high resolution T2 scans (Fig. 9) focussing on the region around an external opening or expected site of fistula (based on prior imaging) is often the most effective way of identifying a tract. It is critical that Hyoscine Butylbromide or other gut paralytic agent is given at the start of the examination to ensure bowel movement artefact is minimised. Heavily T2 weighted, fat saturated and post contrast sequences can also help to delineate tracts, and are therefore routinely used in perianal protocols. If patients are prone to repeated CT imaging then MRI can have an important role to minimise radiation dose, in patients that are not acutely unwell or can manage the requirements of an MRI scan (Figs. 9 and 10).

Ultrasound

Ultrasound can have a similar diagnostic accuracy as fluoroscopic contrast studies for identifying fistulas, reaching up to 87% sensitivity and 90% specificity, however ultrasound has the additional advantage of identifying other extra-luminal disease e.g. collections. In those departments with better access to US than other imaging modalities, it may provide a quick and convenient assessment or provide additional information to aid the interpretation of other tests. The use of hydrogen peroxide inserted through the skin opening can increase the sensitivity of detecting the internal opening [78].

Malignancy and ECFs

In instances when patients have spontaneous or unexpected ECF, underlying malignancy needs to be excluded. Although rare, any mass like areas with irregular or asymmetric wall thickening with an abrupt transition on CT and MRI should raise the suspicion of neoplasia. Malignant transformation associated with longstanding ECF or other fistulating inflammatory disease is well recognised and not only should patients be appropriately counselled, where surgery or curative therapy is not an option, but consideration of surveillance imaging is important. Both squamous and adenocarcinomas are described and the prognosis is poor.

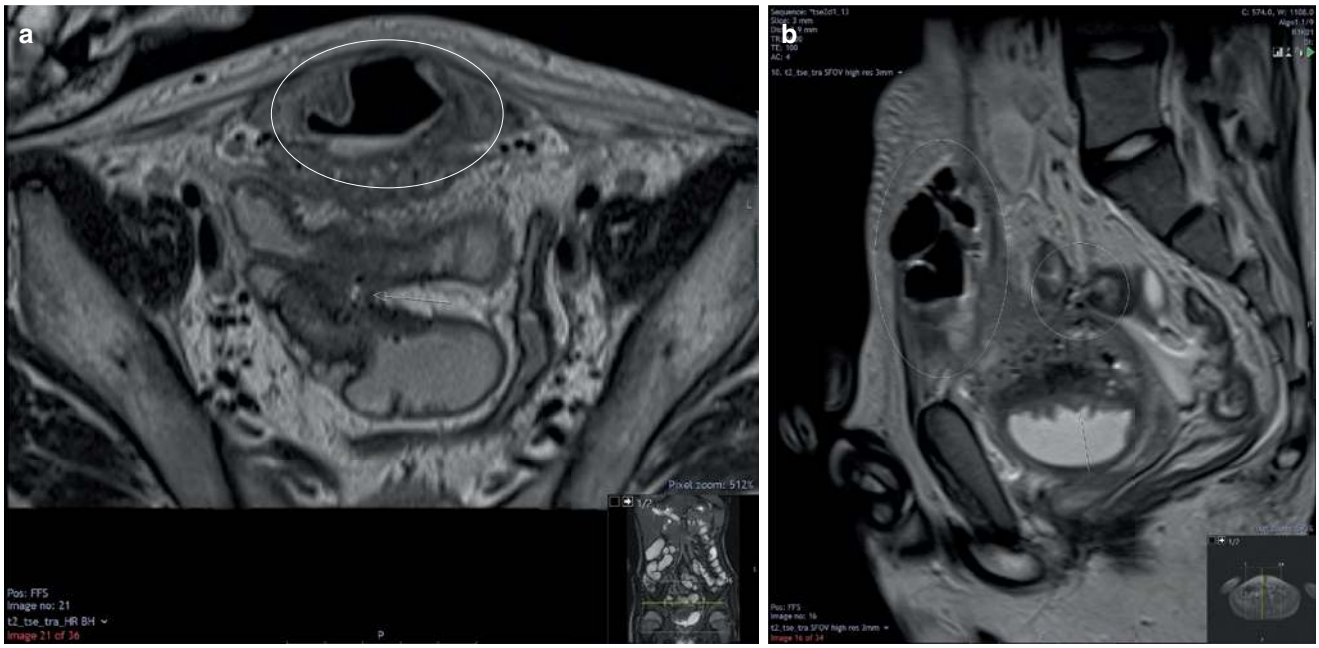

Fig. 9 (**a**) High resolution axial MR T2 sequence shows entero-enteric fistula (arrowed) and this also communicated with a gas containing abscess in the muscle of the anterior pelvic wall (elipse). (**b**) Sagittal MRI T2 sequence shows entero-enteric fistula (circled), with changes extending to the dome of the bladder where there is wall thickening (arrow) and the gas filled collection in the anterior pelvic wall (ellipse)

Abdominal Wall Assessment

Detailed assessment and reporting of the abdominal wall is important in IF patients as often these patients have had previous surgeries and may have a stoma, cutaneous fistula, hernia, or abdominal wall collection. No dedicated imaging of abdominal wall or modification of the imaging techniques is necessary. Most of the necessary information regarding the abdominal wall can be obtained by focused specialist review of previous cross-sectional imaging, especially CT scan.

Assessment should specifically comment on the presence or absence of an abdominal wall hernia. If one is present, the following features should be noted; its location, size of abdominal wall defect (maximum length and width in cm), contents, assessment of loss of domain, complications of the hernia, abdominal wall thickness and quality and evidence of previous surgery (including presence of mesh). The report should also highlight if there are any adhesions and the location of any fistula or stoma in addition to the standard report of the abdomino-pelvic viscera [79].

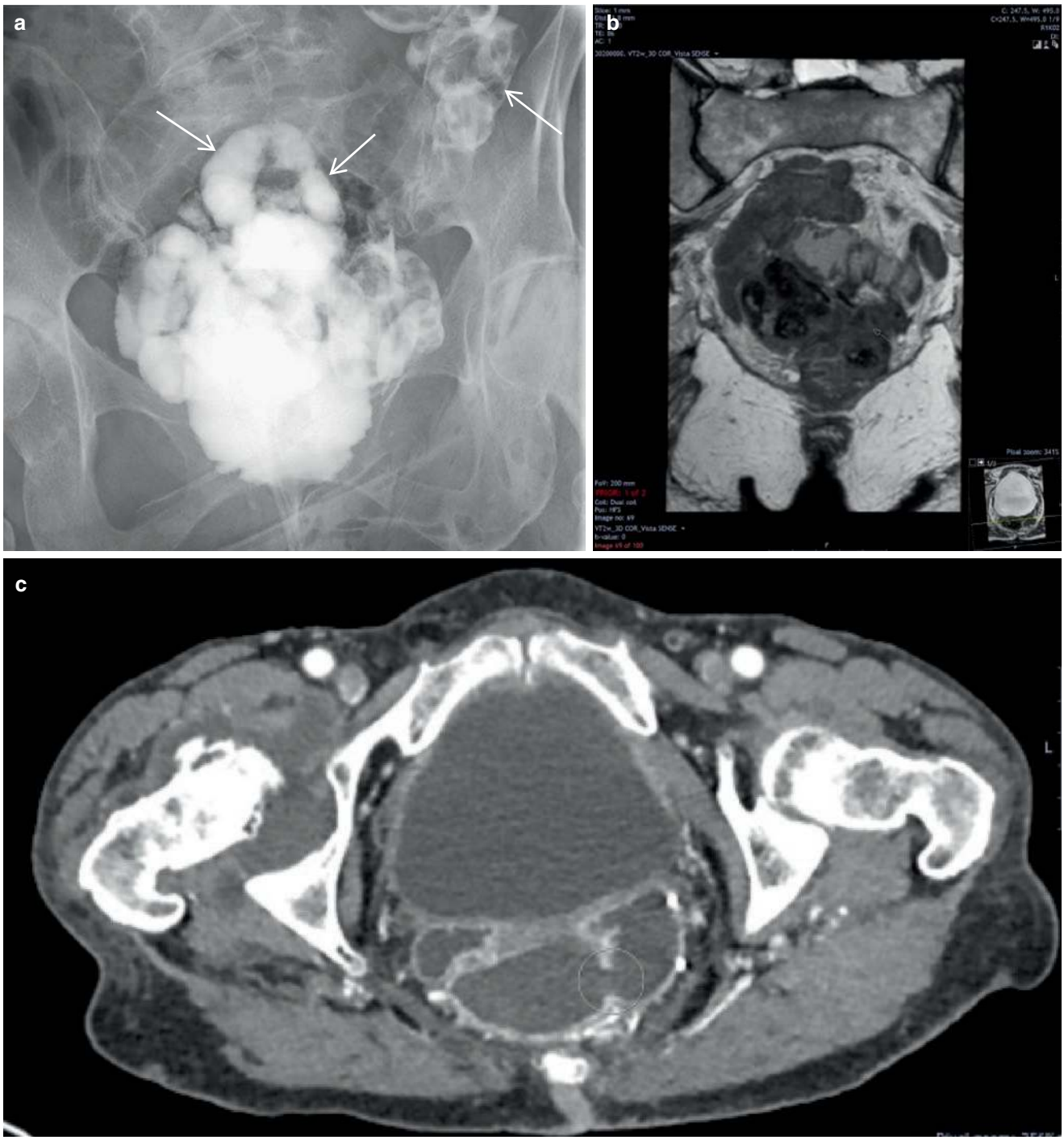

Fig. 10 (**a**). Contrast enema shows abnormal filling of the small bowel (thin arrows), with only small volume of contrast in the descending colon (broken arrow), but the site of fistula was not visible. An MR (**b**) was done, but the site of fistula (arrow) was still hard to identify, until reviewed in conjunction with the CT (**c**), which more clearly shows the entero-rectal fistula (circled)

References

1. Nightingale JMD, Bartram CI, Lennard-Jones JE. Length of residual small bowel after partial resection: correlation between radiographic and surgical measurements. Gastrointest Radiol [Internet]. 1991 Dec;16(1):305–6.
2. Garzelli L, Nuzzo A, Copin P, Calame P, Corcos O, Vilgrain V, et al. Contrast-enhanced CT for the diagnosis of acute mesenteric ischemia. Am J Roentgenol. 2020;215(1):29–38.
3. Davidson J, Plumb A, Burnett H. Adult intestinal failure. Clin Radiol [Internet]. 2010;65(5):395–402.
4. Ilangovan R, Burling D, George A, Gupta A, Marshall M, Taylor SA. CT enterography: review of technique and practical tips. Br J Radiol. 2012;85(1015):876–86.
5. Kuehle CA, Ajaj W, Ladd SC, Massing S, Barkhausen J, Lauenstein TC. Hydro-MRI of the small bowel: effect of contrast volume, timing of contrast administration, and data acquisition on bowel distention. Am J Roentgenol. 2006 Oct;187(4):W375–85.
6. Barber JL, Maclachlan J, Planche K, Furman M, Crespi D, Bab N, Beal I. There is good agreement between MR enterography and bowel ultrasound with regards to disease location and activity in paediatric inflammatory bowel disease. Clin Radiol. 2017;72(7):590–7.
7. Grainger JT, Maeda Y, Donnelly SC, Vaizey CJ. Assessment and management of patients with intestinal failure: a multidisciplinary approach. Clin Exp Gastroenterol. 2018;11:233–41.
8. Silva AC, Pimenta M, Guimarães LS. Small bowel obstruction: what to look for. Radiographics. 2009;29(2):423–39.
9. NELA Project Team. Sixth patient report of the national emergency laparotomy audit. London: RCoA; 2020.
10. Paulson EK, Thompson WM. Review of small-bowel obstruction: the diagnosis and when to worry. Radiology. 2015;275(2):332–42.
11. Maglinte DD, Reyes BL, Harmon BH, Kelvin FM, Turner WW, Hage JE, et al. Reliability and role of plain film radiography and CT in the diagnosis of small-bowel obstruction. AJR Am J Roentgenol. 1996;167(6):1451–5.
12. Miller G, Boman J, Shrier I, Gordon PH. Etiology of small bowel obstruction. Am J Surg. 2000;180(1):33–6.
13. Thompson WM, Kilani RK, Smith BB, Thomas J, Jaffe TA, Delong DM, et al. Accuracy of abdominal radiography in acute small-bowel obstruction: does reviewer experience matter? AJR Am J Roentgenol. 2007;188(3):W233–8.
14. Nicolaou S, Kai B, Ho S, Su J, Ahamed K. Imaging of acute small-bowel obstruction. AJR Am J Roentgenol. 2005;185(4):1036–44.
15. Mayo-Smith WW, Wittenberg J, Bennett GL, Gervais DA, Gazelle GS, Mueller PR. The CT small bowel faeces sign: description and clinical significance. Clin Radiol. 1995;50(11):765–7.
16. Jacobs SL, Rozenblit A, Ricci Z, Roberts J, Milikow D, Chernyak V, et al. Small bowel faeces sign in patients without small bowel obstruction. Clin Radiol. 2007;62(4):353–7.
17. Lazarus DE, Slywotsky C, Bennett GL, Megibow AJ, Macari M. Frequency and relevance of the "small-bowel feces" sign on CT in patients with small-bowel obstruction. AJR Am J Roentgenol. 2004;183(5):1361–6.
18. Ten Broek RPG, Krielen P, Di Saverio S, Coccolini F, Biffl WL, Ansaloni L, et al. Bologna guidelines for diagnosis and management of adhesive small bowel obstruction (ASBO): 2017 update of the evidence-based guidelines from the world society of emergency surgery ASBO working group. World J Emerg Surg. 2018;13:24.
19. Zinther NB, Fedder J, Friis-Andersen H. Noninvasive detection and mapping of intraabdominal adhesions: a review of the current literature. Surg Endosc. 2010;24(11):2681–6. https://doi.org/10.1007/s00464-010-1119-6.
20. Guglielmo FF, Anupindi SA, Fletcher JG, Al-Hawary MM, Dillman JR, Grand DJ, et al. Small bowel crohn disease at CT and MR enterography: imaging atlas and glossary of terms. Radiographics. 2020;40(2):354–75.
21. Balthazar EJ, Birnbaum BA, Megibow AJ, Gordon RB, Whelan CA, Hulnick DH. Closed-loop and strangulating intestinal obstruction: CT signs. Radiology. 1992;185(3):769–75.
22. Duda JB, Bhatt S, Dogra VS. Utility of CT whirl sign in guiding management of small-bowel obstruction. AJR Am J Roentgenol. 2008;191(3):743–7.
23. Balthazar EJ, George W. Holmes Lecture. CT of small-bowel obstruction. AJR Am J Roentgenol. 1994;162(2):255–61.
24. Svatek RS, Fisher MB, Williams MB, Matin SF, Kamat AM, Grossman HB, et al. Age and body mass index are independent risk factors for the development of postoperative paralytic ileus after radical cystectomy. Urology. 2010;76(6):1419–24.
25. Kim MJ, Min GE, Yoo KH, Chang SG, Jeon SH. Risk factors for postoperative ileus after urologic laparoscopic surgery. J Korean Surg Soc. 2011;80(6):384–9.
26. Millan M, Biondo S, Fraccalvieri D, Frago R, Golda T, Kreisler E. Risk factors for prolonged postoperative ileus after colorectal cancer surgery. World J Surg. 2012;36(1):179–85.
27. Chapuis PH, Bokey L, Keshava A, Rickard MJ, Stewart P, Young CJ, et al. Risk factors for prolonged ileus after resection of colorectal cancer: an observational study of 2400 consecutive patients. Ann Surg. 2013;257(5):909–15.
28. Vather R, Josephson R, Jaung R, Robertson J, Bissett I. Development of a risk stratification system for the occurrence of prolonged postoperative ileus after colorectal surgery: a prospective risk factor analysis. Surgery. 2015;157(4):764–73.
29. Moghadamyeghaneh Z, Hwang GS, Hanna MH, Phelan M, Carmichael JC, Mills S, et al. Risk factors for prolonged ileus following colon surgery. Surg Endosc. 2016;30(2):603–9.
30. Vather R, Trivedi S, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. J Gastrointest Surg. 2013;17(5):962–72.
31. Venara A, Neunlist M, Slim K, Barbieux J, Colas PA, Hamy A, et al. Postoperative ileus: pathophysiology, incidence, and prevention. J Visc Surg. 2016;153(6):439–46.
32. Frager DH, Baer JW, Rothpearl A, Bossart PA. Distinction between postoperative ileus and mechanical small-bowel obstruction: value of CT compared with clinical and other radiographic findings. AJR Am J Roentgenol. 1995;164(4):891–4.
33. Frager D, Baer JW, Medwid SW, Rothpearl A, Bossart P. Detection of intestinal ischemia in patients with acute small-bowel obstruction due to adhesions or hernia: efficacy of CT. AJR Am J Roentgenol. 1996;166(1):67–71.
34. Balthazar EJ, Liebeskind ME, Macari M. Intestinal ischemia in patients in whom small bowel obstruction is suspected: evaluation of accuracy, limitations, and clinical implications of CT in diagnosis. Radiology. 1997;205(2):519–22.
35. Zalcman M, Sy M, Donckier V, Closset J, Gansbeke DV. Helical CT signs in the diagnosis of intestinal ischemia in small-bowel obstruction. AJR Am J Roentgenol. 2000;175(6):1601–7.
36. Chuong AM, Corno L, Beaussier H, Boulay-Coletta I, Millet I, Hodel J, et al. Assessment of bowel wall enhancement for the diagnosis of intestinal ischemia in patients with small bowel obstruction: value of adding unenhanced CT to contrast-enhanced CT. Radiology. 2016;280(1):98–107.
37. Schieda N, Fasih N, Shabana W. Triphasic CT in the diagnosis of acute mesenteric ischaemia. Eur Radiol. 2013;23(7):1891–900.
38. Kanasaki S, Furukawa A, Fumoto K, Hamanaka Y, Ota S, Hirose T, et al. Acute mesenteric ischemia: multidetector CT findings and endovascular management. Radiographics. 2018;38(3):945–61.
39. Furukawa A, Kanasaki S, Kono N, Wakamiya M, Tanaka T, Takahashi M, et al. CT diagnosis of acute mesenteric ischemia from various causes. AJR Am J Roentgenol. 2009;192(2):408–16.

40. Acosta S, Alhadad A, Ekberg O. Findings in multi-detector row CT with portal phase enhancement in patients with mesenteric venous thrombosis. Emerg Radiol. 2009;16(6):477–82.
41. Acosta S, Björck M. Modern treatment of acute mesenteric ischaemia. Br J Surg. 2014;101(1):e100–8.
42. Tilsed JV, Casamassima A, Kurihara H, Mariani D, Martinez I, Pereira J, et al. ESTES guidelines: acute mesenteric ischaemia. Eur J Trauma Emerg Surg. 2016;42(2):253–70.
43. Schlussel AT, Steele SR, Alavi K. Current challenges in the surgical management of Crohn's disease: a systematic review. Am J Surg. 2016;212(2):345–51. https://doi.org/10.1016/j.amjsurg.2015.12.027.
44. Mccullagh M, Garvie DC, Dykes EH. A new method of intestinal salvage for severe small bowel ischemia. J Pediatr Surg. 1994;29(9):1231–3. https://doi.org/10.1016/0022-3468(94)90809-5.
45. Thompson JS, Langnas AN, Pinch LW, Kaufman S, Quigley EM, Vanderhoof JA. Surgical approach to short-bowel syndrome. Experience in a population of 160 patients. Ann Surg. 1995;222(4):600–5. https://doi.org/10.1097/00000658-199522240-00016.
46. Thompson JS, Weseman RA, Rochling FA, Grant WJ, Botha JF, Langnas AN, et al. Pre-resection obesity increases the risk of hepatobiliary complications in short bowel syndrome. Nutrients. 2012;4(10):1358–66. https://doi.org/10.3390/nu4101358.
47. Nordgaard I, Hansen BS, Mortensen PB. Colon as a digestive organ in patients with short bowel. Lancet. 1994;343(8894):373–6. https://doi.org/10.1016/s0140-6736(94)91220-3.
48. Pakarinen MP, Pakkasjärvi N, Merras-Salmio L, Koivusalo A, Rintala R. Intestinal rehabilitation of infantile onset very short bowel syndrome. J Pediatr Surg. 2015;50(2):289–92. https://doi.org/10.1016/j.jpedsurg.2014.11.018.
49. Dore M, Junco PT, Andres AM, Sáchez-Galán A, Amesty MV, Ramos E, et al. Surgical rehabilitation techniques in children with poor prognosis short bowel syndrome. Eur J Pediatr Surg. 2016;26(01):112–6. https://doi.org/10.1055/s-0035-1567805.
50. Lodwick D, Dienhart M, Ambeba E, Yacob D, Balint J, Bates DG, et al. Accuracy of radiographic estimation of small bowel dimensions in pediatric patients with short bowel syndrome. J Pediatr Surg. 2016;51(6):953–6. https://doi.org/10.1016/j.jpedsurg.2016.02.059.
51. Hukkinen M, Kivisaari R, Merras-Salmio L, Koivusalo A, Pakarinen MP. Small bowel dilatation predicts prolonged parenteral nutrition and decreased survival in pediatric short bowel syndrome. Ann Surg. 2017;266(2):369–75. https://doi.org/10.1097/SLA.0000000000001893.
52. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35(2):247–307. https://doi.org/10.1016/j.clnu.2016.01.020.
53. Teitelbaum EN, Vaziri K, Zettervall S, Amdur RL, Orkin BA. Intraoperative small bowel length measurements and analysis of demographic predictors of increased length. Clin Anat. 2013;26(7):827–32. https://doi.org/10.1002/ca.22238.
54. Cheng W, Zhang S, Wang J, Zhou C, Li Y, Li J. Three-dimensional CT enterography versus barium follow-through examination in measurement of remnant small intestinal length in short bowel syndrome patients. Abdom Radiol 2018; 43(11): 2955-2962doi: https://doi.org/10.1007/s00261-018-1597-x.
55. Shatari T, Clark MA, Lee JR, Keighley MR. Reliability of radiographic measurement of small intestinal length. Color Dis. 2004;6(5):327–9. https://doi.org/10.1111/j.1463-1318.2004.00603.x.
56. Sinha R, Trivedi D, Murphy PD, Fallis S. Small-intestinal length measurement on MR enterography: comparison with in vivo surgical measurement. AJR Am J Roentgenol. 2014;203(3):W274–9. https://doi.org/10.2214/AJR.13.11944.
57. Wilson NA, Park HS, Lee KS, Barron LK, Warner BW. A novel approach to calculating small intestine length based on magnetic resonance enterography. J Am Coll Surg. 2017;225(2):266–273.e1. https://doi.org/10.1016/j.jamcollsurg.2017.04.009.
58. Smith J, Godfrey E, Bowden D, Hickman K, Sharkey L, Butler A, et al. Imaging of adult intestinal failure. Clin Radiol. 2019;74(8):603–12. https://doi.org/10.1016/j.crad.2018.12.007.
59. Taylor SA, Avni F, Cronin CG, Hoeffel C, Kim SH, Laghi A, et al. The first joint ESGAR/ESPR consensus statement on the technical performance of cross-sectional small bowel and colonic imaging. Eur Radiol. 2017;27(6):2570–82. https://doi.org/10.1007/s00330-016-4615-9.
60. Schindera ST, Nelson RC, DeLong DM, Jaffe TA, Merkle EM, Paulson EK, et al. Multi-detector row CT of the small bowel: peak enhancement temporal window—initial experience. Radiology. 2007;243(2):438–44. https://doi.org/10.1148/radiol.2432060534.
61. Lee SJ, Park SH, Kim AY, Yang SK, Yun SC, Lee SS, et al. A prospective comparison of standard-dose CT enterography and 50% reduced-dose CT enterography with and without noise reduction for evaluating Crohn disease. AJR Am J Roentgenol. 2011;197(1):50–7. https://doi.org/10.2214/AJR.11.6582.
62. Kambadakone AR, Chaudhary NA, Desai GS, Nguyen DD, Kulkarni NM, Sahani DV. Low-dose MDCT and CT enterography of patients with Crohn disease: feasibility of adaptive statistical iterative reconstruction. AJR Am J Roentgenol. 2011;196(6):W743–52. https://doi.org/10.2214/AJR.10.5303.
63. Vandenbroucke F, Mortelé KJ, Tatli S, Pelsser V, Erturk SM, De Mey J, et al. Noninvasive multidetector computed tomography enterography in patients with small-bowel Crohn's disease: is a 40-second delay better than 70 seconds? Acta Radiol. 2007;48(10):105–1060. https://doi.org/10.1080/02841850701589290.
64. Rimola J, Planell N, Rodríguez S, Delgado S, Ordás I, Ramírez-Morros A, et al. Characterization of inflammation and fibrosis in Crohn's disease lesions by magnetic resonance imaging. Am J Gastroenterol. 2015;110(3):432–40. https://doi.org/10.1038/ajg.2014.424.
65. Wnorowski AM, Guglielmo FF, Mitchell DG. How to perform and interpret cine MR enterography. J Magn Reson Imaging. 2015;42(5):1180–9. https://doi.org/10.1002/jmri.24981.
66. Sica J, Burch J. Management of intestinal failure and high-output stomas. Br J Nurs 2007;16(13):772, 774, 776–7. https://doi.org/10.12968/bjon.2007.16.13.24242.
67. Tang Q, Hong Z, Ren H, Wu L, Wang G, Gu G, et al. Nutritional management of patients with enterocutaneous fistulas: practice and progression. Front Nutr. 2020;7:564379. https://doi.org/10.3389/fnut.2020.564379.
68. Menys A, Atkinson D, Odille F, Ahmed A, Novelli M, Rodriguez-Justo M, Proctor I, Punwani S, Halligan S, Taylor SA. Quantified terminal ileal motility during MR enterography as a potential biomarker of Crohn's disease activity: a preliminary study. Eur Radiol. 2012;22(11):2494–501. https://doi.org/10.1007/s00330-012-2514-2.
69. Bickelhaupt S, Froehlich JM, Cattin R, Patuto N, Tutuian R, Wentz KU, Culmann JL, Raible S, Bouquet H, Bill U, Patak MA. Differentiation between active and chronic Crohn's disease using MRI small-bowel motility examinations – initial experience. Clin Radiol. 2013;68(12):1247–53. https://doi.org/10.1016/j.crad.2013.06.024.
70. Lambrou T, Chaudhry NA, Grajo JR, Moser P, Riverso M, Mramba LK, Zimmermann EM. Small bowel stricture is associated with abnormal motility on the cine MRI sequence in patients with Crohn's disease. Eur J Radiol. 2019;118:264–70. https://doi.org/10.1016/j.ejrad.2019.08.001.
71. Cullmann JL, Bickelhaupt S, Froehlich JM, Szucs-Farkas Z, Tutuian R, Patuto N, Dawson H, Patak MA. MR imaging in Crohn's disease: correlation of MR motility measurement with histopathology

in the terminal ileum. Neurogastroenterol Motil. 2013;25(9):749–e577. https://doi.org/10.1111/nmo.12162.
72. Bickelhaupt S, Pazahr S, Chuck N, Blume I, Froehlich JM, Cattin R, Raible S, Bouquet H, Bill U, Rogler G, Frei P, Boss A, Patak MA. Crohn's disease: small bowel motility impairment correlates with inflammatory-related markers C-reactive protein and calprotectin. Neurogastroenterol Motil. 2013;25(6):467–73. https://doi.org/10.1111/nmo.12088.
73. Bickelhaupt S, Wurnig M, Boss A, Patak MA. Correlation between morphological expansion and impairment of intra- and prelesionary motility in inflammatory small bowel lesions in patients with Crohn's disease - preliminary data. Eur J Radiol. 2014;83(7):1044–50. https://doi.org/10.1016/j.ejrad.2014.03.009.
74. Menys A, Taylor SA, Emmanuel A, Ahmed A, Plumb AA, Odille F, Alam A, Halligan S, Atkinson D. Global small bowel motility: assessment with dynamic MR imaging. Radiology. 2013;269(2):443–50. https://doi.org/10.1148/radiology.13130151.
75. Alexander ES, Weinberg S, Clark RA, Belkin RD. Fistulas and sinus tracts: radiographic evaluation, management, and outcome. Gastrointest Radiol. 1982;7(2):135–40. https://doi.org/10.1007/BF01887627.
76. Tonolini M, Magistrelli P. Enterocutaneous fistulas: a primer for radiologists with emphasis on CT and MRI. Insights Imaging. 2017;8(6):537–48. https://doi.org/10.1007/s13244-017-0572-3.
77. Lee SS, Kim AY, Yang SK, Chung JW, Kim SY, Park SH, Ha HK. Crohn disease of the small bowel: comparison of CT enterography, MR enterography, and small-bowel follow-through as diagnostic techniques. Radiology. 2009;251(3):751–61. https://doi.org/10.1148/radiol.2513081184.
78. Maconi G, Parente F, Bianchi Porro G. Hydrogen peroxide enhanced ultrasound-fistulography in the assessment of enterocutaneous fistulas complicating Crohn's disease. Gut. 1999;45(6):874–8. https://doi.org/10.1136/gut.45.6.874.
79. Halligan S, Parker S, Plumb A, Windsor A. Imaging complex ventral hernias, their surgical repair, and their complications. Eur Radiol. 2018;28(8):3560–9.

Insertion, Types and Care of Enteral Feeding Tubes

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Key Points

1. Enteral nutrition (EN) is given for no or insufficient oral intake when it is safe to do so and when there is adequate functioning small bowel present.
2. Nasogastric tubes need the tip position carefully checking with an acidic aspirate (pH < 5) and if doubt a chest radiograph.
3. Gastrostomy tubes are most commonly and most safely inserted at endoscopy.
4. Jejunal tubes may be inserted at the bedside (with or without an electromagnetic devise), during an endoscopy, using radiological screening or at surgery.
5. After gastrostomy insertion feeding may start after 2–4 h, the tube should be on very gentle tension for a week, then this is relaxed and the tube rotated daily and pushed in 2–10 cm once a week.
6. Distal feeding into defunctioned bowel or a fistula is done via a small diameter feeding catheter or balloon catheter providing there is no distal obstruction. The feed may provide all the nutrition required (complete) or a small amount to stimulate motility and be trophic to the mucosa.
7. A buried gastrostomy internal flange (bumper) occurs if there is much traction on a gastrostomy tube. A buried internal flange can, if patent, sometimes be removed by stiffening and pushing the tube inwards, and/or dilating or cutting (with an endoscopic needle knife) the gastric tissue to free the internal flange.

Introduction

Most patients receiving enteral nutrition will have oral (intake) failure most commonly due to neuromuscular disorders, head/neck cancer and occasionally cardio-respiratory diseases or dysmotility/malabsorption problems. If those with IF cannot absorb adequate macronutrients and fluid with an increased intake, dietary/fluid modifications and sip feeds, then enteral feeding may be needed. EN may be given to utilize the gut for longer periods (e.g. with an overnight enteral feed) [1, 2]. Enteral feeding is usually preferred to parenteral nutrition as it is more physiological, less expensive, prevents biliary sludge formation and originally was thought to be associated with less severe complications than parenteral nutrition (PN); however with the safer administration of PN, EN may have a similar incidence of severe complications [3] or more (e.g. after pancreaticoduodenectomy [4]). It was thought to maintain the gut barrier function to prevent endotoxin and bacterial translocation [5–7] which could lead to sepsis and multi-organ failure; however the evidence for this is not convincing [8]. Previous metabolic and septic problems with PN may have related to overfeeding and hyperglycaemia, and less careful attention to the care of the feeding catheter. Now less energy is given especially in critical care so metabolic problems are less frequent; great care is given to the aseptic care of parenteral feeing catheters so septic complications are much less frequent.

EN is usually contraindicated if there is mechanical bowel obstruction, peritonitis or ischaemia, or if there has been a recent major gastrointestinal haemorrhage. Percutaneous abdominal tubes are relatively contra-indicated if a coagulopathy or if a patient has ascites (accumulation needs to be prevented for 7–10 days after the procedure to allow adherence of the gut to the abdominal wall) or the presence of a ventriculo-peritoneal shunt (as it can be infected and cause meningitis) [9, 10].

EN and PN may be used together when PN is being weaned, but generally should not be used together in the

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Table 1 Routes for providing enteral nutritional support

Nasal tube
Nasogastric (NG)
Nasoduodenal/jejunal (ND/NJ)
Pharyngostomy/oesophagostomy
Gastrostomy
Percutaneous endoscopic (PEG)
Percutaneous radiological gastrostomy (PRG) (also called a radiologically inserted gastrostomy (RIG))
Surgical (includes percutaneous laparoscopically assisted gastrostomy (PLAG))
Duodenostomy/jejunostomy
Percutaneous endoscopic gastro-jejunostomy (PEGJ)
Direct percutaneous endoscopic jejunostomy (D-PEJ)
Percutaneous radiologically inserted via gastrostomy (PRGJ or RIGJ)
Surgical (open (using a needle catheter) or laparoscopic)
Distal feeding
Enteroclysis and fistuloclysis

long-term as the management of both becomes very complex and time consuming.

This chapter outlines the methods of inserting enteral feeding tubes and advises upon their subsequent care.

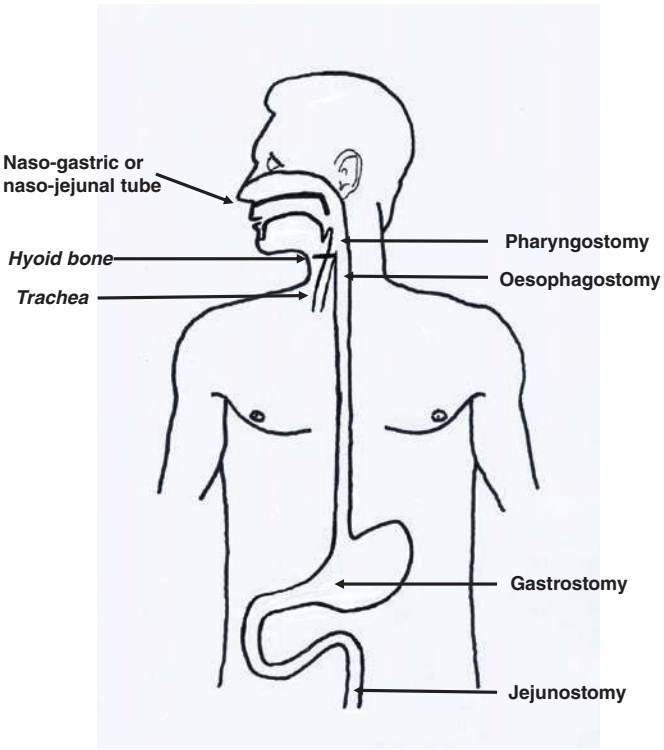

Fig. 1 Enteral routes for feeding into upper gut

Access Routes to the Gut

There are many ways to access the gut (Table 1, Fig. 1) [11]. Direct feeding into the colon/rectum has been successful in the past [12] but is not currently used. If there is a mucus fistula or fistula connecting to defunctioned ileum or colon, saline, a peptide feed or the effluent from a high stoma may be instilled into it to help with fluid/nutrient balance. This distal feeding can give all the nutritional requirements or can give a small amount of feed to help the bowel function/mucosal growth before continuity is surgically re-established. This procedure can be unpleasant and technically demanding ("Distal Feeding and Hydration" chapter).

Nasoenteric Feeding

An enteral feed may be given by a tube passed through the nose into the stomach, duodenum or jejunum (nasogastric, nasoduodenal and nasojejunal feeding). It has become traditional to insert enteral feeding tubes through the nose rather than the mouth as it is thought to be more comfortable for the patient and eliminates the possibility of the tube being bitten. Fine bore naso- or oro-enteral tubes are chosen for short-term feeding (up to 4–6 weeks) and a gastrostomy or jejunostomy tube for long-term enteral feeding.

Feed may be delivered into the stomach if there are no problems with aspiration or inadequate/delayed gastric emptying (e.g. if opioid or anticholinergic drugs including cyclizine have been given). The stomach tolerates hypertonic feeds, higher feeding rates and bolus feeding better than the small intestine. After abdominal surgery, owing to increased sympathetic activity, the stomach may take 1–2 days to regain its motor function and the colon may take 3–5 days, but the motor and absorptive functions of the small bowel usually remain normal [13, 14]. Thus post-pyloric feeding may be started safely within 12 h of surgery/trauma, especially if the patient is already undernourished. Many units wait for at least 24 h to allow for the 'ebb phase' of hypometabolism and some surgeons delay for 5 days, often to 'protect a distal anastomosis' [15, 16]. Clinically the return of hunger, the passage of stomal or rectal wind and the presence of bowel sounds suggests the return of gut function. It is helpful if access for feeding, via the gut, is achieved at the time of surgery (e.g. by a nasojejunal tube or needle jejunostomy). Post-pyloric/jejunal feeding is indicated when there is altered gastric anatomy (e.g. gastrectomy, gastric bypass or Whipple's procedure), gastroparesis, high risk of aspiration or an intolerance of gastric feeding [10].

The passage of a tube through the nose can induce the patient to cough and so the procedure is considered an aerosol (less than 5 μm diameter) generating procedure and FFP3 masks and visas should be worn if the patient has or is at risk of having a disease spread by an aerosol (e.g. COVID) [17].

Nasogastric Tubes

Nasogastric tubes are generally marketed for single use; however, the manufacturers of some tubes advocate cleaning and re-passing of the same tube on the same patient if it is accidentally dislodged. The maximum rate of flow through an enteral feeding system depends mainly upon the tube diameter and length, and less upon the viscosity and temperature of the feed [18]. They are generally only used for 4–6 weeks [11].

Material

Fine-bore nasogastric tubes are made of polyvinyl chloride (PVC), latex, polyurethane or silicone, and are available in a variety of sizes and lengths. Polyurethane is preferred to polyvinyl chloride (PVC) and latex as it is more resistant to kinking. Polyurethane allows the tube wall to be thinner than with silicone, so that while its outer diameter is the same its internal diameter is larger, so allowing high flow rates. Nasogastric tubes made from PVC tend to lose plasticizers after a few days; they become brittle and rarely can cause pressure necrosis of soft tissues. PVC tubes are damaged by radiotherapy. PVC tubes require changing after 7–10 days, whereas polyurethane or silicone tubes can remain in situ for a month. Many tubes are impregnated with a water-activated lubricant to help insertion, and most are radio-opaque.

Diameter

Large-bore Ryles tubes, used for gastric drainage, are uncomfortable and may be associated with rhinitis, oesophageal reflux, and oesophageal strictures. Fine-bore tubes (1.4–4.0 mm diameter, 4–12 Fr) are more comfortable and cause less trauma to the nasopharynx and oesophagus. Fine-bore tubes are more easily displaced by coughing or vomiting than large-bore tubes, and there is a greater chance of them being accidentally inserted into a bronchus, especially in an unconscious patient. The presence of an endotracheal tube does not preclude the tube being accidentally passed down the trachea into the lung.

Quoted tube size is based on external diameter; the internal diameter is usually about 1 mm less. The diameter of a tube is the single most important limitation to flow, and an increase in internal diameter from 1 to 2 mm results in a tenfold increase in flow. The limitation to flow is rarely clinically relevant; for example an 8 FG 100 cm long tube connected to a giving set and a feed container will discharge 100 mL of 24 °C solution (viscosity 4.25 cps which is similar to/higher than most feeds) at a pressure of 75 cm water (about the height of a drip stand) within 5 min [18]. The fine-bore tubes used in clinical practice vary from 1.4 mm (4 FG) for small infants, to 2.7–4.0 mm (8–12 FG) for older children and adults. All commercially available feeds can be administered with good flow through an 8 FG tube though even smaller tubes may suffice (e.g. infants may be fed boluses via a 4 FG tube with no problems). Only if there is a need to give drugs through the tube, or if gastric juice needs to be aspirated regularly in adults, is a larger tube required.

Length

The total length of a nasogastric tube varies between 40 and 90 cm and is selected to ensure a manageable amount of external tubing. The longer the tube, the greater is the resistance to flow [18]. A weighted tip on a nasogastric tube does not make the tube easier to pass or less likely to become displaced [19].

Insertion of Nasogastric Tubes

The method of insertion is outlined in Box 1. The tube must not be forced, and special care must be taken if a tube is considered necessary in a patient with mucositis or oesophageal varices. The tube may be passed through the mouth if there is a severe rhinitis. Soft, pliable nasogastric tubes made of polyurethane or silicone generally have a

Box 1 Passing a Nasogastric Tube at the Bedside

This is considered a clean procedure. Equipment: non sterile gloves and plastic apron, tray, sterile/boiled water, glass of water ± straw, tissues, sterile paper towel, sterile receiver (galipot), receptacle for aspirate, hypoallergenic tape or other fixative, glass of water, lubricating jelly, nasogastric tube (CE marked), enteral syringes of 10 and 50 mL, pH indicator strip (CE marked), measuring tape.

Method

1. Explain the procedure and arrange a signal for patient to give if he/she wants the procedure to stop.
2. Check that the nostrils are patent by asking the patient to sniff with each nostril occluded in turn.
3. Wash hands and dry hands, apply hand rub and assemble the equipment.
4. Put out the equipment. Sterile paper towel onto trolley/tray then put onto it the NG tube, galipot and enteral syringes. Ensure the glass of water, lubricating jelly, hypoallergenic tape and pH paper are near.
5. Put on gloves
6. Position the patient upright and do not tilt the head backwards (if insertion is difficult it can be helpful to put the head forwards and/or turn it to one side).

7. Measure the distance from the nose to an earlobe to the xiphisternum (NEX distance which is 50–60 cm in adults) then add 5–10 cm to this.
8. Mark the tube (if not marked) with the measured distance. If there is a guidewire in the tube, remove it and flush the tube with 10 mL water, then reinsert the guidewire; this allows the wire to be withdrawn freely. Check that the guidewire does not protrude through the end of the tube and that it is freely mobile within the tube.
9. The clearest nostril may be sprayed with lignocaine. Lubricate the tube with a small amount of lubricating jelly (or water).
10. Gently slide the tube backwards along the floor of the clearest nostril. At a distance of 10–15 cm the tube can usually be seen at the back of the pharynx. If possible, at this point ask the patient to take a mouthful of water and hold it. Ask the patient to swallow and at that moment advance the tube 5–10 cm, stop when the swallowing stops and repeat 3–6 times. If the patient becomes distressed, continually coughs or becomes blue, remove the tube. If there is difficulty passing the tube, the patient can turn his/her head either way by 90° and flex the head.
11. When the mark (at 50–60 cm in adults) is reached, stop advancing the tube and gently remove the guidewire. If does not remove withdraw tube gently and twist as it may be coiled Do not attempt to replace the guidewire when the tube is in situ as it may exit from the side of the tube and cause a perforation.
12. Check the tube position by aspirating 2–5 mL gastric juice and check that the pH is less than 5.5 or below using pH indicator strips (CE marked for human aspirate). If so, the tube is in the correct position and can be secured at the nose and feeding begun. If not, the tube may not be in the stomach or the stomach may not be producing acid (e.g. if the patient is taking a proton inhibitor drug); a chest radiograph is needed to confirm that the tube has not entered the lungs. Auscultating for bubbles is unreliable as bubbles can be heard even if the tube is in the lung.
13. Document the procedure: time, indication, consent verbal/written, tube type, size and two health care workers should sign to confirm the pH reading and the position of the tube. If a chest radiograph is needed the name of the clinician confirming the correct position should be recorded.

Additional comments

- If the patient is heavily sedated or has had a general anaesthetic, the head can be flexed to 30° and the larynx lifted anteriorly [22].

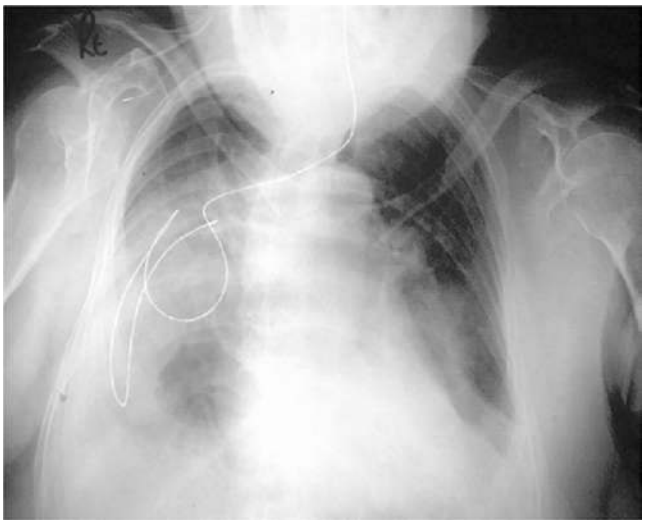

Fig. 2 A NG tube accidentally placed in the right lung

guidewire to aid insertion, while those made of PVC do not. There is still a small risk of misplacement (1.3%) [20], oesophageal or pulmonary perforation. In the UK intrapulmonary or pleural placement of a nasogastric tube with administration of feed or medication or fluid is considered a "never" event that must fully investigated (Fig. 2) [21]. Due to the trauma involved for staff when these never events are investigated it is advised that two staff are present at the insertion to confirm the tube position (with a pH indicator strip). There is a high rate of nasogastric tubes 'falling out'. This 'non-elective removal' has been reported to be as high as 25% within the first 24 h [20].

Checking Position of Nasogastric Tubes

The intra-gastric position of a nasogastric tube should be confirmed before using the tube for feeding or administering medication. This should be carried out every time the tube is used; failure to do so could result in feed or medication being delivered to the lungs. Only checking the gastric pH and chest X-ray are acceptable methods.

Aspiration

Two to 5 mL of gastric juice is aspirated through the nasogastric tube using a 50 mL syringe. A 50 mL syringe exerts less negative pressure and so is less likely than a smaller syringe to create a vacuum and cause damage. The aspirate is checked, using a pH indicator strip (CE marked), and should show an acidic fluid with a pH of between 1 and 5.5 [23–25]. Care in interpreting the pH is advised if little fluid is aspirated and much lubricating jelly has been used, as lubricating jelly has an acidic pH. Fluids aspirated from the respiratory and intestinal tract or from a patient receiv-

ing a proton pump inhibitor should all have an alkaline pH. However some of the occasions in which the tube has been accidentally inserted into the lung in UK have had an acidic pH documented. In future, a means of both measuring pH and detecting a gastric (e.g. pepsin) or intestinal enzyme (e.g. trypsin) may become available.

Chest/Abdominal Radiography

Abdominal radiography is the definitive way to confirm the correct position of a radio-opaque nasogastric tube. Most tubes have radio-opaque markings, or contain a radio-opaque compound (e.g. bismuth trioxide). Although it is a reliable method, it is only indicative of the position of the tube at the time of X-ray, and is therefore not necessarily correct at the time the patient starts feeding, when aspiration should again be done. It may be used as a check on initial placement of the tube if an acidic gastric juice cannot be aspirated. Due to the occurrence of "never events" some units advocate chest radiographs on all patients with a neurological disease or impaired consciousness. Many community hospitals, and patients at home, do not have access to X-ray facilities and so do not have this checking system. When tubes are dislodged frequently (e.g. in patients with neurological problems), repeated X-rays are not practical and the radiation exposure becomes unacceptable. An additional problem is that feeding is delayed while a patient is waiting for a radiograph and its interpretation.

The features on a CXR that show correct position of a naso/oro-gastric tube are: The naso-gastric tube should remain in the midline through thorax down to the level of the diaphragm, it bisects the carina, and is clearly visible below the left hemi-diaphragm (unless situs inversus). Its tip should be approximately 10 cm beyond the gastro-oesophageal junction (i.e. within the stomach). Figure 2 shows a malplaced NG tube.

Laryngoscopy

If the patient is unconscious, the tube can be visualized passing into the upper oesophagus using a laryngoscope or endoscope.

Tests of NG tube position <u>not to be</u> relied upon

1. *Auscultation*

   Air is injected into the stomach via the nasogastric tube and at the same time the observer listens with a stethoscope over the upper abdomen ('whoosh' test); bubbling should be heard and the site where they are loudest is noted. This method can be falsely reassuring and bubbles may be heard (in the epigastrium) when the tube is incorrectly in the lung base. This technique should not be relied upon.

   A feeding tube can be attached to a specially adapted stethoscope; if the tube is in the trachea or bronchi, loud breath sounds are heard [26].

2. *Monitoring bubbling at the end of the tube*

   The end of the tube can be left in a glass of water as the tube is inserted. If the tube then enters the lung, there may be bubbles in the water. Again this is not a method that can be relied upon.

3. *Monitoring for respiratory distress*

   Tubes can be inserted into the lung with no patient distress (until feed is given) especially in neurological disorders.

4. *Observing the appearance of NG tube aspirate*

   The aspirate from the lung can look similar to that from the stomach/duodenum.

5. *Testing the acidity/alkalinity of aspirate using blue litmus paper*

   Only pH indicator strips (CE marked for human aspirate) are considered accurate. A pH of less than 5 is taken to indicate a gastric aspirate. However rarely bronchial secretions, especially if infected, can cause a similar low pH.

Problems

No aspirate in syringe.

If this occurs, check that the correct/usual length of tubing is visible externally and that the tube is firmly secured to the face. If a longer length of tube than expected is visible, the tube may have slipped back and thus needs to be removed or resited. If the tube appears to be of correct length, it may be that the tip is not in contact with gastric contents; in this case, the position of the patient can be changed (i.e. to lie on the left or right side, sit up, etc.) and aspiration again attempted. Alternatively, if some oral intake is possible, the patient can be given a drink to increase the volume of the gastric contents before another attempt is made to aspirate the stomach. If these methods fail, the tube may be advanced a short distance (2–5 cm) and aspiration again tried. This may not be possible with some polyurethane tubes.

Aspirate is not acidic.

This may occur if the patient is taking antacids, H_2 antagonists or proton pump inhibitors. A confirmatory chest radiograph may be needed.

Nasoduodenal and Nasojejunal Tubes

Post-pyloric feeding may be indicated when there is delayed gastric emptying (gastroparesis) or an increased risk of aspiration (large hiatus hernia). Nasoduodenal/jejunal tubes may be single lumen (as for a nasogastric tube but of a longer length) or double lumen, allowing feeding into the small intestine while aspirating gastric secretions.

Insertion of Nasoduodenal/Jejunal Tubes

Post-pyloric tube placement may be difficult, and various techniques have been adopted. They may be inserted at the bedside (Box 2), radiologically, in endoscopy or at an operation. Post pyloric feeding compared to gastric feeding in critically ill patients resulted in a 30% lower rate of pneumonia and an increase in the amount of nutrition delivered to these participants [11, 27, 28].

Bedside Placement

Box 2 Methods for Passing a Nasojejunal Tube at the Bedside

When the tube is in the stomach (60 cm), the guidewire inside the tube can be removed and a 30° bend made 3 cm from the tip. The wire is then carefully replaced. This allows the tube to be rotated to assist its passage through the pylorus [29]. In addition, when the tube is at 60 cm, the patient is turned onto his/her right side and the tube advanced to about 70 cm. This usually results in passage of the tube; if not, the stomach can be rapidly inflated with 500–1000 mL of air before the tube is advanced further [30]. Rotating the tube clockwise and giving 10 mg intravenous metoclopramide may also help the tube pass the pylorus [30]. Sometimes referred to as the 10-10-10 method as 10 mg metoclopramide is given, then there is a wait of 10 min before advancing the tube 10 cm. The tube position should be checked radiologically with a plain abdominal radiograph or ideally screened so that the tube tip is positioned at or beyond the duodeno-jejunal flexure.

It may be advantageous to give metoclopramide (10-10-10 as above) or erythromycin (cisapride in the past) just prior to any insertion procedure to increase gastric emptying and help the tube pass the pylorus. Neostigmine may also be used, but careful cardiac monitoring is needed as it may cause a severe bradycardia.

Auscultation and aspiration techniques may be used to attempt confirmation that the tube is situated beyond the pylorus, but they are not conclusive [31]. If air is injected down the tube during insertion, the loudest place that bubbling is heard (with a stethoscope) is initially on the left side of the abdomen (in the stomach) then, when the tube is past the pylorus, on the right side of the abdomen. In addition, the volume of air that can be aspirated from a post-pyloric tube, after 60 mL air has been instilled, is usually about 10 mL as compared to 40 mL if the tube is in the stomach. A more reliable method is to aspirate fluid which should show a pH change from less than or equal to 4 in the stomach, to greater than or equal to 6 in the duodenum/small bowel.

In an intensive care setting the blind insertion of an NJ tube had a 43% successful placement rate and was most likely to be successful if the greater curve of the stomach was cephalad (higher) than L1-L2 disc [32]. The success rate and time to insert a tube using endoscopy or fluoroscopy was the same (95% taking about 15 min) [33].

A randomized prospective trial in 1993 showed that tubes with weighted tips were less likely than unweighted tubes to pass through the pylorus [34]. This may be because a weighted tip naturally falls into the antrum to a level below that of the pylorus.

Self-Propelling Tubes

A nasojejunal tube which develops a spiral coil when the guidewire is removed (e.g. Bengmark) can be inserted into the stomach and in most patients will pass spontaneously into the small bowel, probably being carried there by the fasting migrating myoelectrical complex. This type of tube may stay in position more reliably than a straight tube [35, 36].

Electromagnetic Guided Tubes

Electromagnetic bedside feeding devices (e.g. Cortrak®) are increasingly being placed with over 60% successful placement [37]. They have an electromagnetic stylet that can be tracked and provide a display of the path of the feeding tube during placement. The system consists of an LCD monitor unit, specific nasoenteral feeding tubes each containing a stylet with a transmitter, and a signal receiver unit. Thus they provide real-time location information on the tube tip placement. There is as with all naso-enteric tubes a risk of accidental placement into the lung [38].

Other Techniques

Other methods for placing a transpyloric tube include the use of ultrasound or a magnet on the tip of the tube and on the abdominal wall (88% achieved transpyloric feeding) [39]. The Kangaroo™ feeding tube with IRIS technology uses direct vision via an integral 3 mm camera as the tube is placed and may have a role in the future.

Image Guidance Insertion

Image guidance (fluoroscopic) techniques are generally successful [40, 41], more so than blind placement and almost as often successful as endoscopic placement [33, 41]. Radiologists may be familiar with the technique as it was used to perform a small bowel enema examination.

Endoscopic Insertion

Endoscopic placement may be difficult [42]. If the nasoenteral tube is grasped with forceps and taken to the distal duodenum/proximal jejunum using a paediatric colonoscope, it easily becomes displaced during withdrawal of the endoscope, even when the guidewire has been left within the tube. It is technically easier to position a long guidewire through an endoscope into the jejunum, and then withdraw the endoscope completely to leave the guidewire in situ. The wire can be re-routed through the nose (using a short tube passed through the nose and out of the mouth). The lubricated nasoenteric tube is passed over the guidewire into the jejunum while being careful to maintain the same length of guidewire outside the patient (Figs. 1 and 3).

Many NJ tubes are passed through an endoscope, ideally using an ultrathin transnasal gastroscope [43], but if a normal gastroscope is used rerouting from the mouth to the nose is required, however it is easy for the tube (especially if not kept stiff with a guidewire) on withdrawal to form a loop in the stomach and this may cause the enteral tube to fall back into the stomach.

An endoscopic nasoenteral feeding tube may have a clip placed at the end of the tube to anchor it to the jejunum and this results in fewer repeat endoscopies than standard endoscopic naso-enteral tube placement [44].

Post Insertion of Jejunal Feeding Tube

A plain abdominal radiograph should be taken 8–12 h after insertion to confirm position, except in pregnant women or patients in whom a tube is replaced at home. A polyurethane tube of 105–145 cm can be expected to last about 10 days; the longer-length tubes can be positioned further into the intestine and allow more free tube outside the nose; they do not block more frequently than shorter ones [45].

Securing a Nasoenteric Tubes with a Nasal Loop (Bridle)

A nasoenteric tube can be secured with a non-allergenic fixative on the maxilla, and the tube can be hooked over the ear.

A technique of making a nasal loop (bridle) for confused patients was described in 1980 [46]. A catheter is passed through one nostril and brought out of the mouth (as done initially for re-routing a tube from the mouth to the nose). Surgical ribbon is taped to the catheter coming out of the mouth. The catheter is pulled gently back out of the nose and a 15 cm length of ribbon is left emerging from one nostril. The procedure is repeated through the other nostril, and the ribbon is cut 15 cm from the nose. Thus ribbon passes into one nostril, goes round the nasal septum, and exits through the other nostril. The ends of the tape are tied through tape fastened round the nasoenteric tube [47]. Subsequently a simpler way of inserting the nasal loop was by inserting magnets attached to the distal ends of the catheter and a probe (magnetic retrieval system). After inserting the catheter into one nostril and the probe into the other, the magnets come in contact posterior to the vomer bone, the probe is withdrawn pulling the catheter and tape out of the nostril leaving tape passing round the back of the nasal septum. The end of a feeding tube is securely connected with the tape [47]. A nasal loop inserted in this way on an intensive care unit resulted in less tube displacement 10% (4 of 40) compared with 36% (18 of 50) whose tube was secured by tape only [48].

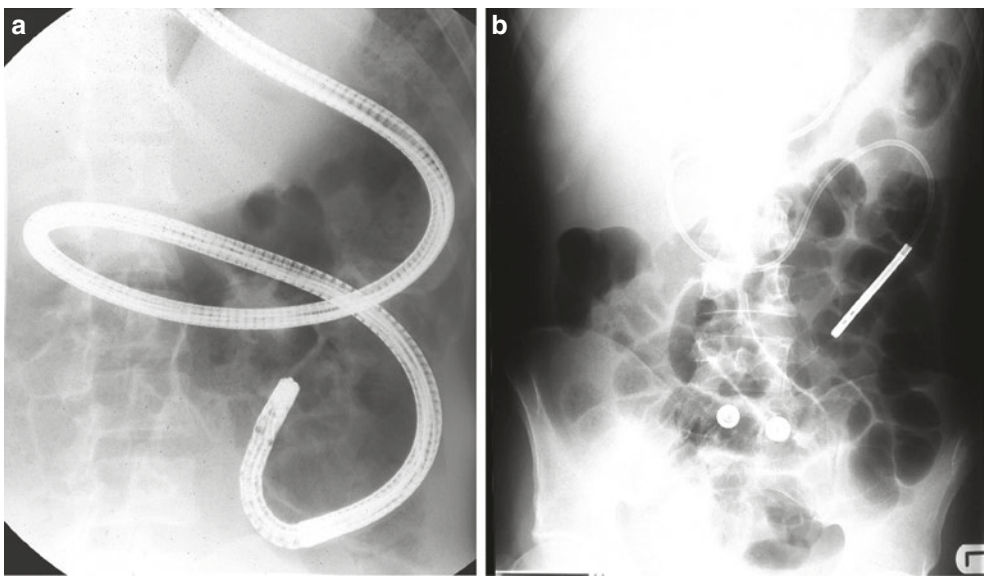

Fig. 3 (**a**) Passage of endoscope (lateral view) into small bowel and guidewire emerging. (**b**) Endoscopically placed nasojejunal tube in situ beyond the DJ flexure

Cervical Pharyngostomy and Oesophagostomy

A tube with its insertion in the neck above the cricoid cartilage is termed a pharyngostomy; one below the cricoid is an oesophagostomy. Either may be performed after maxillofacial surgery, often performed for head/neck cancer. These are basically blind procedures that carry not only the risks of any operation but also the risk of pharyngeal or oesophageal leaks or salivary fistulas. The tubes are just as visible as nasoenteric tubes and are extremely uncomfortable for the patient, as whenever the neck is moved it pulls on the tube. Now that percutaneous endoscopic or radiologically guided enterostomies can be made, usually prior to surgery, pharyngostomy and oesophagostomy are rarely performed except in the very rare circumstance that, for anatomic reasons, a nasoenteric tube, gastrostomy or jejunostomy cannot be placed.

Cervical pharyngostomy was first described by Shumrick in 1967 [49]. It can be performed using open dissection, a percutaneous approach [50], or a combination of both. The pyriform sinus is located with an index finger passed down the lateral pharyngeal wall until below the hyoid bone; a right-angle forceps is inserted through the mouth and pushed out in this position. A small stab incision is made through the skin, then mainly blunt dissection is used to reach the forceps, which are pushed out of the side of the neck. Tape is grasped and pulled back into the pharynx, Kelly forceps hold onto the tape, so are pulled from outside the neck into the pharynx, the proximal end of an already in situ orogastric tube is grasped by the Kelly's forceps and pulled out through the skin incision [51]. If a long-term pharyngostomy is required, a more definitive incision is made along the anterior border of the sternocleidomastoid muscle, and it and the carotid sheath are retracted laterally. The exit site is made as before but the pharyngeal mucosa is sutured to the cervical skin.

Cervical oesophagostomy was described by Klopp in 1951 [52]. The approach is usually on the left side of the neck as the oesophagus lies to the left of the midline in this area. A formal dissection requires a 4–6 cm oblique supraclavicular incision. The sternocleidomastoid muscle is retracted laterally after careful open dissection that does not damage the thyroid or its vessels, trachea, recurrent laryngeal nerve, carotid sheath and contents or thoracic duct. A tube is then inserted through a 5 mm incision in the lateral wall of the oesophagus. The tube feeds into the stomach and either exits through the lower end of the incision or from a separate stab incision [53].

For both procedures the position of the feeding tube tip can be checked as for other nasoenteric tubes.

Gastrostomy Feeding

A gastrostomy may be inserted surgically, endoscopically or under radiological/ultrasound guidance. It means that the patient can be fed without having to swallow and is likely to receive a greater amount of the prescribed feed than from a nasoenteric tube [54, 55]. Gastrostomy feeding devices are currently made from polyurethane or silicone, and may vary in diameter from 9 Fr to 26 Fr. As with nasogastric tubes, the smallest diameter that is adequate for feeding is chosen. Thin tubes are cosmetically most acceptable to patients. Gastrostomy tubes differ in appearance, but share most of the same features. An inner radio-opaque fixation device (a soft flange or a balloon) sits against the anterior stomach wall. It prevents the tube from being accidentally pulled out and, as long as it is held securely against the gastric mucosa, it prevents leakage of gastric contents. An external fixation device is positioned comfortably against the skin and is adjusted to accommodate weight changes. It prevents migration of the tube through the pylorus, and also prevents leakage and soreness due to excessive inward/outward movement of the tube.

Before a gastrostomy is inserted an INR is checked, the procedure may proceed if it is less than 1.5. Clopidogrel is usually stopped 7 days before the procedure and warfarin 5 days [9].

Endoscopically Placed Gastrostomy

An endoscopic gastrostomy can be inserted, under light sedation (e.g. midazolam 2.5 mg) and using local anesthetic, in over 95% of adult patients. A gastrostomy placed at endoscopy is a less expensive procedure than one placed at open operation. It may not be possible to insert an endoscopic gastrostomy safely if a patient has had a gastrectomy, has ascites, hepatomegaly, a neoplastic/infiltrative disease of the gastric wall, an obstructing oesophageal lesion, a coagulation problem or is in the later stages of pregnancy. It may be difficult if the patient is obese and if it is not possible to bring the anterior gastric wall into contact with the anterior abdominal wall.

All techniques involve gastric insufflation to bring the stomach wall into apposition with the abdominal wall, percutaneous placement of a tapered cannula into the stomach, passage of guidewire/thread into the stomach, placement of the gastrostomy and verification of its position. There are two ways in which an endoscope can be used to help position a gastrostomy tube: by a pull (traction) or a push method in which the endoscopist mainly observes the procedure. The tubes inserted by the pull method is commonly referred to as a PEG (percutaneous endoscopic gastrostomy). The pull technique was introduced in 1980 [56] and takes only

15–20 min to perform (Box 3) [57–59]. The original push technique was similar to the pull technique except that a 300 cm flexible-tipped guidewire was inserted into the stomach instead of a thread, the wire was snared and brought out through the mouth, and the gastrostomy tube was then pushed over it down through the mouth and into the stomach [59]. The push technique has subsequently been used to refer to a technique (used by radiology and endoscopy) in which the stomach is first fastened to the abdominal (gastropexy) and then a trochar is inserted and through its sheath a balloon gastrostomy is inserted (see below). No significant differences have been found between the push and pull techniques in terms of procedure time or complications [59, 60].

Antibiotics are usually given (e.g. a single dose of 2.2 g co-amoxiclav 30 min before the procedure) to reduce the risk of a peristomal wound infection [43, 61]. An antiseptic mouthwash before the procedure may also be beneficial.

The external fixation device (disc/plate) is made of non-irritant material and provides a secure external grip on the catheter, keeping it in contact with the skin; it also prevents the tube from kinking/looping. It may alter the tube angle by 90°.

Box 3 Pull Method for Placing a Percutaneous Endoscopic Gastrostomy (Fig. 4)

1. The procedure is explained to the patient/relative/carer and written informed consent obtained. The platelets and INR may need to be corrected if there is a risk of bleeding. The patient is fasted for 6 h before the procedure. Prophylactic antibiotics may be given half an hour before the procedure. Some units may stop H_2 antagonists/PPI for 1–3 days before the procedure, and some carefully clean the mouth with an antiseptic mouthwash immediately before the procedure.
2. The PEG inserter (A1) sets up a trolley near to the endoscopy table and examines the patient's abdomen for scars and enlarged organs. The size and position of the aorta is noted. The patient is sedated with an intravenous injection of a short-acting benzodiazepine. The gastric smooth muscle is relaxed by an intravenous injection of 20 mg hyoscine butylbromide.
3. The endoscopist (A2) performs a full upper gastrointestinal endoscopy, noting in particular any evidence of a hiatus hernia or oesophagitis (duodenal biopsies and test for *Helicobacter pylori* may be done). The patient is turned onto the back. The stomach is distended with air. A1 pushes a finger gently into the epigastric region about halfway between xiphisternum and umbilicus, A2 sees if this is visible in the gastric antrum. The site of maximum indentation is chosen. If no indentation is seen, the endoscope light power is turned to full brightness and A1 observes if the light can be seen through the abdominal wall. Sometimes, on transillumination a shadow from the transverse colon can be seen and this area must be avoided. These two techniques locate the route that the PEG's sheathed trocar (with air valve) will take to enter the stomach. Originally, the site chosen for a gastrostomy was one-third of the distance from umbilicus to left costal margin in the mid-clavicular line. Although the PEG can be inserted anywhere in the abdomen, the rectus abdominis muscles and abdominal creases are best avoided.
4. A1 washes and dries hands, opens the dressing pack, and puts on sterile gloves. Antiseptic solution is poured into a small container. Five milliliters of 1% lignocaine solution is drawn up.
5. A1 cleans a 15 cm area of abdominal skin and puts a small dressing towel below the intended insertion site. Using a small, then a long injection needle, the skin and route to the stomach (including peritoneum) are anaesthetized with about 2–3 mL of 1% lignocaine solution. The longer needle can often be seen by A2 to enter the stomach. If this can be done there is rarely any problem in subsequently inserting the sheathed trocar. The PEG set is opened and tipped onto the open dressing pack.
6. A1 makes a 1–3 mm vertical skin incision about 5 mm deep with a pointed scalpel. The sheathed trocar is carefully inserted along the line by which the long needle entered the stomach; it is advanced with short jabs. Sometimes the needle can only be made to fully enter the stomach with the help of biopsy forceps used by A2. When 1–2 cm of needle are inside the stomach, the trocar is removed to leave the sheath in place; the latter may need a cap over it to prevent air escaping.
7. A narrow long thread is inserted down the sheath. A2 catches this in the stomach with biopsy forceps or a snare and withdraws the thread up into the endoscope. A1 must take care that not all the thread is pulled up into the endoscope. The endoscope is withdrawn and the thread is left coming out of the mouth.
8. The PEG is held by A1 and tied to the thread. A1 then pulls the PEG down through the mouth into the stomach and, using gentle traction, pulls the dilating end of the PEG out onto the abdominal wall.
9. The dilating end of the PEG is cut off and attachments made according to the manufacturer's instructions. The patient returns to the ward with clear written instructions about subsequent care for the next 2 weeks.

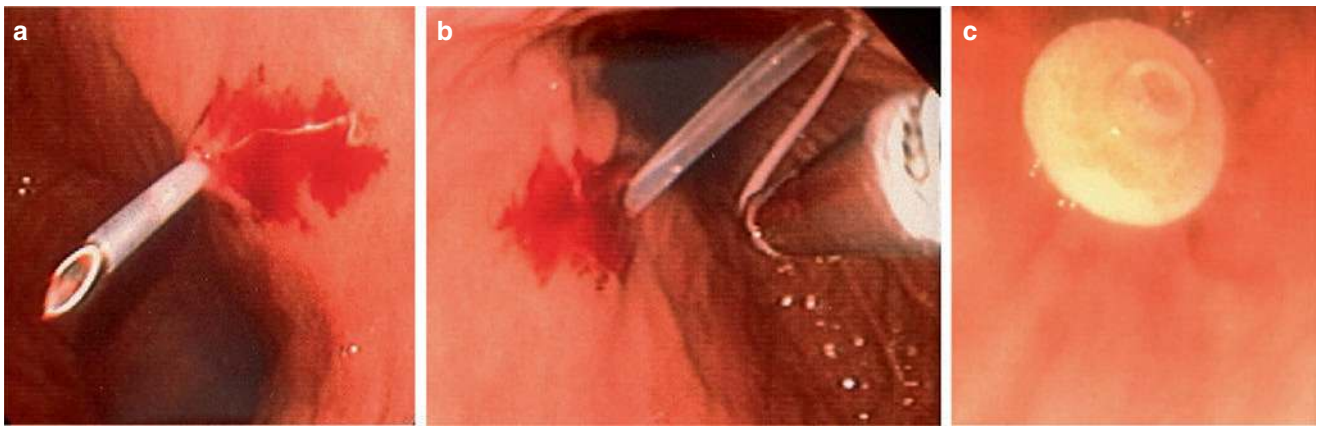

Fig. 4 (**a**) Sheathed needle entering the stomach at the start of a pull PEG insertion. (**b**) Biopsy forceps capture the thread. (**c**) Internal flange at end of the procedure

Problems After PEG Insertion

Complications requiring surgery occur in fewer than 5% of patients; the procedure-related mortality rate is 0.3–2% [62–64]. Most deaths are caused by the underlying illness. The main problems are infection of the insertion site and peristomal leakage [65, 66]. Other rare early problems include peritonitis, septicaemia, tube dislodgement, pulmonary aspiration, bowel perforation, gastro-colic fistula and necrotizing fasciitis [67]. Bleeding problems should be avoided if coagulation abnormalities are corrected before the procedure.

Poor wound healing may occur if the patient is undernourished (e.g. cancer/HIV infection) [66, 67], immunosuppressed or taking steroids or have EDS. Mortality is higher during the first month in patients with previous aspiration or urinary tract infections or those who are more than 75 years old [68].

A benign pneumoperitoneum is common and can be seen on abdominal or chest X-rays in as many as 38% of patients [69, 70]. It is important to recognize this as a normal finding—it does not mean that the patient has a significant bowel perforation.

In the long term, aspiration pneumonia may occur in 23% of patients [71].

Direct Puncture Gastrostomy Insertion

Endoscopically (Push Technique)

A different technique for inserting a PEG without the tube passing down the oesophagus can be done endoscopically. This may reduce the chance of entry site infections as the tube has not passed through the mouth and may also prevent the seeding of an oropharyngeal or oesophageal tumor to the PEG site (risk 0.3–0.5% with a standard pull PEG) [72, 73].

The endoscopic technique involves distending the stomach with air via the endoscope, an assistant injects local anaesthetic into the abdominal wall, and introduces 2–4 stitches (or T fasteners) into the stomach to anchor it to the anterior abdominal wall (gastropexy). Then after making a small stab incision (2 mm) a trocar with a peel away sheath over it is introduced into the stomach (e.g. Pexact®). Under endoscopic observation the trocar is removed, a balloon gastrostomy inserted through it, filled with water, the peel-away sheath is split and removed before gentle traction is applied to the balloon which is fixed to the abdominal wall. Originally a needle was inserted with Seldinger wire then serial dilators were pushed over this to make a tract for a balloon gastrostomy to be inserted [74].

Radiologically

Percutaneous Radiological Gastrostomy (PRG)

A percutaneous radiological gastrostomy (PRG) is also referred to as a radiologically inserted gastrostomy (RIG) or percutaneous fluoroscopic gastrostomy (PFG). PRG can be used as alternative techniques for the placement of a feeding tube into the stomach, if an endoscopically guided tube placement cannot be performed. Of 180 tube attempts a failed gastrostomy tube placement occurred in 15.7% of PEGs and 1.9% of RIGs. Post-procedure aspiration was recognized after 10.5% PEG and 0% PRG attempts [74]. Originally the risk of peritonitis, balloon failure and hence tube displacement, and mortality was lower for a PEG than a PRG [75–77]. However with time the outcome of a PRG has improved and is associated with an equal number or even less complications than a PEG [78, 79]. A study of 133 patients who underwent PRG placement found a 1.5% incidence of major complications requiring operative intervention and a 3% incidence of minor complications [76]. Both PEG and PRG are effective for long-term EN support in selected individuals, PRG may be a better option in patients with motor neurone disease especially if they have significant respiratory impairment [80]. PRG can be performed as an outpatient procedure [81, 82].

The technique for insertion of a PFG is very similar to that performed endoscopically (Box 4) except that it starts

with distending the stomach with air via a nasogastric tube and using ultrasound to position the fasteners (gastropexy) before inserting the trocar; the rest of the procedure is the same [82]. Often a PFG or PFGJ (percutaneous fluoroscopically placed gastrojejunostomy) succeeds when a PEG has not been possible [9, 83, 84], though it does not allow the upper gastrointestinal tract to be carefully inspected.

Box 4 Radiological Method of Placing a Percutaneous Gastrostomy

A gastrostomy tube can be placed using ultrasound or X-ray guidance (fluoroscopically) or both.

1. Ultrasound may be used to determine the position of the liver and transverse colon relative to the stomach. Occasional injections of air into the colon via a rectal tube can be used to delineate the transverse colon, but too much gas makes ultrasound difficult.
2. A nasogastric tube is passed into the stomach, and the stomach is distended with air.
3. Upon selection of a site in the mid-body of the stomach, an aseptic technique is used, gloves are worn, the skin is cleaned and the area draped with towels. The skin, subcutaneous tissues and peritoneum are injected with local anaesthetic.
4. The abdominal wall is punctured with a needle through which a T fastener is passed to anchor the anterior gastric wall to the abdominal wall. One to four of these may be inserted.
5. The abdominal wall between the anchoring clasps is punctured with a needle inside a sheath. Using fluoroscopic guidance, the needle is inserted into the stomach and then withdrawn, leaving the sheath in place.
6. A water-soluble contrast agent may be injected to confirm the position of the sheath within the stomach.
7. A wire is passed into the stomach and the sheath removed. The opening may be dilated using progressively larger dilators. A catheter (pigtail or balloon type) is passed into the stomach over the wire. The wire is removed and the threads to a pigtail catheter released or a balloon inflated.
8. Contrast may again be injected through the catheter to try to ensure that there is no leakage into the peritoneal cavity. If a jejunal tube is needed a catheter can be inserted through the pylorus into the duodenum or jejunum.
9. An external flange (fixing device) is attached and sutured to the skin.

Surgical Gastrostomy

A surgical gastrostomy may be fashioned at the time of other abdominal surgery using the Stamm technique [85]; a laparoscopic technique has also been described [86]. The Stamm technique uses concentric submucosal purse-string sutures (two rows) that invaginate the serosa about a mushroom-tipped tube passed into the anterior stomach wall at the junction of the body and antrum. An exit separate from the laparotomy incision is made for the tube. The gastric serosa is sutured to the peritoneum and transversalis fascia [87].

A surgical gastrostomy is rarely performed as percutaneously inserted gastrostomies are quicker to accomplish, avoid a general anaesthetic, and usually have a lower incidence of stomal leakage and wound infection [88–90]. Two studies have shown no difference in the complications following a PEG, laparoscopic or open gastrostomy [90, 91]. A PEG or, rarely, a balloon catheter can be inserted at the time of surgery, though the latter may be difficult to connect to a giving set and may not last as long.

Button Gastrostomy

When a gastrostomy tract has become established, the catheter may be replaced with a button-type gastrostomy, especially in children [92]. The button-type gastrostomy (14–28 FG) consists of a small catheter with an internal water or saline balloon containing 5–20 mL. It is anchored externally with a flange, and the button opening is flush with the skin. The button has a duckbill anti-reflux valve, which prevents leakage of gastric contents. A feeding extension clicks into it when in use, and a cap fits into it when not in use. It has the advantage of being level with the skin and so more convenient and cosmetically acceptable.

When inserting a button for the first time, the length of the abdominal wall tract is measured by inserting a balloon catheter with measurements along its side. The balloon is inflated with 5 mL air and pulled back, the length of the tract is measured and a suitable size button is selected. If the shaft length is too long, the balloon does not sit close to the gastric mucosa. This may cause leakage of the stomach contents around the button shaft. If the shaft is too short, skincare may be difficult and soreness can result. If the tube is tight or painful, a lateral abdominal X-ray is performed to check that the balloon is in the stomach, not the peritoneal cavity. The balloon volume should be checked every 7 days, as there is always a small loss of volume.

Post-pyloric Feeding

Percutaneous Gastrojejunostomy

If a percutaneous endoscopic gastro-jejunostomy (PEGJ) is to be done, a large (e.g. 15 FG) gastrostomy tube is inserted and through this the jejunostomy tube is passed with a stiffening wire in its centre. The patient is re-intubated with a long endoscope (e.g. a paediatric colonoscope), the end of the jejunostomy tube is grasped by biopsy forceps, and the tube is taken slowly (using the push-pull techniques of colonoscopy) about 30–50 cm distal to the pylorus (at or beyond the duodeno-jejunal flexure). The endoscope is withdrawn to the gastric body while the forceps are advanced to keep the jejunal tube in position. The biopsy forceps let go of the tube and are gently shaken as they are withdrawn to try to prevent the jejunostomy tube from returning into the stomach. When the forceps have been fully withdrawn, the stiffening wire is removed from the jejunostomy tube. The view from the endoscope will show the tube passing through the pylorus. An abdominal radiograph is done to confirm the post-pyloric position of the jejunostomy tube tip. Only when the tip is considered to be in a satisfactory position is the tube cut and connected to the inner gastrostomy tube. Some tubes allow the stomach to be drained at the same time as the jejunal feed is given. If the tube cannot be placed endoscopically, it may be done radiologically (PFGJ or RIGJ), which may be easier if the PEG has been inserted through the greater curve of the stomach.

The procedure can be done through a gastrostomy tube using an ultra-thin endoscope [43, 93].

There have, in the past, been many difficulties with PEGJ tubes [71–73, 94–96]. In particular, PEGJ tubes often become displaced back into the stomach [96] (Fig. 5) or become disconnected and the whole tube passes through the PEG and down the gut. A PEGJ does not necessarily prevent aspiration [94], though a patient with a PFGJ is less likely to develop pneumonia than one with a PEG [97]. Tube blockage, leakage, migration or fracture occurred in 53% of PEGJs compared to 24% of PEGs with a mean follow-up of 275 days [95]. Designs of jejunostomy tube with a distal flexible, non-weighted tip that can easily be grasped with biopsy forceps may be better; though the connection of the jejunostomy tube to the gastrostomy tube can still become detached and result in the tube falling into the gut.

Direct Percutaneous Endoscopic Jejunostomy (D-PEJ)

A technique similar to PEG insertion can be used to insert a direct percutaneous endoscopic jejunostomy (D-PEJ) in patients who have had a gastrectomy. Sometimes a paediatric colonoscope can be positioned in the distal duodenum, the duodeno-jejunal flexure or beyond, and under radiological guidance a needle inserted into the bowel just distal to the scope. If thread can be introduced through a medium-sized needle (the large introducers supplied with a PEG set are usually too big and do not penetrate the bowel) then a PEG-type tube can be inserted in the usual way (to prevent the thread being cut, the needle must be completely withdrawn as the thread is pulled into the endoscope). Radiological screening also helps to prevent other structures (especially the transverse colon) being entered with the needle. The procedure may also be done using double balloon enteroscopy [98].

Surgical Needle Jejunostomy

It is difficult at surgery to manipulate a nasoenteric tube round the duodenum and into the jejunum. It can be difficult to both aspirate the stomach and feed into the small bowel at the same time, though tubes are available to do this. For these reasons a needle jejunostomy is often inserted at the time of

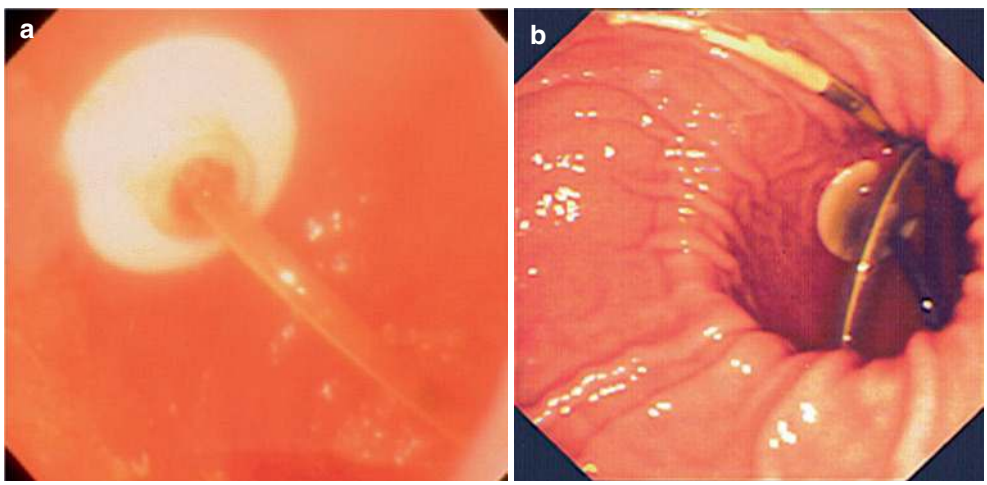

Fig. 5 (**a**) PEGJ in situ. (**b**) PEGJ tube that has become displaced back into the stomach

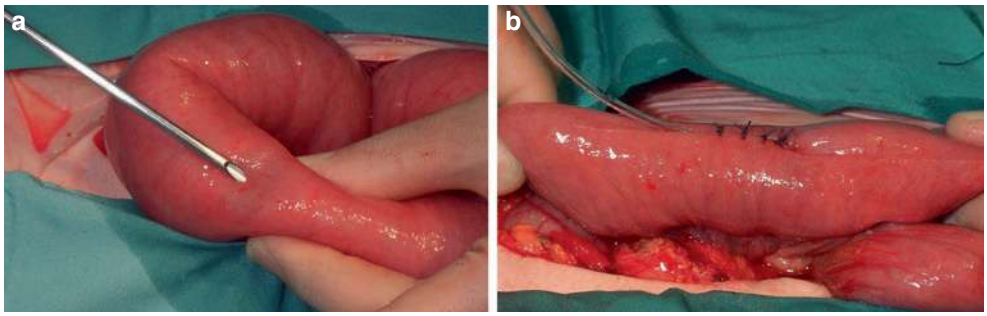

Fig. 6 (**a**, **b**) Insertion of a needle surgical jejunostomy and the Witzel tunnel

operation (Box 5) (Fig. 6) [99–103]. A laparoscopic method of inserting a needle jejunostomy has been described [104]. Complications are common, especially tube dislodgement or obstruction [103, 105], and the outcome is no better than for a well-placed and cared-for surgical tube jejunostomy [106]. The bowel can kink at the catheter entry point, so causing obstruction, or leakage can occur. The incidence of aspiration pneumonia is still high at about 16% [104]. The tube is always left in for 3–5 weeks, even if feeding has stopped, so that a tract can become established and the purse-string suture holding the tube will have dissolved. This may take longer if the patient is taking steroids. There are many types of surgical gastrostomy tubes some have a Dacron cuff that can embed 1–2 cm from the exit site in a similar way to that on a Hickman-type catheter.

Box 5 Surgical Placement of a Needle Jejunostomy

At the end of the laparotomy a needle jejunostomy may be inserted. This takes about 20 min.

1. A loop of jejunum about 10–30 cm distal to the duodeno-jejunal flexure or gastrointestinal anastomosis is selected and orientated. The distance should be sufficiently great to allow tension-free apposition to the abdominal wall.
2. A 1 cm diameter purse-string absorbable suture is placed on the anti-mesenteric border of the jejunum at the site selected for jejunal catheter insertion. The ends are left untied.
3. A submucosal tunnel is created on the anti-mesenteric border using a 12–14 gauge hollow needle with a retractable obturator. With the obturator withdrawn, the needle is pushed into the sero-muscular layer within the purse-string suture. The obturator is advanced and the blunt end used to create an intramural tract for 2.5–5.0 cm before the obturator is withdrawn and the sharp needle is advanced into the lumen. If the needle tip position is uncertain, 10 mL of air can be injected into the bowel and distension observed; if there is resistance the needle is withdrawn and another attempt is made to enter the bowel lumen.
4. If present, the flexible J end of the guidewire is identified and put into the catheter (but not so that it protrudes from the catheter). The catheter (with guidewire) is then advanced through the needle into the bowel lumen.
5. The needle is removed while grasping the catheter within the bowel; the catheter is advanced for 20–45 cm. If necessary, the J end of the guidewire may be advanced to just beyond the distal end of the catheter to help passage. Care is taken to prevent the catheter from kinking or curling within the bowel. The guidewire is removed and the purse-string is tied.
6. In addition to the submucosal tunnel, a short (2–3 cm) Witzel tunnel is often made by suturing two parts of the sero-muscular layer (from the same circumference) together around the catheter, so covering the catheter. The sutures must not be tight enough to cause occlusion of the catheter or to cause tissue necrosis.
7. A second sheathed hollow needle that can be split (or that has a sheath that can be split) is inserted through the left abdominal wall at a position where there will be no tension on the bowel. The catheter is fed through this (or if necessary the needle is removed) and the needle (or introducer) is split and removed.
8. The jejunum is stitched to the anterior abdominal wall using 2–3 sutures around the catheter.
9. The catheter is placed in an external fixative device (retainer) which is sutured with non-reactive monofilament sutures to the skin.
10. The site may be covered with a clear dressing and any attachments are connected to the catheter. Catheter patency is confirmed using 20 mL air, saline or contrast.

Distal Enteral Feeding

Distal enteral feeding includes feeding through the distal limb of an enterocutaneous fistula (fistuloclysis) or through a defunctioned distal small bowel stoma/mucus fistula (enteroclysis). The distal feeding (DF) may be complete/total (CDF) where the aim is to administer all nutrition and hydration (±chyme) via the enteral tube or just trophic (TDF) where it aims only to provide enough nutrition/hydration to maintain bowel structure and function usually before a surgical re-anastomosis [107] ("Distal Feeding and Hydration" chapter). Proximal and distal contrast studies of the bowel are done before starting DF to ensure there is no disease, obstruction or leak present in the distal bowel. The feeding is done by inserting an enteral feeding tube (fine bore nasogastric tube or balloon gastrostomy) more than 5 cm into the distal intestine. A polymeric or semi-elemental feed or chyme may be given, ± added salt through the distal feeding tube. The action of DF in addition to providing nutrition/fluid, is by neural and humeral mechanisms, to reduce upper gastrointestinal secretions and motility, and thus proximal stomal/fistula output and so reducing the amount of nutritional/fluid support needed.

TDF consists of a small volume (100–500 mL/24 h) bolus being given once or twice daily into the distal bowel. It helps maintain the bowels anatomical structure and motility (preventing gut atrophy), so making a surgical re-anastomosis more likely to be successful (easier anastomosis, faster postoperative return of function and a lower chance of an anastomotic leak); but parenteral support may still be needed while this continues.

Care of a Patient Receiving Enteral Feeding

Skin Care

It takes 2–4 weeks after insertion for the anterior gastric or jejunal wall to become adherent to the abdominal wall and then an intraperitoneal leak is improbable. After insertion very low traction without tension should be applied to the tube and the distance from the internal flange to the skin recorded (usually 2–4 cm) for 1 week. It is a common error for the traction to be completely removed after insertion and this can allow a leak/bleed to occur as the stomach has not adhered to the anterior abdominal wall. This is suggested by pain and an increase in the distance between the internal flange and abdominal wall. Each day, after the insertion of a percutaneous gastrostomy or jejunostomy, the site should be cleaned gently with unperfumed soap and water and the tube gently rotated by 90°, but not pushed inwards (till 7–10 days). The gastrostomy tube of a gastrojejunostomy should not at any stage be rotated as it can dislodge the jejunostomy tube. A loose absorbent dressing may be applied. Glycerin hydrogel or glycogel dressing may be used as alternative to classical aseptic wound care in the first weeks. After healing occurs 10–14 days after placement (longer if malnourished or taking steroids) the dressings (if one is needed) are changed once or twice a week [11]. The traction is loosened after 3–5 days and after 7–10 days the external flange (also called a fixing plate or fixing device) is undone and the gastrostomy tube rotated (not if a gastroenterostomy tube) then pushed in (2–10 cm) [11] and, and the skin cleaned and dried [11, 43]. The tube is pulled with very light traction and the external flange is reattached and the distance from the internal flange to the abdominal wall skin noted. There may be 0.5–1 cm between the skin and the external flange. If the external flange is positioned while the patient lies supine, it may be tight when sitting/standing and have to be loosened. The external flange may also need loosening as the patient puts on weight. If the tube is kept too tight and not rotated, epithelial overgrowth (buried bumper) may occur [108, 109].

The skin around a gastrostomy or jejunostomy tube is kept clean and dry to prevent soreness/infection; the use of gauze and talcum powder is discouraged. Creams are kept off the tube as these can cause the external flange to slip. If the external flange slips when dry, it should be replaced.

If a nine FG PEG is used, the skin incision is so small that early PEG problems are very rare [110]; however visceral perforation with peritonitis, fasciitis, and pericatheter leaks are reported [111] in addition to bleeding [43] Leakage of gastric contents onto the skin should not occur if the stoma is healthy and the external flange correctly positioned. When it does happen, however, it can result in extreme soreness partly because of the low pH of the gastric juice. It requires a review of the tube and skin care to prevent recurrence. The skin can be protected by zinc oxide based barrier skin protectants, foam dressing and giving a proton pump inhibitor drug. The formation of granulation tissue may be prevented by regular rotation of the tube. Silver nitrate can be gently applied to areas of excessive granulation tissue but can burn the surrounding skin, so an antibacterial/steroid creams are often preferred.

For showering, bathing and swimming the tube is capped and the site should be covered with a water proof dressing.

Mouth Care

Patients, especially those who have no oral intake, are advised to clean their mouth with a mouthwash and to brush teeth and gums twice daily. They may need artificial saliva if their mouth is very dry. Some patients like to have something to taste (sweet) in their mouths when they receive their EN. For patients on an intensive care unit, the normal or induced production of saliva can be useful because of saliva's natural bactericidal activity. Lemon and glycerine swabs are avoided as they lower the pH in the mouth to 2.3–3.9, which can cause decalcification of teeth.

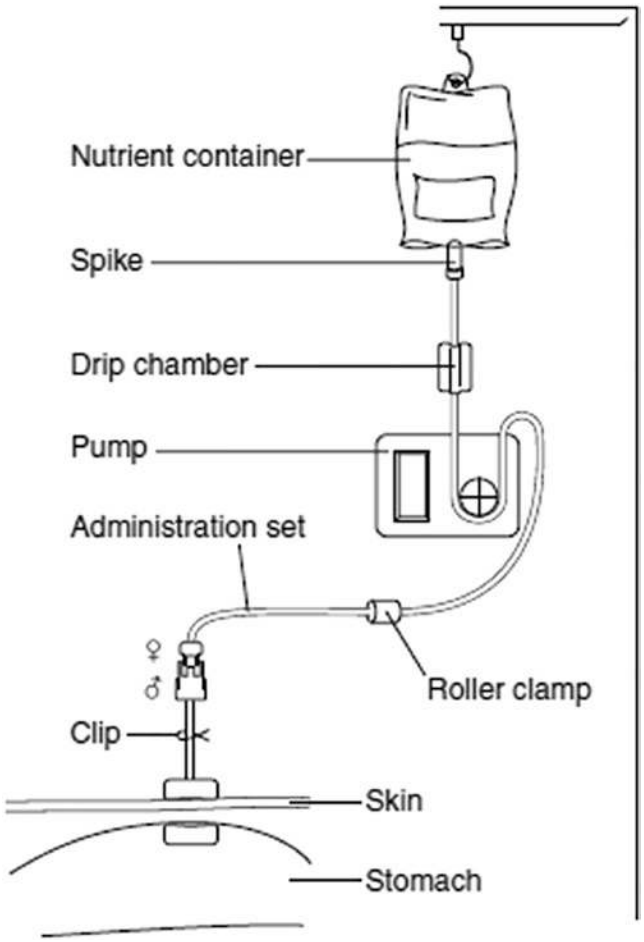

Fig. 7 Diagram of an enteral feed being given through a gastrostomy. Most systems no longer have a drip chamber

Care of the Feeding Tube

Enteral feeding can start 2–4 h after a percutaneous feeding tube has been inserted, there is no evidence to support giving water alone at first [11].

Enteral feeding tubes are used for the administration of feeds, water and, if necessary, medications (Box 6) (Fig. 7); they may become blocked by feed or medication solidifying within the tube. Feed may block the tube if there is a failure to flush the tube, interrupted feeding (e.g. due to a pump malfunction) or if the feed is of a high viscosity and contains whole protein. Acidic fluids with a pH of less than 5 (e.g. gastric acid or fruit juices) and the warmth of the body may cause casein-derived feeds to coagulate and thus block the tube. However, feeds containing free amino acids, small peptides (elemental or peptide feeds), egg albumin or whey proteins do not coagulate at a pH of less than 5 [18, 112] and thus can be used if recurrent blockage occurs. Crushed tablets and potassium and iron preparations are especially likely to block tubes. Many drugs are in a hyperosmolar solution which, in addition to making line blockage more likely, may cause nausea and diarrhoea [113].

To prevent blockage, the tube should be kept clean by flushing with water (usually 30–50 mL of fresh tap water, cooled boiled water or sterile water in accordance with local policy) before and after administering feed or medication. A 50 mL syringe is used for flushing, fitting either directly onto the feeding tube or onto the side port of a giving set. The quantity of water used to flush the tube should be sufficient to clear the tube and meet the patient's fluid requirements. Some units recommend that the tube be flushed weekly with a carbonated drink (e.g. Coca Cola®, 7 Up®, or a sodium bicarbonate solution) or pineapple juice, followed by cooled boiled or sterile water, to prevent blockage. Drugs should not be given through an enteral feeding tube, if possible; if such administration is necessary, they should be obtained in liquid form after establishing compatibility. When more than one medication is required, the tube should be flushed after each medication to prevent the two from mixing within the tube.

Box 6 How to Set Up an Enteral Feed

1. Check the expiratory date on the feed, which should be at room temperature. Record the time/date the feed was set up. Invert the feed container 2–3 times.
2. Wash and dry your hands. (Some units recommend putting on gloves.)
3. Remove the cover from the feeding container and clean the inferior surface with spirit.
4. Close the giving set clamp/roller, then spike the feeding container and attach the giving set.
5. Invert the container and hang it on the drip stand. For gravity feeding, the feeding container should be 1 m above the proximal end of the feeding tube.
6. Remove the distal cap from the tubing and slowly open the roller/clamp to prime the giving set.
7. Flush the feeding tube with the prescribed quantity (usually 50 mL) of cooled boiled or sterile water.
8. Connect the giving set to the feeding tube.
9. Insert the drip chamber or length of tubing into the pump.
10. Set the pump rate, unclamp the giving set and run.

Approximate drip rates[a]	
mL/h	drips/min
125	35
100	28
75	21
50	14
25	7

$$\text{drips / min} = \frac{\text{mL / h} \times 17}{60}$$

[a] The drip rate is affected by viscosity of feed, temperature of feed and giving set material. It is not necessary to know this for most modern pumps

It may be possible to clear a blocked tube by flushing with warm water, a carbonated drink, pineapple juice or sodium bicarbonate solution. Cranberry juice is less effective than Coca Cola® or water in preventing blockage [114]. An alkalinized solution of pancreatic enzymes (Viokase® at pH 7.9 with sodium bicarbonate) is effective in unblocking most lines [115], and the same mixture has been advocated for giving after a feed and a water flush to prevent tube blockage [116]. This solution can be made by adding 5 mL of water to one crushed tablet of Viokase® and one of sodium bicarbonate.

Before the enteral feeding tube is connected to a giving set, air is expelled. Some 'backflow' of gastric contents into tube is normal and is a reassuring sign of the correct position of the tube within the stomach, though it may be perceived by a carer to be a problem.

Some types of gastrostomy or jejunostomy tube have a clip/clamp on the tube to prevent leakage when the feeding ports are open. If left closed when the tube is not in use, these clamps can cause damage to the tube, which may eventually break at the point where the clamp was located.

It may be possible to replace certain parts of an enteral feeding tube (e.g. the Luer lock end) if damaged.

Gastric Aspirates

It is uncommon for a nasogastric tube to be inserted routinely after abdominal surgery to 'decompress the stomach' as patients with a tube in place have more infective complications and it is longer before they can take food orally [117]. Sedative drugs and high circulating catecholamine levels delay gastric emptying. If a gastrostomy or nasogastric tube has been inserted post-operatively or in an intensive therapy unit, the residual volume should not prevent feeding from starting, but care must be taken when aspirating more than 200 mL from a nasogastric tube or 100 mL from a gastrostomy tube [118]. If, more than 2 h after starting to feed, there is an aspirate of more than 200 mL or more than 2 times the hourly feeding rate, gastric emptying is likely to be delayed and extra care is needed, however the feed does not necessarily need to be stopped. Some intensive therapy units aspirate all the gastric contents every 4 h and replace 200 mL. Metoclopramide 10–20 mg three times a day (0.1–0.2 mg/kg in children) orally or intravenously, domperidone 10 mg four times a day, erythromycin 125–250 mg four times a day (3 mg/kg in children over 1 h) or, rarely, neostigmine 1 mg may all be used to increase the gastric emptying rate. Cisapride 10 mg four times a day used to be helpful but has unfortunately been withdrawn. If a high gastric aspirate is preventing feeding, jejunal feeding should be considered.

A fine-bore feeding tube used to aspirate gastric fluid is much more likely to become blocked as the acid coagulates casein-derived protein [119].

Feeding Regimen

Starter Regimens/Feeding Rates

A gastrostomy or jejunostomy is not used for 2–4 h after insertion (though longer after surgery/trauma), then fed is given at 20–45 mL/h for the next 12 h, before being increased (sometimes over 2–4 days) to the amount needed to meet the patient's requirements [120]. Some units starts the feed at 25 mL/h and increases it every 4 h in 25 mL/h increments until the calculated rate is reached. With an overnight feed the rate rarely exceeds 150 mL/h. Often a jejunal feed is started at a slower rate 10 mL/h and gradually increasing and reaching the target by day 6.

With continuous infusions in patients who have had some oral intake in the last week, starter regimens that either dilute [121] or reduce the feed volume [122] are not necessary and may prolong the period of negative nitrogen balance. However, if vomiting/bloating or diarrhoea (not related to antibiotic therapy) occurs, the feed rate may be reduced for a trial period.

Energy/Composition

If high-energy feed is given, hepatic steatosis, osmotic diarrhoea, refeeding syndrome, uraemia or hyper-capnia may occur. Care must be taken not to overfeed a patient who is being ventilated as the energy requirements are likely to be up to 1000 kcal/24 h less than calculated; a feed with less carbohydrate is usually given. Ten to 30% of tube-fed patients will have hyper-glycaemia [123] and may need to be given an oral hypo-glycaemic agent or subcutaneous insulin before starting the feed. It is important not to underfeed patients. Keeping a patient 'nil by mouth' while waiting for investigations, stopping feeding because of a high nasogastric aspirate, cardiac problems or the tube 'falling out' can all worsen the problems of undernutrition.

If a patient has a non-functioning gut and full nutrient requirements are being met by parenteral nutrition, minimal enteral feeding (10 mL/h) with or without added glutamine is often given on the basis that it may preserve the gut's barrier function and prevent villous atrophy, however there is no good evidence in man that it reduces bacterial translocation [124].

Most commercial feeds contain 1.0–1.5 kcal/mL and are nutritionally complete. In the long term, a feed containing fibre (fructo-oligosaccharide) is often given as it may result in a normal formed stool. If a patient is being fed into the jejunum and a polymeric diet has caused symptoms of dumping syndrome, then an isoosmolar peptide feed may be given.

Feeding Method

Gravity, a pump or a syringe can be used to deliver a feed, which may be given continuously, intermittently or by boluses.

Continuous feeding keeps the intragastric pH high/neutral [125]; this used to be thought to protect against haemorrhage from 'stress ulceration' in critically ill patients. If the gastric contents are not acidic, however, they will not be bactericidal and the stomach can become colonized by enteral bacteria [126, 127]. The gastric contents can reflux up the oesophagus and spill over into the lungs where micro-organisms can cause pneumonia and an increased mortality [128]. Administration of an H_2 antagonist (cimetidine) increased the risk of patients on a ventilator developing pneumonia [129]. Bile reflux into the stomach raises gastric pH and ultimately predisposes to colonization of the lower respiratory tract by gastric bacteria [130]. Four Gram-negative bacteria (*Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae* and *Serratia marcescens*) are mainly responsible for stomach-to-airway colonization. At a pH of less than 2.7, all 4 bacterial species are killed within 90 min [131], thus a period free from a feed that allows a normal low gastric fasting pH to be reached should be beneficial. An additional problem in ventilated critically ill patients is that their gastric motility is disrupted, making them more likely to have viable bacteria in their stomach [132].

The time a patient should be rested from a feed has not been determined; Bonten et al. showed that colonization of the stomach, oropharynx and trachea was the same with 4 h fasting every 24 h as with continuous feeding [133]. With 8 h fasting every 24 h, the incidence of pneumonia on an intensive therapy unit fell from 54% to 12% [134]. A break in feeding (probably of 4–8 h) allows both the stomach pH to return to normal and catch-up time to ensure that all of a feed is given.

Continuous and intermittent feeding is usually done via a pump (and no drip chamber), which provides a resistance to flow, so preventing excessive amounts of feed abruptly being delivered into the stomach/small bowel. Whole protein feeds may be of high viscosity but the pump does not need to generate a high pressure [18]. It would be cheaper and simpler for most patients to use gravity feeding with a variable or fixed resistance to control the feeding rate.

In bolus feeding, boluses of 200–400 mL feed are generally given (though 800 mL has been used) into the stomach over 20 min (range 15–60) [135]. Bolus feeding would seem more physiological and akin to what happens in real life. Bolus feeding may cause bloating and diarrhoea and, if given into the jejunum, may cause a dumping type syndrome. Bolus feeding can be done by pouring the feed into an inverted 50 mL syringe which has had the plunger removed. The syringe is then either connected directly to the feeding tube or via an extension tube and the feed is run in slowly. If the rate is too slow the plunger can be replaced and the feed gently injected. The syringes can be washed between uses, depending upon local policies but they do need to be replaced weekly as they become hard to use.

Drugs

Drugs should be given in liquid form and the tube flushed before and after use with 30 mL water [11]. Care should be exercised if digoxin and fibre, or warfarin and vitamin K/E are given together as they may make digoxin and warfarin, respectively, less effective. Sucralfate that is allowed to mix with enteral feed in the stomach or in an enteral tube can form a solid mass and so block the tube. Phenytoin can interact with protein, so it is given 2 h before or 2 h after enteral feeding.

Contamination of Feeds

An enteral feed is an ideal culture medium and can easily become contaminated. The feeding tube itself is also an important reservoir for bacteria, including those that are multi-resistant [136]. The factors that determine whether contamination will cause a problem are the dose of infecting organism, the route of administration (stomach or jejunum) and host resistance, which is reduced in elderly, undernourished or immunosuppressed patients.

Unacceptable contamination of a feed is said to occur when there are more than 10^4 colony-forming units per mL of feed, and levels greater than this have been associated with diarrhoea [137]. In ventilated patients the organisms that contaminate a feed have often come from the gut [130]. Contamination is common if a feed is hung for more than 24 h [138]. It is important that asepsis is maintained in the preparation and delivery of a feed, especially for those patients on the intensive therapy unit, immunocompromised patients, patients taking proton pump inhibitors or H_2 antagonists, and neonates. Hand washing is the single most important measure to prevent contamination. A mask should be worn if the carer has a cold, sore throat or respiratory tract infection. No part of the system that comes into contact with the feed should touch the hands, clothes, skin or any non-disinfected surface [139, 140]. The number of manipulations to a feed should be kept to a minimum. A recessed spike on the giving set helps to reduce the chance of contact and thus contamination of the feed. Bottles with a ring pull that needs decanting should be avoided as the feed is usually poured over the area the thumb has touched to remove the ring. If a feed has to be decanted it should be hung for a short time.

Acidifying an enteral feed preserves gastric acidity and reduces gastric colonization in critically ill patients and thus may reduce the incidence of pneumonia [141].

Patient Position

Patients should always be fed in the semi-supine position (propped up) for nasogastric or gastrostomy feeding and for 30 min after finishing, as there is a high and often unrecognized risk of aspirating the feed. While this position does not prevent aspiration, it reduces its frequency and severity [19].

Equipment

Pumps

Most pumps in Europe give a flow rate that varies from 1 to 300 mL/h and they comply with European Device Standards. It is suggested that no more than 500 mL be given over 4–6 h without a pump. An enteral feeding pump should not be able to generate a pressure of more than 15 psi, and syringes smaller than 50 mL should not be used as they can exceed this pressure. A parenteral nutrition pump should never be used as this generates high pressures. Pumps may have alarms for occlusion, air in the line or low battery.

Several small portable pumps with carrying packs are available and allow feeding to occur while the patient is mobile.

Drip Stands

A large hospital drip stand is often provided, but small bedside stands are available. The LITRE (Looking Into The Requirements for Equipment) group in United Kingdom has designed a small portable drip stand that can be used for carrying a feeding bag for enteral or parenteral nutrition.

Dry Goods

The feeding catheter connects to a flexible giving set, which in turn connects to the nutrient-feeding bag (Fig. 7).

Feeding tube The position of the feeding tube should be regularly checked by looking at the markers on its side to ensure that it has not slipped out. Some jejunal feeding systems allow the stomach to be drained while feeding continues into the jejunum. Tubes with a balloon may not last as long as those with a flange and may need to be changed every 3–6 months or according to the manufacturer's instructions [43]. A PEG tube may last for 2 years, a jejunostomy tube for a shorter time of about 6 months. There is no difference in blockage between an 8, 10 or 12 FG feeding tube, though it is harder to aspirate fluid from the smaller tube [142], and leakage and peristomal infections were not significantly more common with a 20 FG compared to a 12 FG tube [143]. A radiologically placed gastrostomy will last about 6–12 months.

Connectors ENFit is the global enteral feeding device connector design that complies with International Standard (ISO 80369-3). ENFit devices will not be compatible with a Luer connection or any other type of small bore medical connector, so preventing the accidental intra-venous administration of an enteral feed. Unlike current parenteral and oral syringes with male syringe tips that fit into female connectors, the ENFit devices are the opposite. They have *a female* tip on the syringe that will fit around a *male* connector on feeding tubes. All the same, care should be taken to label the delivery system to prevent its contents from being accidentally administered intravenously, especially as adapters that change male Luer lock or push-in connections to female ones are available. 'All parts, joints and connectors of an enteral giving set and catheter shall withstand a linear tensile strength of 15 N without disconnection, rupture or cracking' and there should be no leakage when the system is pressurized to a minimum of 150 kPa with water for 2 min [144].

Giving set/nutrient containers/syringes There may be local policies concerning the feed administration sets and handling procedures. The feed administration set and nutrient containers are discarded after a single use while syringes may be washed and reused.

Disconnecting an Enteral Feed

An enteral feed is disconnected after hands have been washed; the tube is flushed with cooled boiled or sterile water, then capped off. All feeding equipment except syringes is discarded. An open nutrient container can be refrigerated and reused for 24 h only.

Discharge Planning

Before discharge from hospital, the patient/carer must be trained in the setting up/taking down of a feed, flushing the tube, giving medication through the tube, care of the exit site, prevention and treatment of tube blockage, and repair of the hub. They must understand some basic anatomy and physiology as well as how to set up and operate the pump (if used). They must have made arrangements for delivery so that there is an uninterrupted supply of the feed/dry goods. They should have contact numbers in case of illness or if they have problems with the equipment. They should have follow-up appointments arranged. All patients, those receiving enteral nutrition, are reviewed at least annually by a specialist nutrition team.

Monitoring

When an enteral feed is first started, especially if the patient is very undernourished, haemoglobin, clotting, sodium, potassium, urea, creatinine, liver and bone chemistry and magnesium are measured, as is a random urinary sodium concentration. Within the first 24 h of starting the feed the serum phosphate and potassium are measured. These tests, along with serum magnesium, are done at least weekly for 2 weeks, then every 2–12 months depending upon the clinical

condition of the patient. Refeeding problems are common with enteral feeding largely due to the incretin effect ("Refeeding Problems" chapter).

The patient is ideally weighed daily in hospital, but often this is not possible; mid-arm muscle circumference and hand grip dynometry may be determined and measured every week until discharge, then every 2–4 months. After discharge weight, muscle mass/strength, hydration, food intake, complications and quality of life are assessed with routine blood testing that may include serum transthyretin (pre-albumin) [11].

Psychosocial Implications

It is difficult for a patient to feel that he/she is part of the family if he/she cannot eat; fortunately, patients with intestinal failure are usually able to eat normally and use the feeding as a way of getting extra energy, usually at night. They can lead a moderately normal life and can bathe/shower/swim 2–4 weeks after a gastrostomy or jejunostomy has been inserted.

Problems of Enteral Tubes

The long-term problems include over granulation of tissue at the exit site, tube blockage, aspiration, leakage around entry site or at the connection and discharge at exit site and buried bumper. All are covered in "Enteral Nutrition" chapter but buried bumper which occurs due to too much traction being applied to a percutaneous enteral feeding tube is discussed here.

Accidental and Elective Tube Removal/ Replacement

Accidental Removal

A percutaneously inserted tube should not be removed, nor reinserted along the new tract until at least 4 weeks after insertion, as a fibrous tract needs to have become established to prevent intraperitoneal leakage [11, 43]. If a tube becomes displaced in the first 4 weeks then a full new insertion needs to be done. If the tube is inadvertently displaced more than 4 weeks after initial placement, direct replacement can be safely attempted (within 12 h) before the tract closes [11]. A flexible guidewire is often the easiest way of finding the tract. Its soft end can be inserted into the tract. An endoscopist can see the wire emerge in the stomach and can catch it with a polypectomy snare or grasping forceps. The wire is pulled up into the endoscope, which is withdrawn to leave the wire coming out of the mouth. A new PEG is tied to this and pulled into position in the usual way by the assistant at the abdominal wall. Another option is to dilate the tract with dilators of gradually increasing diameter and to insert a button or balloon-type gastrostomy.

Elective/Planned Removal

Planned removal may be by cutting the tube and allowing it to pass, or careful endoscopic A gastrostomy tube with an internal fixation device that deflates can be removed by withdrawing air/water from it and gently pulling. If it does not come out easily, however, it may need to be removed in the same way as a tube with a non-deflating internal fixation device. If a gastrostomy tube is pushed inwards to check that it is free, then pulled upon and transected as near to the skin as possible, it will usually pass through the gut with no problems [145]; however, in a few cases (2%) the tube does not pass [146]. This method may be appropriate if the patient has a normal gut (no Crohn's disease or distal strictures). If a gastrostomy tube with a rigid internal fixation device is removed endoscopically, the tube is pushed 1–2 cm inwards and a polypectomy snare is put over the internal fixation device and tightened round the tube. The tube is cut about 5 cm from its skin entry point and the endoscopist withdraws the scope and tube. The patient is usually kept nil by mouth for 12 h following tube removal. Abdominal fistulae rarely develop, even in patients with Crohn's disease [147].

When a PEG/PEJ tube needs replacement because of breakage/leakage that cannot be corrected with repair kits/replacement parts, it can usually be done endoscopically. The PEG can be transected about 10 cm from the exit site and the new double-looped introducing thread of the new PEG pushed in through the lumen of the old PEG and into the stomach. The closed polypectomy snare from the endoscope is pushed through this loop, and then opened; this traps the thread round the snare. The snare is then put round the internal fixation device and closed; the thread is caught in this and, when the PEG is removed, the thread will again come out of the mouth ready to be attached to a new PEG. An alternative way is to cut a 1 mm hole 5–10 mm from the end of the cut PEG; the introducing thread from the new PEG set is put through the newly cut side hole and tied. The old PEG can then be removed, using a polypectomy snare, as already described. The thread will emerge from the mouth and the new PEG is attached to this and pulled into position in the usual way.

When a PEG is removed it is sometimes replaced with a button, especially in children.

Burried Internal Flange (Buried Bumper)

Traction on an enteral tube (and without pushing it in each week) particularly one with a flat disc can result in the gastric mucosa growing over the disc and eventually occluding it. While the tube may rotate it will not push into the stomach

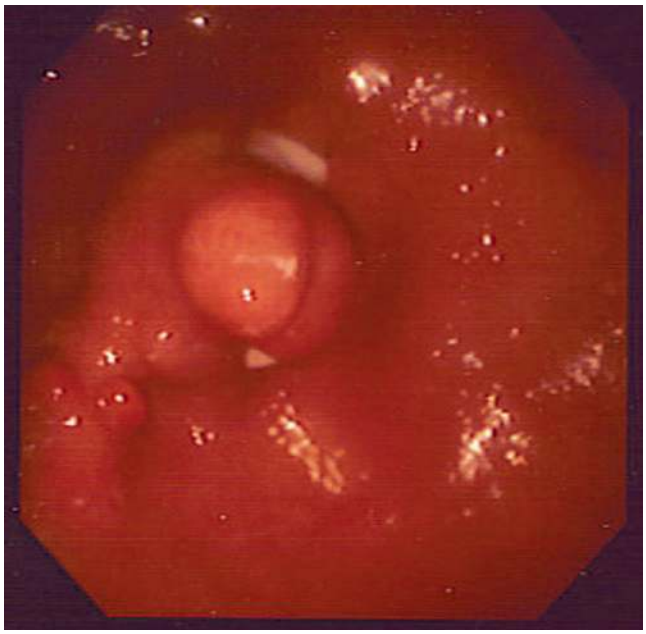

Fig. 8 Burried bumber. As the white of the internal flange (bumber) can be seen, it should be possible to remove

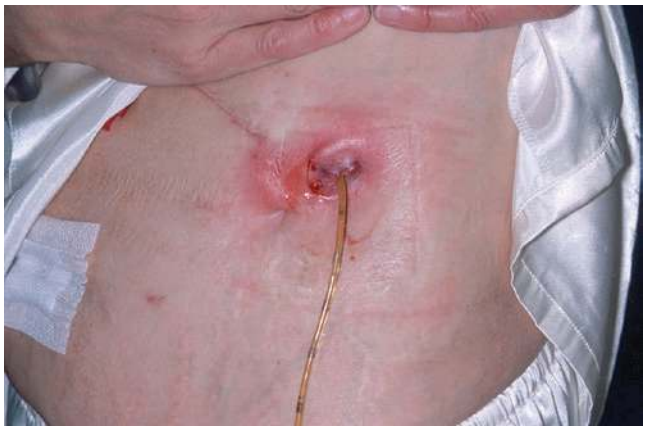

Fig. 9 A PEG tube has almost eroded out of the abdominal wall in a very thin patient. It was removed after injecting local anaesthetic

(this can be hard to tell as the tube may kink within its tract). The flow through the tube with a flush or a feed becomes slow, there may be peristomal leakage, and eventually flow stops completely and it is not possible to flush the tube. At endoscopy some (Fig. 8) or no internal flange (bumper) (Fig. 9) may be seen and the flushing fluid may or not be seen to enter the stomach.

The tube can be cut flush to the skin and left [148], which may be the best option if no internal flange is seen. However if a little flange is visible, it may be possible to remove the enteral tube. There are many techniques described. One is to stiffened the PEG tube, so the tube can be pushed inwards. This can be done with a guidewire (if it will pass into the stomach) or more effectively a oesophageal balloon dilator which is inflated (10–12 mm) when the first 2 cm of dilator is seen in the stomach. This balloon dilator both acts as a stiffener so the tube can be pushed inwards and it may disrupt some of the overgrown tissue so allowing the tube to enter the stomach. If this is not successful radial incisions with an endoscopic needle knife onto the internal flange can aid the balloon's passage into the stomach [43, 149]. If it does not pass it is worth leaving the tube alone on no traction and repeating the procedure a week later, and often the tube relocates easily into the stomach. Another technique with good results reported is to cut the PEG tube short close to the abdominal wall and pass biopsy forceps through the PEG; then through an endoscope pass a snare which is grasped by the biopsy forceps and pulled out; a 2 cm piece of the old PEG tubing is placed through the snare and closed to create a t-piece which is pulled by the endoscope; thus the PEG should emerge into the stomach [150]. A new PEG can usually be reinserted through the old tract.

If the PEG tube cannot be seen at all an abdominal CT scan may help identify its position.

References

1. McIntyre PB, Wood SR, Powell-Tuck J, Lennard-Jones JE. Nocturnal nasogastric tube feeding at home. Postgrad Med J. 1983;59:767–9.
2. Aiges H, Markowitz J, Rosa J, Daum F. Home nocturnal supplemental nasogastric feedings in growth-retarded adolescents with Crohn's disease. Gastroenterology. 1989;97:905–10.
3. Harvey SE, Parrott F, Harrison DA, Sadique MZ, Grieve RD, Canter RR, McLennan BK, Tan JC, Bear DE, Segaran E, Beale R, Bellingan G, Leonard R, Mythen MG, Rowan KM. A multicentre, randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of early nutritional support via the parenteral versus the enteral route in critically ill patients (CALORIES). Health Technol Assess. 2016;20(28):1–144.
4. Perinel J, Mariette C, Dousset B, Sielezneff I, Gainant A, Mabrut JY, Bin-Dorel S, Bechwaty ME, Delaunay D, Bernard L, Sauvanet A, Pocard M, Buc E, Adham M. Early enteral versus total parenteral nutrition in patients undergoing pancreaticoduodenectomy: a randomized multicenter controlled trial (Nutri-DPC). Ann Surg. 2016;264(5):731–7.
5. Moore FA, Moore EE, Poggetti R, McAnena OJ, Peterson VM, Abernathy CM, Parsons PE. Gut bacterial translocation via the portal vein: a clinical perspective with major torso trauma. J Trauma. 1991;31:629–38.
6. Buchman AL, Moukarzel AA, Bhuta S, et al. Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. J Parenter Enteral Nutr. 1995;19:453–60.
7. Kudsk KA, Croce MA, Fabian TC, et al. Enteral versus parenteral nutrition. Effect on septic morbidity after blunt and penetrating abdominal trauma. Ann Surg. 1992;215:503–13.
8. MacFie J. Enteral versus parenteral nutrition: the significance of bacterial translocation and gut-barrier function. Nutrition. 2000;16(7–8):606–11.
9. Itkin M, DeLegge MH, Fang JC, McClave SA, Kundu S, Janne d'Othee B, Martinez-Salazar GM, Sacks D, Swan TL, Towbin RB, Walker TG, Wojak JC, Zuckerman DA, Cardella JF, Interventional

Radiology and American Gastroenterological Association, American Gastroenterological Association Institute, Canadian Interventional Radiological Association, Cardiovascular and Interventional Radiological Society of Europe. Multidisciplinary practical guidelines for gastrointestinal access for enteral nutrition and decompression from the Society of Interventional Radiology and American Gastroenterological Association (AGA) Institute, with endorsement by Canadian Interventional Radiological Association (CIRA) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE). J Vasc Interv Radiol. 2011;22(8):1089–106.
10. Arvanitakis M, Gkolfakis P, Despott EJ, Ballarin A, Beyna T, Boeykens K, Elbe P, Gisbertz I, Hoyois A, Mosteanu O, Sanders DS, Schmidt PT, Schneider SM, van Hooft JE. Endoscopic management of enteral tubes in adult patients—Part 1: definitions and indications. European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2021;53(1):81–92.
11. Bischoff SC, Austin P, Boeykens K, Chourdakis M, Cuerda C, Jonkers-Schuitema C, Lichota M, Nyulasi I, Schneider SM, Stanga Z, Pironi L. ESPEN guideline on home enteral nutrition. Clin Nutr. 2020;39(1):5–22.
12. Randall HT. Enteral nutrition: tube feeding in acute and chronic illness. J Parenter Enteral Nutr. 1984;8:113–36.
13. Woods JH, Erickson LW, Condon RE, Schulte WJ, Sillin LF. Postoperative ileus: a colonic problem? Surgery. 1978;84:527–32.
14. Gluckman DL, Halser MH, Warren WD. Small intestinal absorption in the immediate post-operative period. Surgery. 1966;60:1020–5.
15. Moore EE, Moore FA. Immediate enteral nutrition following multisystem trauma: a decade perspective. J Am Coll Nutr. 1991;10:633–48.
16. Carr CS, Ling KDE, Boulos P, Singer M. Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection. Br Med J. 1996;312:869–71.
17. Jones B. An overview of opinions on nasogastric tubes as aerosol generating procedures during the Covid-19 crisis. Updated 15 Apr 2020. www.bapen.org.uk/pdfs/covid-19/ngt-and-agp-and-ppe-15-04-20.pdf.
18. Elia M, Crozier C, Martin S, Neale G. Flow and aspiration of artificial feeds through nasogastric tubes. Clin Nutr. 1984;2:159–66.
19. Keohane PP, Attrill H, Silk DBA. Clinical effectiveness of weighted and unweighted 'fine bore' nasogastric feeding tubes in enteral nutrition: a controlled clinical trial. J Clin Nutr Gastroenterol. 1986;1:189–93.
20. McWey RE, Curry NS, Schabel SI, Reines D. Complications of nasoenteric feeding tubes. Am J Surg. 1988;155:253–7.
21. Jones BJM. A position paper on nasogastric tube safety "time to put patient safety first". Prepared by the NGSIG (Nasogastric Tube Special Interest Group of BAPEN). 2020. https://www.bapen.org.uk/pdfs/ngsig/a-position-paper-on-nasogastric-tube-safety.pdf.
22. Moore DM, Calcaterra TC. Inserting and securing the nasogastric tube. Laryngoscope. 1987;97:1460.
23. Metheny NA, Clouse RE, Clark JM, Reed L, Wehrle MA, Wiersema L. pH testing of feeding-tube aspirates to determine placement. Nutr Clin Pract. 1994;9:185–90.
24. Metheny N. Minimizing respiratory complications of nasoenteric tube feedings: state of the science. Heart Lung. 1993;22:213–23.
25. Patient safety alert NPSA/2011/PSA002: reducing the harm caused by misplaced nasogastric feeding tubes in adults, children and infants. 2011. http://www.gbukenteral.com/pdf/NPSA-Alert-2011.pdf.
26. Kirby DF, Delegge MH, Fleming CR. American Gastroenterological Association technical review on tube feeding for enteral nutrition. Gastroenterology. 1995;108:1282–301.
27. Jiyong J, Tiancha H, Huiqin W, Jingfen J. Effect of gastric versus post-pyloric feeding on the incidence of pneumonia in critically ill patients: observations from traditional and Bayesian random-effects meta-analysis. Clin Nutr. 2013;32(1):8–15.
28. Alkhawaja S, Martin C, Butler RJ, Gwadry-Sridhar F. Post-pyloric versus gastric tube feeding for preventing pneumonia and improving nutritional outcomes in critically ill adults. Cochrane Database Syst Rev. 2015;2015(8):CD008875.
29. Zaloga GP. Bedside method for placing small bowel feeding tubes in critically ill patients. Chest. 1991;100:1643–6.
30. Schulz MA, Santanello SA, Monk J, Falcone RE. An improved method for transpyloric placement of nasoenteric feeding tubes. Int Surg. 1993;78:79–82.
31. Levy H. Nasogastric and nasoenteric feeding tubes. Gastrointest Endosc Clin N Am. 1998;8(3):529–49.
32. Kurisawa K, Yokose M, Tanaka H, Mihara T, Takaki S, Goto T. Multivariate analysis of factors associated with first-pass success in blind placement of a post-pyloric feeding tube: a retrospective study. J Intensive Care. 2021;9(1):59.
33. Foote JA, Kemmeter PR, Prichard PA, Baker RS, Paauw JD, Gawel JC, Davis AT. A randomized trial of endoscopic and fluoroscopic placement of postpyloric feeding tubes in critically ill patients. JPEN J Parenter Enteral Nutr. 2004;28(3):154–7.
34. Lord LM, Weiser-Maimone A, Pulhamus M, Sax HC. Comparison of weighted vs unweighted enteral feeding tubes for efficacy of transpyloric intubation. Parenter Enteral Nutr. 1993;17:271–3.
35. Bengmark S. Progress in peri-operative enteral tube feeding. Clin Nutr. 1998;17:145–52.
36. Lai CW, Barlow R, Barnes M, Hawthorne AB. Bedside placement of nasojejunal tubes: a randomised-controlled trial of spiral- vs straight-ended tubes. Clin Nutr. 2003;22(3):267–70.
37. Gerritsen A, de Rooij T, Dijkgraaf MG, Busch OR, Bergman JJ, Ubbink DT, van Duijvendijk P, Erkelens GW, Klos M, Kruyt PM, Bac DJ, Rosman C, Tan AC, Molenaar IQ, Monkelbaan JF, Mathus-Vliegen EM, Besselink MG. Electromagnetic-guided bedside placement of nasoenteral feeding tubes by nurses is non-inferior to endoscopic placement by gastroenterologists: a multicenter randomized controlled trial. Am J Gastroenterol. 2016;111(8):1123–32.
38. Bourgault AM, Aguirre L, Ibrahim J. Cortrak-assisted feeding tube insertion: a comprehensive review of adverse events in the MAUDE database. Am J Crit Care. 2017;26(2):149–56.
39. Gabriel SA, Ackermann RJ, Castresana MR. A new technique for placement of nasoenteral feeding tubes using external magnetic guidance. Crit Care Med. 1997;25:641–5.
40. Gutierrez ED, Balfe DM. Fluoroscopically guided nasoenteric feeding tube placement: results of a 1-year study. Radiology. 1991;178:759–62.
41. Ott DJ, Mattox HE, Gelfand DW, Chen NW, Wu WC. Enteral feeding tubes: placement by using fluoroscopy and endoscopy. Am J Roentgenol. 1991;157:769–71.
42. Van Stiegmann GV, Pearlman NW. Simplified endoscopic placement of nasoenteral feeding tubes. Gastrointest Endosc. 1986;32:349–50.
43. Gkolfakis P, Arvanitakis M, Despott EJ, Ballarin A, Beyna T, Boeykens K, Elbe P, Gisbertz I, Hoyois A, Mosteanu O, Sanders DS, Schmidt PT, Schneider SM, van Hooft JE. Endoscopic management of enteral tubes in adult patients - Part 2: peri- and post-procedural management. European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2021;53(2):178–95.
44. Hirdes MM, Monkelbaan JF, Haringman JJ, van Oijen MG, Siersema PD, Pullens HJ, Kesecioglu J, Vleggaar FP. Endoscopic clip-assisted feeding tube placement reduces repeat endoscopy rate: results from a randomized controlled trial. Am J Gastroenterol. 2012;107(8):1220–7.

45. Mathus-Vliegen EMH, Tytgat GNJ, Merkus MP. Feeding tubes in endoscopic and clinical practice: the longer the better? Gastrointest Endosc. 1993;39:537–42.
46. McGuirt WF, Strout JJ. "How I do it"--head and neck. A targeted problem and its solution: securing of intermediate duration feeding tubes. Laryngoscope. 1980;90(12):2046–8.
47. Popovich MJ, Lockrem JD, Zivot JB. Nasal bridle revisited: an improvement in the technique to prevent unintentional removal of small-bore nasoenteric feeding tubes. Crit Care Med. 1996;24:429–31.
48. Gunn SR, Early BJ, Zenati MS, Ochoa JB. Use of a nasal bridle prevents accidental nasoenteral feeding tube removal. JPEN J Parenter Enteral Nutr. 2009;33(1):50–4.
49. Shumrick DA. Pyriform sinusostomy; a useful technique for temporary or permanent tube feeding. Arch Surg. 1967;94:277–9.
50. Gaggiotti G, Orlandoni G, Boccoli G, Caporelli SG, Patrizi I, Masera N. A device to perform percutaneous cervical pharyngostomy (PCP) for enteral nutrition. Clin Nutr. 1989;8:273–5.
51. Lyons JH, Cervical pharyngostomy. A safe alternative for gastrointestinal decompression. Am J Surg. 1974;127:387–91.
52. Klopp CT. Cervical esophagostomy. J Thorac Cardiovasc Surg. 1951;21:490–1.
53. Ketcham AS. Elective esophagostomy. Am J Surg. 1962;104:682–5.
54. Park RHR, Allison MC, Lang J, et al. Randomised comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding in patients with persisting neurological dysphagia. Br Med J. 1992;304:1406–9.
55. Norton B, Homer-Ward M, Donnelly MT, Long RG, Holmes GKT. A randomised prospective comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding after acute dysphagic stroke. Br Med J. 1996;312:13–6.
56. Gauderer ML, Ponsky JL, Izans RJ. Gastrostomy without laparotomy: a percutaneous endoscopic technique. J Pediatr Surg. 1980;15:872–5.
57. Ponsky JL, Gauderer MWL. Percutaneous endoscopic gastrostomy: a nonoperative technique for feeding gastrostomy. Gastrointest Endosc. 1981;27:9–11.
58. Beasley SW, Catto-Smith AG, Davidson PM. How to avoid complications during percutaneous endoscopic gastrostomy. J Pediatr Surg. 1995;30:671–3.
59. Hogan RB, DeMarco DC, Hamilton JK, Walker CO, Polter DE. Percutaneous endoscopic gastrostomy – to push or pull. A prospective randomized trial. Gastrointest Endosc. 1986;32:253–8.
60. Mamel JJ. Percutaneous endoscopic gastrostomy. Am J Gastroenterol. 1989;84:703–10.
61. Lipp A, Lusardi G. Systemic antimicrobial prophylaxis for percutaneous endoscopic gastrostomy. Cochrane Database Syst Rev. 2013;2013(11):CD005571.
62. Ponsky JL, Gauderer MWL, Stellato TA, Aszodi A. Percutaneous approaches to enteral alimentation. Am J Surg. 1985;149:102–5.
63. Larson DE, Burton DD, Schroeder KW, DiMagno EP. Percutaneous endoscopic gastrostomy. Indications, success, complications, and mortality in 314 consecutive patients. Gastroenterology. 1987;93:48–52.
64. Hull MA, Rawlings J, Murray FE, et al. Audit of outcome of long–term enteral nutrition by percutaneous endoscopic gastrostomy. Lancet. 1993;341:869–72.
65. Chowdhury MA, Batey R. Complications and outcome of percutaneous endoscopic gastrostomy in different patient groups. J Gastroenterol Hepatol. 1996;11:835–9.
66. Amann W, Mischinger HJ, Berger A, et al. Percutaneous endoscopic gastrostomy (PEG). 8 years of clinical experience in 232 patients. Surg Endosc. 1997;11:741–4.
67. Fox VL, Abel SD, Malas S, Duggan C, Leichtner AM. Complications following percutaneous endoscopic gastrostomy and subsequent catheter replacement in children and young adults. Gastrointest Endosc. 1997;45:64–71.
68. Light VL, Slezak FA, Porter JA, Gerson LW, McCord G. Predictive factors for early mortality after percutaneous endoscopic gastrostomy. Gastrointest Endosc. 1995;42:330–5.
69. Gottfried EB, Plumser AB, Clair MR. Pneumoperitoneum following percutaneous endoscopic gastrostomy. Gastrointest Endosc. 1986;32:397–9.
70. Pidala MJ, Slezak FA, Porter JA. Pneumoperitoneum following percutaneous endoscopic gastrostomy. Does timing matter? Surg Endosc. 1992;6:128–9.
71. Cogen R, Weinryb J. Aspiration pneumonia in nursing home patients fed via gastrostomy tubes. Am J Gastroenterol. 1989;84:1509–12.
72. Rowell NP. Tumor implantation following percutaneous endoscopic gastrostomy insertion for head and neck and oesophageal cancer: review of the literature. Head Neck. 2019;41(6):2007–15.
73. Siu J, Fuller K, Nadler A, Pugash R, Cohen L, Deutsch K, Enepekides D, Karam I, Husain Z, Chan K, Singh S, Poon I, Higgins K, Xu B, Eskander A. Metastasis to gastrostomy sites from upper aerodigestive tract malignancies: a systematic review and meta-analysis. Gastrointest Endosc. 2020;91(5):1005–1014. e17.
74. Tucker AT, Gourin CG, Ghegan MD, Porubsky ES, Martindale RG, Terris DJ. 'Push' versus 'pull' percutaneous endoscopic gastrostomy tube placement in patients with advanced head and neck cancer. Laryngoscope. 2003;113(11):1898–902.
75. Vidhya C, Phoebe D, Dhina C, Jayne S, Robert F. Percutaneous endoscopic gastrostomy (PEG) versus radiologically inserted gastrostomy (RIG): a comparison of outcomes at an Australian Teaching Hospital. Clin Nutr ESPEN. 2018;23:136–40.
76. Ho C-S, Yee CAN, McPherson R. Complications of surgical and percutaneous non-endoscopic gastrostomy: review of 233 patients. Gastroenterology. 1988;95:1206–10.
77. Grant DG, Bradley PT, Pothier DD, Bailey D, Caldera S, Baldwin DL, Birchall MA. Complications following gastrostomy tube insertion in patients with head and neck cancer: a prospective multi-institution study, systematic review and meta-analysis. Clin Otolaryngol. 2009;34(2):103–12.
78. Cherian P, Blake C, Appleyard M, Clouston J, Mott N. Outcomes of radiologically inserted gastrostomy versus percutaneous endoscopic gastrostomy. J Med Imaging Radiat Oncol. 2019;63(5):610–6.
79. Singh RR, Nah SA, Roebuck DJ, Eaton S, Pierro A, Curry JI, PEG-RIG trial collaborators. Double-blind randomized clinical trial of percutaneous endoscopic gastrostomy versus radiologically inserted gastrostomy in children. Br J Surg. 2017;104(12):1620–7.
80. Allen JA, Chen R, Ajroud-Driss S, Sufit RL, Heller S, Siddique T, Wolfe L. Gastrostomy tube placement by endoscopy versus radiologic methods in patients with ALS: a retrospective study of complications and outcome. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(4):308–14.
81. Odedra D, Nasirzadeh R, Menard A. Safety of outpatient vs inpatient percutaneous radiological gastrostomy tubes in patients with head and neck cancers. Can Assoc Radiol J. 2016;67(4):416–9.
82. Preshaw RM. A percutaneous method for inserting a feeding gastrostomy tube. Surg Gynecol Obstet. 1981;152:658–60.
83. Hicks ME, Surratt RS, Picus D, Marx MV, Lang EV. Fluoroscopically guided percutaneous gastrostomy and gastroenterostomy: analysis of 158 consecutive cases. Am J Roentgenol. 1990;154:725–8.
84. Wollman B, D'Agostino HB, WalusiWigle JR, Easter DW, Beale A. Radiologic, endoscopic, and surgical gastrostomy: an institutional evaluation and meta-analysis of the literature. Radiology. 1995;197:699–704.

85. Stamm M. Gastrostomy by a new method. Med News. 1894;65:324–6.
86. Murphy C, Rosemurgy AS, Albrink MH, Carey LC. A simple technique for laparoscopic gastrostomy. Surg Gynecol Obstet. 1992;174:424–5.
87. Gallagher MW, Tyson KRT, Ashcraft KW. Gastrostomy in pediatric patients: an analysis of complications and techniques. Surgery. 1973;74:536–9.
88. Grant JP. Comparison of percutaneous endoscopic gastrostomy with Stamm gastrostomy. Ann Surg. 1988;207:598–603.
89. Ruge J, Vazquez RM. An analysis of the advantages of Stamm and percutaneous endoscopic gastrostomy. Surg Gynecol Obstet. 1986;162:13–6.
90. Ho HS, Ngo H. Gastrostomy for enteral access. A comparison among placement by laparotomy, laparoscopy, and endoscopy. Surg Endosc. 1999;13:991–4.
91. Stiegmann GV, Goff JS, Silas D, Pearlman N, Sun J, Norton L. Endoscopic versus operative gastrostomy: final results of a prospective randomized trial. Gastrointest Endosc. 1990;36(1):1–5.
92. Gauderer MWL, Picha GJ, Izant RJ. The gastrostomy "button" – a simple, skin-level, nonrefluxing device for long-term enteral feedings. J Pediatr Surg. 1984;19:803–5.
93. Adler DG, Gostout CJ, Baron TH. Percutaneous transgastric placement of jejunal feeding tubes with an ultrathin endoscope. Gastrointest Endosc. 2002;55(1):106–10.
94. DiSario JA, Foutch PG, Sanowski RA. Poor results with percutaneous endoscopic jejunostomy. Gastrointest Endosc. 1990;36:257–60.
95. Wolfsen HC, Kozarek RA, Ball TJ, Patterson DJ, Botoman VA. Tube dysfunction following percutaneous endoscopic gastrostomy and jejunostomy. Gastrointest Endosc. 1990;36:261–3.
96. Henderson JM, Strodel WE, Gilinsky NH. Limitations of percutaneous endoscopic jejunostomy. Parenter Enteral Nutr. 1993;17:546–50.
97. Hoffer EK, Cosgrove JM, Levin DQ, Herskowitz MM, Sclafani SJ. Radiological gastrojejunostomy and percutaneous endoscopic gastrostomy: a prospective, randomized comparison. J Vasc Interv Radiol. 1999;10:413–20.
98. Despott EJ, Gabe S, Tripoli E, Konieczko K, Fraser C. Enteral access by double-balloon enteroscopy: an alternative method of direct percutaneous endoscopic jejunostomy placement. Dig Dis Sci. 2011;56(2):494–8.
99. Delany HM, Carnevale NJ, Garvey JW. Jejunostomy by a needle catheter technique. Surgery. 1973;73:786–90.
100. Delaney HM, Carnevale N, Garvey JW, Moss CM. Postoperative nutritional support using needle catheter feeding jejunostomy. Ann Surg. 1977;186:165–70.
101. Gerndt SJ, Orringer MB. Tube jejunostomy as an adjuvant to esophagectomy. Surgery. 1994;115:164–9.
102. Sarr MG. Needle catheter jejunostomy: an unappreciated and misunderstood advance in the care of patients after major abdominal operations. Mayo Clin Proc. 1988;63:565–72.
103. Eddy VA, Snell JE, Morris JA. Analysis of complications and long term outcome of trauma patients with needle catheter jejunostomy. Am Surg. 1996;62:40–4.
104. Duh Q-Y, Way LW. Laparoscopic jejunostomy using T-fasteners as retractors and anchors. Arch Surg. 1993;128:105–8.
105. Gogen R, Weinryb J, Pomerantz C, Fenstemacher P. Complications of jejunostomy tube feeding in nursing facility patients. Am J Gastroenterol. 1991;86:1610–3.
106. Haun JL, Thompson JS. Comparison of needle catheter versus standard tube jejunostomy. Am Surg. 1985;51:466–9.
107. Farrer K, Culkin A, Small M, Nightingale J, the BIFA Committee. BIFA top tips for distal enteral tube feeding. www.bapen.org.uk/pdfs/bifa/bifa-top-tips-series-9.pdf.
108. Klein S, Heare BR, Soloway RD. The 'buried bumper syndrome': a complication of percutaneous endoscopic gastrostomy. Am J Gastroenterol. 1990;85:448–51.
109. Lipscomb GR, Brown CM, Wardle T, Rees WDW. Blocked gastrostomy tubes. Lancet. 1994;343:801–2.
110. Litchfield BL, Nightingale JMD. Outcomes of percutaneous endoscopic gastrostomy tube insertion 1991–7. Proc Nutr Soc. 1999;58:138A.
111. Chung RS, Schertzer M. Pathogenesis of complications of percutaneous endoscopic gastrostomy. A lesson in surgical principles. Am Surg. 1990;56:134–7.
112. Marcuard SP, Perkins AM. Clogging of feeding tubes. J Parenter Enteral Nutr. 1988;12:403–5.
113. Niemiec PW, Vanderveen TW, Morrison JI, Hohenwarter MW. Gastrointestinal disorders caused by medication and electrolyte solution osmolality during enteral nutrition. J Parenter Enteral Nutr. 1983;7:387–9.
114. Metheny N, Eisenberg P, McSweeney M. Effect of feeding tube properties and three irrigants on clogging rates. Nurs Res. 1998;37:165–9.
115. Marcuard SP, Stegall KL, Trogdon S. Clearing obstructed feeding tubes. J Parenter Enteral Nutr. 1989;13:81–3.
116. Sriram K, Jayanthi V, Lakshmi RG, George VS. Prophylactic locking of enteral feeding tubes with pancreatic enzymes. J Parenter Enteral Nutr. 1997;21:353–6.
117. Cheatham ML, Chapman WC, Key SP, Sawyers JL. A meta-analysis of selective versus routine nasogastric decompression after elective laparotomy. Ann Surg. 1995;221:469–78.
118. McClave SA, Snider HL, Lowen CC, et al. Use of residual volume as a marker for enteral feeding intolerance: prospective blinded comparison with physical examination and radiographic findings. J Parenter Enteral Nutr. 1992;16:99–105.
119. Powell KS, Marcuard SP, Farrior ES, Gallagher ML. Aspirating gastric residuals causes occlusion of small-bore feeding tubes. J Parenter Enteral Nutr. 1993;17:243–6.
120. Wicks C, Gimson A, Vlavianos P, et al. Assessment of the percutaneous endoscopic gastrostomy feeding tube as part of an integrated approach to enteral feeding. Gut. 1992;33:613–6.
121. Keohane PP, Attrill H, Love M, Silk DBA. Relationship between osmolality of diet and gastrointestinal side effects in enteral nutrition. Br Med J. 1984;288:678–80.
122. Rees RGP, Keohane PP, Grimble GK, Frost PG, Attrill H, Silk DBA. Elemental diet administered nasogastrically without starter regimens to patients with inflammatory bowel disease. J Parenter Enteral Nutr. 1986;10:258–62.
123. Vanlandingham S, Simpson S, Daniel P, Newmark SR. Metabolic abnormalities in patients supported with enteral tube feeding. J Parenter Enteral Nutr. 1981;5:322–4.
124. MacFie J, Bradford I, O'Boyle C, Mitchell CJ. Bacterial translocation and nutritional support. Br J Intens Care. 1996: 195–201.
125. Valentine RJ, Turner WW, Borman KR, Weigelt JA. Does nasoenteral feeding afford adequate gastroduodenal stress prophylaxis? Crit Care Med. 1986;14:599–601.
126. du Moulin GC, Hedley-Whyte J, Paterson DG, Lisbob A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of post-operative colonisation of the airway. Lancet. 1982;1:342–5.
127. Garvey BM, McCambley JA, Tuxen DV. Effects of gastric alkalinization on bacterial colonization in critically ill patients. Crit Care Med. 1989;17:211–6.
128. Jacobs S, Chang RWS, Lee B, Bartlett FW. Continuous enteral feeding: a major cause of pneumonia among ventilated intensive care unit patients. J Parenter Enteral Nutr. 1990;14:353–6.
129. Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatality in patients

receiving continuous mechanical ventilation. Am Rev Respir Dis. 1986;133:792–6.
130. Inglis TJJ, Sherratt MJ, Sproat LJ, Gibson JS, Hawkey PM. Gastroduodenal dysfunction and bacterial colonisation of the ventilated lung. Lancet. 1993;341:911–3.
131. Mehta S, Archer JF, Mills J. pH-dependent bactericidal barrier to gram-negative aerobes: its relevance to airway colonisation and prophylaxis of acid aspiration and stress ulcer syndromes – study in vitro. Intensive Care Med. 1986;12:134–6.
132. Dive A, Moulart M, Jonard P, Jamart J, Mahieu P. Gastroduodenal motility in mechanically ventilated critically ill patients: a manometric study. Crit Care Med. 1994;22:441–7.
133. Bonten MJM, Gaillard CA, van der Hulst R, de Leeuw PW, van der Geest S, Stobberingh EE, Soeters PB. Intermittent enteral feeding: the influence on respiratory and digestive tract colonization in mechanically ventilated intensive-care-unit patients. Am J Respir Crit Care Med. 1996;154:394–9.
134. Lee B, Chang RWS, Jacobs S. Intermittent nasogastric feeding: a simple and effective method to reduce pneumonia among ventilated ICU patients. Clin Intensive Care. 1990;1:100–2.
135. McAtear CA, editor. Current perspectives on enteral nutrition in adults. A report by the British Association for Parenteral and Enteral Nutrition; 1999.
136. Bussy V, Marechal F, Nasca S. Microbial contamination of enteral feeding tubes occurring during nutritional treatment. J Parenter Enteral Nutr. 1992;16:552–7.
137. Anderson KR, Norris DJ, Godfrey LB, Avent CK, Butterworth CE Jr. Bacterial contamination of tube-feeding formulas. J Parenter Enteral Nutr. 1984;8:673–8.
138. Kohn CL. The relationship between enteral formula contamination and length of enteral delivery set usage. J Parenter Enteral Nutr. 1991;15:567–71.
139. Anderton A, Aidoo KE. The effect of handling procedures on microbial contamination of enteral feeds. J Hosp Infect. 1988;11:364–72.
140. Anderton A. Reducing bacterial contamination in enteral tube feeds. Br J Nurs. 1995;4:368–76.
141. Heyland DK, Cook DJ, Schoenfeld PS, Frietag A, Varon J, Wood G. The effect of acidified enteral feeds on gastric colonization in critically ill patients: results of a multicenter randomized trial. Crit Care Med. 1999;27:2399–406.
142. Methy N, Eisenberg P, McSweeney M. Effect of feeding tube properties and three irrigants on clogging rates. Nurs Res. 1988;37:165–9.
143. Duncan HD, Bray MJ, Kapadia SA, et al. Prospective randomized comparison of two different sized percutaneous endoscopically placed gastrostomy tubes. Clin Nutr. 1996;15:317–20.
144. Sterile enteral feeding catheters and giving sets for single use. BS EN 1615; 1997.
145. Korula J, Harma C. A simple and inexpensive method of removal or replacement of gastrostomy tubes. JAMA. 1991;265:1426–8.
146. Mollitt DL, Dokler ML, Evans JS, Jeiven SD, George DE. Complications of retained internal bolster after pediatric percutaneous endoscopic gastrostomy. J Pediatr Surg. 1998;33:271–3.
147. Nightingale JMD. Gastrostomy placement in patients with Crohn's disease. Eur J Gastroenterol Hepatol. 2000;12:1073–5.
148. Kejariwal D, Aravinthan A, Bromley D, Miao Y. Buried bumper syndrome: cut and leave it alone! Nutr Clin Pract. 2008;23(3):322–4.
149. Mueller-Gerbes D, Hartmann B, Lima JP, de Lemos Bonotto M, Merbach C, Dormann A, Jakobs R. Comparison of removal techniques in the management of buried bumper syndrome: a retrospective cohort study of 82 patients. Endosc Int Open. 2017;5(7):E603–7.
150. Hollingworth T, Boger P, Clarke E, Patel P, Rutter C, Smith T, Rahman I, PWE-006. The T-piece pull technique removal of PEG buried bumpers – a quick novel endoscopic technique. Gut. 2019;68:A176–7.

Formulation and Administration of Enteral Feeds

Gil Hardy and Hazreen Abdul Majid

Key Points

1. Enteral nutrition (EN) is generally accepted to be the first choice for nutrition support of most patients. However, EN and/or parenteral nutrition (PN) are both equally efficacious, if prescribed and used appropriately
2. There is no good evidence for trophic EN. It is suggested to give either EN or PN. A combination of both may be used when converting from PN to EN or when EN is insufficient to meet energy requirements, at the discretion of the multidisciplinary nutrition support team (NST).
3. After the stomach, all parts of the gut can absorb water, macro-nutrients, minerals and vitamins, so some nutrition from EN will be absorbed in all parts of the small and large intestine.
4. Distal enteral tube feeding (DETF)/fistuloclysis whereby EN or gastrointestinal secretions (chyme) is administered through an enterocutaneous fistula in the distal bowel can be effective.
5. Enteral feeds (EF) divide into three main formula types, standard (whole protein), peptide (semi-elemental) and specialized formulas. EF then further sub-divides into, oral/sip feeds and tube feeds.
6. Most liquid EF are ultra high temperature (UHT) sterilised, but heat processing can destroy some vitamins (e.g. all B vitamins especially thiamine and vitamin B_6, folic acid and pantothenic acid) and heat-sensitive amino acids (e.g. glutamine and cysteine). Extra vitamins and some individual amino acids may need to be supplemented.
7. Enteral feeding tubes (EFT) are increasingly used as vehicles for administering medications, but pharmaceutical advice should be taken to avoid drug-nutrient interactions (DNI) and managed by the multidisciplinary NST.
8. To avoid tube blockage, the tube should be flushed with water before and after feeding. Tubes should also be flushed before and after any medication is administered.
9. Quality assurance procedures should be followed to avoid contamination of EF during administration, but most contamination may not be clinically relevant unless a patient is immuno-suppressed, is taking drugs to inhibit gastric acid production, or is being fed directly into the small bowel.
10. Protein deficiency decreases absorption of vitamin A, dietary fat decreases calcium absorption, copper and zinc supplements inhibit iron absorption, whereas vitamin C enhances absorption of non-haem iron.
11. Do not aim to achieve the full energy target with early EN. Early feeding that exceeds actual energy expenditure is harmful. Hypocaloric early EN appears to be safe and can frequently meet protein targets.
12. There are published practical guidelines for prescribing and administering EN for paediatric and adult, surgical and critically ill patients.

Introduction

In considering the nutritional support of hospital patients the general, almost obligatory, rule that has been promulgated in recent years is 'if the gut works, use it'. However with the recent advancement in research, it is crucial to ensure at least the patients are fed [1]. Delivering early nutrition therapy, generally within 48 h in the ICU [2], primarily by the enteral route, is now seen as a proactive therapeutic strategy that may reduce disease severity, diminish complications, decrease length of stay (LOS) in the ICU, and favourably impact patient outcomes [3]. Nutrition support via enteral nutrition (EN) and/or parenteral nutrition (PN) for patients is

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Table 1 General principles and precautions for using early EN (EEN) in critically ill patients at risk of intolerance

Starting and continuing EEN	Start EN at a slow rate (10–20 mL/h) while carefully monitoring abdominal/gastrointestinal symptoms
	Increase EN slowly once previous symptoms are resolving and no new symptoms occur
	Do not increase EN in cases of intolerance or new symptoms, such as pain, abdominal distension or increasing intra-abdominal pressure. In these circumstances EN should be either continued at a slow rate or ceased depending on the severity of symptoms and suspected underlying sinister pathology (e.g. mesenteric ischaemia)
Energy target during EEN	Do not aim to cover full energy target with EEN. The optimal energy and protein target in the early phase of acute critical illness is not known. EEN that exceeds actual energy expenditure appears harmful and should be avoided [12, 13], whereas hypocaloric EEN may be safe [14–16]
Monitoring and protocolised management of GI dysfunction during EEN	In case of gastric retention without other new abdominal symptoms use prokinetics and/or postpyloric feeding in a protocolised way [17]. Monitoring gastric residual volume (GRV) is typically conducted to observe signs of feeding intolerance, but a meta analysis of 4 RCT provided no evidence that returning residual gastric aspirates provides more benefits than discarding them [18] (chapter "Insertion, Types and Care of Enteral Feeding Tubes").
	During introduction and increasing the rate of EN, measurement of intra-abdominal pressure (IAP) provides an additional numeric value to detect negative dynamics of IAP during EN in patients with severe abdominal pathology, hypoperfusion or fluid overload
Individualized approach	For patients with diminished consciousness and inadequate swallowing, precautions to prevent aspiration of gastric contents may be useful, including considering post pyloric feeding
	Premorbid health and course of the acute illness may differ between patients with similar diagnose; therefore an individual approach should always be applied

crucial with no superiority for either, if prescribed and used appropriately. EN is claimed to: be physiological, improve gastrointestinal function, prevent bacterial translocation and improve patient outcome while being less expensive than PN.

There is no documented evidence for reduced bacterial translocation or improved intestinal function in humans, although there are animal data [4] which show that intestinal mass, mucosal weight, villus height and disaccharidase activity all decrease in animals fed with PN compared with EN. Although there is no direct evidence that patient outcome or safety is better, there are studies which show fewer complications with EN compared with PN. These include patients with pancreatitis [5], following a total gastrectomy [6] and after hepatic resection [7]. There are fewer septic complications [5] and natural killer cell activity is higher in patients fed with EN compared with PN [7]. The frequently quoted paper in favour of EN, by Moore et al. [8], is a meta-analysis of eight studies (six unpublished). Their analysis shows no difference between EN and PN in non-infectious complications, mortality rates or length of hospital stay. However, more septic complications were noted with PN in patients who had had abdominal trauma. A comprehensive review of published prospective randomized controlled trials by Lipman [9] concluded that with the exception of reduced septic morbidity in abdominal trauma (which was offset by an increased incidence of EN-related complications) the only significant difference between EN and PN was the lower cost of EN. A more recent study of critically mechanically ventilated patients concluded that ventilator-associated pneumonia rates, ICU and hospital lengths of stay, ICU and hospital mortality rates of patients receiving PN were not significantly different than those receiving EN [10].

A balanced approach to the route of nutrition support therapy is appropriate. It is important to consider the nutritional support requirements of each individual patient, then choose the most appropriate route of delivery for that patient. Guidelines, as proposed by Blaser et al. [11] for successfully feeding critically ill patients suggest giving early EN in order to meet nutritional goals (Table 1). It is important that individualised approach to be used to ensure nutritional optimization.

History, Ingredients and Manufacturing

Various mixtures of milk, egg, beef or chicken broth, wine, brandy and pancreatic tissue have been administered to patients rectally since Ancient Egyptian times [19]. John Hunter in 1790 successfully used a 'tube' passed through the mouth into the stomach to feed a patient who was unable to swallow due to 'paralysis of the muscles of deglutition'. The 'tube', which was designed by a watchmaker, consisted of eel skin wrapped round a flexible whalebone and was attached to a pig's bladder which acted as a reservoir. Hunter recommended that jellies, eggs beaten with a little water, sugar and wine or milk should be given as food [20].

Today whole protein enteral feeds (EF) are made from milk components (e.g. calcium caseinates) or soya protein isolates as the predominant protein sources, various oils (e.g. soya, corn or safflower) as lipid sources, and ingredients derived from corn starch (e.g. maltodextrin), sucrose, and glucose as sources of carbohydrate. Some have insoluble and/or soluble fibre added. The protein sources in semi-elemental EF (peptide or elemental diets) are based upon the

products of hydrolysis of milk components (caseinates, whey protein and lactalbumin) or soy protein, with some specific amino acids and medium-chain triglycerides added. Most EF intended for use as sole source of nutrition, are fortified with essential vitamins, minerals and trace elements. Some also contain other nutrients such as choline, taurine, arginine and glutamine.

Manufacturers of EF invariably endeavour to achieve maximum nutrient content in minimum volume. Technological challenges for new product R&D involve packaging development to ensure the final product maintains nutritional, microbiological and organoleptic integrity. Sensory assessment is important during the product development stage. The elderly have different perceptions of taste and smell to younger people, and it is now known that further alterations occur during hospitalisation. Sensory testing is initially conducted 'in-house' but then usually involves consumer and patient panels that must be conducted according to the Medical Nutrition Industry Code of Conduct [21]. Finally, extensive stability testing in the laboratory is required to establish shelf life, pilot production runs and larger scale-up for industrial processing.

Stability

The stability of macro- and micro-nutrients depend upon the exposure of the EF to heat, pH, light and air (Table 2). Heat processing to produce a sterile liquid feed can destroy some vitamins (e.g. all B vitamins especially thiamine and vitamin B_6, folic acid and pantothenic acid) and heat-sensitive amino acids (e.g. glutamine and cysteine). Hence glutamine and cysteine are absent from most commercial EF. The amount of vitamin and amino acid lost will depend on the time for which heat is used to destroy harmful organisms. Thiamine is more stable to heat at low pH, but when the pH is high, losses are considerable. Riboflavin is unstable at high pH and is light-sensitive. Vitamin A losses can occur if light and air are not rigorously excluded. Vitamin C is the least stable of all the vitamins; it is readily oxidized in air, a process which is catalysed by heat, light, high pH and the presence of copper and/or iron. Whilst vitamin C is partially protected by the addition of bisulphite, thiamine destruction is accelerated. Vitamin E is relatively stable to heat but oxidized in the presence of air. Average nutritional claims for the content of EF are those which are declared on the label.

Table 2 Vitamin and amino acid stability in EF

Heat
Vitamins
B vitamins (especially thiamine and B_6), folic acid and pantothenic acid
Amino acids
Cysteine and glutamine
Light
Vitamin A and riboflavin
pH
Riboflavin and thiamine at high (alkaline) pH
Air
Vitamins A, C and E all oxidize

Most liquid, ready-to-use feeds are filled aseptically into cartons, plastic containers or glass bottles. These are then subjected to ultra-high temperatures (UHT) to kill any bacteria present. A temperature of about 143–152 °C is maintained for 5–10 s. The resultant sterile feed will keep for several months but variable losses of vitamin C and folic acid may occur during storage. It is difficult to give precise values for expected losses, and they will be accentuated when the containers are opened and exposed to air. However, if they are kept in the closed carton in which they are transported, the contents will be protected from light and oxygen. The process of freeze drying has been used for over 50 years, and was refined during World War II in order to supply huge quantities of dried plasma and penicillin to the armed forces. It is now used extensively in the pharmaceutical industry as one of the best methods for preserving biological materials and for protecting heat-sensitive drugs. It has also been successfully adopted for producing some EF.

Manufacturers generally fortify EF to levels designed to compensate for losses, which occur during processing. In addition, most manufacturers have rigorous quality assurance programmes designed to test levels of all nutrients during the 'quarantine' period after products are manufactured, but before they are released for sale, to ensure that nutrient levels, which are listed on the labels, are accurate. Most companies also conduct routine stability trials to determine the average levels of nutrients over the shelf-life of the product. Feeds can usually be stored at room temperature unopened for up to 1 year.

Formulations

The type of EN formulation used, as for PN, is directly dependent on the nutrient needs and goals of therapy for the patient [22]. EF divide into three formula types, standard (whole protein), peptide (semi-elemental) and specialized formulas. EF then fall into two different categories, oral/sip feeds and tube feeds:

Oral (or Sip) Feeds

Most prescribable sip feeds are nutritionally complete and can be used as sole source of nutrition. However, in general they should only be used to supplement a patient's diet to

Table 3 Nutritional considerations for enteral feed constituents

1.	Protein source (whole protein, peptides or amino acids)
2.	Carbohydrate content and source (e.g. lactose free)
3.	Fat content and source (long-chain triglycerides (LCT) vs. medium-chain triglycerides (MCT))
4.	Energy density
5.	Energy distribution (i.e. % of energy supplied by protein, carbohydrate and fat)
6.	Fibre content, type and source
7.	Renal solute load
8.	Electrolyte composition
9.	Lactose/gluten content
10.	Vitamin and mineral content (i.e. volume required to supply RNI)
11.	Osmolality
12.	Viscosity
13.	Palatability and patient acceptance

Table 4 Classification of prescribable enteral products in UK[a]

1.	Oral supplements (sip feeds)—to provide greater nutritional value and/or energy density to the diet
2.	Polymeric tube feeds—nutritionally complete feeds with high/whole protein, maltodextrin, LCT, PUFA/ MUFA, immune modulating formula and often fibre
3.	Elemental/peptide feeds for sip and/or tube feeding—mono/oligo-peptides and mono/oligo-saccharides which may be more easily digested and absorbed (but have a high osmolality, especially the elemental diet)
4.	Disease-specific formulae—for short bowel, liver or renal failure
5.	Modular diets (e.g. powdered carbohydrate or protein supplements—to individualize a patients diet)
6.	Feeds for inborn errors of metabolism (e.g. phenylketonuria)
7.	Infant formulas (e.g. lactose free feeds or those which do not contain cow's milk)

[a] This list is not exhaustive and does not include gluten-free foods or low protein foods

achieve optimum nutrition. There is a wide range of 'ready-to-use' commercial sip feeds.

Tube Feeds

Tube feeds are administered as nutrition support via a naso-enteric tube (for short term) or via a percutaneous endoscopic gastrostomy (PEG) or jejunostomy (for long term). They are nutritionally complete and can be safely given as the sole source of nutrition. These include whole protein feeds for patients with 'normal' gut function, peptide feeds often used for jejunal feeding, and specialised feeds (free amino acids hence hyperosmolar) to treat some patients with malabsorption such as Crohn's disease. Some of the nutritional considerations relating to EF are shown in Table 3.

A comprehensive list of prescribable EF (classified as 'Borderline Substances') can be found in the British National Formulary (BNF) [23]. Unlike in the USA, very little EN 'compounding' is carried out in UK pharmacy departments. EN products can be classified into seven groups (Table 4).

Protein

In the UK it is common to refer to protein requirements for EN and nitrogen requirements for PN. The eight essential amino acids (EAA) (in adults: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine) cannot be manufactured by the body but can be used to make the non-essential amino acids (NEAAs), which provide most of an individual's metabolic need for nitrogen. The quality of protein is as important as the quantity. Whilst chemical scores based on reference standards for egg or milk proteins provide useful data, they do not take into account imbalances in protein amino acid patterns, different digestion rates and absorption of specific amino acids and losses during processing. Published data based on actual protein and EAA requirements for humans that accommodate age and lifestyle factors, allow reasonably accurate amounts to be determined. Nevertheless, most enteral and parenteral products have a lower protein quality value when compared to egg or milk.

Glutamine

Glutamine is key for immune function as the primary fuel for proliferation of lymphocytes, production of cytokine, and macrophage phagocytic and secretory activities [24]. Glutamine is also the precursor for amino acids, proteins and nucleotides synthesis, and also ammonia genesis in the kidneys [25]. Since glutamine is available abundantly from animal and plant-based protein sources, individuals consuming a balanced diet can easily meet their nutritional requirements for glutamine. However during periods of metabolic stress or catabolic conditions, such as critical illness, sepsis, burns, post-surgery, and malnutrition; glutamine becomes conditionally essential, as the demand for glutamine increases drastically. Recent research has shown that glutamine can positively affect gut health by supporting the gut microbiome, gut mucosal wall integrity, and by modulating the inflammatory response [26]. Because glutamine is heat labile, standard EF do not contain adequate amounts of glutamine, due to losses during the manufacturing process. Therefore, glutamine may be provided to those individuals as modular supplements in the form of the more heat-stable glutamine dipeptides.

Arginine

Just like glutamine, arginine is also a conditionally essential amino acid during metabolic stress and trauma, due to the increased protein turnover and energy requirements of the immune system. Arginine is involved in various metabolic pathways. It is converted into biologically active compounds such as ornithine, nitric oxide, polyamines and citrulline. Hence, arginine is involved in the modulation of immune function, regulation of blood flow, angiogenesis and also wound healing [27]. Arginine is stable to heat processing and can therefore be formulated into EN regimens. All protein-based enteral feeds contain theoretically between 3 and 5 g arginine per 1000 kcal (4200 kJ) whilst some have been further enriched with additional free amino acid. Lower infection rates and reduced hospital stays have been reported with these arginine-enriched diets, but it remains difficult to interpret the potentially beneficial effects of arginine supplementation because of its co-administration with other immune-stimulating nutrients during many trials [28].

Nucleotides

Nucleotides plays an important role in the structural integrity of DNA and RNA, especially in the development of immune system, and differentiation of rapidly growing cells, such as: skin, intestinal mucosal, lymphocytes, etc [29]. During periods of rapid growth, tissue injury, infection and certain disease states, the physiological demand for nucleotides beyond de novo synthesis [30]. Hence, they are also incorporated into immune-enhancing formulas.

Carbohydrate

Carbohydrate is an essential component of enteral feeds, however Recommended Nutrient Intakes (RNIs) have not been published [24]. Most enteral feeds are designed to supply a non-protein calorie to nitrogen ratio of between 94:1 and 154:1. These proportions of energy and protein help to ensure that the carbohydrate in the feed is used for energy.

Lipids

Lipids are included in most enteral feeds as they act as a source of energy to help meet energy requirements and to minimize endogenous protein catabolism. Unlike carbohydrate and protein, lipids do not contribute to osmolality. Enteral formulas contain essential fatty acids like alpha-linolenic acid (omega-3 fatty acid), linolenic acid (omega-6 fatty acid) and other polyunsaturated fatty acids (PUFAs) as they cannot be synthesized *de novo*, and have to be consumed from the diet.

In peptide-based enteral formulas, fractionated coconut oil is often added as a source of medium-chain triglycerides (MCTs) for better absorption. MCTs are absorbed directly into the lymphatic system, hence, may minimize steatorrhea in patients with malabsorption.

Vitamins and Minerals

Enteral formulas whether to be used as sip or tube feeds, that are intended for use as sole source of nutrition; are fortified with essential vitamins, minerals and trace elements adequate to supply the RNI in volumes about 1–2 L [31]. The RNIs are a guide to the requirements for healthy individuals, therefore may not be representative of the micronutrient requirements of metabolically-stressed patients, who will have increased requirements for nutrients due to changes in metabolism. Therefore, some enteral formulas contain higher amounts of micronutrients, which will be beneficial for patients, in account for the increased nutrient requirements [32]. Recommendations for adult and paediatric daily micronutrient requirements in EN and PN have been published by ASPEN [33] and ESPEN [34] and for paediatric requirements by ESPEN/ESPGHAN [35].

Osmolality

Osmolality is the measure of the size and quantity of ionic and molecular particles within a defined volume, usually in the measure of mOsm/kg of water. A standard enteral formula of approximately 300 mOsm/kg of water is considered "isotonic" as it falls within the normal physiologic range of the human body. However, with energy and nutrient-dense formulas, the osmolality of the formula increases as more molecular particles are present within the same amount of volume. Generally, commercially available enteral feeds are tolerated by most individuals. Tolerance to higher osmolality formula may vary according to different medical conditions and gut integrity. Patients with gastrointestinal diseases or on jejunal tube feeding may experience intolerance such as osmotic-induced diarrhoea, when given high osmolality enteral feeds at a high rate. Therefore, it is advisable to start the enteral feeds at a lower infusion rate and advance gradually, and to monitor the patient for gastrointestinal intolerances. Patients with a high output jejunostomy may need a solution with an osmolality near to 300 mOsm/kg and a sodium content of 90–120 mmol/L (chapter "Management of a High Output Stoma, Jejunotomy or Uncomplicated Enterocutaneous Fistula"). In some units additional sodium

is added (using aseptic procedures) to the feeding bag prior to administration, but this will increase the osmolality.

Feeding Routes/Administration

The choice of feeding route is determined by alimentary tract function, previous gastrointestinal surgery (e.g. gastrectomy), accessibility of the gastrointestinal tract (GIT), practicality of using the GIT and patient preference. In patients who are able to eat, but unable to meet their nutritional requirements with everyday food and drink, fortified foods or sip feeds can help to increase intake of energy, protein and other nutrients.

In those who are unable to eat, but have a functioning GIT, tube feeds may be administered via a nasogastric tube in the short-term, or a gastrostomy or jejunostomy in the long-term. Nasogastric feeding is the most common form of tube feeding, and can be used to meet total nutritional requirements, or to complement oral or parenteral nutrition. A gastrostomy (most commonly a PEG) or jejunostomy is used for patients who are expected to require tube feeding for longer than about 3 weeks. Jejunostomy feeding is used when the stomach cannot be used (e.g. if patient has had a gastrectomy) and the patient has otherwise a functioning GIT. Jejunostomy feeding has been successfully used to feed patients after liver transplantation [36]. In patients who do not have adequate functioning gut, or whose nutritional goals cannot be met by EN, parenteral feeding is indicated.

Delivery Techniques

For most tube-fed patients, a feeding pump is used to deliver the feed. Pump controlled feeding can be continuous or intermittent. In the hospital setting, continuous feeding is the most common. For patients who require feeding at home, intermittent feeding allows more flexibility and freedom. In addition, when feeding is stopped for 4 or more hours each day, the gastric pH drops to below 2.5 and this has the additional advantage of having an antibacterial effect. Gravity or bolus feeding, which supplies 100–400 mL of feed over 10–30 min several times a day, can be used with stable patients who may find it better psychologically. However, if not introduced carefully, it can increase the incidence of diarrhoea, cramps, nausea, bloating and/or abdominal discomfort [37] (chapter "Enteral Nutrition").

Tube Blockage

Tube blockage can occur in enterally fed patients and may lead to the EFT needing to be replaced. Protein coagulation, which occurs at low pH, is usually the cause of blockage and may be aggravated by the administration of medications through the tube. To avoid tube blockage, the tube should be flushed with water before and after feeding, and some advocate every 4 h during feeding. Tubes should also be flushed before and after any medication is administered and certain medications should never be mixed as this may cause EF to become unstable, thus increasing the potential for the tube to become blocked (see below). Along with other measures (chapter "Insertion, Types and Care of Enteral Feeding Tubes"), a suspension of pancreatic enzymes and bicarbonate can prevent tube blockage and decrease the rate of tube occlusion tenfold [38] (e.g. a Creon® capsule dissolved in 10 mL 8.4% sodium bicarbonate).

Diarrhoea

Much research has been undertaken to understand and define the pathogenesis of enteral feeding-related diarrhoea. Factors such as antibiotics, high osmolality feed, lactose intolerance, contaminated feeds, laxatives and overflow incontinence have all been implicated (chapter "Intestinal Adaptation"). A systematic review of 26 studies has shown that diarrhoea can be moderated by fibre in patients receiving EN [39] and fibre is well tolerated within 72 h of feeding in ICU [40]. However, the addition of prebiotics (fermentable fibre), which lead to specific changes in the composition and/or activity of gut microbiota that benefit the well-being and health of the host) in minimising diarrhoea in ICU settings remain inconclusive [41]. In addition, a meta-analysis of 30 trials with 2972 patients had shown the potential use of probiotics in reducing VAP infections but high quality clinical trials are needed in a broader selection of patients to substantiate this interesting and low cost approach for diarrhoea prevention [42].

Administration and Compatibility of Drugs with Enteral Nutrition

Providing optimal nutrition therapy is as vital to patient outcome as prescribing the correct drug, but as our knowledge of clinical nutrition and pharmaconutrition has expanded, so too have the complexities of the nutrition and drug therapies that patients are prescribed. The two extremes of nutritional status i.e. malnutrition and obesity, can both influence drug disposition and drug absorption when administered with EF in infancy and childhood; pregnancy and lactation; and especially in the elderly. Around 10% of the population in most western countries is over the age of 65 but this relatively small percentage of patients uses more than a third of all medicines prescribed. Moreover, polypharmacy or multiple drug therapy and malnutrition are more prevalent in older

people. It is estimated that over 40% of home enteral tube feeding (HETF) patients are over 70 years old and the majority will have a permanent feeding device with only 20% using nasogastric tubes.

As a result of the heightened awareness of the benefits of home artificial nutrition (HAN) support, EF are now increasingly seen as a useful vehicle for administration of medications. However, interactions between drugs and nutrients in an EF can cause an alteration of the pharmacokinetics of the drug or nutrient (bioavailability, distribution, metabolism, excretion) leading to compromised nutritional status. Drug-nutrient interactions (DNI) can be categorised as: physical, pharmaceutical, pharmacological, physiological, pharmacokinetic or pathophysiological and may occur when certain medications are administered together with EF, causing reduced absorption of the medication or nutrients, or tube blockage. Factors contributing to DNI have been comprehensively listed by Rollins in Table 5 [43]. The clinical consequences of an interaction are related to alterations in the disposition and effect of the drug or nutrient and can include nutritional deficiencies, drug toxicity or loss of therapeutic efficacy.

Typical DNI usually occur during absorption in the gastrointestinal tract. For example, there is a reduction in absorption of phenytoin when an EF is being administered at the same time. Hence, adjustments to the timing of feeds and phenytoin administration are needed, whereby the EF is stopped for 2 h before administration of intravenous phenytoin; and plasma levels of phenytoin need to be monitored routinely [43]. Additionally, protein deficiency decreases absorption of vitamin A, dietary fat decreases calcium absorption, copper and zinc supplements inhibit iron absorption, whereas vitamin C enhances absorption of non-haem iron by binding and solubilising ferric iron. Another example of DNI involves warfarin, whereby the effect of medication is dependent on the vitamin K content of the EF. In such cases, once feeding has been established and the patient will be on long term EN, INR should be monitored routinely and dosage of warfarin should be adjusted accordingly [43]. Most drugs contain excipients that could also interact with an EF. Sorbitol, used as a solubilizing agent and as a sugar-free sweetener in liquid formulations can cause severe cramping and diarrhoea. It has now been eliminated from some drugs, such as paediatric antibiotics, but it is wise to check with the drug manufacturer. Nevertheless, it must be remembered that these actions will breach the product licence of the drug. Consequently, adding an oral medication directly into the EF is generally discouraged in favour of direct enteral bolus or via the EFT after consultation with the pharmacist.

Table 5 Factors contributing to drug-nutrient interactions (adapted from [43])

Administration related	Tube characteristics size, length, material
Regimen	Continuous, cyclic, intermittent or bolus
	Flushing fluid (e.g. water) frequency and volume
Site of feeding	Gastric, duodenal or jejunal
Medication	Tablet, capsule, solution, elixir (contains alcohol), syrup (contains sugar), suspension
	Osmolality and viscosity of liquids
	Excipients: sorbitol, alcohol, stabilizers
Absorptive environment	Acid, base, hydrophilic or lipophilic
Therapeutic index	Important if narrow
Formula	Protein content - intact, hydrolysed, caseinate, isolated milk protein, soy, whey
	Components affecting GI motility: lipid content, osmolality, viscosity
	Vit K content
Disease related factors	Visceral protein and GI motility/digestive enzymes and mucosal absorption

DNI in patients on EN can be avoided or minimised by the following: avoid mixing drug and the EF formula, change the route of administration, change the drug dosage form to a therapeutic equivalent, change the EN formula, use minimum drug dose, dilute the drug and flush EFT before and after dosing. Liquid solutions or liquid suspensions of drugs are preferred and can be administered directly via the EFT. Tablets or capsules, need to be either crushed and dissolved, or opened and dissolved in water before administering through the EFT. When administering medication via the EFT, it is advisable to flush with 20–30 mL of water before and after the medication is administered. If adding more than one drug, flush the EFT with 10 mL of water between the different medications. Mixing drugs together and adding medications directly into the EF is generally discouraged in favour of direct enteral bolus. Modified or extended release tablets, enteric coated tablets or capsules, cytotoxics, and hormones should not be administered as the pharmacokinetic properties (bioavailability, distribution, metabolism, excretion) of the medication may be significantly altered.

The US Pharmacopoeia [44] contains release characteristics of drug dosage forms and data on DNI with EF or EFT. The BPNG Handbook of Drug Administration via Enteral Feeding Tubes provides legal, practical and technical aspects that clinicians should consider for safe and effective prescribing and administration of drugs via EFT [45]. Whenever possible a licensed formulation should be used but the individual drug monographs in the book provide guidance on alternative medications when appropriate. Nevertheless, it must be remembered that administering a crushed or opened oral drug or an intravenous drug via an EFT usually falls outside the drugs product licence. There could be a risk of inaccuracies in dosing, tube blockage or an adverse patient reaction—in which case the drug manufacturer is no longer accountable, but the responsible health pro-

fessional could be liable for any adverse reaction experienced by their patient. The ASPEN Enteral Nutrition Handbook [1] contains the latest recommendations on safe practices and new information on preparation, labelling, and dispensing of EN. It provides a step-by-step, practical guide to caring for patients receiving EN therapy. The ASPEN website [46] also has useful references including updates on the ASPEN ENFit® project to standardise enteral connections in accordance with the ISO standards [47]. The US FDA is in the process of developing guidance for the pharmaceutical industry on oral drug products for ETF. The draft guidance, which is out for public consultation, will cover in vitro testing and labelling recommendations for manufacturers to ensure oral drug quality and bioequivalence when evaluating a drug's suitability for administration via an EFT [48].

Administration of drugs via an EFT has implications for all members of the multidisciplinary NST. In particular, the pharmacist has several responsibilities to ensure the correct drug formulation is prescribed and that clinical colleagues are aware of the legal implications of using an unlicensed drug. Rational drug or nutrition therapy requires clinical management based on accurate interpretation of symptoms, correct diagnosis and sufficient knowledge about drugs to select the right medicine and administer it in the right dose for the optimum length of time by the most appropriate route. More comprehensive education on DNI in EN will enable health care providers to better manage their patient's clinical outcome.

Feed Contamination

Safety must be a primary focus for the preparation and administration of an EF. According to the ASPEN Safe Practices for Enteral Nutrition Therapy Task Force [49] before any drug is considered for administration via an EFT, the pharmacist should be consulted, who can ensure that national equivalents of OSHA and NIOSH [50, 51] are complied with for the use of hazardous drugs in hospital settings. Additionally, the patient should be assessed to determine whether they can tolerate and manage oral administration of the prescribed licensed medication. Detailed practice recommendations have been compiled by ASPEN [49].

Microbial contamination of EF can occur during preparation, decanting and assembly of mixed or ready-to-use products, or more commonly during the subsequent manipulation of the feeding system and might be a source of nosocomial infection [52, 53]. It has been assumed that micro-organisms present in a feed administered into the gut (especially the stomach), will be destroyed by gastric acid and digestive enzymes, in the same way as food. Hence, infection control procedures have remained less stringent for EN than those for PN. However, the risk and magnitude of contamination is directly related to the type and number of manipulations of the system and the use (or non-use) of aseptic techniques [54]. Nurses often do not wash their hands before handling EN systems but micro-organisms detected in patient's feeds can be transferred from nurses' hands or from patients themselves [55, 56]. Typical organisms isolated from EF include the skin contaminants *Staph. epidermidis* and Gram-negative bacilli. Retrograde spread of organisms from the patient, via the giving set, to the EN container have been reported [57]. Microbiological contamination of EFT may be due to the practice of flushing the tube with tap water [58]. The practice of flushing and rinsing giving sets when changing EN containers is common in the USA, but rinsing may be unnecessary if the sets are changed at least every 24 h [59]. Historically, hang-time for paediatric formulas has been only 4 h, but by using sterile closed EN systems hang times may be extended up to 24 h [49].

Several policies and procedures intended to minimize EN contamination have been published in USA and Europe [48]. Anderton et al. [60] published guidance notes for the British Dietetic Association and recommended that at no time should any internal part of the nutrient container or giving set be allowed to come into contact with hands, clothes or surrounding surfaces. Contamination is more likely in patients on an ICU if EF are reconstituted or diluted with non-pasteurized water rather than with sterile water. Contamination of a EF may not be clinically relevant unless a patient is immuno-suppressed, is taking drugs to inhibit gastric acid production, is being fed directly into the small bowel or if there is an enteropathic organism in the feed. As such patients may not be immediately identified, it is therefore recommended that EFs are always prepared and administered using aseptic technique.

Other Feeding Options That Need Microbiological Monitoring

Blenderised food is becoming increasingly popular with HEN patients. It involves administering liquidised or pureed table food vi an EFT. There may be physiological benefits such as improvement in symptoms of vomiting, reflux and abnormal bowel habits for some tube-fed individuals. Additionally, the parents and carers of some tube-fed children report social and emotional benefits. Nevertheless, this mode of EN has been met with caution, by some professionals who consider there could be increased risks of nutrient deficiencies, blockage of EFT or infection, in comparison to commercial EF. The UK BDA has produced a position statement designed to inform dietitians and ensure effective, evidence-based patient care [61].

Chyme reinfusion (CR) into the distal gut is known to improve nutritional status of patients with high output enter-

ostomies but use has been limited by complicated equipment, safety concerns and low patient acceptance. However, recent clinical experiences in Europe and Australasia [62] have demonstrated that the procedure can be microbiologically safe, reduce dependency on PN and improve gut rehabilitation before surgery (chapter "Distal Feeding and Hydration").

It is important for a multidisciplinary NST, ideally comprising a physician, dietitian, pharmacist, nurse and a microbiologist, to have an ongoing quality assurance programme for EN and PN. The team approach to quality assurance with the key participation of the pharmacist and/or microbiologist has been previously advocated by Anderton, [63] who proposed an adaptation of the food industry's Hazard Analysis Critical Control Point (HACCP) system for the preparation and administration of EF that has been successfully employed over the years [64].

References

1. Malone A, et al. ASPEN enteral nutrition handbook. 2nd ed. Colorado: ASPEN; 2019. ISBN eBook: 978-1-889622-39-2.
2. Singer P, et al. ESPEN guideline on clinical nutrition in the intensive care. Clin Nutr. 2019;38:48–79.
3. McClave SA, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. JPEN J Parenter Enteral Nutr. 2009;33:277–316.
4. Levine GM, et al. Role of oral intake in maintenance of gut mass and disaccharide activity. Gastroenterology. 1974;67(5):975–82.
5. Kalfarentzos F, et al. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. Br J Surg. 1997;84(12):1665–9.
6. Sand J, Luostarinen M, Matikainen M. Enteral or parenteral feeding after total gastrectomy: prospective randomised pilot study. Eur J Surg. 1997;163(10):761–6.
7. Shirabe K, et al. A comparison of parenteral hyperalimentation and early enteral feeding regarding systemic immunity after major hepatic resection—the results of a randomized prospective study. Hepatogastroenterology. 1997;44:205–9.
8. Moore FA, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. Ann Surg. 1992;216(2):172–83.
9. Lipman TO. Grains or veins: is enteral nutrition really better than parenteral nutrition? A look at the evidence. JPEN J Parenter Enteral Nutr. 1998;22(3):167–82.
10. Altintas ND, et al. Effect of enteral versus parenteral nutrition on outcome of medical patients requiring mechanical ventilation. Nutr Clin Pract. 2011;26:323–9.
11. Blaser AR, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med. 2017;43(3):380–98.
12. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med. 2014;370(13):1227–36.
13. Weijs PJ, et al. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care. 2014;18(6):1–10.
14. Heart TN. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA. 2012;307(8):795.
15. Arabi YM, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. N Engl J Med. 2015;372(25):2398–408.
16. Casaer M, Van den Berghe G. Permissive underfeeding of standard enteral feeding in critically ill adults. N Engl J Med. 2015;18(2015):1.
17. Blaser AR, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM working group on abdominal problems. Intensive Care Med. 2012;38(3):384–94.
18. Wen Z, et al. Is discard better than return gastric residual aspirates: a systematic review and metaanalysis. BMC Gastroenterol. 2019;19:113.
19. Randall RJHT, Caldwell MD. In: Randall RJHT, Caldwell MD, editors. The history of enteral nutrition, in clinical nutrition: enteral and tube feeding. Philadelphia: WB Saunders; 1990.
20. Hunter J. A case of paralysis of the muscles of deglutition cured by an artificial mode of conveying food and medicines into the stomach. Trans Soc Imp Med Chir Know. 1793;1:182–8.
21. British Specialist Nutrition Nutrition Association Medical Nutrition Industry Code of Conduct. 2020.
22. Randall HT. Sixth annual Jonathan E. Rhoads lecture. Enteral nutrition: tube feeding in acute and chronic illness. JPEN J Parenter Enter Nutr. 1984;8(2):113–36.
23. British National Formulary (BNF). 2020. www.bnf.org.
24. Apostolopeulou A, et al. Effects of glutaine supplementation on critically ill paients. Nutrition. 2020;78:110960. https://doi.org/10.1016/j.nut2020.110960.
25. Cruzat V, et al. Glutamine: metabolism and immune function, supplementation and clinical translation. Nutrients. 2018;10(11):1564.
26. Deters BJ, Saleem M. The role of glutamine in supporting gut health and neuropsychiatric factors. Food Sci Human Wellness. 2021;10:149–54.
27. Tong BC, Barbul A. Cellular and physiological effects of arginine. Mini Rev Med Chem. 2004;4(8):823–32.
28. Patel JJ, Miller KR, Rosenthal C, Rosenthal MD. When is it appropriate to use arginine in critical illness. Nutr Clin Pract. 2016;31:438–44.
29. Ding T, et al. Nucleotides as optimal candidates for essential nutrients in living organisms: a review. J Funct Foods. 2021;82:104498.
30. Hess JR, Greenberg NA. The role of nucleotides in the immune and gastrointestinal systems: potential clinical applications. Nutr Clin Pract. 2012;27(2):281–94.
31. British Nutrition Foundation. Nutrition requirements. London: British Nutrition Foundation; 2019. http://www.nutrition.org.uk.
32. Iacone R, et al. Micronutrient content in enteral nutrition formulas: comparison with the dietary reference values for healthy populations. Nutr J. 2016;15(1):30.
33. Sriram K, Lonchyna V. Micronutrient supplementation in adult nutrition therapy: practical considerations. JPEN J Parenter Enteral Nutr. 2009;33:548–63.
34. Shenkin A. Trace elements and vitamins in PN and EN. In: Sobotka L, editor. Basics of clinical nutrition. ESPEN. 4th ed. Prague: Galen; 2011. p. 273.
35. Hardy G. Micronutrient deficiencies in intestinal failure. In: Duggan C, Gura K, Jaksic T, editors. Clinical management of intestinal failure. New York: CRC; 2012. p. 283.
36. Wicks C, et al. Comparison of enteral feeding and total parenteral nutrition after liver transplantation. Lancet. 1994;344(8926):837–40.
37. Todorovic VE, et al. Methods of artificial nutritional support, in a pocket guide to clinical nutrition. Birmingham: British Dietetic Association; 1997.
38. Sriram K, et al. Prophylactic locking of enteral feeding tubes with pancreatic enzymes. JPEN J Parenter Enter Nutr. 1997;21(6):353–6.

39. Zaman MK, et al. Fiber and prebiotic supplementation in enteral nutrition: a systematic review and meta-analysis. World J Gastroenterol. 2015;21(17):5372.
40. Fu Y, et al. Relationship between dietary fiber intake and short-chain fatty acid–producing bacteria during critical illness: a prospective cohort study. JPEN J Parenter Enteral Nutr. 2020;44(3):463–71.
41. Majid HA, et al. Additional oligofructose/inulin does not increase faecal bifidobacteria in critically ill patients receiving enteral nutrition: a randomised controlled trial. Clin Nutr. 2014;33(6):966–72.
42. Manzanares W, et al. Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis. Crit Care. 2016;20(1):1–19.
43. Rollins CJ. Drug-nutrient interactions in patients receiving enteral nutrition. In: Boullatta J, Armenti V, editors. Handbook of drug-nutrient inteactions. 2nd ed. New York: Humana Press; 2010. p. 367–410.
44. United States Pharmacopoeia (USP). Hazardous drugs-handling in healthcare settings. 2013. https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/usp-nf-notices/m7808_pre-post.pdf.
45. White R, Bradnam V. In: White R, Bradnam V, editors. BPNG handbook of drug administration via enteral feeding tubes. 3rd ed. London: Pharmaceutical Press; 2015.
46. ASPEN Enteral Nutrition Resources. www.nutritioncare.org
47. Guenter P, Lyman B. ENFit® enteral nutrition connectors: benefits and challenges. Nutr Clin Pract. 2016;31:769–72.
48. US FDA. Oral drug products administered via enteral feeding tube: in vitro testing and labeling recommendations: guidance for industry. Silver Spring, MD: US FDA; 2021. https://www.regulations.gov.
49. Boullata J, et al. ASPEN safe practices for enteral nutrition therapy. JPEN J Parenter Enteral Nutr. 2017;41:15–103.
50. NIOSH list of antiplastic and hazardous drugs in healthcare settings. CDC USA 2014. Publication no. 2014-138.
51. OSHA Occupational Safety and Health Administration. Technical manual. Section VI. Chp2. 2016.
52. Anderton A. Microbiological aspects of the preparation and administration of naso-gastric and naso-enteric tube feeds in hospitals—a review. Hum Nutr Appl Nutr. 1983;37(6):426–40.
53. Fagerman KE, et al. Effects of time, temperature, and preservative on bacterial growth in enteral nutrient solutions. Am J Hosp Pharm. 1984;41(6):1122–6.
54. Anderson K, et al. Bacterial contamination of tube-feeding formulas. JPEN J Parenter Enter Nutr. 1984;8(6):673–8.
55. Kohn CL. The relationship between enteral formula contamination and length of enteral delivery set usage. JPEN J Parenter Enter Nutr. 1991;15(5):567–71.
56. Thurn J, et al. Enteral hyperalimentation as a source of nosocomial infection. J Hosp Infect. 1990;15(3):203–17.
57. Payne-James JJ, et al. Retrograde (ascending) bacterial contamination of enteral diet administration systems. JPEN J Parenter Enter Nutr. 1992;16(4):369–73.
58. Bussy V, Marechal F, Nasca S. Microbial contamination of enteral feeding tubes occurring during nutritional treatment. JPEN J Parenter Enter Nutr. 1992;16(6):552–7.
59. Anderton A. Bacterial contamination of enteral feeds and feeding systems. Clin Nutr. 1993;12:S16–32.
60. Anderton A, Howard J, Scott D. Microbiological control in enteral feeding. Guidance for the British Dietetic Association. Hum Nutr Appl Nutr. 1986;40A:163–7.
61. Durnan S, et al. BDA position paper on the use of blenderised feeds with EFT. 2019.
62. Liu C, et al. A review of chyme reinfusion: new tech solutions for age old problems. J Royal Soc. 2022. https://doi.org/10.1080/03036758.2022.2117832.
63. Anderton A. What is the HACCP (hazard analysis critical control point) approach and how can it be applied to enteral tube feeding? J Hum Nutr Diet. 1994;7(1):53–60.
64. JinXiu L, et al. Application of HACCP in enteral nutrition preparation department. J Food Saf Qual. 2019;10:1054–105.

Access for Parenteral Support

Arun Abraham, Geert Wanten, and Jeremy M.D. Nightingale

Key Points

1. Assessment prior to the insertion of a central feeding catheter consists of examining for evidence of previous venous thrombosis or its predisposing factors (dehydration and sepsis).
2. Reviewing current medication including anti-coagulants.
3. The choice of catheter is influenced by the underlying diagnosis for Intestinal Failure (IF), predicted duration of parenteral support (PS), the frequency and composition of the PS mixture, intravenous medication needed, the person who will be setting up the infusion, the patient and IF team preference.
4. A catheter needed for long-term home PS is usually tunnelled to reduce the risk of dislodgement.
5. If possible ultrasound is used to help placement of all central feeding catheters commonly into the jugular or subclavian veins.
6. The routes for parenteral nutrition can be described according to the position of the catheter tip as large, medium or small vein feeding.
7. A central vein catheter tip needs to be at the atrial/caval junction. If more proximal the risk of thrombosis increases.
8. An arteriovenous fistula is an effective way to give parenteral support and should be considered if many catheter-related blood stream infections (CRBSI) have occurred.

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Introduction

Venous access is essential for providing parenteral support (PS) (nutrition and/or fluids and electrolytes) to patients with Intestinal Failure (IF). PS is required when the gut is not functioning, is functioning insufficiently, is being left to 'rest' or if enteral nutrition is unsuccessful [1]. Successful outcomes for the management of PS venous catheters relate not only to obtaining venous access but more importantly to the skilled after care of the catheters provided initially by nursing staff (chapter "Nursing Care of Patients Receiving Home Parenteral Support"). This chapter provides a practical guide about central and peripheral feeding catheter insertion. It is helpful for all members of a nutrition support team (NST)/ IF team to have an understanding of the considerations made in obtaining and maintaining venous access.

Indication of PN

The most common indication for intravenous nutrition support is short term reversible (type I) IF during the peri-operative phase, however the duration of nutritional support is widely variable from a few days in the initial post-operative days when an ileus may occur, to a several weeks for those who are severely malnourished due to underlying disease or requiring gut rest. Some of these patients may progress to having medium term reversible (type II) intestinal failure depending upon the severity of the underlying disease. In some cases, patients with an abdominal catastrophe need long-term (type III) IF as a consequence of an extensive bowel resection usually due to a disease process or ischaemia.

Preserving Venous Access

Preservation of venous access is important both for fluid/nutrition delivery and medication administration. An intravenous catheter may need to be changed due to a catheter-

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related blood stream infection (CRBSI), venous thrombosis or due failure of the device. An underlying pro-thrombotic condition (e.g. inflammation, dehydration or a coagulopathy) that will contribute to a hypercoagulable state and thus venous thrombosis should be detected and managed. Dehydration which is often due to fluid losses and/ or poor compliance with the oral must be avoided as in addition to predisposing to venous thrombosis makes venous detection more difficult [2]. Medication (e.g. cyclizine) inserted into a PS catheter can cause damage and an increased the risk of occlusion. Venous thrombosis is often irreversible and therefore contributes to a loss of venous access. Thrombosis of more than two major veins is an indication for discussion about an isolated small bowel transplant (chapter "Intestinal Transplantation"). Preserving access is very relevant to a small number of long-term (type III) IF patients who may require renal replacement therapy.

PN Composition

The lower osmolality of some formulations of parenteral nutrition may be compatible with a short term peripheral infusion (small vein), however there are limitations with many of these formulations as they do not meet the higher energy/volume requirements needed by some patients (lower volume and glucose content). Some of the components of parenteral nutrition (especially glucose and electrolytes) can cause a high osmolality which in theory could lead to irritation of the vein's endothelium and so predispose to thrombosis but surprisingly this has not been shown in one study [3]. The amino acids used in parenteral nutrition may have a low pH and can affect the final pH of the admixture and this may increase the risk of thromboembolism. Therefore on theoretical grounds parenteral nutrition, especially if long-term and of high osmolality (greater than 600 mOsmol/kg), and/or with low pH may be best delivered into the circulation at a point of maximal dilution (e.g. the vena cava/atrial junction).

Central and Peripheral Vein Nutrition

The routes for parenteral nutrition can be described according to the position of the catheter tip as large, medium or small vein feeding (Table 1, Fig. 1). Previous descriptions have addressed the site of catheter insertion as either central

Table 1 Parenteral nutrition routes

Catheter tip	Venous insertion site	Type of nutrition
Large vein	Subclavian/jugular/cephalic vein	Central
	Brachial vein in cubital fossa (PICC)	Central
Medium vein	Brachial vein in cubital fossa	Peripheral
Small vein	Vein on back of hand	Peripheral

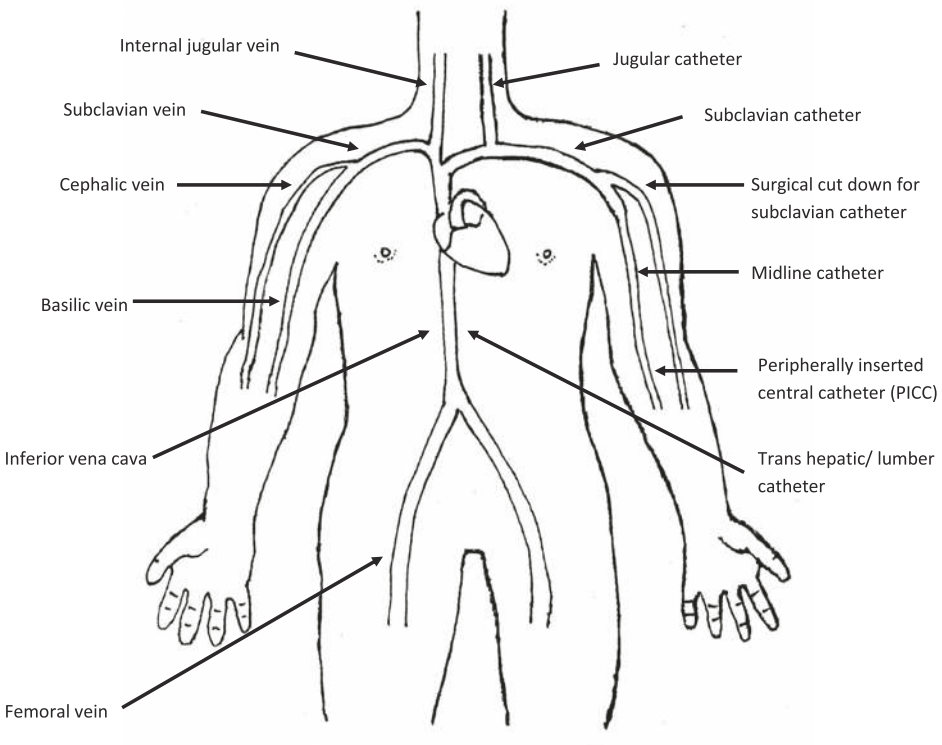

Fig. 1 Schematic venous anatomy and sites for large and medium vein cannulation for the administration of parenteral nutrition

or peripheral. This may lead to confusion as peripheral nutrition may be given through a short cannula with its insertion site and tip in a small vein (e.g. on the back of the hand or on the forearm), or via a catheter inserted into the basilic vein with its tip in the axillary vein.

Nomenclature is most clear when both insertion site and catheter tip position are named (e.g. with peripherally inserted central catheters (PICCs)). PICCs are long small diameter catheters inserted into the basilic vein in the cubital fossa with their tip at the superior vena caval (SVC)/right atrial (RA) junction.

Catheter Materials (Types and Size)

The ideal catheter material is flexible, strong, chemically inert, non-thrombogenic, radio-opaque and does not kink. It should have a measurement scale on its side. The wall of the vein may be damaged by pressure, if the catheter material is relatively inflexible, and this can lead to thrombosis [4]. Small diameter flexible catheters that effectively float in the bloodstream are less likely to cause injury.

The chemical composition of a catheter has not changed and remains an important factor in causing thrombophlebitis of peripheral veins. Most plastics contain additives that may produce a chemical phlebitis. Rubber, polyethylene, polyvinylchloride, Teflon® and uncoated polyurethane are all thrombogenic [4–8]. For parenteral nutrition either a polyurethane-hydromer or silicone elastomer (also called silicone rubber or silastic) catheter is used because they are biologically relatively inert. When compared, thrombophlebitis occurred less frequently with a polyurethane-hydromer coated catheter [9–11].

The coating of a polyurethane-hydromer catheter contains a hydrophobic polymer made from polyvinylpyrrolidone and anisocyanate prepolymer. When a hydromer-coated catheter is wetted, water is absorbed onto the coating and the resulting gel acts as a barrier between the blood and the catheter material so that platelets do not adhere to it. This gives the practical advantage that when wetted by body fluids (e.g. blood) the catheter becomes slippery, which makes the passage of the catheter through a peripheral vein relatively easy and so less likely to cause trauma to the vein. It also has the advantage of being physically stronger than a silicone elastomer catheter, allowing its external diameter to be reduced; in addition, it does not easily kink. Thus polyurethane-hydromer catheters are used when the insertion site is a medium or small vein. Silicone elastomer catheters, which are soft and flexible, are commonly used for long-term central vein feeding where they can last for 10 years without problems.

Some catheters have an antimicrobial (e.g. minocycline) incorporated into the material [12]. Other catheters have an extra cuff (VitaCuff®) containing collagen impregnated with silver ions; the collagen cuff swells to 2–3 times its original size and the silver acts as an antimicrobial [13]. Antimicrobial catheters are not routinely used in current practice due to limited difference in outcome [14, 15].

A central catheter internal diameter is variable but usually 6.6–9.6 FG and a PICC is 2–6 FG. To avoid thrombosis the catheter vein ratio should be 45% or less [16, 17].

Choice of Catheter

The choice of catheter is influenced by the underlying diagnosis for IF, predicted duration of PS, the frequency and composition of the PS mixture, intravenous medication needed, the person who will be setting up the infusion, the patient and IF team preference. In acute IF the choice of catheter for patient care may be different to that of patients requiring a catheter for PS at home. At the onset of IF after an abdominal catastrophe, due to their physiological and metabolic instability, a patient often requires access for multiple therapies. The onset may be more insidious when IF is limited to an episode of illness that fails to resolve or when there is a decline in gut function on a background of chronic illness. The dependence on intravenous support may changes after surgery that either resects bowel or brings more into continuity.

The Bard Groshong valve is a three-way valve incorporated into the tip of a large-vein catheter which, in the absence of a negative or positive pressure, remains in the closed position. It opens inward when negative pressure is applied for aspiration and outward with positive pressure used for infusion. It should prevent blood from the venous circulation entering the lumen, so making catheter occlusion less common, and should reduce the risk of air entering the catheter. While generally performing well, [18] they were no better than Hickman-type lines in terms of CRBSI or thrombosis formation, and they malfunctioned more frequently [19].

For long-term home PN a tunnelled catheter is preferred as the risk of dislodgement after 2 weeks is minimal (Fig. 2) [20].

Peripherally Inserted Central Catheter

In patients with acute IF, a multiple lumen peripherally inserted central catheter (PICC) may be considered initially and then later changed to a tunnelled catheter if long-term home PN is appropriate. As they are relatively easy to insert and remove, there is a growing tendency to use a PICC to deliver HPN for a short time (e.g. less than 3–6 months). However, they remain less ideal for long-term parenteral feeding due to the risk of dislodgement of the catheter as there is no cuff to anchor the catheter to soft tissues. The exit site position on the arm restricts normal arm movement making daily living activities difficult and almost impossible if

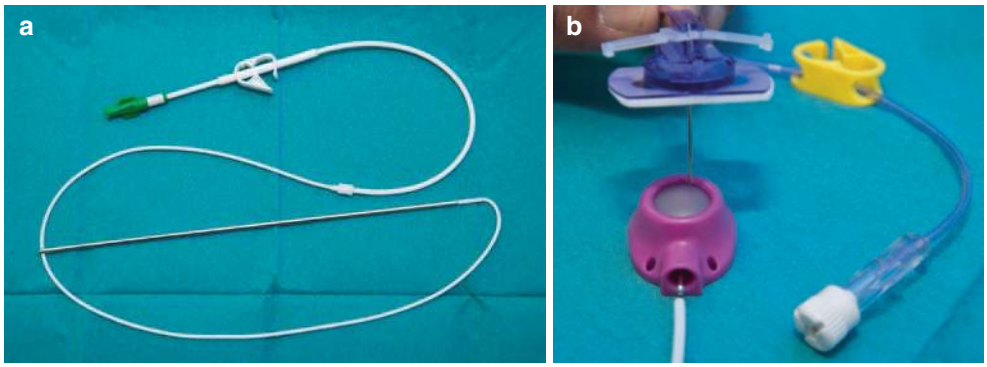

Fig. 2 Types of catheter for long-term PS. (**a**) Cuffed single lumen feeding catheter for long-term use with insertion needle attached. (**b**) Implantable port for long-term feeding (or medication) with external insertion needle attached

the patient is doing the procedures themselves. There is an increased incidence of thrombosis when a larger diameter PICC is used and if there is an underlying malignancy [21]. In other countries such as Canada there is an established practice in using PICC for HPN [22]. They are not suitable for patients who use crutches or a wheelchair.

Implanted Subcutaneous Port

An implanted subcutaneous port is used by some centres for HPN [23]. The first fully implantable venous access device or reservoir device (port) appeared in 1982 [24]. Since that time they have gained in popularity and are now used widely and have few complications [25]. They consist of a vascular catheter attached to a subcutaneous port. The port segment is a cone-shaped chamber made of stainless steel, titanium or plastic covered with a self-sealing compressed silicone septum that can be punctured up to 2000 times by a non-coring needle. Ports are available in single or dual lumen configurations with a pre-attached or attachable silicone rubber or polyurethane catheter. The advantage of an implantable port over other catheters is the cosmetic appearance as it is concealed under the skin and therefore would be an ideal solution for those who prefer the appearance, do not require frequent infusions or wish to swim. However, if patients require daily infusions the advantage of concealed lumen is lost when the Huber needle is left in situ for 5–7 days a week. Daily puncture of the skin overlying the port can lead to ulceration and imflammation of the skin over time. Port site infections can easily lead to CRBSI; salvaging a port when infected is difficult partly due to the reservoir and they usually have to be completely replaced [23].

Preparation

Marking of Catheter Exit Site

The nutrition nurse specialist will discuss with the patient the possible sites for the catheter to exit the skin (especially if a long-term catheter). He/she will then mark at least two appropriate sites with permanent ink that will not come off when the skin is cleaned.

Table 2 Key features included in the WHO surgical checklist [26]

Confirmation of patient, surgical site
Comorbidities and medications identified (anticoagulation)
Allergies specified
Sedation and local anaesthetic identified
Infection precautions
Equipment (instruments/ultra sound/X ray compatible table) confirmed
Post procedure care identified

Place for Procedure

Ideally a large vein feeding catheter is inserted in the radiology department using ultrasound and fluoroscopy. Long-term tunnelled catheters (e.g. a Hickman type catheter or implanted port) are most commonly inserted. Fluoroscopy is useful to ensure the tip of the catheter is at the cavo-atrial junction at the time of placement. Placement of a catheter with the help of fluoroscopy or in interventional radiology should especially be considered to assess and navigate venous anatomy if changed by thrombosis or if there have been several catheter placements.

WHO Surgical Safety Checklist

For any invasive procedure it is recommended to have a checklist to decrease errors or misadventure and a version of the WHO surgical safety checklist is most commonly used [26]. All members of team are present for the WHO check list to appraise patient factors and discuss any issues anticipated for the procedure. The key features within the sign in, time out and sign out headings are listed below (Table 2) [26].

Venous Anatomy Assessment

Multiple visible veins on the chest are suggestive of collaterals (Fig. 3) and should raise concerns about chronic occlusion. A large dilated internal jugular vein seen on ultrasound should raise concern about occlusion of central large veins. Patients who have had multiple central venous catheters, prolonged intensive care stay, multiple episodes of sepsis, or an indwelling catheter for a few years, or have a thrombophilia disorder, or are transitioning from paediatric to adult services are at risk of compromised vascular access. Their venous anatomy may be assessed with the help of a CT (or MRI) venogram. There should always be a high index of suspicion for a venous thrombosis; however assessment of venous anatomy for a long term HPS patient is undertaken only when there is a clinical concern. A comprehensive review of venous anatomy is important prior to undertaking a placement of a new catheter for an existing HPN patient. It is also useful to have upper limb venograms in high risk patients prior to placement of PICC.

New Methods

For non-invasive venous imaging there are developing techniques that use the property of haemoglobin (concentration and oxygenation) as a strong absorber of visible and near-infrared (NIR) light (650 and 950 nm) to show the size and site of veins. For visualising superficial veins (e.g. for venous cannulation/PICC insertion) NIR imaging [27], with or without transillumination, can be used. For deeper veins NIR can be combined with ultrasound imaging (photoacoustic imaging). There are smartphone apps being developed that provide an NIR function.

Equipment

Ultrasound

Ultrasound has changed the practice of insertion of central venous catheters with a significant decrease in incidence of complications [28]. A linear probe with high frequency is used. The probe is placed in a horizontal as well as longitudinal plane to assess the anatomy (Fig. 4a, b). When the probe is placed in horizontal plane the vascular structures appear circular, whereas when the probe is placed in a longitudinal plane it appears as tubular. Veins are collapsible and therefore can be compressed when pressure is applied. Arteries may be compressed; however there is a distinct pulsatile appearance to them. Further confirmation is possible with help of Doppler. The blue colour on Doppler (blood flowing away from the probe) identifies the veins. Red colour on Doppler identifies the artery with blood flow in the opposite direction. If the veins are not collapsible with absence of flow (there is no colour on Doppler) a thrombus must be considered (Fig. 5).

The ultrasound setting should be confirmed to avoid automatic time out.

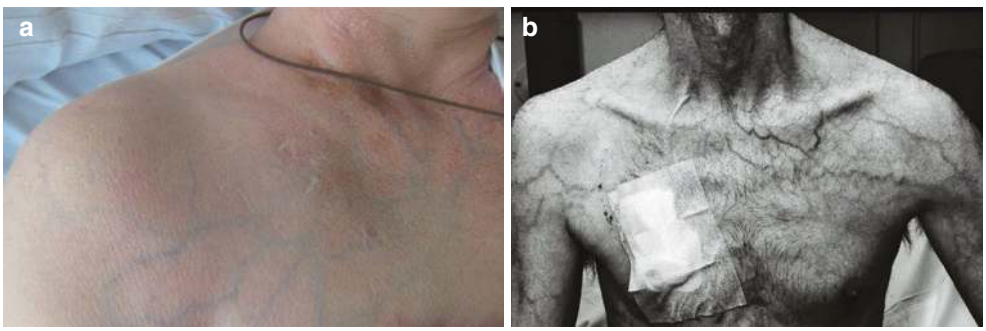

Fig. 3 Collaterals on the upper chest wall due to previous superior vena caval thrombosis. (**a**) Difficult to see and (**b**) very obvious

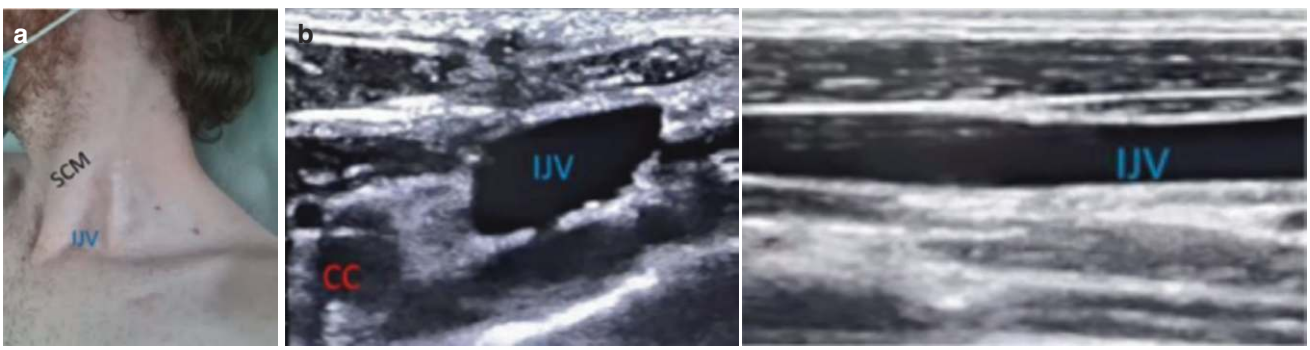

Fig. 4 (**a**) Picture of neck showing position of the internal jugular vein (IJV) (*SCM* sternocleidomastoid muscle). (**b**) Ultrasound of IJV showing size of vein horizontally (*CC* common carotid artery) and (**c**) longitudinally

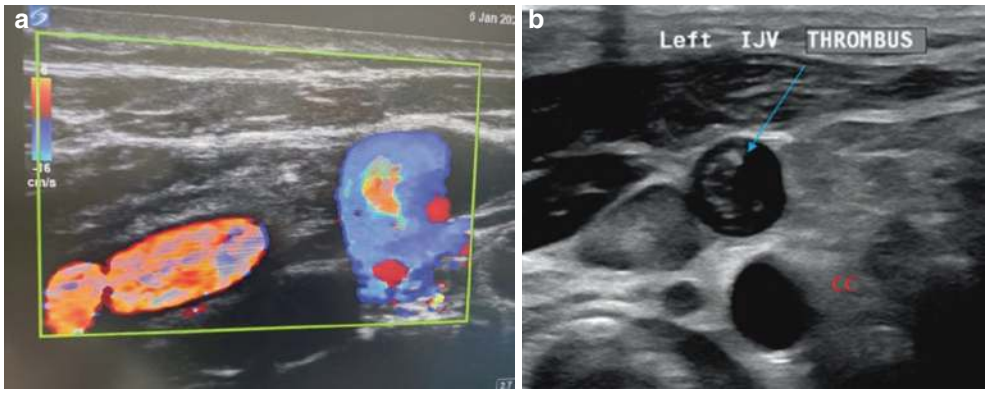

Fig. 5 (**a**) The direction of flow red towards the probe and blue away. (**b**) Thrombus in IJV (internal jugular vein) and common carotid artery (CC) posteriorly

Local Anaesthetics/Sedation

Most of the tunnelled CVCs can be inserted under local anaesthetic. A volume of 15–20 ml of 1% lidocaine is required particularly for the tunnel. Local anaesthetic volume can be increased if 0.25% levobupivacaine hydrochloride (Chirocaine®) is used however it is preferred not to use local anaesthetic with adrenaline. The syringes used for local anaesthetic should be clearly labelled to avoid the error of accidental flushing of catheter with local anaesthetic. Some patients would prefer to have the procedure done under sedation or general anaesthetic due to discomfort or anxiety. General anaesthetic would be essential if a patient cannot lie still. Prophylactic antibiotics are not routinely administered.

Consent and Exit Site

Patient is consented and the exit site marked. Discussion with patient about exit site is important as the catheter can be insitu for a significant period, therefore patient preference should be considered with regards to clothing and ability to care for the catheter. The exit site should be away from the crease of axilla as the skin flora from axilla are different from those on the chest wall [29]. Males patients should have their chest hair trimmed. If the femoral vein is used the exit site may be marked on the lower abdomen or thigh. If a patient is very confused and at risk of pulling the catheter, it can be tunnelled onto the back between the scapulae.

Position

The patient is placed in supine position with table tilted with slight head down. The table should be compatible with X-ray fluoroscopy. Patient may be monitored with an ECG tracing, as well as pulse oximetry. ECG monitoring is useful to detect early arrhythmias caused by the guide wire (if placed into the heart).

Insertion of Large Vein Central Venous Catheter

The operator assess venous anatomy to confirm the site of insertion and then washes hands with surgical scrub, puts on sterile gown, gloves and completes the instrument check. The skin is cleaned with Chlorhexidine in alcohol solution [30–33] and allowed to dry. The site is kept sterile by applying sterile drapes exposing the lateral side of neck as well as the exit site. Head drapes are useful to cover hair and head to maintain a sterile field. The surgical drapes must be adjusted on side of the face to avoid covering patients face completely as this would cause anxiety for patients. The introducer needle is primed with 10 ml syringe with approx. 5 ml of saline in the syringe. It is important to ensure there are no air bubbles in the syringe to help assess if there has been a puncture of lung during the procedure.

Internal Jugular Veins

When internal jugular veins (IJV) are used, the point of entry of catheter should be as low as possible into the root of the neck. If the point of entry is higher in the neck this would lead to an acute angulation of catheter when the catheter is tunnelled under the skin which can lead to occlusions of catheter in the future. A catheter placed as low as possible in IJV will curve anterior to the clavicle forming an arch when tunnelled under the skin which is apparent in a lateral view chest X-ray.

IJV's are commonly used to support acute care and a quad lumen central venous catheter (CVC) may be in situ as the patient recovers and requires support for long term parenteral nutrition. A tunnelled CVC may be placed in the opposite side or the same side if the quad lumen CVC is placed in a more cranial position. The placement of two catheters in the same vein for a prolonged period of time can compromise flow in the vein which can lead to thrombosis, [17, 34] and if one catheter becomes infected, there is a risk of it infecting the other. It is often less difficult to pass the guidewire from the right side than the left. There is some suggestion that the right side has lower risk of thrombosis than the left, possibly due to the catheter being angulated at the junction of the SVC and brachiochephalic vein [35].

Subclavian Vein

Subclavian veins (SC) have always been considered as the vein of choice for PN [36]. as the catheter exit site is not obviously visible, is relatively easy to tunnel from the insertion site and was thought to have a lower incidence of CRBSI. However the introduction of ultrasound reduced the risk of insertion related complications (pneumothorax/haemopneumothorax and arterial puncture) [28]. As it was technically more difficult, with ultrasound, to find and cannulate the subclavian vein there has been a move towards the preferred first insertion site being the internal jugular vein. There is very little difference in the risk of CRBSI from whichever vein a tunnelled CVC is inserted [37]. However, many patients would prefer to have a catheter in the SC for cosmetic reasons as the catheter is not visible over the clavicle (Fig. 6). Rarely a SC catheter may be compressed between the first rib and clavicle (pinch off syndrome).

Femoral Vein

Non tunnelled CVC's placed in a femoral vein are considered to have very high risk of CRBSI. However, for tunnelled CVC's, there is very little difference in rate of CRBSI between the femoral and other sites [37–39]. The catheter can be tunnelled on to the antero-lateral part of thigh or onto the lower abdominal wall taking care to avoid any large collaterals that may have appeared due to a supra-cardiac thrombosis. The risk of a more distal thrombosis with a tunnelled femoral CVC is unknown, partly because most patients needing a femoral catheter have had a thrombosis and are already anticoagulated.

Cardiac and Transhepatic Insertion of a Central Catheter

Rarely all major veins are thrombosed and it is necessary for the cardiothoracic surgeons to insert a feeding line through a

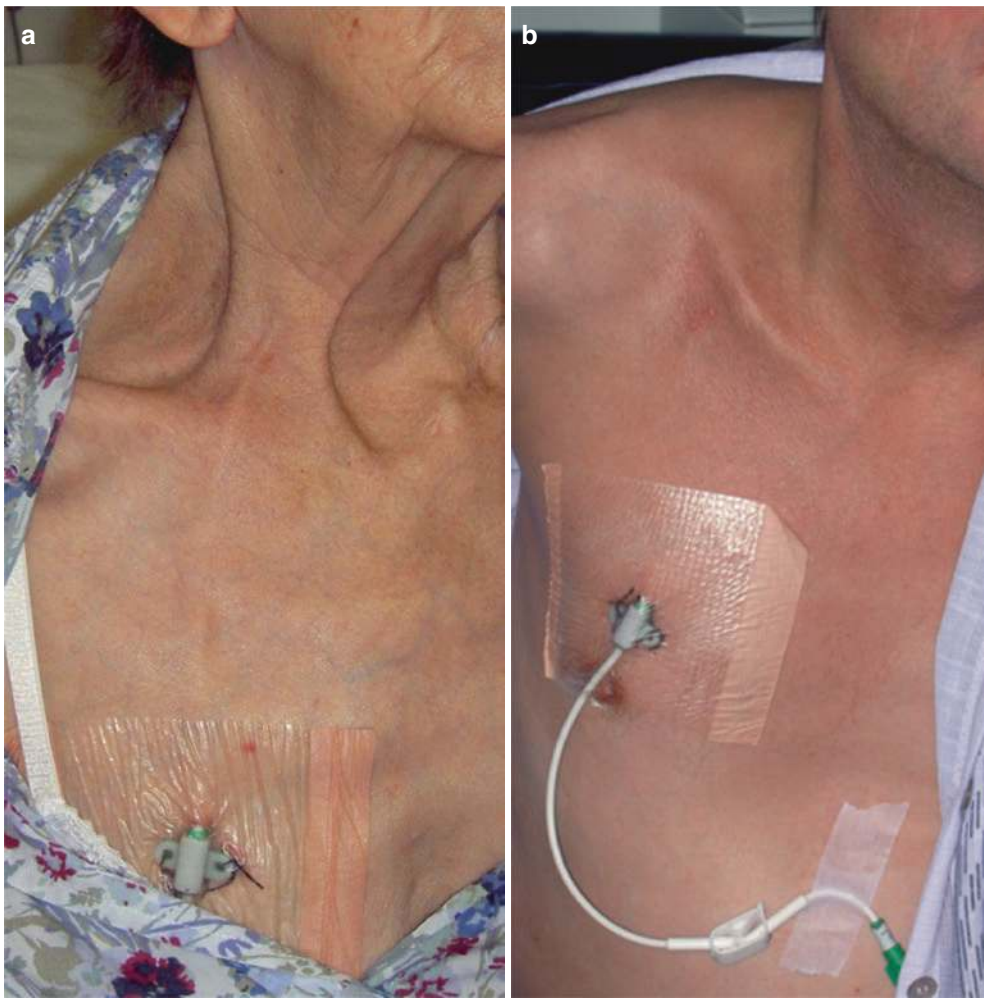

Fig. 6 A recently places (**a**) internal jugular and (**b**) subclavian long-term Hickman type feeding catheter. Note the visible catheter in its tunnel above the clavicle in the jugular insertion

right anterior thoracotomy and through the right atrial appendage into the right atrium [40, 41]. A catheter may be inserted radiologically through the liver and into the inferior vena cava. This technique has mainly been reported in children [42].

Large Vein Catheter Insertion

Boxes 1–4 show the detail about inserting a catheter into a large vein: using ultrasound/radiology (Box 1), directly into the subclavian vein without ultrasound/radiology (Box 2) or surgically using the cephalic vein (Box 3) and the insertion of an implantable port (Box 4). ECG guidance (especially if from an electrode at the tip of the catheter) has helped in knowing when the tip of a catheter is within the right atrium. A catheter tip in the right atrium near the sino-atrial node may cause an atrial tachycardia (often when feed is given) [43]. In most care settings a catheter is placed with radiological screening and the use of ultrasound guidance. In the rare circumstances when this is not possible bedside placement may be performed (Box 2).

Box 1. Ultrasound Aided Cannulation of a Large Vein

1. A sterile probe cover is used to cover the ultrasound transducer. Venous anatomy is confirmed by compressing the vein. The trajectory of insertion needle noted, and skin marked for local anaesthetic. Local anaesthetic is checked and administered about a 1 cm under the skin raising the level of the skin with some blanching. When infiltrating local anaesthetic care must be taken to avoid any small air bubbles which can cause the images to be compromised. The ultrasound probe is used to familiarise the operator with the anatomy.
2. The introducer needle is used to pierce the skin under direct vision. The linear probe is placed horizontally across the vein and needle is positioned at the midpoint of the linear probe (usually marked on the probe). This allows a clear view of the posterior wall and surrounding structures. There are many methods used for cannulation with ultrasound. Most commonly used is the "crepe" method where needle is placed at a small angle to the probe and advanced under direct vision. The probe is tilted as the needle is advanced to ensure the tip of the needle is always in view (Fig. 7). It is important to assess the tip of the needle constantly in relation to the vein. In patients who are underfilled or in older patients with tougher venous wall the introducer needle may not cannulate the vein despite complete indentation of the anterior wall of the vein. Continuous firm pressure with the needle will enable to pierce through the anterior wall of the vein. Cannulation is confirmed by free flow of venous blood into syringe on aspiration and the needle is then tilted towards the skin. The syringe is disconnected keeping the needle steady and guide wire is passed. Absence of pulsatile bleeding from the needle before insertion of guide wire is reassuring. The needle is removed, and ECG tracing is checked to ensure the rhythm is unchanged and the position of the guide wire is confirmed with fluoroscopy.
3. The guide wire is secured, and the skin is incised at the site of cannulation by 0.5 cm. It is good practice to have the full length of the needle under direct view. This is possible when the needle is introduced along the longitudinal plane. However, in some anatomical locations a horizontal plane is more suitable, in such circumstances when the needle is introduced along the horizontal plane it is important to ensure the tip of the needle is always under direct view. It is not possible to have the full length of the needle under direct view when introduced along the horizontal plane and therefore there is a greater risk of piercing the posterior wall of the vein due to difficulty in assessing the tip of the needle. The images seen in horizontal plane can easily led to error in confirming the tip of the needle and therefore the probe must be adjusted regularly to confirm the tip of the needle by identifying the absence of the needle (Fig. 8).
4. The dilator with a peel away sheath is now inserted over the guidewire using a Seldinger technique. When inserting the dilator resistance is felt at the site of cannulation. The dilator is advanced firmly with constant pressure, after a few seconds the resistance gives way and the dilator can be pushed in without any significant resistance. If excess resistance is felt ensure the skin incision is adequate prior to advancing again.
5. Once the dilator is inserted and guide wire secured, a subcutaneous tunnel needs to be formed. Local anaesthetic is infiltrated subcutaneously from the exit site to the entry site (cannulation of vein) with a series of injections. An incision is made at the

marked exit site and the line tunnelled with help of a tunneller (usually a metal rod). The tunneller attached to the catheter is removed via the wound in the neck and the catheter pulled through under the skin. Occasionally some resistance is felt at the clavipectoral fascia. The cuff is pulled through approximately halfway between the clavicle and the marked exit site. The catheter is cut from the tuneller and placed on the chest wall and assessed for positioning and length with the help of fluoroscopy before cutting the catheter to length. If the procedure is not done under fluoroscopy, measurements can be made from the manubrium to predict desired length. If the catheter is placed too far into the right atrium it is easier to withdraw later as long at the cuff is not close (within 3 cm) of the exit site, however if the catheter is too high it cannot be pushed further inwards. Patients with COPD and kyphosis may require further adjustments to the length of the catheter due to their distorted thoracic anatomy. The guide wire and the detachable part of the dilator is removed, and the catheter is then inserted into the vein via the "peel away" sheath. The "peel away" sheath is peeled apart, and catheter tip is positioned with help of fluoroscopy.

In femoral catheter placements the tunnel may be better placed in the outer lateral aspect of thigh as opposed to on the lower abdominal wall.

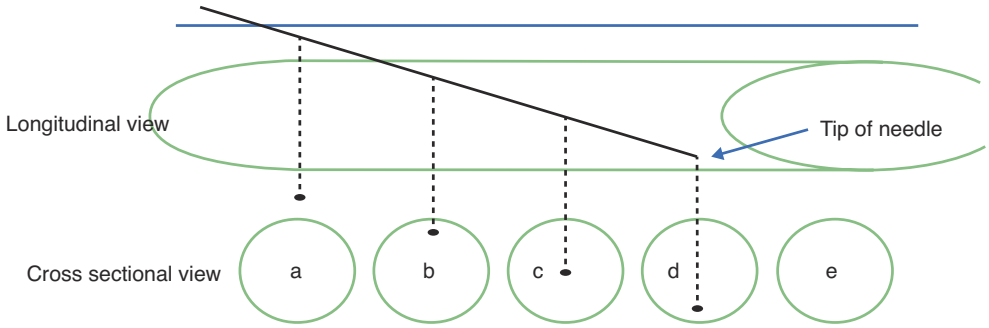

Fig. 7 Diagram to show the different U/S views as the needle is advanced into a large vein. This diagram demonstrates the tip of the needle at points (a) to (e) as the probe is advanced along the vein. The tip of the needle should be confirmed by absence of needle as in point (e)

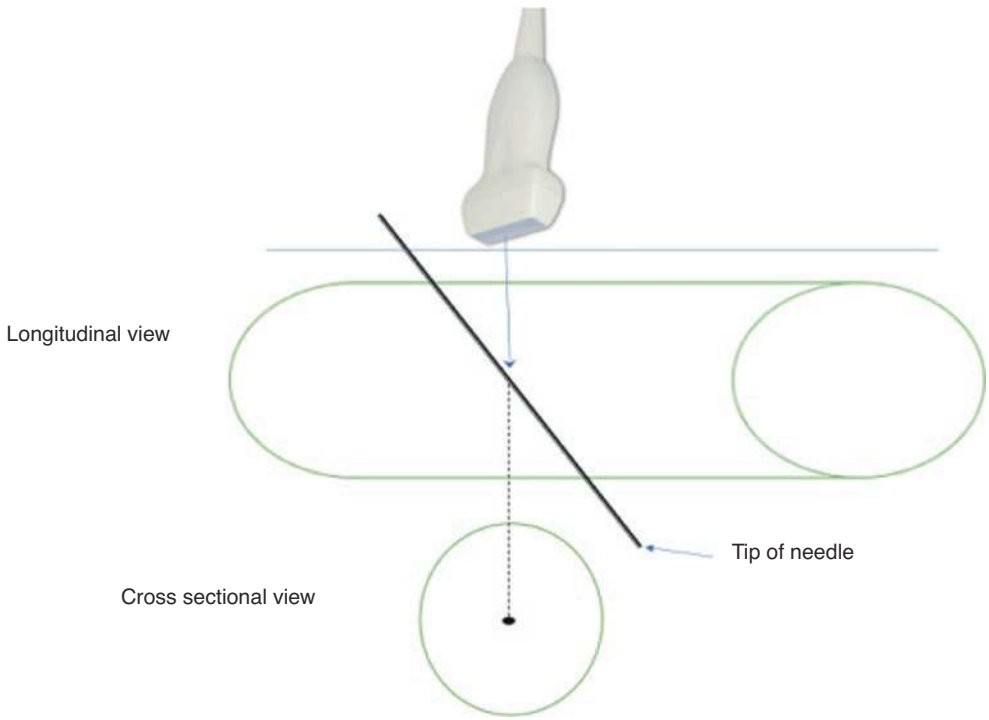

Fig. 8 Diagram to show the tip of the needle which has passed through the vein and is not in position for a guidewire insertion. It demonstrates the limitations of a cross sectional U/S view in which you can see only a small portion of the needle and falsely gives the impression that the tip of the needle is in the centre of the vein

Box 2. Long-term cuffed Subclavian Catheter Placement (*Subclavicular Approach to Large Vein Catheterization without Radiology Often Done at Bedside or in a Dedicated Room)*

The equipment needed is variable but includes a gown, gloves, sterile drapes, needles, syringes, dissecting scissors, scalpel, suturing equipment, cleaning solution, local anaesthetic, a feeding line (Hickman or the smaller Broviac type of line), tunneller, split introducer, Seldinger wire and needle.

1. Patient lies supine, ideally with the head and shoulders positioned lower than the body (some put a small sandbag or rolled pillow between the shoulders). The operator selects the right or left subclavian vein. There is a tendency to choose the right as there is less risk of damaging the thoracic duct and thus of causing a chylothorax. The side furthest away from any abdominal stomas or fistulae is chosen. If the right subclavian vein is selected, the following anatomical landmarks are noted: the tip of the left shoulder, supra sternal notch, the junction of the lateral one-third and middle two-thirds of the right clavicle, the site of the right internal jugular vein and carotid artery.
2. The operator 'scrubs up', puts on a sterile gown and gloves, then checks the equipment on the operating trolley.
3. The operator cleans the chosen site with a chlorhexidine in spirit solution. Sterile drapes are put over the patient's hair and round approximate 30 cm^2 of skin, which leaves all anatomical landmarks visible except the left shoulder tip, which can be felt.
4. Once the skin is dry, a local anaesthetic (lignocaine 1%) is injected intradermally about 1–2 cm below the junction of the lateral one-third and medial two-thirds of the clavicle. An assistant then holds the patient's right hand and pulls gently down towards the patient's feet. The patient turns their head away from the operator and the head of the operating table is lowered. The needle is changed to a longer one, reintroduced and passed under the clavicle, then it is redirected aiming to pass both under the sternal notch and at the left shoulder tip for a distance of about 5 cm. The syringe aspirates every few millimetres before injecting local anaesthetic, usually the subclavian vein will be encountered.
5. The operator may change their gloves, then make a small 1 cm transverse skin incision over the site of the intradermal local anaesthetic injection. Blunt dissection may be done (closed scissors are inserted and opened) to make it easier for the introduction of a splittable introducer. Then the 18 gauge needle from the catheterization pack is connected to a 10–20 ml syringe (some fill this with saline) and advanced in the same way as for the local anaesthetic, with gentle suction being applied from the syringe until there is a good flashback of venous blood into the syringe indicating that the vein has been entered. Holding the needle still, the syringe is removed and the soft end of the guidewire is pushed gently down the needle for a distance of about 30 cm. Hardly any pressure is put on the guidewire. Keeping the guidewire in position, the needle is withdrawn.
6. While the guidewire is left in position and covered lightly with a piece of sterile gauze, the subcutaneous tunnel is made. The tunnel is usually about 15 cm long, the exit site is chosen to be approximately midway between the mid point of the sternum and the nipple position of a man. The exit site should be on a flat area of chest, well away from the moist warm potentially bacteria prone axilla. Skin creases should be avoided. This aids security and comfort by making the catheter easier to anchor, and it reduces the chance of bacterial infection. Local anaesthetic is inserted at the exit site and along the line of the tunnel with 3–4 injections. A small 1 cm vertical incision is made at the exit site. Blunt dissection is performed by opening and closing surgical scissors in the line of the tunnel for a distance of about 7 cm from the exit site. The tunnel is created by pushing, with a rotating action, either a hollow plastic tube into the exit site and up towards the entry site or attaching the feeding catheter to a sharp-ended metal tunnelling rod and pushing this up. Some blunt dissection is usually needed to get the tunnelling instrument out of the entry site. Care should also be taken to maintain a superficial approach so that the Dacron® cuff will easily be felt below the skin. A single pass

may reduce the chances of the patient developing a haematoma, infection or pain.

7. The catheter may be primed with either saline or heparinized saline, reducing the risk of air entering the venous circulation. The catheter is positioned in the tunnel either by putting it into the hollow plastic tunneller or it is pulled behind a metal rod. The dacron cuff is positioned halfway up the tunnel. It must not be at the exit site as cuffs situated adjacent to the exit site readily become infected, which can lead to the loss of the catheter.
8. The tunnelling rod is removed from the catheter, and the length of catheter needed estimated by lying the catheter on the chest wall in the shape of the subclavian vein and SVC (usually about 15–20 cm of catheter will be needed). The catheter is then cut. Care needs to be taken not to contaminate the catheter.
9. The rigid dilator surrounded by the splittable introducer are advanced over the guidewire, checking that the guidewire remains free all the time until the wings of the splittable introducer are close to the patient's skin. The guidewire and rigid introducer are removed leaving the splittable introducer in position. The catheter is then quickly fed through the splittable introducer (forceps may be needed). If the catheter cannot immediately be fed into the splittable introducer the operator may temporarily place their thumb over the splittable introducer to reduce bleeding and prevent air from entering the venous circulation.
10. The working field may be covered and the catheter tip position checked radiologically. However, with experience the operator can achieve a good position. The ideal position for the tip is the SVC/RA junction.
11. If the position is good, the splittable introducer is slowly peeled apart as the catheter is advanced into the vein (non-toothed forceps may be needed to prevent the catheter coming out), until the entire catheter is in place and the sheath has been completely split and removed.
12. Five millilitres of 50 units/ml heparin is instilled into the lumen of the catheter and the line is either capped or connected to a saline infusion.
13. One stitch is put over the insertion and exit site. The long threads from the exit site are tied round the catheter to help prevent it from being pulled out. The entry and exit sites may be sprayed with povidoneiodine. Adhesive sterile gauze dressings are placed over the cannulation and exit sites (Fig. 2). The catheter is curled round or over the dressing and taped to prevent traction.
14. The patient is advised to stay in bed for 2–3 h for the effect of sedation to wear off. A postero-anterior chest radiograph is taken about 3 h after the procedure to check the catheter tip position (Fig. 9) and to warn of a pneumothorax. If the catheter tip position is satisfactory then parenteral nutrition may be started.

Providing the catheter is mechanically stable and not infected, connective tissue will grow into the interstices of the cuff over the following 6 weeks. Sutures are removed after 2–3 weeks, but if the patient is receiving corticosteroids they are left in for at least 5 weeks.

Insertion of non-cuffed short-term feeding line.

If a non-cuffed line is used, the tunnel may be much shorter (5–10 cm). After the subclavian vein has been cannulated, the central needle is withdrawn leaving a plastic sheath in situ, the catheter is fed quickly through this for a measured distance (marks on the catheter usually make this easy). The plastic sheath is removed then the tunnel is made. Local anaesthetic is applied, but no incision made at the exit site. In order to reduce the risk of piercing the catheter with the tunnelling needle, the tunnelling needle without its plastic sheath is pushed from the entry site down the tunnel and out of the exit site. The exit site may need to be enlarged to about 2 mm. About 5 mm of plastic sheath is then pushed gently onto the needle at the exit site. The tunneller needle is gently pulled while the plastic sheath is pushed until the plastic sheath exits from the entry site. The tunneller needle is removed, the catheter is fed down this and the plastic cannula withdrawn. The attachments are put on the end of the feeding line, which is then flushed. A plastic clip, sutured to the skin may be used to hold the line in position.

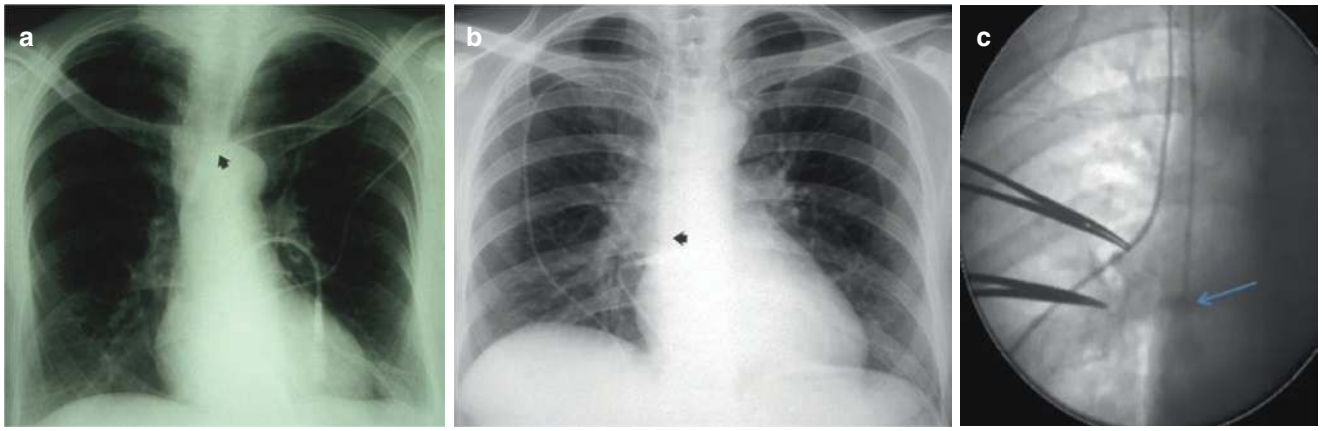

Fig. 9 Chest radiographs after insertion of a central venous catheter. (**a**) Catheter tip (arrowed) too proximal and at high risk of causing a central vein thrombosis. It should be replaced and not used for PN. (**b**) Ideal placement of a central catheter and (**c**) good flow of contrast (arrowed) shown in a well-placed central venous catheter

Box 3. Cephalic Vein Approach to the Subclavian Vein

The cephalic vein lies in the deltopectoral groove and is well placed for surgical insertion of a long-term venous feeding catheter. After injecting local anaesthetic, a 1–3 cm incision is made approximately 1–2 cm below the lateral end of the clavicle. The cephalic vein in the clavipectoral fascia is identified and is controlled by proximal and distal ligatures. A subcutaneous tunnel is created in the same way as described in the percutaneous approach, with the tunnelling rod and catheter exiting at the subclavicular incision. The required length of the catheter is decided and advanced into the cephalic vein via a venotomy made between the proximal and distal ligatures. The tip of the catheter is located at the SVC/RA junction. The ligatures supporting the catheter are tied. The lumen is checked by venous aspiration and flushed with heparinized saline. The clavicular incision is sutured with a subcutaneous catgut suture first, then finally with 2–3 silk skin sutures, which are left in for approximately a week. The exit site of the catheter is secured using the same method as the percutaneous approach.

Box 4. Implantable Port Insertion

After the procedure in Box 1 has been done the procedure to place a subcutaneous port begins. A subcutaneous pocket in made by dissecting a subcutaneous space over the chest wall at the marked site. After the catheter is inserted, tunelled and the position confirmed the port is connected the end of catheter and inserted into a subcutaneous pocket. The port may be anchored in the subcutaneous space with an absorbable suture. Immediately after a port has been placed, an access needle is placed in the port and heparin is locked into it. This is done because swelling and inflammation will make access to the port very difficult for the next week. It is especially important to do this if the port is not going to be used within the next 4 days. When the noncoring needle is in place it must be secured safely and comfortably in place with a sterile gauze dressing.

Unable to Advance Guide Wire

Occasionally there is difficulty in advancing the guidewire after the wire has been inserted into a vein. The tip of the wire may remain at the confluence of brachiochephalics. Manipulation of the wire under fluoroscopy helps to place it in the RA however if the wire does not fall in place with ease there should be a high index of suspicion of an occlusion or stenosis. Ideally an on-table venogram will help reassess the anatomy and so make insertion easier. However if this is not possible further attempts may be made after a detailed assessment of venous anatomy with CT or MR imaging. It is not safe to advance a dilator if the guide wire has not passed into the distal RA.

Venous anatomy on the right side often lies in straight line to RA and therefore placement is less complicated. Left sided catheter placements may require some manipulation of the catheter particularly at the confluence of right and left brachiochephalic veins when the catheter tends to flip upwards into the right brachiocephalic vein. The thoracic duct is on the left side and can be damaged during jugular/subclavian puncture. The left common iliac veins are often anatomically placed at a steep angle to IVC and hence it is easier to use the right side.

Securing the Catheter (Excluding Implantable Port)

The catheter is secured with a 2′0 prolene stitch at the exit site. The sutures at the exit site are kept in place for about 6 weeks to allow the dacron cuff to completely embed in soft tissues. Some of the catheters come with a fixation device, however when they are used it becomes difficult to clean around the exit site. This ensures that the catheter does not get displaced when used regularly. The entry site the neck is closed with absorbable sutures.

After Catheter Insertion

The position of the tip of the central vein catheter is crucial in preventing thrombophlebitis leading to endothelial injury and a SVC thrombosis. This thrombosis may also be promoted by a low pH and/or high osmolality PS infusion. Therefore the tip should be ideally placed at vena cava-atrial junction [44, 45]. This can be confirmed either by fluoroscopy at the time of placement of catheter or by CXR after the catheter is placed. It is worth noting that in women if the catheter cuff is placed close to breast tissue, the tip of catheter is different when they are supine compared to that seen on an erect CXR. This is due to the movement of the cuff which is anchored to the soft tissue of the breast.

Complications of Large Vein Cannulation

Arterial puncture and pneumothorax were common prior to use of ultrasound in venous access practice. Insertion-related complications are reported in 3–12% patients [46] (Table 3) and are less if they are inserted by a nutrition team [47].

Counter Puncture

The venous wall may have resistance and not give way when advancing the needle under US guidance resulting in indenting the anterior wall of the vein and approximating on to the posterior wall, predisposing to risk of counter puncture. The risk can be avoided by applying constant gentle pressure with the needle for some time to allow the needle to pass through the anterior wall of the vein. The root of the neck has a neuro vascular bundle as well as the apex of the lung present. Occasionally the subclavian artery lies posterior to IJV at the root of neck and can be injured by counter puncture without any immediate signs of bleeding. If the US guiding probe is pressed too hard on the neck, the veins may be collapsed making cannulation difficult.

Venous Wall Tear

The risk of tearing the venous wall is substantial if excessive force is used with dialator, furthermore “twisting movement along with excessive force” may lead to a spiral tear of the vein which is difficult to repair [48]. To prevent this complication when introducing the dilator, a firm pressure should be applied.

Malposition

When using a subclavian approach, the catheter can pass up into the jugular vein, a clue to this is that the patient may complain of a pain in their ear when the guidewire is

Table 3 Insertion-related complications of central vein catheterization

• Counter puncture
• Venous wall tear
• Malposition (cardiac arrhythmia’s or perforation)
• Arterial puncture (haemothorax or haemomediastinum)
• Pneumothorax
• Air or catheter embolism
• Nerve injuries (brachial plexus, phrenic or recurrent laryngeal nerve)
• Thoracic duct damage

inserted. If the procedure is done under fluoroscopy the guide wire can be positioned correctly. The catheter can advance into the ventricle or pass into the opposite subclavian vein. The catheter can be redirected using radiological guidance or it may (especially if cuffed) need to be replaced. Rarely the guidewire can induce cardiac arrhythmias, if so it is withdrawn, or cardiac perforation and tamponade have been described. Rarely a catheter can be malpositioned in the pleural cavity or mediastinum and this will cause a pleural or pericardial effusion respectively when the feeding is started.

Artery Puncture

There should be a high index of suspicion of arterial puncture if blood appears bright red when passing the guidewire in to vein. This may be misleading if patient is having a general anaesthetic. Arterial punctures may occur if the needle has gone through the posterior wall of the vein. If so, the needle is removed, and firm pressure applied for 5 min. If the carotid or subclavian artery is injured and the patient's coagulation status is normal, another attempt can be made on the same side. After passing the guidewire repeat assessment with ultrasound to confirm placement of wire in the vein will help decrease the risk of arterial injury with the dilator. Blood can collect in the pleural space (haemothorax) or mediastinum (haemomediastinum) following subclavian arterial puncture. If haemothorax is moderate a wide bore surgical chest drain should be inserted to drain blood from the pleural cavity.

Injury to the common femoral artery is managed by applying direct pressure over it. Rarely the injury leads to retroperitoneal haematoma.

The catheter entry site is observed for signs of bleeding after catheter insertion and blood pressure is monitored. If bleeding occurs, a pressure dressing is applied over the exit site and coagulation studies may be performed.

Haematoma

The needle may be dislodged if the guidewire cannot be inserted in to vein after an initial flash back. To avoid a haematoma and allow a second attempt on the same side it is better to pull the needle out and apply pressure for 5 min.

Pneumothorax

If air is aspirated during cannulation of the subclavian vein (or less commonly the jugular vein), a pneumothorax is likely to develop. This is often not apparent until several hours after the procedure when the patient complains of pleuritic chest pain and breathlessness; a physical examination reveals tachypnoea, tachycardia, a hyperresonant lung with reduced breath sounds. An immediate post-insertion chest radiograph may have been normal; hence one is usually done about 3 h after insertion if there is concern of pneumothorax. A small pneumothorax may be asymptomatic and can be left alone, larger ones can be aspirated and only rarely is a formal chest drain insertion needed [49].

Air/Catheter Embolism

The risk of air embolism is higher in cannulation of supracardiac veins due to change thoracic pressure during breathing. Care is taken to ensure a closed system is always maintained during the procedure, furthermore patient is positioned tilted head down to decrease the risk of air embolism. If an air embolism is ever suspected (e.g. if the catheter suddenly becomes detached) the catheter is clamped as near to the skin as possible and the patient is positioned on their left side with their head tilted downwards. Rarely part of the catheter can break away and pass as an embolus which may get dislodged in lungs depending on the size of the fragment. An attempt should be made to retrieve large fragments wedged in Right atrium with help of interventional radiology. Small fragments that embolise to the lungs can be left alone but if an abscess develops may have to be surgically removed.

Nerve Injuries

If the introduction needle hits the brachial plexus, numbness and tingling can develop in the arm and/or specific muscles can become weak. The exact pattern of weakness depends upon which part of the brachial plexus has been damaged. A neuropraxia can follow and may take several months to resolve. Rarely the phrenic nerve is damaged resulting in diaphragmatic paralysis; the recurrent laryngeal or vagus nerves can also be damaged causing hoarseness.

Thoracic Duct Damage

This can occur from left subclavian vein cannulation and rarely causes a chylothorax.

Peripherally Inserted Central Catheter (PICC) Insertion

As nutrient infusions into small or medium-sized veins are associated with a high risk of thrombophlebitis, it is preferable to site the tip of feeding lines in a large vein. This was first reported in 1975 [50] and can be done using a long catheter inserted into a medium-sized vein. A PICC is made of radio-opaque silicone rubber or polyurethane-hydromer and comes with a single (4Fr) or dual lumen (5Fr). PICCs are inserted into

the basilic, median cubital or cephalic veins in the ante-cubital fossa and the tip of the PICC terminates at the SVC/RA junction. Their insertion can be done at the patient's bedside by a trained nurse [51]. or at interventional radiology if there are concerns of previous thrombosis or abnormal anatomy related to deformities such as severe kyphoscoliosis. The common sites for PICC are the upper limb basilic veins. In common with large vein catheters they may be open ended or have Groshung valve incorporated into the tip. Often PICC's are used at the initial setting of abdominal catastrophe or medium term (type II IF) whilst the patient recovers and stabilised for parenteral nutrition support. Basilic vein often has a good calibre and runs medially away from the neurovascular bundle, however there are variations in anatomy such as small basilic vein with most of the venous drainage via accompanying veins of brachial artery. In some cases, if patients do have upper limb thrombosis, saphenous vein may be considered along with anticoagulation and expert nursing care as access in these circumstances is high risk. Some PICC's are compatible with administration of IV contrast for CT imaging which may be a consideration if access is difficult. As PICCs are placed by cannulating a peripheral vein, they are easier to insert, associated with fewer insertion complications than centrally placed lines [52].

PICCs remain less ideal for long-term parenteral feeding due to the risk of dislodgement of the catheter as there is usually no cuff to anchor the catheter to the soft tissues. The exit site position on the arm restricts normal arm movement making daily living activities difficult and sometimes challenging for the patient if they are doing the procedures themselves.

Box 5. Insertion Procedure for a PICC

The equipment needed includes a gown, gloves, sterile drapes, cleaning solution, local anaesthetic, PICC line, securing mechanism (Securecath®, Steri-strips® and Stat-lock®) and a plastic dressing (e.g. Opsite IV 3000®), Ultrasound and micro puncture kit. The choice of number of lumens is determined by the frequency and type of therapy the patient requires, however it is considered best practice to a use single lumen if the access is required only for administration of PS [53–55]. A tourniquet is applied to distend the veins.

1. The area of insertion is assessed with ultrasound (if available) for a suitable vein before the operator scrubs. The site should be sufficiently above the bend of elbow or 2–3 cm below to prevent kinking of catheter when bending the elbow.
2. The operator 'scrubs up' and puts on sterile gown and gloves.
3. Using strict aseptic technique the skin is prepared with chlorhexidine in spirit.
4. The required length of PICC line is measured pre-insertion in anticipation of the final tip location.
5. An ultrasound may be used to aid cannulation of the basilic vein in the mid arm (similarly to the technique for cannulation of large veins) with a micro-puncture needle (21Gauge).
6. If cannulation was unsuccessful it is important to remove the needle and apply pressure for 5 min to prevent a haematoma and also allowing a second attempt. If there is a haematoma around the vein it is better to abandon the procedure and attempt again a few days later.
7. Once cannulation is confirmed with free flow of venous blood a micro wire is inserted whilst the needle is held steady. The needle is removed over the wire. When PICC is inserted at bed side it is important to ensure the wire is advanced freely to have the assurance that the catheter can be advanced. Inability to advance wire freely should raise concerns about abnormal venous anatomy or thrombosis therefore further attempts should be done only after assessment of venous anatomy and possibly in interventional radiology.
8. A 4 or 4.5 Fr dilator is passed over the guide wire and the catheter is placed through a peel away sheath.
9. If there are good dilated veins, venous cannulation may be achieved with help of 14g needle and catheter inserted, however this is suitable only for those catheters where the hub may be attached after placement of the catheter such as the Groshung valved catheters.
10. In advancing the catheter at the junction of subclavian and jugulars, there is tendency for the catheter tip to follow cranially into IJV. To prevent this, the arm is often abducted and the patient is asked to turn their head towards the operator and to flex head with chin touching clavicle. Alternatively, you may ask another person to press on jugular vein whilst advancing catheter.
11. Lubricating the line with sterile normal saline may help insertion. The PICC line (Fig. 10a) is then gradually advanced until the measured point. It is preferable to insert the catheter slightly longer than the estimated length as the catheter cannot be advanced further at later time if the site of the tip is unsatisfactory when the sterile felid is lost, but it can be easily pulled back in to the correct position.
12. The catheter is secured (e.g. Secure-cath®, with Steri-strips® and a Stat-lock® dressing). A small gauze square or release dressing is placed over the entry site, then a plastic dressing (e.g. Opsite IV

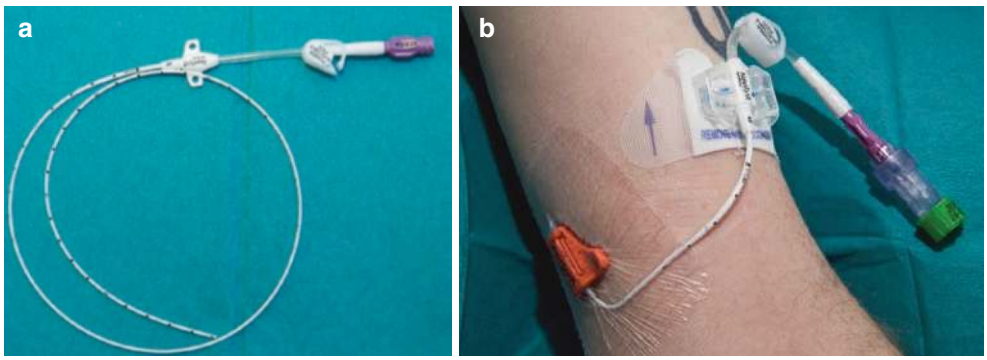

Fig. 10 (**a**) PICC catheter and (**b**) its dressing in the cubital fossa after insertion

3000®) is applied over the exit site for security, a light bandage (or Tubigrip®) is applied again for security and comfort (Fig. 10b)

13. A chest X-ray is taken to ascertain the position of the catheter tip.
14. If the catheter tip is displaced in IJV, a jet flush of 10 ml saline often helps the catheter to fall in place. The catheter may also align itself in SVC over 24 h. If conservative measures fail the catheter may be rewired at bedside again or with help of interventional radiology. It is important to note that the catheter must not be used when it is not placed correctly.

Small-Vein Nutrition

After the introduction of Intralipid® allowed feeding solutions to become less hyperosmolar, it again became possible to consider parenteral nutrition through a small vein [56]. Small-vein parenteral nutrition is administered through a short plastic cannula inserted into the small veins on the forearm, on the back of the hand, or on the scalp of babies. The limiting feature of this type of parenteral feeding is the high incidence of thrombophlebitis which means that a cannula does not often remain patent for more than 3 days [57–60]. It is recommended that a cannula used for feeding in a small vein is re-sited every 1–2 days. This type of feeding is rarely used now that PICCs can be relatively easily inserted.

Managing Access with Complications

Catheter Related Blood Stream Infections (CRBSI)

If catheter is infected and decision is made to remove the catheter, the insertion of a new catheter should take place only after adequate treatment of infection to avoid seeding of infection to the new catheter [61]. It is preferable for patient to be apyrexial for a 2–10 days and any possible metastatic infection treated prior to insertion of a new tunnelled catheter [62]. The interval between removal of catheter and insertion new has been variable in asymptomatic patients, usually the duration is 48 h between the removal of old catheter and insertion of new catheter, however there is very little evidence to support this practice. Negative blood culture is often considered to ensure the infection has been treated particularly with fungus or staphylococcus aureus CRBSI. Rewiring of an infected catheter is often not successful [43], however in extreme cases where the access is very poor, antibiotics is delivered through the infected catheter and later changed over a guide wire with further delivery of antibiotics via the new catheter.

Exit Site Infection

Failed salvage of exit site infection [43] will require a new catheter with a new tunnel away from the old tunnel. Sometimes the opposite site has to be considered due to extent of inflammation or type of organism (pseudomonas) affecting the exit site.

Occluded and Fractured Catheter (Rewiring)

Prior to any intervention with catheter it is important to assess for possible CRBSI. If there is any suggestion of CRBSI it is safer to remove the catheter and insert a new catheter in keeping with CRBSI management. Occlusion of a catheter is not uncommon and often managed with lock solutions; but if unsuccessful a new catheter is inserted. A fracture of the catheter may occur at the exposed part of catheter and is often managed with a repair. Both scenarios can be managed by rewiring a new catheter over a guidewire.

For a short term uncuffed catheter the catheter is dissected at the point of insertion and looped out. The proximal end is secured to prevent dislodgement in to the vein and cut. The old catheter is removed over guide wire and a dilator inserted.

Occasionally there may be scaring at the site of insertion which will prevent advancing the dilator, this should be suspected if there is resistance when the old catheter is pulled out. A new catheter is placed subcutaneously with a new tunnel as described earlier and the catheter inserted. For a cuffed catheter an incision is made over the cuff or at the point of insertion to release the catheter from the soft tissue. The catheter is cut after securing it with a Halstead mosquito clip. A guide wire is inserted, and the old catheter removed over the guide wire. Cannulating with an 18G venflon® into the catheter and flushing may help if the guide wire cannot be passed through the catheter.

In both these scenarios the tip of the old catheter should be sent for culture and sensitivity to determine if there is an infection and thus will help in guidance of antibiotics if patient becomes unwell in the near future.

Thrombosis

In patients with long-term (type III) IF the objective is to maintain access and prevent further loss of venous access from thrombosis (chapter "Central Vein Thrombosis"). The strategy adopted varies depending on the clinical presentation and extend of thrombus.

Acute Thrombosis

In acute thrombosis the patient should be anticoagulated with LMWH injections and will require urgent CT or MR venogram to assess the extent of thrombosis. If the thrombus extents beyond the tip of the catheter; the catheter cannot be used for parenteral nutrition or infusion of crystalloids. However, the catheter may be used as an access for thrombolytic therapy after discussion with a vascular radiologist. If there is a significant stenosis in SVC or large veins contributing to thrombosis, angioplasty may be required prior to insertion of a new catheter ensuring the tip of the catheter is distal to stenosis [63] (chapter "Central Vein Thrombosis").

If the thrombus is proximal to the tip of the catheter and not causing any significant life or limb threatening symptoms the catheter may be used after a 2–5 days of anticoagulation. It is best practice to take blood for a thrombophilia screen prior to anticoagulation. In continuing to use the catheter the access is maintained, and the other veins are preserved for use in the future.

Chronic Thrombosis

Patients with established thrombosis around the catheter may require the catheter to be changed for non-infective mechanical problems (fracture or occlusion). It is preferable to change the catheter over a guidewire to maintain access if possible; however, it is useful to review venous anatomy with a recent venogram prior to placement of new catheter.

Other Considerations

Pacing Wires

Pacing wires are usually placed in left subclavian. It is safer to place tunnelled catheters or PICC under fluoroscopy to avoid any potential dislodgement. Furthermore, the right side is preferable to decrease the number of devices in left brachiocephalic. The tip of the catheter is placed in proximal SVC as a compromise. Infection can cross from an infected PS catheter to a pacing wire. It may be less likely to occur when a fibrin sheath fully covers both the pacing and PS catheters.

Haemodialysis

Patients requiring renal replacement therapy require preservation of venous access for dialysis or venous anastomosis of graft kidney to iliac veins. Insertion of tunnelled catheter is preferred to the contralateral side of AV fistula, usually AV fistula is on the left side and therefore tunnelled catheter on Right IJV would be the safest option. PICC is best avoided to prevent any thrombosis which may compromise life span of AV fistula.

Chemotherapy and PN

Oncology patients receiving PN as well as chemotherapy will require two separate lumens for infusion one for PN and one for chemotherapy due to concerns about compatibility of the oncology medication with PN. This may be delivered with two separate devices or a dual lumen device. The risk has to be balanced between thrombosis due two simultaneous devices versus the risk of CRBSI due to dual lumens even though one may not be used in the long-term. The choice is determined by the probable duration of PN as well as the number of chemotherapy sessions anticipated.

Removal of a Feeding Catheter

Prior to removal of any vascular access device it is important to have information about catheter insertions, complications especially CRBSI and venous thrombosis. The clinician must also be aware if a patient is anticoagulated or on anti-platelet medication. Management of anticoagulation around the procedure will vary depending on the indication for anticoagulation as well as indication for removal of a vascular access device. These procedures are performed under local anaesthetic. Implantable ports should be removed in a setting where surgical dissection can be done with adequate support usually

in a surgical theatre setting. Tunnelled catheters may be removed in a procedure room by an experienced operator with adequate emergency support. A PICC can be removed at the bedside, the length of the line removed should be recorded and the catheter tip should be sent for culture and sensitivity.

Box 6. Tunnelled Catheter Removal

Tunnelled catheters have a cuff that would have embedded to soft tissue under the skin. Removal of the cuff is essential in removing the catheter completely. The cuff may not be placed near the exit site however should be palpable along the line. In some patients the cuff may be difficult to palpate due to subcutaneous fat if they are nutritionally replete particularly if the catheter were placed at time of severe malnourished state. A 1–2 cm transverse incision is made at the superior aspect of the cuff. The soft tissue is separated with blunt dissection down to the line and cuff. The catheter is grasped with a pair of forceps and the fibrous sheath "usually off white" around the catheter formed during the time the catheter has remained in situ is defined. A careful longitudinal linear incision is made along the catheter to avoid transection of catheter and this will remove the fibrous sheath and reveal the white of the catheter. The catheter should be grasped with help of Halstead mosquito forceps between the sleeves of the fibrous sheath and pulled with gentle traction (Fig. 11). This should enable the catheter to be pulled out of the vein completely. The tip of the catheter should have a clean-cut edge suggesting the catheter has not fractured. The length of the catheter as well as comparison with a previous CXR also helps in assessing if the catheter was removed without fragmenting. Occasionally the catheter feels adherent on traction with no movement if they have been in situ for a few years. This is often due to scarring of the venous wall at the site of insertion and requires continued gentle traction for few minutes without fracturing the catheter. Rarely if the catheter is firmly adherent, despite a few minutes traction, another incision is required at the site of entry to dissect down to the vein. This may require input from the vascular services. Once the line is removed from the vein the cuff can be dissected away from the soft tissue with a combination of blunt and sharp dissection. Haemostasis is often achieved by applying firm pressure for a few minutes. Closure of the skin is done with an absorbable suture (e.g. 3′0 vicryl); once satisfactory haemostasis is achieved however in cases of an infected tunnel the wound should be packed to allow for adequate drainage of infection. It is prudent to send the tip of the catheter for culture and sensitivity so as to provide microbiological guidance should patient become febrile/unwell.

On rare occasions when removal of catheter is unsuccessful, and patient requires transfer, it is best to ligate and fix the catheter to soft tissue at the site of dissection.

When tunnelled femoral catheters are removed it is prudent to ensure post procedure, patient remains on bed rest for 4 h to check for delayed bleeding from the sheath or at the site of dissection.

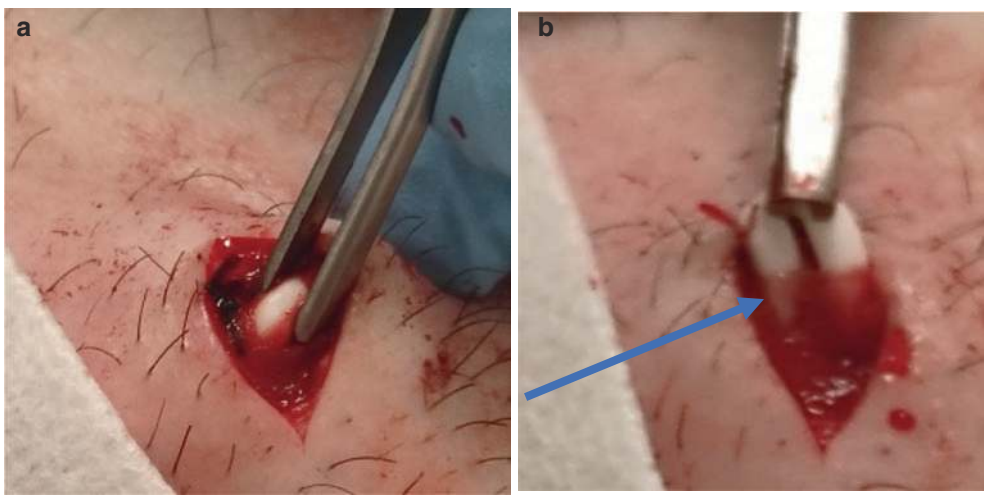

Fig. 11 (**a**) Catheter identified after incising the sheath around the catheter just above the cuff, (**b**) arrow shows the sheath as the catheter is being removed

Box 7. Removal of an Implanted Port

Port-A-Cath can be removed under local anaesthetic however dissection required in releasing the port is more extensive. Some patients who are restless or combative have required sedation with help of anaesthetic support. Incision is made over the previous incision often at the junction of catheter and port. The fibrous sheath is incised, and the catheter removed like that of the tunnelled catheters. The port may be anchored to soft tissues at four corners from the base of the port to soft tissue with non-absorbable suture. The fibrous capsule around the port is incised followed by traction on the port. The sutures if present are cut whilst the port is on traction to remove the port completely. There is a capsule firmly adherent to soft tissue pocket which may be left in situ if there is no evidence of infection. Removal of the capsule may be considered if the pocket appears infected and it may be necessary to consider packing the wound to allow drainage of infection.

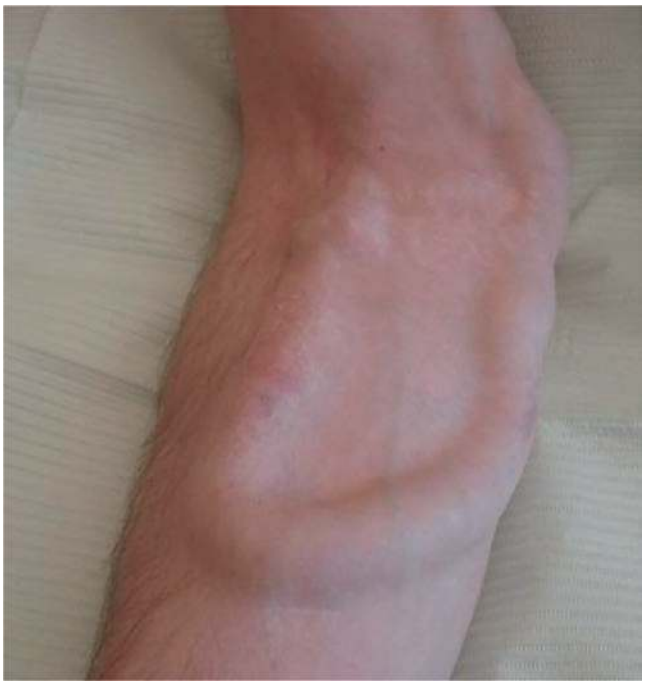

Fig. 12 An arteriovenous fistula in the right cubital fossa

Arteriovenous Fistulae for Venous Access in HPN Patients

While CVCs or implantable ports are standard for long-term parenteral nutrition administration, a surgically created arteriovenous fistula (AVF) was the only available type of venous access at the inception of this treatment in the late 1960s. Upon the introduction of intravenous catheters in the 1970s AVFs became rare, also because of their high complication rate that was associated with the use of xenologous (bovine) or prosthetic (polytetrafluoroethylene-like) graft materials leading to shunt occlusion and thrombosis [64].

From the start of the HPN program in Nijmegen (Netherlands) in 1969, besides CVCs there has been a continued use of AVFs in patients with a high CVC infection rate. In 1983, a series of 7 patients using AVFs was reported [64]. Later, the group described their oldest patient who has currently remained well on HPN with an AVF for more than 45 years [65].

The notion that AVFs may still be a valuable alternative to CVCs was corroborated in a retrospective analysis of 127 HPN patients, comprising 194 AVF access years [66]. Bloodstream infections (BSI) were extremely rare (0.03/year) for AVFs compared to tunneled CVCs (1.37/year), although occlusion was more frequent (0.6 versus 0.35/year). Of note later taurolidine locks (not feasible in AVFs) were started which brought the CRBSI rate down to 0.6/year [67].

Currently the first choice for an AVF is the autogenous radiocephalic shunt on the fore-arm (Fig. 12), or less ideally, in the lower extremity. When the quality of these peripheral vessels is insufficient, more proximal fistulae such as the brachiocephalic or brachio-basilic AVF are considered at the elbow and upper-arm region. In case these options fail, graft implants may be used as a vascular conduit to construct an AVF, whenever possible with the use of an autologous transposed vein, most commonly the great saphenous vein (GSV). Such graft AVFs may also be created on the thoracic wall.

For reasons outlined above, the use of prosthetic materials such as PTFE to create AVFs for the purpose of HPN [68] is avoided. Importantly, following their creation it usually takes a maturation period of around 6 weeks before AVFs are available for (self)-puncturing by the patient or caregiver. For follow up and surveillance patients are provided with a stethoscope to detect changes in the pitch of the murmur and loss of thrill over the AVF at an early stage that might indicate stenosis, mostly at the level of the anastomosis. In this case, balloon dilation of the stenosis by the interventional radiologist usually can solve the problem. Also for this reason, regular check-ups (usually at 6-month intervals) with evaluation through ultrasound of the shunt flow to detect such abnormalities are required, and also to rule out severely increased shunt blood flow (which may become more than 3 l/min) that might lead to cardiac failure.

Thus AVFs may be a valuable alternative to other modalities to provide HPN as long as the expertise to adequately address any of the associated complications is available.

References

1. Hamilton H, O'Byrne M, Nickolai L. Central lines inserted by clinical nurse specialists. Nurs Times. 1995;91:38–9.
2. Kelly J, Hunt BJ, Lewis RR, Swaminathan R, Moody A, Seed PT, Rudd A. Dehydration and venous thromboembolism after acute stroke. QJM. 2004;97(5):293–6.
3. Kane KF, Cologiovanni L, McKiernan J, Panos MZ, Ayres RC, Langman MJ, Lowes JR. High osmolality feedings do not increase the incidence of thrombophlebitis during peripheral i.v. nutrition. JPEN J Parenter Enteral Nutr. 1996;20(3):194–7.
4. Handfield-Jones RPC, Lewis HBM. Rubber tubing as a cause of infusion thrombophlebitis. Lancet. 1952;1:585–8.
5. Indar R. The danger of indwelling polyethylene cannulae in deep veins. Lancet. 1959;1:284–6.
6. Madan M, Alexander DJ, McMahon MJ. Influence of catheter type on occurrence of thrombophlebitis during peripheral intravenous nutrition. Lancet. 1992;339:101–3.
7. Nachnan GH, Lessin LS, Motomiya T, Jensen WN. Scanning electron microscopy of thrombogenesis on vascular catheter surfaces. N Engl J Med. 1972;286:139–40.
8. Borow M, Crowley JG. Evaluation of central venous catheter thrombogenicity. Acta Anaesthesiol Scand. 1985;Suppl 81:59–64.
9. Everitt NJ, Madan M, Alexander DJ, McMahon MJ. Fine bore silicone rubber and polyurethane catheters for delivery of complete intravenous nutrition via a peripheral vein. Clin Nutr. 1993;12:261–5.
10. Linder L-E, Curelaru I, Gustavsson B, Hansson H-A, Stenqvist O, Wojciechowski J. Material thrombogenicity in central venous catheterization; a comparison between soft, antebrachial catheters of silicone elastomer and polyurethane. J Parenter Enter Nutr. 1984;8:399–406.
11. di Costanzo J, Sastre B, Choux R, Kasparian M. Mechanism of thrombogenesis during total parenteral nutrition: role of catheter composition. JPEN J Parenter Enteral Nutr. 1988;12(2):190–4.
12. Darouiche RO, Raad II, Heard SO, et al. A comparison of two antimicrobial-impregnated central venous catheters. N Engl J Med. 1999;340:1–8.
13. Denny DF Jr. Placement and management of long-term central venous access catheters and ports. Am J Roentgenol. 1993;161:385–93.
14. Loveday HP, Wilson JA, Pratt RJ, Golsorkhi M, Tingle A, Bak A, Browne J, Prieto J, Wilcox M. UK Department of Health. epic3: national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. J Hosp Infect. 2014;86(Suppl 1):S1–70.
15. Gilbert R, Brown M, Rainford N, Donohue C, Fraser C, Sinha A, Dorling J, Gray J, McGuire W, Gamble C, Oddie SJ, PREVAIL trial team. Antimicrobial-impregnated central venous catheters for prevention of neonatal bloodstream infection (PREVAIL): an open-label, parallel-group, pragmatic, randomised controlled trial. Lancet Child Adolesc Health. 2019;3(6):381–90.
16. Sharp R, Cummings M, Fielder A, Mikocka-Walus A, Grech C, Esterman A. The catheter to vein ratio and rates of symptomatic venous thromboembolism in patients with a peripherally inserted central catheter (PICC): a prospective cohort study. Int J Nurs Stud. 2015;52(3):677–85.
17. Spencer TR, Mahoney KJ. Reducing catheter-related thrombosis using a risk reduction tool centered on catheter to vessel ratio. J Thromb Thrombolysis. 2017;44(4):427–34.
18. Delmore JE, Horbelt DV, Jack BL, Roberts DK. Experience with the Groshong long-term central venous catheter. Gynecol Oncol. 1989;34:216–8.
19. Pasquale MD, Campbell JM, Magnant CM. Groshong versus Hickman catheters. Surg Gynecol Obstet. 1992;174:408–10.
20. Kovacevich DS, Corrigan M, Ross VM, McKeever L, Hall AM, Braunschweig C. American Society for Parenteral and Enteral Nutrition guidelines for the selection and care of central venous access devices for adult home parenteral nutrition administration. JPEN J Parenter Enteral Nutr. 2019;43(1):15–31.
21. Liem TK, Yanit KE, Moseley SE, Landry GJ, Deloughery TG, Rumwell CA, Mitchell EL, Moneta GL. Peripherally inserted central catheter usage patterns and associated symptomatic upper extremity venous thrombosis. J Vasc Surg. 2012;55(3):761–7.
22. Hortencio TDR, Arendt BM, Teterina A, Jeejeebhoy KN, Gramlich LM, Whittaker JS, Armstrong D, Raman M, Nogueira RJN, Allard JP. Changes in home parenteral nutrition practice based on the Canadian Home Parenteral Nutrition Patient Registry. JPEN J Parenter Enteral Nutr. 2017;41(5):830–6.
23. Santacruz E, Mateo-Lobo R, Riveiro J, Nattero L, Vega-Piñero B, Lomba G, Sabido R, Carabaña F, Arrieta FJ, Botella-Carretero JI. Infectious complications in home parenteral nutrition: a long-term study with peripherally inserted central catheters, tunneled catheters, and ports. Nutrition. 2019 Feb;58:89–93.
24. Niederhuber JE, Ensminger W, Gyves JW, Liepman M, Doan K, Cazzi E. Totally implanted venous and arterial access system to replace external catheters in cancer treatment. Surgery. 1982;92:706–12.
25. Howard L, Claunch C, McDowell R, Timchalk M. Five years' experience in patients receiving home nutritional support with the implanted reservoir: a comparison with the external catheter. J Parenter Enter Nutr. 1989;13:478–83.
26. Braham DL, Richardson AL, Malik IS. Application of the WHO surgical safety checklist outside the operating theatre: medicine can learn from surgery. Clin Med (Lond). 2014;14(5):468–74.
27. Francisco MD, Chen WF, Pan CT, Lin MC, Wen ZH, Liao CF, Shiue YL. Competitive real-time near infrared (NIR) vein finder imaging device to improve peripheral subcutaneous vein selection in venipuncture for clinical laboratory testing. Micromachines (Basel). 2021;12(4):373.
28. Hind D, Calvert N, McWilliams R, Davidson A, Paisley S, Beverley C, Thomas S. Ultrasonic locating devices for central venous cannulation: meta-analysis. BMJ. 2003;327(7411):361.
29. Davis CP. Normal flora. In: Baron S, editor. Medical microbiology, Chap. 6. 4th ed. Galveston: University of Texas Medical Branch at Galveston; 1996. https://www.ncbi.nlm.nih.gov/books/NBK7617/.
30. Blot K, Bergs J, Vogelaers D, Blot S, Vandijck D. Prevention of central line-associated bloodstream infections through quality improvement interventions: a systematic review and meta-analysis. Clin Infect Dis. 2014;59(1):96–105.
31. Lai NM, Lai NA, O'Riordan E, Chaiyakunapruk N, Taylor JE, Tan K. Skin antisepsis for reducing central venous catheter-related infections. Cochrane Database Syst Rev. 2016;7(7):CD010140.
32. Darouiche RO, Wall MJ Jr, Itani KM, Otterson MF, Webb AL, Carrick MM, Miller HJ, Awad SS, Crosby CT, Mosier MC, Alsharif A, Berger DH. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. N Engl J Med. 2010;362(1):18–26.
33. Chaiyakunapruk N, Veenstra DL, Lipsky BA, Saint S. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. Ann Intern Med. 2002;136(11):792–801.
34. Debourdeau P, Farge D, Beckers M, Baglin C, Bauersachs RM, Brenner B, Brilhante D, Falanga A, Gerotzafias GT, Haim N, Kakkar AK, Khorana AA, Lecumberri R, Mandala M, Marty M, Monreal M, Mousa SA, Noble S, Pabinger I, Prandoni P, Prins MH, Qari MH, Streiff MB, Syrigos K, Büller HR, Bounameaux H. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. J Thromb Haemost. 2013;11(1):71–80.
35. Verso M, Agnelli G, Kamphuisen PW, Ageno W, Bazzan M, Lazzaro A, Paoletti F, Paciaroni M, Mosca S, Bertoglio S. Risk factors for upper limb deep vein thrombosis associated with the

use of central vein catheter in cancer patients. Intern Emerg Med. 2008;3(2):117–22.
36. NICE. National Institute for Health and Care Excellence. Nutritional support in adults: oral supplements, enteral and parenteral feeding. Clinical guideline [CG32]; 22 Feb 2006. https://www.nice.org.uk/guidance/cg32/chapter/1-Guidance#parenteral-nutrition-in-hospital-and-the-community.
37. Ge X, Cavallazzi R, Li C, Pan SM, Wang YW, Wang FL. Central venous access sites for the prevention of venous thrombosis, stenosis and infection. Cochrane Database Syst Rev. 2012;(3):CD004084.
38. Marik PE, Flemmer M, Harrison W. The risk of catheter-related bloodstream infection with femoral venous catheters as compared to subclavian and internal jugular venous catheters: a systematic review of the literature and meta-analysis. Crit Care Med. 2012;40(8):2479–85.
39. Abraham A, Sawbridge D, Coultier A, Teubner A, Bond A, Taylor M, Lal S. Are femoral tunnelled central venous catheters safe to use for HPN? Gut. 2019;68:A174. gut.bmj.com.
40. Hayden L, Stewart GR, Johnson DC, Fisher MM. Transthoracic right atrial cannulation for total parenteral nutrition- case report. Anaesth Intensive Care. 1981;9(1):53–7.
41. Birnbaum PL, Michas C, Cohen SE. Direct right atrial catheter insertion with video-assisted thoracic surgery. Ann Thorac Surg. 1996;62(4):1197.
42. Qureshi AM, Rhodes JF, Appachi E, Mumtaz MA, Duncan BW, Asnes J, Radavansky P, Latson LA. Transhepatic Broviac catheter placement for long-term central venous access in critically ill children with complex congenital heart disease. Pediatr Crit Care Med. 2007;8(3):248–53.
43. Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M, ESPEN. ESPEN guidelines on parenteral nutrition: central venous catheters (access, care, diagnosis and therapy of complications). Clin Nutr. 2009;28(4):365–77.
44. Cadman A, Lawrance JA, Fitzsimmons L, Spencer-Shaw A, Swindell R. To clot or not to clot? That is the question in central venous catheters. Clin Radiol. 2004;59(4):349–55.
45. Petersen J, Delaney JH, Brakstad MT, Rowbotham RK, Bagley CM Jr. Silicone venous access devices positioned with their tips high in the superior vena cava are more likely to malfunction. Am J Surg. 1999;178(1):38–41.
46. Mughal MM. Complications of intravenous feeding catheters. Br J Surg. 1989;76:15–21.
47. DeJong PCM, von Meyenfeldt MR, Rouflart M, Wesdorp RIC, Soeters PB. Complications of central venous catheterization of the subclavian vein: the influence of a parenteral nutrition team. Acta Anaesthiol Scand. 1985;Suppl 81:48–52.
48. Gibson F, Bodenham A. Misplaced central venous catheters: applied anatomy and practical management. Br J Anaesth. 2013;110(3):333–46.
49. Porcel JM. Chest tube drainage of the pleural space: a concise review for pulmonologists. Tuberc Respir Dis (Seoul). 2018;81(2):106–15.
50. Hoshal VL. Total intravenous nutrition with peripherally inserted silicone elastomer central venous catheters. Arch Surg. 1975;110:644–6.
51. Merrell SW, Peatross BG, Grossman MD, Sullivan JJ, Harker WG. Peripherally inserted central venous catheters. Low-risk alternatives for ongoing venous access. West J Med. 1994;160:25–30.
52. Brown J. Peripherally inserted central catheters: use in home care. J Intravenous Nurs. 1989;12:144–7.
53. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, Lipsett PA, Masur H, Mermel LA, Pearson ML, Raad II, Randolph AG, Rupp ME, Saint S, Healthcare Infection Control Practices Advisory Committee (HICPAC) (Appendix 1). Summary of recommendations: guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52(9):1087–99.
54. Raman M, Gramlich L, Whittaker S, Allard JP. Canadian home total parenteral nutrition registry: preliminary data on the patient population. Can J Gastroenterol. 2007;21(10):643–8.
55. Kuizon D, Gordon SM, Dolmatch BL. Single-lumen subcutaneous ports inserted by interventional radiologists in patients undergoing chemotherapy: incidence of infection and outcome of attempted catheter salvage. Arch Intern Med. 2001;161(3):406–10.
56. Deitel M, Kaminsky V. Total nutrition by peripheral vein: the lipid system. Can Med Assoc J. 1974;111:152–4.
57. Isaacs JW, Millikan WJ, Stackhouse J, Hersh T, Rudman D. Parenteral nutrition of adults with a 900 milliosmolar solution via peripheral veins. Am J Clin Nutr. 1977;30:552–9.
58. Khawaja HT, Campbell MJ, Weaver PC. Effect of transdermal glyceryp trinitrate on the survival of peripheral intravenous infusions: a double-blind prospective clinical study. Br J Surg. 1988;75:1212–5.
59. Nordenstrom J, Jeppsson B, Loven L, Larsson J. Peripheral parenteral nutrition: effect of a standardised compounded mixture on infusion phlebitis. Br J Surg. 1991;78:1391–4.
60. May J, Murchan P, MacFie J, Sedman P, Donat R, Palmer D, Mitchell CJ. Prospective study of the aetiology of infusion phlebitis and line failure during peripheral parenteral nutrition. Br J Surg. 1996;83:1091–4.
61. Chin BS, Han SH, Lee HS, Jeong SJ, Choi H, Kim CO, Choi JY, Song YG, Kim JM. Risk factors for recurrent catheter-related infections after catheter-related bloodstream infections. Int J Infect Dis. 2010;14(1):e16–21.
62. Daneman N, Downing M, Zagorski BM. How long should peripherally inserted central catheterization be delayed in the context of recently documented bloodstream infection? J Vasc Interv Radiol. 2012;23(1):123–5.
63. Gabe S, Willsmore J, Oke S, Nightingale J and the BIFA Committee. British Intestinal Failure Alliance (BIFA) Guideline. Detection and treatment of catheter-related thrombosis in patients receiving home parenteral support. 2021. https://www.bapen.org.uk/pdfs/bifa/management-of-central-vein-thrombosis-in-patients-receiving-hps.pdf.
64. Engels LG, Skotnicki SH, Buskens FG, van Tongeren JH. Home parenteral nutrition via arteriovenous fistulae. JPEN J Parenter Enteral Nutr. 1983;7(4):412–4.
65. Versleijen M, Vissers R, Wanten G. Excellent quality of life after 31 years of parenteral nutrition via an arteriovenous fistula. Eur J Clin Nutr. 2008;62(10):1253–4.
66. Versleijen MW, Huisman-de Waal GJ, Kock MC, Elferink AJ, van Rossum LG, Feuth T, Willems MC, Jansen JB, Wanten GJ. Arteriovenous fistulae as an alternative to central venous catheters for delivery of long-term home parenteral nutrition. Gastroenterology. 2009;136(5):1577–84.
67. Wouters Y, Theilla M, Singer P, Tribler S, Jeppesen PB, Pironi L, Vinter-Jensen L, Rasmussen HH, Rahman F, Wanten GJA. Randomised clinical trial: 2% taurolidine versus 0.9% saline locking in patients on home parenteral nutrition. Aliment Pharmacol Ther. 2018;48(4):410–22.
68. Driessen W, van der Meijden W, Wanten G, van Hoek F. Long-term patency rate of the translocated autologous saphenous vein versus prosthetic material in vascular access surgery for haemodialysis and parenteral nutrition. J Vasc Access. 2021:11297298211013133.

Formulation of Parenteral Nutrition Regimens

Gil Hardy and Michael Charles Allwood

Key Points

1. All parenteral nutrition (PN) compounding must be performed under strict aseptic conditions and under pharmacy control.
2. Multiple chamber bags (MCBs) have the lipid, carbohydrate and protein components physically separated, have long shelf lives (e.g. 1 year) and do not need refrigeration, before mixing, by rolling the bag just before the infusion begins.
3. MCBs can be triple chamber "All-in-One" (AIO), or double chamber "2 in 1" without intravenous lipid emulsion (ILE),
4. MCBs do not contain trace elements or vitamins which must be added aseptically or administered separately.
5. 'Bespoke' or 'tailored' PN bags can be compounded up to 2–3 weeks before administration but generally have all the necessary vitamins and trace elements included.
6. The shelf life of bespoke bags and MCB after mixing under aseptic conditions can be up to 21 days.
7. Interactions between PN components arise from physico-chemical incompatibility and/or chemical degradation that can lead to precipitation, loss of nutritional or pharmacological efficacy, and possible toxicity due to hazardous degradation products. The greatest risk of precipitation is from the formation of insoluble calcium phosphate salts.
8. The most significant limitations on stability of complete AIO PN regimens are high cation concentrations and poor control of air content and air ingress into PN mixtures during compounding and storage. The use of air impermeable bags is essential.
9. There is a loss of vitamins and other nutrients from PN mixtures after compounding due to chemical degradation (e.g. ascorbic acid and thiamine), adsorption onto the surface of the infusion bag or administration sets (e.g. vitamin A and E), and by light catalysed photodegradation. Consequently, exposure to direct sunlight must be avoided.
10. All PN systems, i.e. bags, and ideally the giving set, should have a light protective covering and an in-line 1.2 μm filter. Administration should be well away from a sunny window or at night.

Introduction

Since the first edition of this textbook, the major international professional societies, ASPEN (American Society for Parenteral and Enteral Nutrition) and ESPEN (European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism)) have published important clinical practice guidelines for parenteral nutrition (PN) prescribing, preparation and administration [1–3]. AuSPEN (Australasian Society for Parenteral and Enteral Nutrition), European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), ESPEN and ASPEN have produced clinical guidelines for trace elements and vitamins [4–8], and international expert consensus recommendations for micronutrients in adult and paediatric PN have been recently published [9, 10]. Additionally, the United Kingdom NHS Pharmaceutical Quality Control Committee has published protocols for assessing PN stability [11]. Where appropriate, the recommendations of these expert bodies will be incorporated into this chapter.

PN-is a complex prescription therapy that is indicated in a wide spectrum of clinical situations, from surgical and intensive care unit (ICU) patients, who may require short term nutritional support (for a few days/weeks), to patients relying on long-term PN for survival because of severe impairment in gastrointestinal (GI) function. A PN regimen typically includes 40–50 components, including; amino acids, glucose and lipids, multivitamins and trace elements.

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In the past PN has been associated with significant adverse effects when the therapy is used inappropriately. Safe prescribing and use is an essential component of PN therapy that requires a thorough knowledge of indications, requirements for protein and energy, macro and micro-nutrients, fluid homeostasis and acid-base balance, together with basics of sterility and infection control and associated complications. PN is administered with increasing frequency at home (HPN) or in long-term care facilities. Regardless of the setting or the number of patients receiving the therapy, classification of PN as a high-alert medication requires healthcare institutions to develop evidence-based policies and procedures to promote safe administration, and to validate the competency of those responsible for preparation and administration of this complex intravenous therapy [1]. In depth education on PN should be included as a standard component of acute care and home care training. This applies equally to all health professionals caring for PN patients and clear communications are essential.

This chapter outlines the components of a PN regimen, reviews reasons for their choice and clinical requirements, summarises the recommendations from recent guidelines and expert groups, for safely preparing and administering PN, and reviews key features relating to the stability and compatibility of PN admixtures.

Components of a PN Solution

When PN first became a treatment option in the 1960s (then often called 'hyperalimentation') [12], all components were separately administered from bottles of high strength glucose, protein hydrolysates or amino acids, with or without intravenous lipid emulsion (ILE). To some of these macronutrient containers, electrolytes and micronutrients were added by ward staff. Infusion systems comprised multiple lines with two-or three-way taps, connected to the central venous access device (CVAD). The risk of the line becoming infected was high due to contamination from changing infusion containers and handling the administration lines. Extrinsic contamination was later found to be significantly reduced if PN admixtures were compounded under strict aseptic pharmaceutical conditions. Subsequently, the single 'Big Bag' and all-in-one (AIO) systems for PN were developed and introduced in the late 1970s [13, 14].

As the clinical benefits of the AIO system were increasingly recognized by clinicians, the demand for more nutritionally complete mixtures and bags with shelf-lives greater than 24 h produced new challenges for pharmacists, who needed to ensure the stability and compatibility of these complex admixtures. This means that careful formulation and strict mixing protocols must be followed during compounding. Pharmacy-operated compounding services, either by commercial companies or hospital-based, are now common and have made a major impact on reducing infection risks in patients receiving PN. Most adult patients can be supported nutritionally with a range of standardized regimens.

Protein

Currently available solutions supply all the traditionally termed 'essential' and 'non-essential' L-amino acids. Some paediatric amino acid preparations contain the aminosulfonic acid, taurine, to alleviate taurine deficiency. However, the 'conditionally essential' amino acids; glutamine and cysteine are not usually included because of solubility and/or potential stability problems. Dipeptide additive solutions are available as a vehicle for less soluble heat-labile amino acids, e.g. glycyl-L-glutamine dipeptide, N(2)-L-alanyl-L-glutamine dipeptide and glycyl-L-tyrosine. These are chemically and heat stable but are hydrolysed to free glutamine, glycine, alanine or tyrosine in plasma and tissues [15].

Amino acid solutions are available in concentrations ranging from 5% to 15% with or without some electrolytes. High strength solutions with Nitrogen contents up to 30 g/L allow more concentrated formulations to be compounded when administration volume is important. Around the world protein may be prescribed as either g. protein equivalent/g. amino acids or g. Nitrogen [16].This may be confusing for some health professionals and it is now time for some international agreement on a standard terminology. In the meantime, the most common method of determining PN efficacy is to measure nitrogen balance. A factor of 6.23 can then be used to convert Nitrogen to protein/amino acids.

Energy

There is no longer debate as to which is the best energy source. It is generally recognised that glucose, lipids and amino acids are essential energy substrates but may play different roles in certain clinical situation for optimizing the efficiency of energy utilization and minimizing metabolic complications. Providing the administered substrate is adequately utilized, there is no difference in the efficacy of glucose or lipids with regards to protein sparing. Most centres use an admixture of glucose, amino acids and an ILE for AIO PN, but some still advocate the separate infusion of ILE administered weekly to provide essential fatty acids (EFA).

It is conventional, though illogical, to describe the energy given in PN as "non-protein energy" and the protein/amino acid energy is not usually stated, in contrast to enteral nutrition (EN) where the total energy content of a feed is indi-

cated. However, it must be remembered that amino acids are metabolically important energy substrates for cells of the immune system and should be included in total energy calculations. Moreover, Nitrogen itself is NOT a source of energy, thus the terms 'non-nitrogen calories or energy' are incorrect and should not be used.

Carbohydrate

Glucose is the carbohydrate of choice for PN and is available in concentrations ranging from 5–70% w/v, sometimes in combination with electrolytes. Alternative carbohydrate sources do not offer any advantages over glucose. The energy value of anhydrous glucose is approximately 4 kcal/g. When glucose monohydrate is used (as in USA) then a figure of 3.4 kcal/g is used.

Advantages

- Inexpensive and readily available
- Effectively metabolized in the presence of insulin
- Stimulates insulin release so encouraging nitrogen retention in muscles.

Disadvantages

- Concentrated solutions are hypertonic so preventing peripheral infusion
- Hyperglycaemia and glycosuria may occur
- Essential fatty acid deficiency can occur if used as the only energy source.

Lipid

ILE have low osmolality and allow large amounts of energy to be administered in a relatively small volume. Historically, ILE consisted of soya bean oil (SO) long-chain triglycerides (LCT) with chain lengths of 16–20 carbon atoms. These products have been used safely and with good clinical acceptance for over 50 years. More recently concerns have been expressed about the immunosuppressive pro-inflammatory effects of high doses of LCT and the adverse effects of phytosterols, present as impurities in SO. Newer ILE, were developed towards the end of the twentieth century, formulated from coconut oil (CO) or olive oil (OO) and/or fish oil (FO). Medium chain triglycerides (MCT) with chain lengths of 6–10 carbon atoms from CO are metabolised via a carnitine-independent fatty acid transport system [17]. Mono-unsaturated fatty acids (MUFA) with 9 carbon atoms, derived from OO are less immunosuppressive than LCT. and FO ILE contain anti-inflammatory long chain omega-3 poly unsaturated fatty acids (PUFA). Clinical experiences with the newer generation ILE provide evidence that the role of lipids extends beyond that of energy substrates. Lipids may influence prostaglandin and leukotriene synthetic pathways to beneficially modify the patient's response to illness [18–20].

All ILE are emulsified with egg lecithin derived phospholipids to mimic the structure of chylomicrons and contain 5% glycerol, to ensure the products are isotonic. A variety of ILE with different combinations of MCT/LCT/MUFA/PUFA and ω-3FA, are available as 10%, 20% or 30% w/v concentrations. The energy value of lipid is approximately 9 kcal/g, but glycerol contributes 1 kcal/g. Hence the energy contribution of a 10% ILE is 1.1 kcal/mL, a 20% ILE is 2.0 kcal/mL and 30% ILE is 3.0 kcaL/mL.

Advantages

- High energy content
- Isotonic allowing peripheral infusion
- Source of essential fatty acids (EFA) and vitamin E.

Disadvantages

- Expensive compared to glucose
- Lipids may interfere with routine blood tests
- Some patients may have reduced ability to clear lipid
- Risk of catheter occlusion with complex AIO regimens
- Pharmaceutical limitations on stability and shelf life.
- Increased susceptibility to microbial growth

Electrolytes

Various electrolyte salts are available as small volume parenteral injections (SVP) for inclusion into PN regimens. Examples are sodium (as chloride or acetate), potassium (as chloride or phosphate), phosphate (as mono- and dibasic potassium salts or organic compounds), magnesium (as sulphate or chloride) and calcium (as chloride, sulphate or gluconate). Organic phosphate injections, such as glucose-1 phosphate, glycero-phosphate and fructose-1,6-diphosphate reduce the possibility of calcium phosphate precipitation in PN mixtures. The phosphate group on these compounds is covalently bonded and thus is not ionized for precipitation as insoluble calcium phosphate. Some SVP and particularly calcium gluconate, can be contaminated with aluminium, which may be a problem for patients with renal impairment and preterm infants [21].

Micronutrients

While EN products and oral supplements usually include sufficient micronutrients to ensure basic nutritional completeness, Chemical and temperature stability considerations preclude vitamins from being incorporated into PN admixtures until closer to the time of administration. Fixed dose combinations and some individual micronutrients are available commercially as additives for compounding to meet specific clinical requirements. When micronutrients are administered intravenously they are 100% bioavailable and undergo the same metabolic and elimination pathways as corresponding minerals provided by oral feeding.

Trace Elements

Over a dozen trace elements are thought to be essential to biological functions, but only 9 are routinely supplemented in PN regimens. Metabolic rates after elective surgery may increase by 10–20% and with severe sepsis by up to 50%. When the metabolic rate increases there is a greater requirement for trace elements, partly because all essential trace elements are involved in enzyme-catalysed reactions, many of which are central to intermediary metabolism. There are also multiple sites from which large amounts of zinc, copper, manganese can be lost from fistula or diarrhoea during surgery or trauma [22].

The provision of precise amounts of micronutrients is therefore difficult due to uncertainty about how much to give and in what chemical form. In addition, the amino acid and other PN products may be contaminated with trace elements. Contamination has been reported for zinc, copper, manganese, chromium, selenium and most recently iron [23, 24]. Contamination levels vary between manufacturers and between lots from the same manufacturer. Consequently a daily amount to prevent clinical deficiency states must be provided in accordance with the guideline recommendations referenced earlier [4–10].

Standard PN solutions do not contain trace elements because of the aforementioned chemical stability considerations and need to be added to the PN solution shortly before administration to the patient. Trace elements may interact with vitamins, amino acids and other trace elements. Because these interactions become more significant when concentrations differ markedly from recommended daily intakes, administration of supplemental trace elements in a fixed combination single solution, has been advocated in order to maintain balance [25].

The compatibility of trace elements, especially iron, with lipid-containing PN remains controversial. Tu et al. [26] showed that the addition of small quantities of trace elements (including some iron) does not affect the physicochemical stability of ILE during storage for several days and that therapeutic doses of iron can be suitably admixed with lipid-containing (AIO) PN solutions. Nevertheless, these data have not been confirmed by other researchers and caution is still advised when considering adding iron to PN [27].

Vitamins

A number of commercial multivitamin preparations for parenteral use are available which provide the recommended daily requirements of vitamins Products with higher thiamine content may be advantageous when thiamine deficiency is anticipated or when a relatively carbohydrate-rich feeding regimen is used, in order to avoid refeeding syndrome (RFS). A continuing problem is the loss of vitamins from PN mixtures after compounding, whether due to chemical degradation, light catalysed peroxidation, by exposure to ultraviolet light, adsorption onto the surface of the infusion bag or administration sets. Because of these potential chemical losses the patient may not receive an adequate vitamin intake according to the prescription to maintain vitamin status. Light protection of the PN container and exclusion of air during compounding can help to minimise these losses [28, 29].

Water

Water makes up most of a PN regimen with the quantity varying according to a patient's needs. If large amounts are needed this is usually given in conjunction with isotonic sodium chloride, which is usually lost from the body with water.

Peripheral Parenteral Nutrition Formulations

When central vein access is limited, peripheral parenteral nutrition (PPN) should be considered for ≤5–7 days but can be given for up to 14 days if required. PPN can provide a safe, efficient and cost-effective short term route for nutrition delivery in a variety of clinical situations [30]. The most important complication limiting the use of PPN is thrombophlebitis, largely due to administering high osmolarity solutions into a small calibre vein. The major contributors to the osmolarity are glucose, amino acids and electrolytes with a greater incidence of thrombophlebitis noted from increasing electrolyte content, especially potassium. Consequently, standard PN regimens are not suitable for peripheral administration as their hyperosmolarity increases the risk of thrombophlebitis when infused into smaller veins. The likelihood of thrombophlebitis is reduced when the PPN regimen con-

tains ILE [31] and has an osmolarity of less than 900 mOsm/L [32, 33]. Given the low electrolyte composition of PPN, due to limitations with osmolarity, the patient's electrolyte levels should be checked prior to administration in order to minimise the risk of refeeding syndrome (RFS). Good administration and monitoring procedures, based on evidence-based practices, with careful surveillance for the signs of thrombophlebitis that include warmth, tenderness and pain in the affected area, often accompanied by redness and swelling, can ensure the success of PPN. The addition of heparin and hydrocortisone to infusions has been used to reduce the incidence of peripheral vein thrombophlebitis. Timmer and Schipper [34] have shown that the 'osmolality rate' (osmolarity × infusion rate) correlates more with peripheral vein thrombosis than osmolarity alone.

Compounding Standards and Regulations

All PN compounding must be performed under strict aseptic conditions and under pharmacy control. In the UK PN is a Prescription Only Medicine and all hospital pharmacy compounding units are strictly controlled by the Medicines and Healthcare products Regulatory Agency (MHRA). Pharmacies must have a Manufacturer's licence for compounding licensed PN products with a marketing authorisation (MA), or a Specials licence for compounding small batches of unlicensed products or a Section 10 exemption from licensing [35, 36]. Within Europe, individual countries have their own regulations controlling compounding pharmacies [37] and in the USA, ASPEN recommends that all healthcare organisations with 'in-house' compounding facilities shall comply with USP Chapter <797> standards [38].

Those hospitals without licensed Aseptic Units may contract their PN compounding to an outside manufacturer or compounder. A decision to outsource PN compounding requires that the commissioning pharmacy should exercise due diligence to monitor that the outsourcer operates within the jurisdiction of the MHRA, or in the USA follows USP <797> guidelines.

Procedures involved in providing a PN compounding service are described in detail by Austin and Stroud [35] and a useful Summary table of twelve recommendations for ordering, order review, compounding and labelling/dispensing of PN is included in the ASPEN Clinical Guidelines [33]. Risk management advice for health professionals performing PN compounding, by the NHS Pharmaceutical QA Committee [11], include considerations of the compounding processes, the final container choice, stability, exclusion of air and light protection, storage temperature and infusion period. Controlling impurities such as Aluminium, that has been regulated in the USA for over 20 years [39], is now a BP requirement for UK manufacturers [40].

Standard commercially available 'ready-to-use' PN products may be viable options to aseptically compounded PN products, when compliance with USP Chapter <797> and other national guidelines is not feasible [1]. Multi chamber bags (MCB) are designed to reduce the risk for instability or precipitation. Macronutrient components of the PN formulation are separated in individual chambers by a seal, until just prior to activation and administration. The contents of the chambers should be mixed and any additives made aseptically under pharmaceutical conditions, prior to dispensing the PN prescription. If MCB are used in home care then patients and/or caregivers shall be provided with thorough training regarding the procedure for properly mixing the contents before use [1, 37, 41].

Stability and Compatibility of PN Solutions

Since PN solutions are complex mixtures, there are two categories of interactions between components that can potentially take place in compounded PN admixtures: physico-chemical incompatibility leading to precipitation, and chemical degradation leading to loss of nutritional or pharmacological efficacy, and possibly enhanced toxicity from hazardous degradation products. Avoiding precipitation and minimizing degradation requires an understanding of the major reasons why they occur in certain PN regimens. The chemical composition and physical properties of PN admixtures vary greatly between regimens depending on the amino acid source, ILE type, the particular electrolyte salts used, the relative concentrations of ingredients and the final volume. In describing the potential chemical and physical interactions that can take place, it is important to realize that each regimen is chemically unique. Extrapolation of stability data from one to another regimen requires a full understanding of all the factors that can influence stability.

Physical Incompatibility

Electrolytes

The most common cause of precipitation in PN mixtures is due to calcium phosphate insolubility [35–37]. Factors influencing the solubility of calcium phosphate in PN admixtures are multi-factorial, but the most important variable is pH [42]. The final pH of a mixture is influenced by the following factors:

The amino acid product. Differences in pH, that can vary from around pH 5 to greater than 7 are important due to the strong buffering capacity of individual amino acids that are the major controllers of pH in the final PN admixture [43].

The phosphate source. Inorganic phosphates are strong buffers but potassium dihydrogen phosphate injection (acid

phosphate) has a very low pH c.5 while disodium hydrogen phosphate has a pH around 8. Thus, the choice of phosphate injection can have a marked effect on final pH of the PN mixture [42].

The Buffering Capacity of Amino Acids and Inorganic Phosphate

The chemical equilibrium for inorganic phosphate salts in water is shown in Fig. 1. Note that pH is the controlling factor for which phosphate species actually predominate in any particular solution. In PN admixtures, the optimum pH lies between 5 and 7 but will depend on the amino acid source, final concentration and phosphate source. At pH 5, the dihydrogen-phosphate salt predominates, while at pH 7, the predominate salt is the mono-phosphate species [42].

Calcium mono-hydrogen phosphate is 60 times less soluble than the dihydrogen salt. As the pH increases, there is an increasing likelihood of precipitation. Since the most important cause of precipitation in PN admixtures is the formation of insoluble calcium phosphate, the calcium source needs to be considered [42].

Parenteral Calcium comes in two forms, as inorganic or organic salts: calcium chloride and calcium sulphate for injection, which are fully ionized in aqueous solution, or calcium gluconate injection which is only partially ionized in aqueous solution. These salts behave differently in PN admixtures, and precipitation is most likely with the chloride salt. Calcium gluconate is therefore preferred to reduce the risk of precipitation in PN mixtures [44] But there is a further complication. The degree of ionization of calcium gluconate is only slightly influenced by pH, but is substantially affected by temperature [42]. Raising the temperature increases the dissociation of calcium gluconate, so paradoxically, PN admixtures containing calcium gluconate stored in the refrigerator are less likely to precipitate, compared with PN admixtures at room temperature. More importantly, is the possible risk of precipitation in the administration set, as the PN infusion warms to body temperature, especially within the canopy of a neonatal cot. Consequently, a limit of 76 mg Ca per kg and a molar Ca:P ratio of 1.3:1 is recommended for neonatal PN regimens [33]. Note also the concerns about high aluminium levels in calcium gluconate injection as previously indicated [39].

Other factors that can also affect calcium phosphate solubility in PN admixtures are summarized in Table 1.

Other Possible Causes of Precipitation

There are some other possible causes of precipitation, but all are far less likely than calcium phosphate. Most are associated with trace elements and usually take many days to become evident [46, 47]. In contrast, calcium phosphate precipitates appear within 24 h of compounding. Significant trace element interactions can cause precipitation in PN admixtures. These include:

- Copper and sulphide (a degradation product of cysteine found in Vamin®, Vaminolact® and Primene products [47].
- Iron and phosphate (only reported with Synthamin® with electrolyte-containing PN mixtures) [47].
- Selenium and vitamin C at acidic pH [48].

In summary, the greatest risk of precipitation is from formation of insoluble calcium phosphate salts. In clinical practice, it is normally possible to achieve adult nutritional

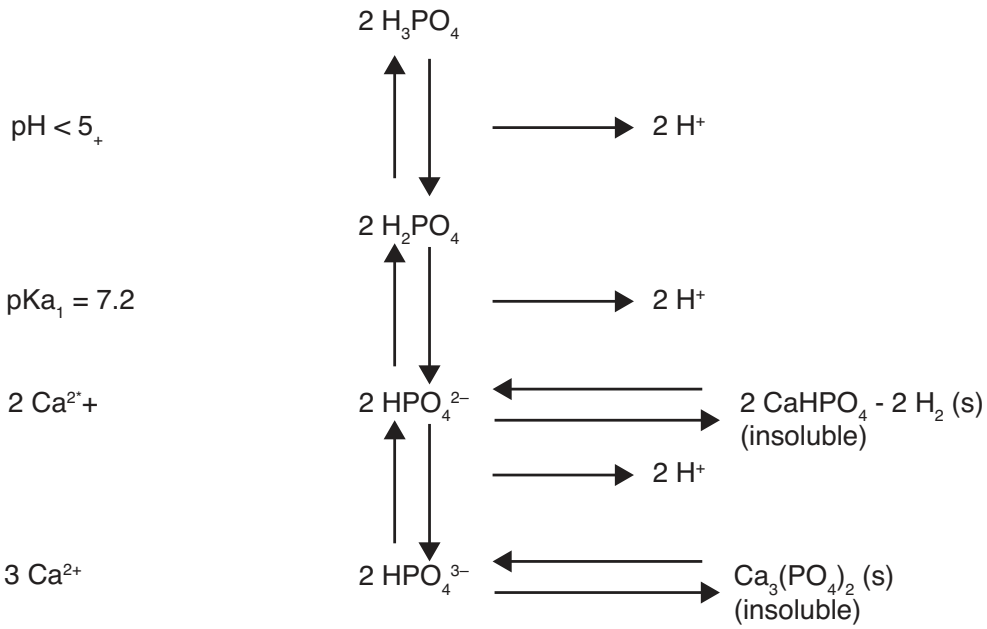

Fig. 1 Speciation of phosphate salts in parenteral nutrition mixtures

requirements without running the risk of calcium phosphate precipitation. Nevertheless, in neonates and small children, because of their greater needs for these essential compounds, it is very difficult to formulate PN regimens without creating a potentially incompatible admixture. Insolubilities can be minimised by using an organic source of phosphate, such a sodium glycerophosphate [45] with covalently bonds so there are no free phosphate ions present. Thus, the risk of forming an insoluble salt with calcium is minimised, so phosphate requirements for neonates and small children are more easily achieved.

Intravenous Lipid Emulsions

It is now routine practice to include intravenous lipid emulsions (ILE) in most PN formulations. An intravenous oil-in-water emulsion is manufactured using a homogenization process to form a very fine emulsion, egg lecithin being the emulsifying agent. Each lipid particle is kept separate by the fact that the surface is covered in the negative charges of phospholipid 'tails' around its surface. Consequently, charge repulsion maintains the emulsion in a stable state [49].

Since the average globule size is around 3–400 nm (0.3–0.4 μm), small enough to pass through the smallest capillaries, the essential requirement of any ILE after being added to a PN admixture, is that this size does not increase to the extent that it might block these capillaries. This forms the basis for deciding if the AIO regimen remains within acceptable limits. Most ILE contain added sodium oleate (c. 0.3%) as an additional surfactant to enhance the physical stability of the emulsion. Such ILE are also more stable and can tolerate both lower and higher concentrations of amino acids and glucose after dilution in a PN regimen [50].

In compounding a PN admixture, ILE is mixed with a whole range of other compounds, which, crucially, include electrolytes and specifically, cations. These positively charged ions can neutralize the negative surface charges of the oil globules. The particles start to come together as aggregates and form small clumps. Since oil is lighter than water, these aggregates tend to float to the surface and form a 'cream' layer (just like the "top-of-the-milk") (Fig. 2). Gentle shaking can disperse these clumps. Therefore, the formation of a cream layer is not normally considered hazardous because the particles remain discreet. However, if the particles start to coalesce to form larger oil globules, this is more hazardous, but can usually only be detected by careful particle-size analysis [51].

Table 1 Factors that effect calcium phosphate solubility in PN mixtures

Factor	Likely effect	Reason for effect
Magnesium concentration	Reduces likelihood of precipitation	Magnesium phosphate more soluble than calcium phosphate salts [33]
Amino acid source	May decrease or increase solubility and/or precipitation	Some amino acids specifically bind calcium and reduce salt formation, thus enhancing solubility [43]
Organic phosphate	Removes risk of calcium precipitation	Phosphate is in an organic covalent form (e.g. glycerophosphate or glucose phosphate) and so calcium phosphate does not precipitate [45]

Causes of destabilisation in AIO PN mixtures

- HIGH concentrations of calcium and magnesium
- LOW pH
- LOW relative volumes of ILE
- LOW concentration of amino acids
- HIGH ratio of acidic to basic amino acids

Fig. 2 Stages of All-in-One PN admixture instability over time

Factors that enhance stability of AIO admixtures

- HIGHER glucose concentrations, but within an upper limit
- Second emulsifying agent—sodium oleate

In fact, it requires relatively large concentrations of cations to significantly reduce these surface charges, but divalent cations are much more efficient charge neutralizers. So, in practice it is the concentration of divalent cations, which is the most important cause of destabilisation. There have been attempts to quantify the destabilising effect of cations. Although the relatively simple equations used in colloid science are more applicable to simple ILE and cannot always be applied to the more complex AIO admixtures, calculating the critical aggregation number (CAN) from the Schultz-Hardy equation [49]. can be a useful indicator and has been used for stability predictions of paediatric PN regimens [52].

The USP <729> provides pharmaceutical specifications describing stability methods and acceptance criteria defined as the "percentage of fat residing in globules larger than 5 µm (PFAT5) for a given ILE is not to exceed 0.05%". It is claimed that PFAT5 can also applied to final PN admixtures [53] and that PFAT5 has been validated for both the ILE from the manufacturer and as a total nutrient admixture (TNA) from the compounder in both animal models and human subjects [54]. Nevertheless, although the principle of PFAT5 is sound, as with the CAN approach, there are concerns that the USP monograph cannot be applied accurately to all AIO admixtures and that the recommended light obscuration techniques will not pick up the smaller lipid droplets which may have an important role in indicating instability. A recent study by Zhao B et al. [55]. that assessed the stability of MCT/LCT-based PN admixtures by measuring mean droplet diameter (MDD), PFAT5, pH, and osmolality, reported that all TNA met USP <729> but there were some significant differences between MDDs and PFAT5s.

To date, the USP standards have not been officially accepted in the UK or Europe but PFAT5 is used by some manufacturers, as part of routine stability testing for PN admixtures [56]. Other testing laboratories prefer a combination of assessments methods based on visual, microscopic and particle size analysis (e.g. laser diffraction, light obscuration) together with their extensive historical laboratory comparative data to determine and predict AIO PN stability.

The ASPEN consensus recommendations for a stable AIO PN regimen [1, 33], provide a useful 'rule of thumb' and can be summarised as follows:

Glucose >10% (excluding PPN)
Amino Acids >4%
Lipid >2%
Ca/Mg <20 mEq (10 mmol)/L
Na/K <200 mEq (mmol)/LNB: Stability information should never be extrapolated between PN admixtures with different commercial sources of amino acids and/or ILE.

Chemical Degradation

Most PN components are remarkably stable after compounding, at least during the normal shelf lives of PN admixtures, and in particular the 30-day shelf life most commonly used in practice. It is important to consider stability at two stages: (a) during storage after compounding and (b) during administration. There are three possible chemical mechanisms for the degradation of specific PN ingredients (Table 2) primarily involving vitamins. Thus, it is often the addition of vitamins that subsequently limits the shelf life of PN admixtures [57–62].

Vitamin C (Ascorbic Acid) Oxidative Degradation

Ascorbic acid is the least stable ingredient in any PN admixture and some loss during compounding, storage and administration is inevitable. There are two important factors to note from the degradation pathway for ascorbic acid in Fig. 3.

First, the initial reaction is reversible; this is important because dehydro-ascorbic is equally biologically functional. Second, the degradation involves oxygen which can originate from:

1. Air in infusion solutions and additives—glucose, electrolytes, water for reconstituting vitamins, (but not amino acid infusions or ILE, both of which are usually protected by a nitrogen gas overlay).
2. Air in the bag after compounding, if not removed prior to sealing
3. Air which dissolves in the infusions during the filling process especially as solutions pass through the filling lines
4. Oxygen permeating through the bag wall during storage.

Oxygen reacts with ascorbic acid rapidly, catalysed by copper ions [63, 64]. Within an hour or two, the oxygen will have reacted to reduce ascorbic acid to dehydroascorbic acid

Table 2 Chemical mechanisms for PN degradation

Reaction	Most important candidate(s)
1 Oxidation	Vitamin C (ascorbic acid)
2 Reduction	Vitamin B_1 (thiamine)
3 Photodegradation	Vitamin A (retinol) Vitamin E (tocopherol)

[64]. This in turn is further oxidized and/or hydrolysed to keto-gulonic acid, so the amount of ascorbic acid degraded depends almost entirely on the amount of oxygen present in the PN admixture after compounding.

It can be expected that the quantity of ascorbic acid degraded after compounding a typical 2–3 L adult formulation will amount to 40–60 mg [63]. The amount the patient receives depends on the quantity of oxygen in the PN bag, and on the type of bag used. Degradation will continue as oxygen permeates through the semi-permeable wall of PVC or EVA PN bags, accounting for a further loss of 10–15 mg per day [64]. In an EVA bag, the maximum shelf life must therefore be only 3–5 days, because of the high oxygen permeability of the plastic. This phenomenon can be minimised by using multi-layered bags, which are virtually impermeable to oxygen. A comparison of ascorbate (AA + DHAA) degradation in single layer EVA versus multi-layered bags is illustrated in Fig. 4. Note how degradation is initially rapid, but then the rate of losses level off to almost zero, after a few hours. This is accounted for by the initial reaction with dissolved oxygen already in the PN admixture. Once all the oxygen has reacted, no further degradation of ascorbic acid takes place. Thus, in multi-layered bags, which are now commonly used in UK and some other countries, the shelf life of PN admixtures can be extended, commonly up to 30 days, provided the initial compounding is undertaken efficiently, to minimise aeration during filling, and any residual air is removed before sealing the bag [63–65].

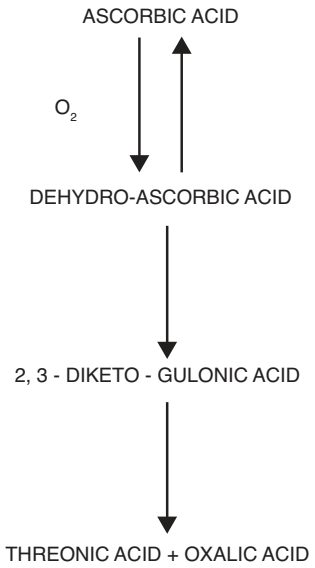

Fig. 3 Ascorbic acid degradation pathway

Unfortunately, the plastic films used to fabricate MCB's are also semi-permeable to oxygen. Consequently, following removal of the outer wrap, mixing of the main ingredients and the addition of multi-vitamins, degradation of ascorbic acid will occur as described above, such that shelf lives should be restricted to 48–72 h, including infusion time. The shelf lives of these products can be further extended to at least 60 days, usually in a high GMP industrial facility, by re-packaging the MCB (after mixing and adding vitamins), in a gas-impermeable overwrap. Any remaining air between the MCB and its overwrap is replaced by nitrogen gas before sealing the overwrap under vacuum. An oxygen scavenger is also commonly included.

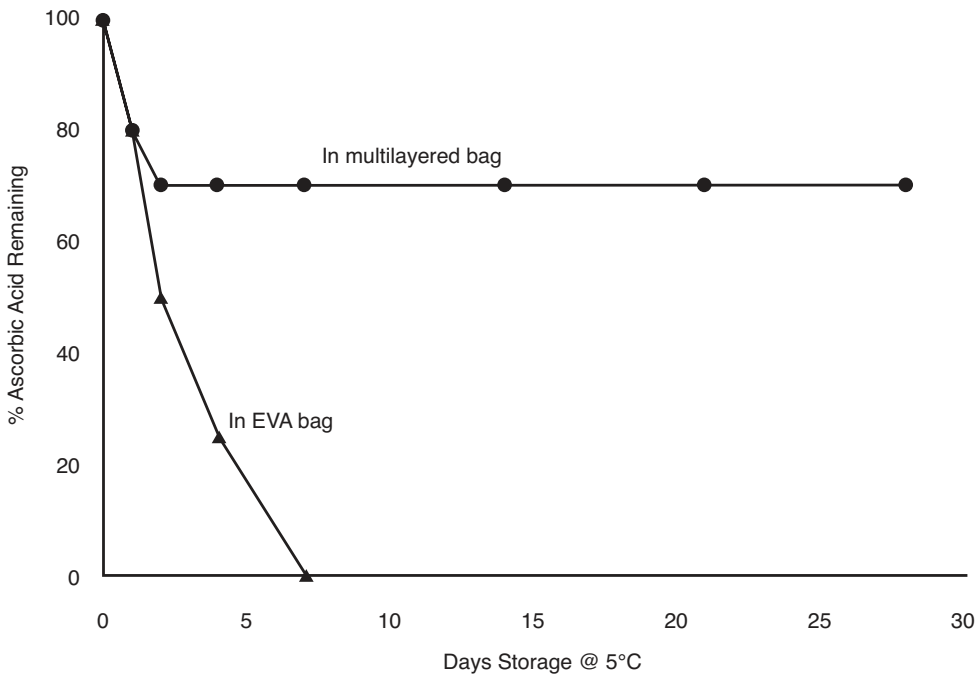

Fig. 4 Degradation of ascorbate in PN mixture during storage

Vitamin B_1 (Thiamine) Reduction

Thiamine is degraded by a reduction reaction with sodium metabisulphite [33]. Historically, some amino acid infusions contained sodium metabisulphite as a reducing agent to prevent oxidation of amino acids during manufacture and storage. In the absence of metabisulphite, thiamine is stable for at least 28 days in PN mixtures [66].

Vitamin A (Retinol) Photodegradation

The most light-sensitive ingredient of any PN admixture is retinol (vitamin A) [28, 67]. Many factors can influence the rate of light induced retinol degradation during PN administration, including the time of day, the position with respect to light from the window, volume in bag, infusion rate, ILE in the admixture and the presence/absence of a light protecting cover over the PN bag [28, 67].

But note the following important points:

- Since degradation is caused by exposure to ultraviolet light (below 350 nm wavelength), only daylight degrades retinol [67]
- Artificial light contains very little UV emission
- Photodegradation will occur both in the bag and in the administration set as the solution is infused, if the system is not protected [65].

Drug Additions to PN Mixtures

It is generally recommended that drugs should NOT be added to PN admixtures unless absolutely necessary. According to ASPEN [33] a decision to make drug additions should be supported by data on the physicochemical compatibility and stability of the medication and of the final admixture, under conditions of typical use. In addition, clinical data on the expected therapeutic advantages of incorporating the drug into the PN admixture should be available. Evidence is available which identifies the compatibility and stability of specific drugs in particular PN admixtures [68, 69]. The most commonly added drugs are, the histamine type 2 receptor antagonists, heparin, insulin:

H_2 Antagonists

Cimetidine is stable in PN regimens, and shelf lives of up to 28 days have been indicated in certain mixtures [52]. In contrast, ranitidine is far less stable. Half-lives of only a few days are indicated in many regimens, although it is possible to extend this in multi-layered bags, and/or by adding vitamin C, as ranitidine degradation is by light-induced oxidation [70–73].

Heparin

Heparin is commonly added to PN regimens for neonates, but great care is necessary to avoid destabilizing the ILE in AIO admixtures, or when lipid-free PN admixtures mix with ILE via a Y-set. Standard heparin interacts with the emulsifying agent in ILE, in the presence of calcium ions, to form calcium-heparin bridges [74]. The emulsion rapidly destabilizes and cracks within a few minutes. This risk can be avoided by using low molecular weight heparin [52].

Insulin

Insulin infusions may be required for poorly controlled diabetic patients or for those patients developing insulin resistance. Addition of insulin to PN regimens has also been advocated to promote anabolism but this can lead to further metabolic disturbances. Moreover, if added to the PN admixture, insulin can partially adher to the plastic container and giving set, limiting its bioavailability. Addition is therefore discouraged [33, 35].

Various other medications such as hydrocortisone or albumin have been demonstrated to have only limited stability and short shelf lives [33] Overall, limited or inconclusive stability, bioavailability and the potential for introducing contamination make the addition of all non-nutrient medications undesirable and generally not recommended

FDA Recommendations for Compounding During the Covid 19 Pandemic and Other Particles [75]

Personnel who compound sterile drugs such as PN are required to use PPE to reduce the risk of microbes and other particles present on human skin, hair and clothing contaminating the product they are preparing. Where PPE are in short supply, the FDA recommends that compounding practices can be modified as follows

- Use other PPE, if obtainable, that confer equal protection
- Preserve the existing supply of PPE by
  - Limiting the number of personnel conducting aseptic activities
  - Reducing compounding activities

Mitigation strategies to reduce the risk of contamination relating to compounding without standard PPE, include

- Increase the frequency of cleaning compounding areas and gloves
- Increase the frequency of environmental monitoring
- Use standard PPE beyond the designated shelf life, if stored appropriately
- If no other PPE are available:
  - Reuse masks during the same shift but do not share between personnel
  - Reuse masks on subsequent days, only if stored correctly and free from defects
  - Use an appropriate agent to disinfect masks
  - If sterile gloves are unavailable, non sterile gloves may be disinfected and used, after checking material and manufacturers recommendations
  - Foot covers should not be reused

PN Administration After Compounding

PN administration errors that occur at the point of patient contact are less likely to be intercepted and more likely to cause harm. Two relatively simple precautions to be taken are:

1. To protect the PN system from oxygen and light
2. To filter the PN before reaching the patient.

1. It has been well known since the pioneering work with AIO in Montpelier, France [13] that some components of PN admixtures are susceptible to oxidation and light catalysed degradation. Photooxidation is defined as a "a chemical reaction occurring as a result of absorption of light in the presence of oxygen". The presence (or absence) of oxygen is therefore key to the stability of nutrients in aqueous solution. This phenomenon has been well demonstrated in our laboratories over the past 30–35 years [67] and the point is made in the introduction to the UK NHS advisory paper on PN Stability published in 2016 [11] As indicated earlier, vitamins, and ILEs appear to be the most susceptible to photooxidation when exposed to intense sunlight, including the ultraviolet range in the presence of air, but ambient light can also have significant effects [76, 77].

   Cressex and colleagues [78, 79] most recently demonstrated that premature neonates, and the critically ill are most susceptible to light induced oxidative stress. In consequence the most recent guidance from ESPEN [79] and ASPEN [80] make recommendations to light protect PN systems for premature babies and neonates and the regulatory agencies, MHRA and EMA have now made this a requirement for PN manufacturers [81, 82].

   In practice it has long been a standard recommendation in UK for *all* PN systems to be protected from light [29, 35, 76].
2. In-line filters during PN administration reduce the potential for patient harm due to particulates, microprecipitates, microorganisms, and air emboli. The most recent advice from ASPEN [83] and ESPEN [84] for inclusion of a filter in a PN administration system follows the much earlier UK recommendations from BPNG [85, 86].

   It is now generally recommended to use a 1.2 micron in-line filter for administration of all PN regimens, whether AIO or '2 in 1' PN (without lipid) or ILE when separately infused [83].

   Single use filters should be placed as close to the catheter hub for AIO admixtures or below the Y-site where the amino acid/dextrose admixture and ILE co-infuse [83] and should be changed according to the manufacturer's guidelines, typically every 24 h. Due to the potential for contamination and subsequent release of endotoxin, filters should not be connected to the PN system in advance but should be primed with fluid immediately before initiating the infusion.

   When an occluded filter triggers pump alarms, the PN infusion should be stopped and the PN pharmacist should review the PN formulation to determine if incompatibility issues are the cause of the problem and to recommend appropriate action.

Practical Tips for Maintaining Stability During PN Administration

- Use an in-line 1.2 μm filter for all PN [83]
- Avoid exposure to direct sunlight [76, 81, 82]
- Protect the bag content with a light excluding cover [76]
- If possible, light protect the giving set; not protecting the set will lead to some nutrient losses [76]
- Administration at night or well away from a window will reduce losses substantially [76].
- The ILE in AIO admixtures may offer some protection to vitamin degradation but will itself be subjected to peroxidation [76].

Procedures to Follow Before PN Administration

Various Check Lists have been published for final inspection of a PN admixture [11, 33, 35].

Key points include:

- Compare label to prescription
- Compare calculated weight to actual weight
- Visually check for:
  - Colour changes
  - Precipitates
  - Leaks
  - Phase separation
- Establish an expiry date
- **IF IN DOUBT 'THROW IT OUT'**

Parenteral Nutrition Education and Training

PN errors caused by insufficient competency and poor proficiency with automatic compounding devices (ACD) are areas of concern. A lack of competency-based educational curriculum in schools of pharmacy or pharmacy technician training programmes in preparation of sterile products and admixtures, may contribute to PN errors [33].

PN compounding and administration errors often stem from failure to adhere to the verification steps of PN which parallel the "five rights" of medication safety: Right patient, Right drug, Right dose, Right route and Right time. For PN these rights must include; confirmation of Patient identity, visual inspections, verification of PN label, documentation to trace container and administration set to point of origin, and independent double checks by nurses. Since non compliance with labelling and set tubing changes can lead to pump errors, some have advocated a 'sixth right' to ensure the Right Pump and Accessories are used to administer the PN [87].

Educating pharmacy and clinical staff about the proper use and effectiveness of double checks and procedures for reporting errors, near misses and barriers to safe practice in a non punitive environment are essential [33].

References

1. Ayers P, et al. ASPEN parenteral nutrition safety consensus recommendations. J Parenter Enteral Nutr. 2014;38:296–333.
2. Singer P, et al. ESPEN guideline on clinical nutrition in the ICU. Clin Nutr. 2019;38:48–79.
3. Muhlebach S, et al. In: Sobotka L, editor. How to prepare PN admixtures: role and function of the pharmacist in basics in clinical nutrition. 4th ed. Czech Republic: Galen; 2011.
4. Osland E, et al. Australasian Society for parenteral and enteral nutrition guidelines for supplementation of trace elements during parenteral nutrition. Asia Pac J Clin Nutr. 2014;23:545–54.
5. Osland EJ, Ali A, Nguyen T, Davis M, Gillanders L. Australasian society for parenteral and enteral nutrition (AuSPEN) adult vitamin guidelines for parenteral nutrition. Asia Pac J Clin Nutr. 2016;25(3):636–50.
6. Venek K, et al. A.S.P.E.N. Position paper: recommendations for changes in commercially available parenteral multivitamin and multi–trace element products. Nutr Clin Pract. 2012;27:440–91.
7. Bronsky J, Campoy C, Braegger C, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: vitamins. Clin Nutr. 2018;37(6, Part B):2366–78.
8. Domellöf M, Szitanyi P, Simchowitz V, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: iron and trace minerals. Clin Nutr. 2018;37(6, Part B):2354–9.
9. Blaauw R, Osland E, Sriram K, et al. Parenteral provision of micronutrients to adult patients: an expert consensus paper. J Parenter Enteral Nutr. 2019;43(Suppl 1):S5–S23.
10. Hardy G, et al. Parenteral provision of micronutrients to pediatric patients: an expert consensus paper. J Parenter Enteral Nutr. 2020;44(Suppl 2):S5–S23.
11. Anon. NHS Pharmaceutical Quality Control Committee. A standard protocol for deriving and assessment of stability. Part 4- parenteral nutrition. 2016. www.medicinesresources.nhs.uk/en/Communities/NHS/UKQAInfoZone.
12. Dudrick SJ, et al. Long term total parenteral nutrition with growth development and positive nitrogen balance. Surgery. 1968;64:134–42.
13. Solassol C, Joyeux H, Etco L, Pujol H, Romieu C. New techniques for long term intravenous feeding: an artificial gut in 75 patients. Ann Surg. 1974;179:519–22.
14. Hardy G. Ten years TPN with 3 litre bags. Pharm J. 1987:H526–8.
15. Furst P. New parenteral substrates in clinical nutrition. Eur J Clin Nutr. 1994;48:607–16.
16. Hardy G, Kleck S, Chourdakis M, Majid H. Towards an international metrology for clinical nutrition. JPEN J Parenter Enteral Nutr. 2019;43:445.
17. Richelle M, Deckelbaum RJ, Vanwyenberg V, Carpentier Y. Lipoprotein metabolism during and after a 6-h infusion of MCT/LCT vs LCT emulsion in man. Clin Nutr. 1997;16:119–23.
18. McMahon MM, et al. Parenteral nutrition in adults in clinical management of intestinal failure management by Gura K et al. Boca Raton: CRC; 2009. p. 135–43.
19. Martindale RG, et al. Lipids in parenteral nutrition. J Parenter Enteral Nutr. 2020;44:S7–S20.
20. Abbasoglu O, et al. Fish oil–containing lipid emulsions in adult parenteral nutrition: a review of the evidence. J Parenter Enteral Nutr. 2019;43:48–470.
21. Gura K. Aluminium contamination in PN products. Curr Opin Clin Nutr Metab Care. 2014;17:551–7.
22. Hardy G, Reilly C. Technical aspects of trace element supplementation. Curr Opin Clin Nutr Metab Care. 1999;2(4):277–85.
23. Pluhator-Murton MM, Fedorak RN, Audette RJ, Marriage BJ, Yatscoff RW, Gramlich LM. Trace element contamination of total parenteral nutrition. 1. Contribution of component solutions. J Parenter Enteral Nutr. 1999;23(4):222–7.
24. Menendez AM. Iron contamination in paediatric TPN mixtures. Colorado: Poster ASPEN; 2018.
25. Harraki B, Guiraud P, Rochat MH, Alary J, Favier A. Interactions related to trace elements in parenteral nutrition. Pharm Acta Helv. 1995;70:269–78.
26. Tu YH, Knox NL, Biringer JM, Eichman ML, Schweinsberg PD, Howard JR. Compatibility of iron dextran with total nutrient admixtures. Am J Hosp Pharm. 1992;49:2233–5.
27. Zemrani B, et al. Trace element provision in parenteral nutrition in children. Nutrients. 1819;2018:10.
28. Allwood MC. The influence of light on vitamin A degradation during administration. Clin Nutr. 1982;1:63–70.
29. Hardy G, Ball P, McElroy B. Basic principles for compounding AIO PN admixtures. Curr Opin Clin Nutr Metab Care. 1998;1:291.
30. Carey S. Protocol for use of peripheral parenteral nutrition. AuSPEN. 2018. www.auspen.org.

31. Pineault M, Chessex P, Piedboeuf B, Bisaillon S. Beneficial effect of co-infusing a lipid emulsion on venous patency. J Parenter Enteral Nutr. 1989;13:637–40.
32. Correia MI, Guimaraes J, de Mattos LC, Gurgel KC, Cabral EB. Peripheral parenteral nutrition: an option for patients with an indication for short-term parenteral nutrition. Nutr Hosp. 2004;19:14–8.
33. Boullata JI, Gilbert K, Sacks G, Labossiere RJ, Crill C, Goday P, et al. A.S.P.E.N. clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. JPEN J Parenter Enteral Nutr. 2014;38:334–77.
34. Timmer JG, Schipper HG. Peripheral venous nutrition: the equal relevance of volume load and osmolarity in relation to phlebitis. Clin Nutr. 1991;10:71–5.
35. Austin P and Stroud M. Technical services. In: Prescribing adult intravenous nutrition. London: Pharm Press; 2007. p. 232–44.
36. NICE guideline [CG32] Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. 2006. www.nice.org.uk/guidance/cg32.
37. Muhlbach S, Driscoll HG. Pharmaceutical aspects of parenteral nutrition support. In: Sobotka L, editor. Basics in clinical nutrition. 4th ed. Czech Republic: Galen; 2011. p. 373–84.
38. USP <797>. Guidebook to pharmaceutical compounding-sterile preparations. Rockville, MD: USP Convention; 2008.
39. Gura KM, Puder M. Recent developments in aluminium contamination of products used in parenteral nutrition. Curr Opin Clin Nutr Metab Care. 2006;9(3):239–46.
40. British Pharmacopoeia. Parenteral nutrition solutions, vol. 3. London: HMSO; 2020.
41. BPNG position statement on the use of MCB for adult PN. www.bpng.co.uk/pdf/.
42. Allwood MC. The compatibility of calcium phosphate in paediatric TPN infusions. J Clin Pharm Ther. 1987;12:293–301.
43. Hardy G, Cotter R, Dawe R. The stability and comparative clearance of TPN mixtures with lipid. In: Johnstone IDA, editor. Advances in clinical nutrition. London: MTP Press; 1983. p. 241–60.
44. Muhlebach S and Driscoll DF. Stability and compatibility of PN admixtures 384=390 In: Basics in clinical nutrition 4th 2011 Lubos Sobotka Galen. Czech Republic.
45. Ronchera-Oms CL, Jimenez NV, Peidro J. Stability of parenteral nutrition admixtures containing organic phosphates. Clin Nutr. 1995;14:373–380.46.
46. Harraki B, Guiraud P, Rochat MH, Fussellier M, Favier A. Influence of copper, iron, and zinc on the physicochemical properties of parenteral admixture. J Parenter Sci Technol. 1993;47(5):199–204.
47. Allwood MC. The compatibility of four trace elements in total parenteral nutrition infusions. Int J Pharm. 1983;16:57–63.
48. Hardy IJ, Sill-Steffens R, Hardy G. Sodium selenite stability in intravenous solutions. Clin Nutr. 2004;23:827.
49. Davis SS. The stability of intravenous fat emulsions. In: Johnstone IDA, editor. Advances in clinical nutrition. London: MTP Press; 1983. p. 213–40.
50. Allwood M, Kierney M. Compatability and stability of additives in PN admixtures. Nutrition. 1998;14:697–708.
51. Driscoll DF, Nehne J, Peterss H, Klutsch K, Bistrian BR, Niemann W. Physicochemical stability of intravenous lipid emulsions as all-in-one admixtures intended for the very young. Clin Nutr. 2003;22:489–95.
52. Watrobska-Swietlikowska D, et al. Evaluation of physical stability of AIO PN admixtures for pediatric homecare. Nutr Hosp. 2015;31:236–43.
53. Boullata J, et al. Summary of proceedings and expert consensus statements: lipids in PN. J Parenter Enteral Nutr. 2020;44:S7–S20.
54. Klang M. PFAT5 and the evolution of lipid admixture stability. J Parenter Enteral Nutr. 2015;39(Supp 1):69S–71S.
55. Zhao B, et al. Physical stability of medium-chain triglyceride/long-chain triglyceride emulsion injections from 5 manufacturers in high-concentration electrolyte–based total nutrient admixture. J Parenter Enteral Nutr. 2020;45:1275–84.
56. Personal Communications Baxter and BBraun (UK).
57. Allwood MC. Stability of vitamins in TPN solutions stored in 3 L bags. Br J Intraven Ther. 1982;3:22–6.
58. Billion-Rey F, Guillaumont M, Frederich A, Aulanger G. Stability of fat-soluble vitamins A (retinol palmitate), E (tocopherol acetate) and Kl (phylloquinone) in total parenteral nutrition at home. J Parenter Enteral Nutr. 1993;17:56–60.
59. Dahl GB, Svensson L, Kinnander NJG, Zander M, Bergstrom UK. Stability of vitamins in soybean oil fat emulsion under conditions simulating intravenous feeding of neonates and children. J Parenter Enteral Nutr. 1994;18:234–9.
60. Dahl GB, Jeppson RI, Tengbom HJ. Vitamin stability in a TPN mixture stored in an EVA plastic bag. J Clin Hosp Pharm. 1986;11:271–9.
61. Schmutz CW, Martinelli E, Muhlebach S. Stability of vitamin K assessed by HPLC in total parenteral nutrition. Clin Nutr Suppl. 1992;12:169.
62. Chen MF, Boyce W, Triplett L. Stability of B vitamins in mixed parenteral nutrition solution. J Parenter Enteral Nutr. 1983;7:462–4.
63. Allwood MC. Factors influencing the stability of ascorbic acid in total parenteral nutrition infusions. J Clin Hosp Pharm. 1984;9:75–85.
64. Allwood MC, Brown PE, Ghedini C, Hardy G. The stability of ascorbic acid in TPN mixtures stored in a multilayered bag. Clin Nutr. 1992;11:284–8.
65. Proot P, De Pourco L, Raymakers AA. Stability of ascorbic acid in a standard total parenteral nutrition mixture. Clin Nutr. 1994;13:273–9.
66. Kearney MJ, Allwood MC, Neal T, Hardy G. The stability of thiamine in total parenteral nutrition mixtures stored in EVA and multilayered bags. Clin Nutr. 1995;14:295–301.
67. Allwood MC, Plane JH. The wavelength-dependent degradation of vitamin A exposed to ultraviolet light. Int J Pharm. 1986;31:1–7.
68. Bouchoud L, et al. Compatability of intravenous medications with PN. JPEN J Parenter Enteral Nutr. 2013;37:416–24.
69. Cardoba D, et al. Review of drug stability on PN admixtures. Clin Nutr. 2013;8:e135–40.
70. Allwood MC, Martin H. The long term stability of cimetidine in total parenteral nutrition. J Clin Pharm Ther. 1996;21:19–21.
71. Allwood MC, Martin H. The stability of ranitidine in TPN mixtures. Clin Nutr. 1995;14:171–6.
72. Baumgartner TG, Henderson GN, Fox J, Gondi U. Stability of ranitidine and thiamine in parenteral nutrition solutions. Nutrition. 1997;13:547–53.
73. Puzovic M, Kukee-Jekovic M, Hardy G. Compatibility of Ranitidine with selected PN admixtures. Nutrition. 2008;24:500–1.
74. Wong C, Allwood MC, Everett NJ, McMahon MJ. Physical stability of a series of adult peripheral all-in-one admixtures containing heparin and hydrocortisone. BAPEN Proc. 1993;5–6.
75. FDA-2020-D-1136. www.fda.gov.regulatory-information/.
76. Allwood MC. Light protection during parenteral nutrition infusion: is it really necessary? Nutrition. 2000;16(3):234–5.
77. Ferguson TI, Emery S, Price-Davies R, Cosslett AG. A review of stability issues associated with vitamins in parenteral nutrition. e-SPEN J. 2014;9:e49–53.
78. Chessex P, et al. Shielding parenteral nutrition from light improves survival rate in premature infants. J Parenter Enteral Nutr. 2017;41(3):378–83.
79. Lavoie JC, Chessex P. Parenteral nutrition and oxidant stress in the newborn: a narrative review. Free Radic Biol Med. 2019;142:155–67.

80. Robinson DT, et al. ASPEN position paper: recommendations for photoprotection of parenteral nutrition. Nutr Clin Pract. 2021;36(5):927–41.
81. Pharmacovigilence Risk Assessment Committee (PRAC). New product information wording—extracts from PRAC recommendations on signals. Amsterdam: European Medicines Agency Publication; 2019. https://www.ema.europa.eu/en/documents/other/new-product-information-wording-extracts-prac-recommendations-signals-adopted-8-11-july-2019-prac_en.pdf.
82. Parenteral nutrition products:light protection required to reduce the risk of serious adverse effects in premature neonates. www.mhra.gov.uk/2019.
83. Worthington P, et al. Update on the use of filters for parenteral nutrition: an ASPEN position paper. Nutr Clin Pract. 2021;36(1):29–39.
84. Puntis J, Hojsak I, Ksiazyk J, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: organisational aspects. Clin Nutr. 2018;37(6 Pt B):2392–400.
85. Bethune K, et al. Use of filters during the preparation and use of PN: position paper from BPNG. Nutrition. 2001;17:403–8.
86. Ball PB. Intravenous in-line filters: filtering the evidence. Curr Opin Clin Nutr Metab Care. 2003;6:319–25.
87. Guenter P, et al. Standardized competencies for parenteral nutrition administration: the ASPEN Model. Nutr Clin Pract. 2018;33:295–304.

Designing Parenteral and Enteral Regimens

Nicola Vernon, Beth Rye, and Jeremy M.D. Nightingale

Key Points

1. Enteral nutrition (EN) feeding alone is used when there is a functional and accessible gastrointestinal tract.
2. Parenteral nutrition (PN) is used when there is a non-functioning or short gut, inaccessible, inadequate, or unsafe EN route.
3. A patient's nutrient (including fluid) requirements start with understanding their current anatomy and physiology.
4. Assessing the macronutrient requirements starts with calculating the total energy needed, then determining the protein component and then dividing the remaining energy between carbohydrate and lipid.
5. The total volume of water and amount of electrolytes (sodium, potassium, calcium, magnesium, phosphate and chloride) needed is determined by firstly calculating their baseline requirements, with additions made for any gastrointestinal losses, for example from vomiting, stool, stoma or fistulas.
6. After macronutrient, fluid and electrolyte needs have been assessed the vitamin and mineral requirements are calculated.
7. Both EN and PN requirements involve also considering a patient's; oral intake, degree of gastro-intestinal absorption and losses (e.g., from stoma/fistula).
8. The initial requirements provide guidance for the primary EN and PN regimen, with it being essential to undertake careful monitoring until a stable regimen has been established.
9. Over-time, the requirements and subsequent EN/PN regimen may change as the clinical needs of a patient changes or adaptation of the gastrointestinal tract occurs.
10. In addition to a patient's nutrient requirements, it is also important, when designing a EN and PN regimen, to consider a patient's personal wishes and quality of life.

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Introduction

Wide ranges of enteral nutrition (EN) and parenteral nutrition (PN) regimens are required for different types of patients with intestinal failure. The patients range from the premature newborn infants with necrotizing enterocolitis to adults with a short bowel, and from those requiring short-term nutritional support in hospital to long-term support at home. The regimens must be of proven efficacy and based on an understanding of nutrient requirements in the different groups of patients.

In general, the gut is used for EN if it is accessible and functional. These requirements are usually less complex than those for PN, as the components given are essentially the requirements based upon current/desired growth or weight. The nutritional and fluid requirements for patients needing PN are very variable, largely because these patients continue to eat and absorb some nutrition from their gastrointestinal (GI) tract. In addition, they may have large fluid losses from one or more stomas or fistulas. It is relatively unusual for a patient to depend totally upon parenteral nutrition for their nutritional requirements, unless they have a bowel obstruction, a gastric/duodenal stoma/fistula or severe dysmotility.

This chapter considers how requirements vary with clinical state in both adults and children, including neonates. The nutrient requirements of growing children vary with age, but recommendations at any specified age are based on extrapolations from other age groups. Enteral feeds come from the manufacturers already compounded

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with all the components, including vitamins, minerals and trace elements added, while parenteral feeding bags are generally compounded specifically for an individual patient (bespoke), where most of the components need to be specified. Although increasingly patients are being given ready-made ("off the shelf") multi-chamber PN bags, that are especially useful if there is a problem with compounding and during a pandemic. Greatest emphasis will be given to the design of a PN regimen, which is covered before an enteral regimen. It will show how patients are established, then stabilised on a regimen and how this is adjusted with time.

Parenteral Nutrition Regimens

After an assessment has been performed (Table 1), there need to be clear objectives for when PN is begun (e.g. treat dehydration/undernutrition, reduce diarrhoea, reduce obstructive symptoms, improve nutritional status for surgery etc) and criteria for stopping (e.g. oral intake resumed, surgical resolution, adaptation has occurred, unethical etc). It is important that when patients commence PN, that they are managed by a multidisciplinary nutrition support team consisting at least of a clinician, dietitian, specialist nurse and pharmacist [1].

Table 1 Assessment prior to starting nutritional support

1. Underlying illness and co-morbidities
2. Gastrointestinal anatomy (e.g. length of small bowel, fistula(s) etc)
3. Fluid status (e.g. gut losses, oral/intravenous intake, urine output etc)
4. Nutritional status (Body mass index (BMI), percentage weight loss, mid arm muscle circumference) and current oral/enteral intake
5. Outcome targets
6. Growth in children

Table 2 How to work out an adult parenteral regimen

1 Calculate total energy using appropriate kcal per kg body weight; will need to factor in age, BMI and clinical condition. Add additional physical activity level as appropriate
2 Calculate amino acid requirement by firstly calculating the protein requirement; 0.8–2 g/kg/day, then divide by 6.25 g to calculate nitrogen. Add repletion if appropriate (0.1 gN per kg weight lost)
3 Calculate amino acid energy: gN × 27
4 Calculate maximum amount of fat allowed (1.5 g fat/kg)[a]
5 Calculate carbohydrate energy as: Total energy − (fat energy + amino acid energy)
6 Calculate fat: carbohydrate calorie ratio and ensure it is about 40:60
7 Check safety of derived glucose, amino acid and lipid infusion rates
8 Calculate/estimate volumes of water, sodium, potassium, magnesium, calcium and phosphate

[a] Many nutrition units divide the non-amino acid energy by 2 to give a fat: CHO energy ratio of 50:50. The exact ratio then is varied so that all the contents of a commercial lipid container are used in the feeding bag

The Overall PN Regimen

PN requirements are based upon a careful assessment, which if the patient is eating will involve an estimate of how much total fluid/nutrition is being absorbed and lost in secretions. Whilst the initial regimen will be relatively standardised for the hospital, the regimen and subsequent prescription at home will be designed around not only the patient's nutritional needs but also their wishes and preferences (e.g. nights off feed, duration/timing of feed, frequency of lipid, desired weight, frequency of deliveries etc.), to allow an adequate quality of life.

Anatomical Considerations

If the gut is short (includes an entero-cutaneous fistula that drains all gut contents) but has normal function, then the long-term type of nutritional/fluid support can be predicted from a knowledge of the small intestinal length in circuit and the presence or absence of a colon in continuity. With time (up to 3 years), patients with a colon in continuity are likely to have a degree of anatomical (villus hypertrophy) and functional adaptation (slowing transit and improvement in some biochemical pathways) so that less PN support is needed. This is not the case for patients with a jejunostomy whose nutritional/fluid requirements change little with time [2].

Initial Stabilisation of PN Regimen in Hospital

The formulation of a PN regimen is a stepwise approach aiming to optimise a patients nutritional and hydration status. The stepwise reasoning behind the design attempts to provide enough macronutrients to maintain or improve nutritional status, enough nitrogen to optimise tissue nitrogen deposition, alongside the fluid, electrolyte, and micronutrient (vitamin/mineral) needs of the patient (Table 2). This is whilst dealing with the constraints such as volume restrictions for PN stability and/or maximum safe doses of macronutrients (for example by compromising on the less critical carbohydrate: fat ratio), and/or maximum and safe doses of the infusion of electrolytes.

Energy: Adults

Energy is administered in parenteral admixtures containing macronutrients with different energy densities: carbohydrates (CHO) (~3.75 kcal/g glucose), fats (9.4 kcal/g), and

amino acids (~27 kcal/g nitrogen). To know the quantity of each of these to provide in a PN (or EN regimen), it is firstly important to ascertain what a patients total energy expenditure (TEE) and thus overall energy requirements are.

Whilst total energy intake (EI), can be readily calculated from the intake of individual macronutrients with known energy densities, TEE over a prolonged period of time, can only be accurately and directly calculated by continuous 24-h calorimetry or tracer techniques such as the gold standard method of doubly labelled water [3]. As this is often not realistic in clinical practice, more often, TEE is calculated by adding together the perceived components of TEE (Table 3). In sick patients a period of negative energy balance, particularly over a prolonged period of time, depletes the body of glycogen, fat and protein. This negative energy balance can be corrected by administering more energy than TEE. In general, about 0.2 g of tissue are accreted for every kcal deposited under anabolic conditions.

Previously predictive equations were used to estimate basal metabolic rate (BMR) such as Harris and Benedict 1919 [4], Schofield 1985 [5] and Henry 2005 [6], with additional factors for metabolic stress, DIT and physical activity added as appropriate [7] to subsequently estimate the TEE. However, the latest recommendations for energy calculations are based on firstly using energy values per kilogram of bodyweight or per kilogram of fat free mass, which vary dependent on a patients age, disease state and body mass index, to estimate REE [8] (Table 4). Onto this calculation for estimating REE, is then added a combined factor for DIT and physical activity, also known as a PAL (Table 5), as appropriate. Whilst these calculations for estimating TEE for patients vary dependent on age, disease state and BMI, the TEE commonly falls within the range 20–35 kcal/kg/day [9, 10, 12], and rarely more than 40 kcal/kg/day [13].

Care should be taken not to provide excess energy as occurred in the 1970/80 s and which resulted in hyperglycaemia, liver function test abnormalities and high rates of infection. With often requirements being adjusted to promote weight gain in those under nourished (BMI <18 kg/m^2) and to avoid over feeding in obesity (BMI >30 kg/m^2) (Table 4). Particularly in the obese population, regular anthropometry is important to monitor changes in body composition and prevent rapid muscle loss.

Table 3 Components of total energy expenditure

1 Resting energy expenditure (REE) (which is basal metabolic rate (BMR) ± metabolic stress)
2 Diet induced thermogenesis (DIT)
3 Physical activity

Table 4 Guidelines for estimating resting energy expenditure [8–11]

BMI <18.5 kg/m^2	25–30 kcal/kg
BMI 18.5–30 kg/m^2	20–25 kcal/kg
BMI >30 kg/m^2	Mifflin St-Jeor (MSJ) Equation: Men: 10 × weight (kg) + 6.25 × height (cm) × (age) +5 Women: 10 × weight (kg) + 6.25 × height (cm) × (age) − 161

Table 5 Combined diet induced thermogenesis and physical activity level (PAL) [8]

Description	PAL
In bed and immobile	1.00–1.10
In bed and/or sitting out	1.10–1.20
Limited mobility	1.2–1.25
Sedentary	1.25–1.40

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Once the overall energy requirements (TEE) have been calculated, this total is split between the two main energy sources in parenteral nutrition: carbohydrate and lipid. Whilst the ratio of glucose to lipid starts at 50:50 (or 60:40) at first, this ratio is not critical and varies between centres. Within the first month the glucose to lipid ratio is reduced to approximately 70–85% from glucose and 15–30% from lipid, and particularly if the patient is for long term HPN [12]. However, if a central line catheter tip becomes high (in SVC or brachiocephalic vein) and replacement is not an immediate option the feed may be adjusted to have a much lower osmolality (to reduce the risk of venous thrombosis) by relying on a high lipid, low glucose content.

Other clinical factors to consider when calculating a patient's estimated energy requirements are:

- **Basal Metabolic Rate (BMR):** BMR is classically measured in relaxed, motionless subjects after an overnight fast in thermoneutral ambient conditions. Its most important determinant is the size of the lean body mass. Equations that estimate BMR from body weight and height are popular and have been established from measurements of BMR in large numbers of healthy volunteers. These equations include the Roberston-Reid [14], Fleish [15] and Harris-Benedict [4] equations, which have been found to overestimate BMR of healthy volunteers by a mean of 0%, +2.5% and + 4.1% respectively [16]. However, these equations do not necessarily apply to patients with disease (e.g. sepsis which frequently accompanies intestinal failure (IF)), undernutrition, or disturbances in hydration (e.g. oedema).
- **Stress factor**: sepsis increases BMR by 5–40% [17, 18], fever raises BMR by approximately 13% per °C rise in body temperature [7]. Intestinal irradiation, chemotherapy, bowel infarction and major surgery also raise BMR (0–30%).

- **Physical activity**: intestinal failure (IF) patients, who are bed-bound or mechanically ventilated and minimally active, have an estimated physical activity component of about 10% of BMR. In contrast, ambulant adult IF patients receiving cyclic nocturnal PN at home have been reported to have a physical activity component of about 30% of BMR [19]. Similar, if not higher, values occur in children.
- **Growth/repletion**: additional energy is required for tissue repletion or for normal growth in children (about 5 kcal/g of tissue deposited [20]). A positive energy balance (EI > TEE) of about 500 kcal/day in adults can achieve slow weight gain, but faster repletion can be achieved with higher intakes.
- **Diet-induced thermogenesis**: enteral or parenteral feeding induces a rise in energy expenditure that is proportional to the EI (DIT approximates to 10% of the metabolizable EI) [19–21].
- **Malabsorption:** in patients with intestinal failure enteral tube feeding may be poorly tolerated and the absorption is poor (50% or more of the energy may not be absorbed), so that nutrients may have to be given in increased amounts and often continuously. Oral and enteral intake is taken into account with an estimate of a malabsorption factor. In patients with a short bowel and jejunostomy at 100 cm from the duodeno-jejunal flexure approximately 40% of the oral diet is absorbed and at 50 cm only 20% [22].

Carbohydrate: Adults

Fructose, xylitol, sorbitol and glycerol all have their potential merits as carbohydrates in PN but glucose (e.g. dextrose monohydrate at 3.4 kcal/g) is both popular and most widely available. Calorimetric studies by King et al. [23]. have shown that infusing dextrose (as the sole non-protein energy source) at approximately 7 g/kg/day will produce a non-protein respiratory quotient (npRQ) of approximately 1.0 in patients with mild metabolic stress. At this point, fat oxidation gives way completely to oxidation of glucose. With more rapid glucose infusions, up to about 30% of the extra glucose infused will be diverted into synthesis of new fat, a process that dissipates a large amount of the extra energy infused. In severely stressed patients with intestinal failure (e.g. peritonitis, post-radiotherapy enteritis) net fat oxidation (npRQ <1) is likely to persist despite glucose infusions [24]. As a result, such high rates of glucose infusion should normally be avoided.

Glucose requirements can be set at 3–6 g/kg/day [12]; being aware that excess glucose provision can cause problems particularly with causing hyperglycaemia or abnormal liver function tests. Glucose oxidation rate can be calculated (4–7 mg × kg × 60 × 24/1000 × 4) to give an indication of the maximum amount of glucose that can be utilized per 24 h. However, it is possible to exceed these requirements in malnourished patients requiring weight gain.

Glucose-only regimens are often discouraged initially because they are often associated with higher volumes and osmolalities, result in higher rates of carbon dioxide production (a possible clinical disadvantage in pulmonary disease), and they are more likely to produce hyperosmolar complications and essential fatty acid deficiency, than those that contain fat.

Lipid: Adults

Adult fat infusions are increased cautiously to a dose that does not usually exceed 1.5 g fat/kg/day or 0.15 g fat/kg/h and aims to provide no more than 50% of the non-nitrogen energy needed. During cyclic PN, gross lipaemia at 6 h after ending the infusion indicates the need to reduce the dose of lipid administered since continuation may lead to impaired reticuloendothelial and immune function and impaired gas diffusion across the lung. During continuous lipid infusions, plasma triglycerides are typically kept below 400 mg/dL. 20% lipid emulsions may be preferable to 10% lipid emulsions because of their lower phospholipid:triglyceride ratio, which is associated with less inhibition by phospholipid lysosomes of the clearance of infused triglycerides from plasma.

The infusion of a minimum of 0.5 g fat/kg/day will prevent essential fatty acid (EFA) deficiency, which can develop rapidly on continuous glucose-amino acid infusions in the absence of lipid. Conversion of infused fatty acids to longer polyunsaturated fatty acids (PUFA), which are necessary for brain development, is slow in infants. Since PUFA are not available for intravenous use, they are given enterally if tolerated.

During the preparation of fat emulsions for intravenous use, soya-bean oil or coconut oil are fractionated yielding long-chain triglycerides (LCT) (14–24 carbon atoms) or medium-chain triglycerides (MCT) (6–12 carbon atoms) [24], emulsified by addition of phosphatidyl-choline and rendered isosmolar to plasma by the addition of glycerol. While there are many advantages of giving lipid, it is not considered appropriate to give it with no glucose, partly because some tissues have a particular preference or need for glucose (leucocytes, repairing tissues, brain), and partly because lean tissue is more rapidly accreted in the presence of glucose. In addition, large doses of parenteral lipids can have detrimental effects.

Most patients are provided with lipid, in particular in those patients with little enteral intake. Long-term intravenous lipid provision is kept below 1 g/kg/day (i.e. 500 mL 20% intralipid provides 1000 kcal, approximately 100 g lipid) as above this chronic cholestasis is common [25]. A 20% soya-based lipid emulsion given once weekly is adequate to prevent essential fatty acid deficiency. If a patient is having no lipid and has a dry skin they can apply 10 mL sunflower or safflower oil to their skin daily [26, 27].

Medium-Chain Triglycerides

Compared to LCTs, MCTs are more soluble in phospholipid, and are present in higher concentrations on the surface of fat droplets, which makes them more accessible to tissue lipases. Their greater tissue availability is complemented by their ability to cross the hepatocyte mito-chondrial membrane independently of carnitine [27]. Therefore, MCT are cleared more rapidly from plasma, and are oxidized more rapidly than LCT. They are also alleged to cause less depression of immune function [28] and to be more effective in sparing protein in the catabolic patient. Their energy density (8.3 kcal/g) is only slightly lower than that of LCT (9.4 kcal/g). Since MCT do not contain essential n3- and n6-fatty acids (EFAs), commercial preparations are only available as a 50:50 MCT/LCT admixtures. Their use might be considered in the following situations:

- *Patients with PN-associated liver dysfunction*; Balderman et al. [29] found that PN-associated rises in transaminases, liver size and liver density occurred less frequently with MCT/LCT infusions than with LCT infusions alone.
- *Patients at risk of infusional hyperlipidaemia;* the half-life of infused MCT is only about half that of LCT. The faster clearance of MCT droplets may be due to their smaller size and less inhibition of lipoprotein lipase (LPL) by fatty acids released during their hydrolysis, and their metabolism by different biochemical pathways (see above).

Nitrogen: Adults

RIV for total amino acids (AA) have been largely based on nitrogen (N) balances, and RIV for specific amino acids on additional measurements of circulating and tissue concentrations. The doses of amino acids, which yield approximately 27 kcal/g nitrogen, required to meet patient requirements [30] can be calculated (Table 6). Many patients with intestinal failure will be nutritionally depleted through malabsorption or protein-losing enteropathy, and they may require extra nitrogen (up to 0.1 g nitrogen/kg/day) to replete the protein losses. The nitrogen is more likely to be retained in depleted patients than non-depleted patients in energy balance. Furthermore, approximately 1–2 mg nitrogen is retained per kcal of energy administered in excess of energy expenditure in non-stressed patients, and possibly more in depleted patients. In metabolically stressed patients, nitrogen losses may exceed 20 g/day, and positive balances are difficult to achieve, even with increased energy and nitrogen intake [31]. Large nitrogen losses are documented in sepsis, major trauma and burns. An unstressed patient with normal organ function will require 0.14 g–0.2 g nitrogen/kg/day [32]. If a patient has a low muscle mass and requires more nitrogen 0.3 g–0.6 nitrogen/kg/day may be used [33].

It has been customary in some countries, including the UK, not to include nitrogen energy (usually 200–300 kcal) in the quoted total energy in a PN regimen (unlike with enteral nutrition where the total energy quoted includes the nitrogen energy).

Table 6 Approximate recommended intakes of intravenous amino acids [8, 9, 30]

Metabolic stress	Example	Nitrogen (g/kg/day)[a]
Nil	Healed extensive intestinal resection	0.128–0.16
Mild	Mild Crohn's disease in small intestinal remnant	0.192
Moderate	Crohn's fistula with abscess	0.24
Severe	Intestinal failure associated with acute pancreatitis or severe infection	0.32
In obese patients: BMI >30 kg/m^2: use 75% of the value estimated from actual weight BMI >50 kg/m^2: use 65% of the value estimated from actual weight		

[a]One gram of nitrogen is equivalent to approximately 7.33 g of intravenous amino acids or 6.25 g of oral protein. Give extra 0.1 g N per kg of body weight lost. One mole of amino acid (typically ~110 g) contains one mole of water (18 g) derived from the hydrolysis of protein

Specific Amino Acids

Most commercial parenteral nutrition solutions lack glutamine because of concerns about its instability (spontaneous degradation to ammonia and pyroglutamic acid). However, free glutamine can be added to PN solutions shortly before use. The alternative is to use a stable dipeptide (e.g. alanyl-L-glutamine). Glutamine is a non-essential amino acid that acts as a carbon and nitrogen carrier, e.g. between skeletal muscle, which produces glutamine, and the small intestine, which utilizes it. Glutamine is an important oxidative fuel for the enterocyte, an essential precursor for nucleotide synthesis [34], which is necessary during rapid cell division (especially epithelial and immune cells) and a regulator of acid base balance. In rats, glutamine-enriched PN has been reported to reduce intestinal villus damage after 5-fluorouracil (5-FU) administration [35], minimize intestinal disuse-atrophy [36] and restore mucosal integrity associated with experimental endotoxaemia [37]. In man, although intravenous glutamine supplementation may improve postoperative nitrogen balance, [38] beneficial effects on mucosal growth and absorption are not proven [39, 40] or are limited to case studies [41]. However, PN regimens enriched with glutamine have been reported to improve nitrogen balance and reduce hospital stay in patients undergoing bone marrow transplantation and major colonic surgery [42, 43]. Other amino acids, which have putative benefits, but which have not always been present in PN solutions include arginine, which may be an important immuno-nutrient, and taurine, which may act as an oxidant scavenger during persistent inflammation.

Energy and Nitrogen: Children

Pre-term infants when starting PN, are often started on 6–10 mg dextrose/kg/min, whilst monitoring glucose tolerance, which usually improves with post-natal age. Newborn infants are at risk of developing tissue carnitine deficiency, and infants of low gestational age are at an even greater risk [44]. MCT may be used in such patients because they enter the mitochondrion in a carnitine-independent fashion, where they are oxidized to ketone bodies. Hyperketonaemia, which may have detrimental effects, is prevented by concomitant administration of LCT and/or glucose. MCT have a lower affinity for plasma albumin. This property, together with their faster clearance from plasma, makes them less prone to displace bilirubin from its binding sites on albumin. This minimizes the danger of brain damage by free bilirubin, which crosses the blood–brain barrier. In newborn infants an initial, continuous, separate, infusion of less than 1 g fat/kg/day is slowly increased to a maximum of 3 g fat/kg/day. Higher infusion rates are more likely to have adverse consequences including impaired pulmonary gas exchange, and possibly reduced host defense against bacteraemia (a common accompaniment of necrotizing enterocolitis) [45].

An infant tolerating 7 mg/kg/min of intravenous dextrose can be started cautiously on a paediatric amino acid solution (PAA) increasing to a maximum of 0.34 g N (approximately 2.5 g AA/kg/day) while monitoring serum ammonia and urea levels. Modern PAA contain an amino acid mixture that aims to establish a circulating amino acid profile that is similar to that of healthy breast-fed term infants (or to that of umbilical cord-blood in pre-term infants) [46]. However, this cannot always be achieved because some amino acids are unstable, too acidic, or potentially toxic. Furthermore, several solutions contain a variety of 'non-essential' amino acids that may become conditionally essential during the metabolic demands of refeeding. The following are examples: arginine, because its synthesis may not meet the demands of the urea cycle, and because of possible immune-enhancing properties; cysteine, because of absence of cystathionase in fetal liver; and taurine [47], because low circulating concentrations are observed in infants receiving long-term PN. The low taurine concentrations may result from the loss of taurine-conjugated bile salts in patients without a functioning terminal ileum or due to an inadequate supply of its precursor (cysteine) in PN admixtures. Therefore, it is recommended that these amino acids are included in neonatal PN solutions.

Fluid and Electrolytes: Adults

Typical daily intakes of water, sodium, and potassium in adult patients without abnormal gastrointestinal fluid losses are about 2.5–3.0 L, 90 mmol and 80 mmol respectively. However, changes in the underlying condition of the patient, particularly large variations in the loss of gastrointestinal effluents, will affect these requirements. Patients with intestinal failure may have variable losses of fluids and electrolytes from stool, stoma, or fistulae. A clinical guide to the additional quantities of electrolytes that need to be replaced can be established from the composition of different intestinal effluents (chapter "Normal Intestinal Anatomy and Physiology"), with patients with an end-jejunostomy having the highest losses of water, sodium, and divalent cations. Overall, in patients with intestinal failure, it is important to replace these losses, especially where there are large fluid outputs.

For the initial regimen, baseline fluid and electrolyte requirements are calculated (Tables 7 and 8), with the standard ranges initially assuming normal organ function and no intestinal losses. Depending on the clinical situation, intestinal anatomy and subsequent gastrointestinal losses of the patient, additional fluid, sodium, potassium, and magnesium may be required. Table 9 provides some indication of the amount of electrolytes lost in different gastrointestinal secretions, to guide the increased amount required. However, when using these requirements as a baseline, it is also important to consider the clinical situation of the patient. Examples of this include; whilst each litre of most effluents contains about 100 mmol of sodium, acute disease may reduce the capacity of the kidneys to excrete a sodium and water load, predisposing to dilutional hyponatraemia and refeeding oedema. Potassium and magnesium depletion will aggravate renal water handling, while protein-losing enteropathy will produce further sodium retention through hyperaldosteronism. PN regimens should also consider potassium losses from gastrointestinal effluents, renal losses due to diuretics or amphotericin [49], glucose-induced entry of the ion into cells, and deposition into lean tissue such as muscle (approximately 3 mEq of K+ per gram nitrogen deposited) [50].

Furthermore, it is also important to consider, when calculating electrolyte requirements that renal calcium reabsorption is lower during PN induced diuresis [51] and may also be influenced by poor vitamin D status resulting from malabsorp-

Table 7 Estimation of fluid requirements before GI losses considered [48]

18–60 years old	35 mL/kg body weight
>60 years old	30 mL/kg body weight
Pyrexia	Add 2–2.5 mL/kg for each °C body temperature is above 37 °C

Table 8 Estimation of electrolyte requirements before GI losses considered [8]

Sodium	1–1.5 mmol/kg
Potassium	1–1.5 mmol/kg
Magnesium	0.1–0.2 mmol/kg
Calcium	0.1–0.15 mmol/kg
Phosphate	0.5–0.7 mmol/kg or 10 mmol/1000 Kcal
Chloride	1–1.5 mmol/kg

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tion, which is associated with low intestinal levels of calcium-binding proteins [52]. It has long been known that the plasma phosphate concentration can drop precipitously during refeeding, especially with glucose (no fat) regimens, due to intracellular shifts, which partly result in the formation of intracellular high energy phosphate bonds. Lastly it is important to consider that chronic intestinal losses of divalent cations are worsened by the presence of fat in the diet [53], and are not reversed by octreotide [54] or omeprazole [55].

As medical and dietary therapy is maximised, (e.g. for high output jejunostomy—restricting oral hypotonic fluid restriction, sipping an oral glucose-saline solution and taking anti-diarrhea and anti-secretory drugs) and/or adaptation of the GI tract occurs over time, losses will reduce. Consequentially, the fluid and electrolyte requirements may need to be recalculated and subsequent adjustments to the content of the PN regimen undertaken.

Micronutrients: Vitamins and Trace Elements

The reference intake value (RIV) for vitamins have been largely based on studies of oral intake, with additional increments for disease and repletion of stores. The recommendations are also based on measurements of vitamin status and on losses during preparation, storage and administration of PN admixtures (e.g. photo-degradation of vitamin A, oxidation of vitamin C), thus the RIV of vitamins for PN is often higher than that for EN (Tables 10 (adult) and 11 (children)).

Table 9 Approximate daily volume and composition of intestinal Secretions produced in response to food (from chapter "Normal Intestinal Anatomy and Physiology")

	Volume (L)	pH	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)	HCO_3^- (mmol/L)	Mg^{2+} (mmol/L)	Ca^{2+} (mmol/L)
Saliva	0.5	7	45	20	44	60	0.7	1.3
Gastric juice	2.0	2	10	10	130	0	0.5	2.0
Pancreatic juice	0.6	8	140	10	30	0	0.2	0.3
Hepatic bile	0.9	7	145	5	100	28	0.6	2.5
Small bowel secretion	1.8[a]	7	138	6	141	<5	<0.1	2.5
Serum		7.4	140	4	100	24	1.0	2.4
Jejunostomy fluid		6	100	15	–	–	4.2	16.1

[a] This fluid is released and absorbed on the mucosa and rarely needs to be taken into account in calculating fluid losses, estimates of its electrolyte composition are unreliable

Table 10 Adult recommended vitamin intakes in enteral and parenteral regimens[a]

	Enteral adult (b) dose/day	Parenteral adult (c) dose/day	Comments
Vitamin A µg (retinol equivalents)	700	3300 IU	Increased losses in steatorrhoea, high losses in nephrotic syndrome, low storage in liver disease; enteral requirement in IF patients typically 3000–15,000 µg/day [56]
Vitamin D (cholecalciferol) µg	0–10	5	Increased losses in steatorrhoea, routine PN supplementation may induce hypercalcaemia and osteomalacia [56]; adult recommendations assume adequate sunlight exposure; IF patients need typically 4000 µg/day by enteral route
Vitamin E (alpha-tocopherol) µg[a]	>4000	10,000–50,000	Requirements depend on iv or enteral intake of PUFA, selenium supplementation decreases requirements; enteral requirements of IF patients typically 34,000 µg/day [56]
Vitamin K µg[d]	1 µg/kg/day	10 mg menadione/week	Increased losses in steatorrhoea, increased requirements in neonatal period and during broad spectrum antibiotic treatment
Vitamin B_1 (thiamine) µg	900 (males) 800 (females)	1200–5000	Increased requirements during high carbohydrate intake
Vitamin B_2 (riboflavine) µg	1300 (males) 1100 (females)	3600	Contribution by colonic bacteria unquantified, accelerated flavoprotein breakdown in catabolic patients interferes with assessment of requirements
Niacin µg	6600 µg (NE) per 1000 kcal	40,000	Low intakes of tryptophan, pyridoxine or riboflavine may increase requirements
Vitamin B_6 (pyridoxine) µg	1400 (males) 1200 (females) or 15 µg/g protein	4000	Malabsorbed in diseased/bypassed small intestine, requirements related to total amino acid metabolism (co-factor in transaminases, decarboxylases, etc)
Vitamin B_{12} (cobalamin) µg	1.5	3	Malabsorbed in ileal resection or bypass, utilised by small intestinal bacteria which reduce its bioavailability
Folic acid µg	200	400	Sulfasalazine reduces absorption, alcoholism increases requirements
Vitamin C (ascorbic acid) µg	40,000	100,000	Enteral administration further increases risk of oxalate stones in SBS—colon patients. Critically-ill patients probably need 500,000 µg/day iv
Panthotenic acid µg[d]	3000–7000	15,000	
Biotin µg[d]	10–200	60	Bioavailability of biotin synthesised by colonic bacteria unknown

a Amounts not adjusted for absorption or excess loss of nutrient
[b] Amounts based on oral Reference Nutrient intakes ([d] or safe intake) [57]
[c] Refers to patients without excess gastrointestinal loss [56, 58, 59]

Table 11 Child recommended vitamin intakes in enteral and parenteral regimens[a]

	Enteral	Enteral	Parenteral	Parenteral	
	dose/day Preterm (b, c) dose/kg/day	Term (d) dose/day	Dose/day Preterm (e) dose/kg/day	Term (e) dose/kg/day	Comments
Vitamin A μg (retinol equivalents)	99–248	350	500	700	Preterm infant invariably depleted at birth. PN-related toxicity reported in infants at doses above 1300 μg/day
Vitamin D (cholecalciferol) μg	Up to 5.0	8.5	4	10	Concentration in preterm formulas should not exceed 3 μg/100 kcal
Vitamin E (alpha-tocopherol)[a] μg	At least 660	400 μg/g PUFA	2800	7000	Preterm formulas should contain at least 0.9 mg/g PUFA. Large iv doses induced liver failure in preterm infants
Vitamin K μg[f]	Nil	10	80	200	Phytoquinolone recommended. Synthetic water-soluble preparation causes dose dependent toxicity. Preterm infants need 0.5–1.0 mg im at birth, then 2–3 μg/kg weekly till breast-fed
Vitamin B_1 (thiamine) μg	22–413	200	350	1200	Supplementation of preterm breast milk (20 μg/100 kcal) only if milk is heat-treated
Vitamin B_2 (riboflavine) μg	66–990	400	150	1400	Renal clearance of excess iv dose reduced in preterm infant
Niacin μg	90–800	3000	6800	17,000	Preterm formulas should contain at least 800 μg/100 kcal
Vitamin B_6 (pyridoxine) μg	39–413	200	180	1.0	Preterm formulas should contain at least 15 μg/g protein and/or 300 μg/100 kcal
Vitamin B_{12} (cobalamin) μg	At least 0.17	0.3	0.3	1000	Marked elevation of serum B_{12} reported in preterm infants receiving 600 μg/kg/day iv
Folic acid μg	At least 66	50	56	140	Red cell folate levels adequate in preterm infants receiving 75 μg/kg/day iv
Vitamin C (ascorbic acid) μg	8300–66,000	25,000	25,000	80,000	Preterm infants need lower doses than term infants to maintain normal plasma ascorbic acid levels (>34 μmol/L)
Panthotenic acid μg[f]	At least 330	1700	2000	5000	Preterm formulas should contain at least 300 μg/100 kcal

[a] Amounts not adjusted for absorption or excess loss of nutrient
[b] Data from ESPGAN 1987 [60]
[C] Data from Lucas 1991 [61]
[d] Amounts based on oral Reference Nutrient intakes ([f] or safe intake) [62]
[e] Data from Greene et al. 1988 [63]

The RIV and subsequent parenteral doses of trace elements have been largely based on those for oral intake, multiplied by a factor for absorption, which varies from <0.1 to 1.0, depending on the trace element. Further adjustments are made to consider losses in GI effluents and measurements of trace element status. For many trace elements, RIV is often much lower in PN than EN (Tables 12 (adult) and 13 (children)). This is because only proportions of trace elements are absorbed via the GI tract. Prolonged excess administration of trace elements can lead to toxicity because the regulatory role of the gut is bypassed (e.g. the gut is the only major site regulating iron status within the body). Toxicity may also occur because of reduced excretion of trace elements in urine (e.g. when there is renal impairment) or in bile (e.g. of manganese when there is liver impairment).

Vitamins and trace elements are included in PN regimens, especially if there is no enteral nutrition or poor GI absorption. However, where ready-made multi-chamber PN bags are used, the infusion of the vitamins and trace elements must be undertaken separately, or an assessment made on if there is adequate access and absorption via the enteral route. The vitamins and trace elements for PN come as commercially ready-made preparations (Tables 14 and 15) which generally provide amounts in excess of basal requirements as they are intended for patients who are nutritionally depleted. Depending on the vitamin and trace element status of the patient and enteral absorption, these preparations can be given daily or on alternate days. Additional supplementation of vitamins and trace elements, particularly iron, vitamin D, and selenium, may be needed in addition to PN if serum levels remain low upon monitoring.

Adjustment of PN Regimen During Hospital Stay and the Final Script for HPN

Often during the hospital stabilisation period, sepsis is treated, and a stoma/fistula output becomes more established, as does the patients oral intake. Fluid balance usually dominates the clinical picture and a stable regimen, particularly regarding establishing the regimens water and electrolytes. Fluid balance, weight, clinical symptoms/sign of

Table 12 Adult recommended mineral and trace element intakes in enteral and parenteral regimens[a]

	Enteral adult (b) dose/day	Parenteral adult (c) dose/day	Comments
Sodium (Na) mmol	70	50–100	Healthy gut absorbs >95%, IF patients may require more than 200 mmol/day. Intestinal losses increase during high enteral intake and decrease during ORS administration
Chloride (Cl) mmol	70	50–100	Healthy gut absorbs >90%, IF patients may need more than 200 mmol/day
Potassium (K) mmol	90	50–100	Suspend K administration if oliguria develops
Calcium (Ca) mmol	17.5	6–10	Healthy gut absorbs up to 40%, IF patients may need up to 120 mmol/day [56] patients with a functioning colon have lower Ca requirements [64]
Phosphorus (P) mmol	17.5	20–40	Healthy gut absorbs 50–60%, IF patients need up to 40 mmol/day
Magnesium (Mg) mmol	12.3	6–12	Healthy gut absorbs up to 75%, for clinical hypomagnesaemia give 17 mmol Mg iv over 30 min before starting TPN: steatorrhoea, nephrotoxic drugs, alcohol increase requirements [65]
Zinc (Zn) µmol	142	38–62	Oral phytate, Ca, Zn reduce absorption, IF patients require 1200 µg (18 µmol) per litre of intestinal effluent, renal losses of Zn increased during amino acid infusions
Copper (Cu) µmol	19	4.7–7.8	Oral phytates, Vitamin C, Cd, Zn reduce absorption, diarrhoeal losses not proportional to effluent volume, increase Cu intake in diarrhoea, reduce intake in liver dysfunction
Chromium (Cr) µmol[d]	0.48	0.19–0.29	Glucose loading increases urinary clearance
Selenium (Se) µmol	0.95	0.51–1.01	High losses in pus + fistula fluids
Manganese (Mn) µmol[d]	25	1.1–1.8	Absorption: adults <4%, neonates up to 50%, >90% excreted in bile
Molybdenum (Mo) µmol[d]	0.52–4.17		Excreted mostly in urine, significant increased losses in short bowel syndrome; 300 µg (3 µmol)/day iv recommended in SBS patients [66]
Iodine (I) µmol	1		PN addition of 1 µg (0.008 µmol)/kg/day recommended only in depleted patients

[a] Amounts not adjusted for absorption or excess loss of nutrient
[b] Amounts based on oral Reference Nutrient intakes ([d] or safe intake) [57]
[c] Refers to patients without excess gastrointestinal losses [56, 58, 59]

dehydration (thirst/dry mouth)/over hydration (oedema, raised JVP) are assessed daily and blood tests (renal and liver function) undertaken as needed (usually 2 or more times a week). A urine output of greater than 1000 mL/24 h with a random urine sodium of 20 mmol/L or more is desirable. The energy given depends upon the oral intake, estimated absorption (which can be better predicted if a bowel length has been measured either at surgery or more commonly radiologically) [71], blood glucose and weight/muscle mass targets (which should increase in hospital). The regimen is adjusted until these are all within desirable ranges and weight/muscle mass is on the appropriate trajectory.

The HPN prescription is formulated towards the end of the patient's hospital admission when they are clinically stable and when they are consuming a similar amount of food and drink each day. Depending upon their nutritional and fluid status they are reviewed in outpatients 1–8 weeks after discharge and subsequently every 3–6 months.

Monitoring and Adjusting the HPN Regimen in Outpatients

During the multi-disciplinary clinic (MDT) visit, a brief clinical examination assessing hydration (postural blood pressure), nutritional status and underlying condition is performed. Weight, mid arm muscle circumference, triceps skinfold thickness is measured so BMI and mid arm muscle mass can be calculated, along with handgrip dynamometry and an oral intake diet history. Blood tests including renal, liver function, along with mineral (especially magnesium), trace elements and vitamins (mainly fat-soluble ones) [10] are taken and a random urine for sodium concentration is collected. Over time intestinal adaptation in patients with a retained colon may reduce the parenteral requirement for fluid, energy, nitrogen, and electrolytes. In addition, it is common for a patient's oral intake to improve at home, and this may result in less PN being needed.

Table 13 Child recommended mineral and trace element intakes in enteral and parenteral regimens[a]

	Enteral preterm (b, c) dose/kg/day	Enteral term (d) dose/day	Parenteral preterm (e, f) dose/kg/day	Parenteral term (f, g) dose/kg/day	Comments
Sodium (Na) mmol	1.3–3	9	3–5	2–4	Beware of hyponatraemia due to high insensible water loss, hypotonic diarrhoea, immature renal tubular Na reabsorption
Chloride (Cl) mmol	1.4–3.2	9	3–5	2–3	Doses of Cl above 6 mmol/kg/day may cause hyperchloraemic acidosis
Potassium (K) mmol	2–5	20	1–2	2–3	Beware of non-oliguric hyperkalaemia due to immature distal tubular secretion of K
Calcium (Ca) mmol	1.9–5.7	13.1	1.5–2.2	0.2–1.2	During low fluid intakes Ca and PO4 in PN should be in a 1:1 molar ratio and should not exceed 15 mmol/l [63]
Phosphorus (P) mmol	1.8–4.8	12.9	1.5–2.2	1–2	
Magnesium (Mg) mmol	0.3–0.8	2.3	0.3–0.4	0.12–0.5	Danger of hypermagnesaemia in renal insufficiency
Zinc (Zn) µmol	9.3–27.9	61	6.1	3.8	PN intakes refer to stable infant [67]; 2–3 times more Zn may be required during diarrhoea
Copper (Cu) µmol	1.6–3.1	3.1	0.32	0.32	PN intakes refer to stable infant [67]; do not administer iv Cu in cholestasis
Chromium (Cr) µmol[h]			0.004	0.004	Do not supplement preterm enteral formulas routinely
Selenium (Se) µmol		0.13	0.025	0.025	Do not supplement preterm enteral formulas routinely
Manganese (Mn) µmol[h]	0.04–0.24	0.3	0.018	0.018	1 µg (0.018 µmol)/kg/day induces positive Mn balance in infants without diarrhoea [67]; withhold iv Mn in cholestasis; monitor Mn status by serum levels [56] and MRI [68]
Molybdenum (Mo) µmol[h]		0.015–0.05	0.003	0.003	Do not add Mo routinely to enteral formulas or short term PN regimens [67]
Iodine (I) µmol	0.09–0.58	0.39	0.008	0.008	Infants absorb extra iodine from topical disinfectants

[a] Amounts not adjusted for absorption or excess loss of nutrient
[b] Data from ESPGAN, 1987 [60]
[c] Data from Lucas, 1991 [61]
[d] Amounts based on oral Reference Nutrient intakes ([h]or safe intake) [62]
[e] Data from Yu, 1992 [69]
[f] Data from Greene et al, 1988 [63]
[g] Data from Poole 1983 [70]

Table 14 Sources of parenteral micronutrients

Trace element	Addaven (µmol/10 mL)	Nutryelt (µmol/10 mL)	Tracutil (µmol/10 mL)
Zinc	77	153	50
Copper	6	4.7	12
Selenium	1.0	0.9	0.3
Iron	20	18	35
Manganese	1	1	10
Chromium	0.2	0.19	0.2
Molybdenum	0.2	0.21	0.1
Iodine	1.0	1.0	1.0
Fluoride	50	50	30

Table 15 Sources of parenteral vitamins

Fat soluble vitamin	Vitlipid adult	Cernevit
Vitamin A (µg)	990	1000
Vitamin E (µg)	9.1	10.2
Vitamin K (µg)	150	–
Vitamin D (µg)	5	5
Water soluble vitamin		
Vitamin B_1 (µg)	3.1	3.5
Vitamin B_2 (µg)	4.9	4.1
Vitamin B_6 (µg)	4.9	5.5
Niacin (µg)	40	46
Folic acid (µg)	400	414
Vitamin B_{12} (µg)	5.0	6.0
Biotin (µg)	60	69
Vitamin C (µg)	11	125

Factors with HPN That May Result in Adjusting the Feeding Regimen

Poor Sleep

Patients are often kept awake at night by the pump noise and/or its bright lights and they may get up 2–3 times during the night to pass urine. These problems can be reduced by having nights free from feed, keeping the feed volume as low as is possible to maintain hydration and running the feed through as fast as is safe. Whilst one of the main aims is to give the feed on as few nights as possible, this can usually be easily done in patients with a colon in continuity but not in patients with a jejunostomy who rapidly become salt and water depleted and need fluid daily. Some patients prefer to feed during the day and may have a backpack containing a pump and the feeding bag.

Cramps

Many complain of cramps during the feed [72]. This may be due to a low sodium concentration feed that is given quickly or due to sodium depletion. In the long-term these can be corrected by increasing the sodium content in the feed, but in the short-term immediate relief can be obtained by taking oral table salt. Magnesium depletion may also contribute.

Thirst

While thirst is most commonly due to water and sodium depletion, it can also be due to high concentrations of sodium in the feed. A low random urinary sodium gives an indication of the cause.

Faint/Nausea When Feed Stops

This can be due to reactive hypoglycaemia and may be avoided if the feed is slowed gradually over the last hour of feeding; also known as ramping the feed.

Unwell After Feeds Containing Lipid

Many patients complain of malaise, joint pains and/or nausea after a lipid feed. It can be given less frequently (e.g. once a week) or occasionally it is omitted altogether. Alternatively, sometimes changing to a different lipid preparation helps.

Frequent Feeding Bag Deliveries (Feed Bag Stability)

If a bag has good stability, it may be delivered every 2 or more weeks. If not, then it may be weekly. Stability is more likely to be a problem if there is lipid in the feed or if the feed is of a very large volume (e.g. 4 l or more).

Enteral Nutrition Regimens

The calculations for energy requirements are the same as for parenteral nutrition, however the nitrogen supplied is quoted in grams of protein. Examples of typical commercial enteral feeds are shown in Table 16. Whilst the composition of the commercial enteral feeds is set and unable to be manipulated, occasionally more sodium chloride (to bring the total sodium concentration to 100 mmol/L) is added to the feed, in patients with high output stomas or fistulae while trying to keep the osmolality near to 280–300 mOsm/kg.

Although early minimal enteral feeding (MEF) (e.g. 200 mL/day in adults) does not contribute significantly to nutrient requirements, it may help to reduce PN-associated intestinal atrophy and minimise trans-intestinal bacterial translocation. The addition of low-dose enteral feeding to intravenously fed rats has been reported to increase nitrogen retention, reduce bacterial translocation [73] and reduce PN-associated increases in macromolecular lactose permeability [74]. MEF increases neonatal gut motility and promotes the release of gut trophic hormones, such as gastrin and enteroglucagon. Enteral feeding has been reported to reverse PN-induced enterocyte atrophy in human volunteers [75] and to preserve intestinal mucosal integrity in PN-fed

Table 16 Composition of typical enteral feeds per 100 g

	Polymeric (ca 1 kcal/mL)[a]	Monomeric (ca 1 kcal/mL)[b]	Elemental (ca 0.75 kcal/mL)
Energy (Kcal)	440	440	364
Fat:CHO:Protein energies (kcal)	38:49:13	38:49:13	17:71:12
CHO (g)	60 (maltodextrin)	59 (maltodextrin)	70
Lactose	0.17	0	0
Protein	13.8 (whey protein)	13.8 (peptides, 86% of MW <1000)	10.0 (as amino acids)
Gluten	Nil	Nil	Nil
Glutamine (g)	Nil	Nil	0.09
Fat (g)	18 (arachis oil)	18 (sunflower + MCT oils)	6.64 (arachis oil)
LCT:MCT	100:1	17:83	100:1
Fibre	Nil	Nil	Nil
Osmolality (mOsm/kg)	269	389	684

[a] IF patients with normal transit time and good pancreatic function may absorb LCT

[b] Moderate osmolality, peptide content, and MCT supplementation are desirable properties in IF patients, fibre supplementation should be considered

critically ill patients [76]. These effects have been ascribed to a variety of nutrients/physicochemical properties of the feed, including its tonicity [77] and the presence of peptides [78], which have higher intestinal transport rates and higher capacity for transport than that for free amino acids [79]. Enteral glutamine has been reported to improve splanchnic blood flow in rats [80] and to reduce small intestinal damage in dogs receiving therapeutic doses of radiation [81]. However, no benefits have been observed in adult human patients suffering from 5-FU-induced mucositis [82].

Carbohydrate that is not absorbed in the small intestine (including fibre present in some enteral feeds) is fermented to short-chain fatty acids, which are subsequently absorbed for further metabolism in human tissues. Such a process can provide a substantial amount of energy (up to 4 MJ/day in a group of patients with IF) [83] and result in improved intestinal adaptation, as in rats with a short bowel [84]. Long chain triglycerides (LCT) have also been reported to improve mucosal height and leucine balance in rats with a short bowel [85]. The theoretical advantages of arginine [86] or nucleotide [87] supplementation merit further clinical evaluation. Exposing the ileal remnant to fat [88] or starch [89] retards gastric emptying (the 'ileal brake') [90] through release of peptide YY [57]. Enteral feeding is also sometimes given to distal defunctioned bowel either to give complete distal feeding or in a small amount as trophic distal feeding (see chapter "Distal Feeding and Hydration").

Neonates requiring PN (e.g. sick pre-term infants, infants recovering from necrotizing enterocolitis) may be gradually started on mother's milk or a pre-term formula, fortified with phosphate and other additives as necessary, aiming to deliver daily 110–165 kcal/kg of energy and 0.46–0.64 g N/kg in protein for pre-term infants, and 115 kcal/kg and ~ 0.29 g N/kg for term infants [61]. When enteral feeds are not tolerated MEF (e.g. 1 mL of infant formula per hour) should be encouraged.

References

1. Nightingale JMD. Nutrition support teams: how they work, are set up and maintained. Frontline Gastroenterol. 2010;1:171–7.
2. Nightingale JMD, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces the need for parenteral therapy, increases the incidence of renal stones but does not change the high prevalence of gallstones in patients with a short bowel. Gut. 1992;33:1493–7.
3. Westerterp KR. Doubly labelled water assessment of energy expenditure principle, practice, and promise. Eur J Appl Physiol. 2017;117:1277–85.
4. Harris JA, Benedict FG. A biometric study of basal metabolism in man. Washington: Carnegie Institute; 1919. Carnegie Institute publication no. 279.
5. Schofield EN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr. 1985;39:5–21.
6. Henry CJK. Basal metabolic rate studies in humans: measurement and development of new equations. Public Health Nutr. 2005;8(7a):1133–52.
7. Weekes E, Soulsby C. Estimating nutritional requirements for adults. In: Todorovic V, Micklewright A, editors. A pocket guide to clinical nutrition. 4th ed. Birmingham: The Parenteral and Enteral Nutriiton Group of the British Dietetic Association; 2011. p. 3.1–3.30.
8. Cope C, Culkin A, Judges D, Mafrici B, Soulsby C, Weekes E. Estimated nutrition requirements for adults. In: Todorovic V, Mafrici B, editors. A pocket guide to clinical nutrition. 5th ed. Birmingham: The Parenteral and Enteral Nutriiton Group of the British Dietetic Association; 2018. p. 3.1–3.98.
9. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and paediatric patients. JPEN J Parent Enteral Nutr. 2002;26(1):1SA–138SA.
10. National Institute of Clinical Excellence (NICE). Nutrition support for adults oral nutrition support, enteral tube feeding and parenteral nutrition. Clinical guideline, vol. 32. London: National Institute of Clinical Excellence (NICE); 2006.
11. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51:241–7.
12. ESPEN. Guidelines on parenteral nutrition: home parenteral nutrition (HPN) in adult patients. Clin Nutr. 2009;28:467–79.
13. Koea JB, Wolfe RR, Shaw JH. Total energy expenditure during total parenteral nutrition: ambulatory patients at home versus patients with sepsis in surgical intensive care. Surgery. 1995;118:54–62.
14. Robertson JD, Reid DD. Standards for the basal metabolism of normal people in Britain. Lancet. 1952;262:940–3.
15. Fleish PA. Le metabolism basal standard et sa determination au moyen du 'Metabocalculator'. Helv Med Acta. 1952;1:23–43.
16. Pullicino E. Aspects of energy metabolism in hospitalised patients. London: CNAA, British Lending Library; 1991. p. 59. Identification Number DX 96679.
17. Bessey PQ, Wilmore DG. In: Kinney JM, Jeejeebhoy KN, Hill G, Owen O, editors. Nutrition and metabolism in patient care. Philadelphia: WB Saunders; 1988. p. 676.
18. Elia M. Artificial nutritional support. In: Badenoch J, editor. Medicine International, vol. 82. Oxon: Medicine Group (UK) Ltd; 1990. p. 3392–6.
19. Pullicino E, Coward A, Elia M. Total energy expenditure measured by the doubly labelled water technique. Metabolism. 1993;42:58–64.
20. Roberts SB, Young VR. Energy costs of fat and protein deposition in the human infant. Am J Clin Nutr. 1988;48:951–5.
21. Pullicino E, Goldberg G, Elia M. Energy expenditure and substrate metabolism measured by 24-hour whole-body calorimetry in patients receiving cyclic and continuous total parenteral nutrition. Clin Sci. 1991;80:571–82.
22. Nightingale JMD, Lennard-Jones JE, Walker ER, Farthing MG. Jejunal efflux in short bowel syndrome. Lancet. 1990;336:765–8.
23. King RFGJ, McMahon MJ, Almond DJ. Evidence for adaptive diet-induced thermogenesis in man during intravenous nutrition with hypertonic glucose. Clin Sci. 1986;71:31–9.
24. Jiang ZJ, Zhang S, Wang X, Yang N, Zhu Y, Wilmore D. A comparison of medium-chain and long-chain triglycerides in surgical patients. Ann Surg. 1993;217:175–84.
25. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med. 2000;132:525–32.
26. Press M, Hartop PJ, Prottey C. Correction of essential fatty-acid deficiency in man by cutaneous application of sunflower-seed oil. Lancet. 1974;2:597–9.

27. Bach AC, Frey A, Lutz O. Clinical and experimental effects of medium-chain triglyceride-based fat emulsion: a review. Clin Nutr. 1989;8:223–35.
28. Sedman PC, Sonners SS, Ramsden CW, Brennan TG, Guillou PJ. Effects of different lipid emulsions on lymphocyte function during total parenteral nutrition. Br J Surg. 1991;78:1396–9.
29. Baldermann H, Wicklmayer M, Rett K, Banholzer P, Dietze G, Mehner H. Untersuchungen zur Veranderung des Sonographiebefundes der Leber unter parenteraler Ehrnahrung mit LCT bzw. MCT/LCT Lipidlozungen. Infus Ther. 1988;15:140–7.
30. Elia M. The effects of nitrogen and energy intake on metabolism of normal, depleted and injured man. Considerations for practical nutritional support. Clin Nutr. 1992;1:173–92.
31. Saffle JR, Medina E, Raymond J, Westenskow D, Kravitz M, Warden G. Use of indirect calorimetry in the nutritional management of the burned patient. J Trauma. 1985;25:32–9.
32. Elia M. Artificial Nutritional Support. Med Int. 1990;82:3392–6.
33. Keys A, Brozek J, Henschel A, et al. The biology of human starvation. Minneapolis, MN: University of Minnesota Press; 1950.
34. Newsholme EA, Carrie AL. Quantitative aspects of glucose and glutamine metabolism by intestinal cells. Gut. 1994;35(suppl 1):S13–7.
35. Bai MX, Jiang ZM, Liu YW, Wang WT, Li DM, Wilmore DW. Effects of alanyl-glutamine on gut barrier function. Nutrition. 1996;12:793–6.
36. Hwang TL, O'Dwyer ST, Smith RJ, Wilmore DW. Preservation of the small bowel mucosa using glutamine-supplemented parenteral nutrition. Surg Forum. 1986;37:56–8.
37. Bai M, Jiang Z, Ma Y. Glutamine-enriched nutritional solutions attenuate bacterial translocation in rats after 60% intestinal resections. Chung Hua I Hsuesh Tsa Chih. 1996;76:116–9.
38. Stehle P, Zander J, Mertes J, Albers S, Puchstein C, Lawin P, Furst P. Effect of parenteral glutamine peptide supplements on muscle glutamine after major surgery. Lancet. 1989;1:231–3.
39. Tremel H, Kienle B, Weilemann S, Stehle P, Furst P. Glutamine dipeptide-supplemented parenteral nutrition maintains intestinal function in the critically ill. Gastroenterology. 1994;107:1595–601.
40. Hornsby-Lewis L, Shike M, Brown P, Pearlstone D, Brennan MF. L-glutamine supplementation in home total parenteral nutrition patients: stability, safety and effects on intestinal absorption. JPEN J Parenter Enter Nutr. 1994;18:268–73.
41. Allen SJ, Pierro A, Cope L, Macleod A, Howard CV. Glutamine supplemented parenteral nutrition in a child with short-bowel syndrome. J Paediatr Gastroenterol Nutr. 1993;17:329–32.
42. Morlion B, Stehle P, Wachtler P, Sichoff HP, Koller M, Furst P, Puchstein C. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study. Ann Surg. 1998;227:302–8.
43. Ziegler TR, Young LS, Benfell K, et al. Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation. A randomized, double blind, controlled study. Ann Intern Med. 1992;116:821–8.
44. Penn D, Ludwig B, Schmidt-Sommerfield E, Pascu F. Effect of nutrition and tissue carnitine concentration in infants of different gestational ages. Biol Neonate. 1985;47:130–5.
45. Lipsky CL, Spear ML. Parenteral nutrition in necrotizing enterocolitis. Clin Perinatol. 1995;22:389–409.
46. Rassin DK. Protein requirements in neonates. In: Lebenthal E, editor. Textbook of gastroenterology and nutrition in infancy. New York: Raven Press; 1989. p. 288.
47. Geggel HS, Ament ME, Heckenlively JR, Diedre A, Martin BS. Nutritional requirements for taurine in patients receiving long-term parenteral nutrition. N Engl J Med. 1985;312:142–6.
48. Tyler DS. Fluid and electrolytes. In: Lyerly HK, editor. The handbook of surgical intensive care. 2nd ed. Chicago: Year Book Medical Publishers; 1989. p. 223–50.
49. Bernardo JF, Murakami S, Branch RA, Sabra R. Potassium depletion potentiates amphotericin B-induced toxicity to renal tubules. Nephron. 1995;70:235–41.
50. Moore F. Energy and the maintenance of the body cell mass. JPEN J Parenter Enteral Nutr. 1980;4:228–60.
51. Lipkin EW, Benedetti TJ, Chait A. Successful pregnancy outcome using total parenteral nutrition from the first trimester of pregnancy. JPEN J Parenter Enter Nutr. 1986;10:665–9.
52. Staun M, Jarnum S. Measurement of 10 000-molecular weight calcium-binding protein in small-intestinal biopsy specimens from patients with malabsorption syndromes. Scand J Gastroenterol. 1988;23:827–32.
53. Ovesen L, Chu R, Howard L. The influence of dietary fat on jejunostomy output in patients with severe short bowel syndrome. Am J Clin Nutr. 1983;38:270–7.
54. Ladefoged K, Christensen KC, Hegnhopj J, Jarnum S. Effect of a long-acting somatostain analogue SMS 201–995 on jejunostomy effluents in patients with severe short bowel syndrome. Gut. 1989;30:943–9.
55. Nightingale JM, Lennard-Jones JE. The short bowel syndrome: what's new and old? Dig Dis. 1993;11:12–31.
56. Jeejeebhoy K. Nutrient requirements and deficiencies in GI diseases. In: Sleisenger S, Fordtran J, editors. Gastrointestinal disease: pathophysiology/diagnosis/management, vol. 2. 5th ed. Philadelphia: WB Saunders; 1993. p. 2017–47.
57. Savage AP, Adrian TE, Carolan G, Chatterjee VK, Bloom SR. Effects of peptide YY (PYY) on mouth to caecum intestinal transit time and on the rate of gastric emptying in healthy volunteers. Gut. 1987;28:166–70.
58. Elia M. Special nutritional problems and the use of enteral and parenteral nutrition. In: Weatherall DJ, Ledingham JGG, Warrel DA, editors. Oxford textbook of medicine. New York: Oxford University Press; 1996. p. 1314–26.
59. Shills M. Parenteral nutrition. In: Shils M, Olson J, Shike M, editors. Modern nutrition in health and disease. 8th ed. Philadelphia: Lea and Feibiger; 1994. p. 1430–58.
60. Committee on Nutrition and Feeding of the Preterm Infant, European Society of Gastroenterology and Nutrition. Nutrition and feeding of the preterm infant. Acta Paediatr Scand. 1987;Suppl 336:3–14.
61. Lucas A. Feeding the pre-term infant. In: Ballabriga A, Brunser O, Dobbing J, Gracey M, Senterre J, editors. Clinical nutrition of the young child, vol. 16. New York: Raven Press; 1991. p. 317–36.
62. Department of Health. Dietary reference values for food energy and nutrients for the United Kingdom, report on health and social subjects No. 41. London: HMSO; 1991.
63. Greene HL, Hambridge MK, Shanler R. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report on the subcommittee on paediatric parenteral nutrient requirements from committee on clinical practice issues of the American society for clinical nutrition. Am J Clin Nutr. 1988;48:1324–42.
64. Grinstead WC, Pak CY, Krejs GJ. Effect of 1,25-dihydroxyvitamin D3 on calcium absorption in the colon of healthy humans. Am J Phys. 1984;247:G189–92.
65. Freeman JB. Magnesium requirements are increased during parenteral nutrition. Surg Forum. 1977;28:61–2.
66. Abumrad NN. Molybdenum: is it an essential trace metal? Bull N Y Acad Med. 1984;60:163–71.
67. Zlotkin S, Atkinson S, Lockitch G. Trace elements in nutrition for premature infants. Clin Perinatol. 1995;22:223–40.
68. Ono J, Harada K, Kodaka R, et al. Manganese deposition in the brain during long term total parenteral nutrition. JPEN J Parenter Enter Nutr. 1995;19(4):311–2.
69. Yu V, Macmahon RA. Intravenous feeding in the preterm neonate. In: Yu V, editor. Intravenous feeding of the neonate. London: Edward Arnold; 1992. p. 240–9.

70. Poole RL. Electrolyte and mineral requirements. In: Kerner JE, editor. Manual of paediatric parenteral nutrition. New York: Wiley; 1983. p. 129–36.
71. Nightingale JMD, Bartram CI, Lennard-Jones JE. Length of residual small bowel after partial resection: correlation between radiographic and surgical measurements. Gastrointest Radiol. 1991;16:305–6.
72. Elphick DA, Baker M, Baxter JP, Nightingale JM, Bowling T, Page KB, McAlindon ME. Muscle cramps are the commonest side effect of home parenteral nutrition. Clin Nutr. 2009;28:351–4.
73. Sax HC, Illig KA, Ryan CK, Hardy DJ. Low dose enteral feeding is beneficial during parenteral nutrition. Am J Surg. 1996;171:587–90.
74. Illig KA, Ryan CK, Hardy DJ, Rhodes J, Locke W, Sax HC. Total parenteral nutrition induced changes in gut mucosal function: atrophy alone is not the issue. Surgery. 1992;112:631–7.
75. Buchman AL, Moukarzel AA, Bhuta S, et al. Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. JPEN J Parenter Enter Nutr. 1995;19:453–60.
76. Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW. Effects of enteral and parenteral nutrition on gut permeability in the critically ill. Am J Respir Crit Care Med. 1995;152:1545–8.
77. Weser E, Babbitt J, Vandeventer A. Relationship between enteral glucose load and adaptive mucosal growth in the small bowel. Dig Dis Sci. 1985;30:675–81.
78. Cosnes J, Evard D, Beaugerie L, Gendre JP, Le Quintrec Y. Improvement in protein absorption with a small-peptide-based diet in patients with high jejunostomy. Nutrition. 1992;8:406–11.
79. Steinhard HJ. Comparison of enteral resorption rates of free amino acids and oligopeptides. Leber Magen Darm. 1984;14:51–6.
80. Houdijk AP, Van Leeuwen PA, Boermeester MA, et al. Glutamine-enriched enteral diet increases splanchnic blood flow in the rat. Am J Phys. 1994;267:G1035–40.
81. Kemberg S, Souba W, Dolson D, Salloum R, Hautamaki R. Prophylactic glutamine protects the intestinal mucosa from radiation to injury. Cancer. 1990;66:62–8.
82. Jebb SA, Osborne RJ, Maugham TS, Mohideen N, Mack P, Shelley MD, Elia M. 5-Fluorouracil and folinic acid-induced mucositis: no effect of oral glutamine supplementation. Br J Cancer. 1994;70:732–5.
83. Nordgard I, Hansen BS, Mortensen PB. Importance of colonic support for energy absorbtion as intestinal failure proceeds. Am J Clin Nutr. 1996;64:221–31.
84. Aghdassi E, Plapler H, Kurian R, et al. Colonic fermentation and nutritional recovery in rats with massive small bowel resection. Gastroenterology. 1994;107:637–42.
85. Vanderhoof JA, Grandjean CJ, Kaufman SS, Burkley KT, Antonson DL. Effect of high percentage Medium chain triglyceride diet on mucosal adaptation following massive bowel resection in rats. JPEN Parenter Enteral Nutr. 1984;8:685–9.
86. Cynober L. Can arginine and ornithine support gut functions? Gut. 1994;35:S42–4.
87. Grimble GK. Dietary nucleotides and gut mucosal defence. Gut. 1994;34:S46–51.
88. Pironi L, Stanghellini V, Miglioli M, et al. Fat-induced ileal break in humans: a dose-dependent phenomenon correlated to the plasma levels of peptide YY. Gastroenterology. 1993;105:733–9.
89. Layer P, Zinsmeister AR, Dimango EP. Effects of decreasing intraluminal amylase activity on Starch digestion and postprandial gastrointestinal function in humans. Gastroenterology. 1986;91:41–8.
90. Spiller RC, Trotman IF, Higgins BE. The ileal brake-inhibition of jejunal motility after ileal fat perfusion in man. Gut. 1984;25:365–74.

Nursing Care of Patients Receiving Home Parenteral Support

Cathy Cawley and Mia Small

Key Points

1. The aim of nursing care of patients receiving home parenteral support (HPS) is for the patient to understand their condition, treatment and potential complications and so feel in control and able to enjoy an acceptable quality of life (QOL).
2. An intravenous catheter with the minimum number of lumens to meet the vascular access needs of the patient should be used so as to reduce the risk of catheter-related complications.
3. A peripherally inserted central catheter (PICC), tunnelled cuffed Hickman™ type catheter or totally implanted port can be used for home parenteral support (HPS).
4. The choice of device should be made between the clinical team and the patient/carer and take into account an assessment of the patient's veins (ultrasound/venography). The catheter/vein ratio should be 45% or less.
5. Catheter manipulations should be kept to a minimum, and an aseptic non-touch technique (ANTT) should be used for all procedures. Key elements of the technique include hand decontamination, not touching key parts, ensuring that sterile items do not come into contact with non sterile ones, and effective disinfection of the needle free connector/catheter hub.
6. Patient discharge on HPS requires a collaborative multidisciplinary approach which covers;
   - Funding
   - Delivery of the prescribed parenteral support
   - The ancillary items required to administer it
   - Who is going to care for the CVC
   - Ongoing support and information about how to obtain advice quickly.

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Introduction

The loss of a major organ's function challenges the integrity of the whole person. Although the primary changes may be physical they have an impact on how the person thinks and feels and this can impact upon future enjoyment of life.

Some patients with intestinal failure (IF) experience only a short illness before complete recovery whereas others such as those with an entero-cutaneous fistula may have longer periods of illness, possibly being left with a stoma an open wound, or in some cases both. A few are left permanently affected requiring long-term enteral and/or parenteral support. All patients require the same level of attention to their needs. Even those who appear to have responded well to treatment and achieved excellent clinical outcomes may be left with disabling fears resulting from their experiences.

Hospital admissions can be prolonged and the external world shrinks to that around the bedside, with the healthcare team, particularly nurses who usually spend most time with the patient, becoming the focus of social contact. Interactions take place while the nurse is giving personal care and treatment. As progress is commonly very slow and the care required exacting, for example changing a fistula appliance, nursing such patients can be physically and emotionally demanding.

Support systems to maintain the well-being of nurses, enabling them cope with the stress resulting from the care of patients with IF need to be built into departmental organization. This can be achieved through strong leadership from an expert clinical nurse, staff development programs, an open environment where feelings can be shared and the clinical governance systems provide a framework for safe, up to date evidence based, low risk practice during hospital care, rehabilitation and ongoing treatment at home. Obtaining and maintaining physiological stability often takes priority over other aspects of care because the physiological consequences of intestinal failure can threaten survival and impair other functions, such as the ability to think clearly, understand and learn.

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This chapter aims to outline the nursing care of patients receiving HPS. It is recognised that the set up and continuation of HPS at home will vary from country to country. Examples from the process in England where there is a national framework agreement for the supply of HPS services are given for reference. Where specific products are mentioned, this is for information only and should not be seen as an endorsement. The chapter will cover the patients' understanding of intestinal failure, equipment used, the procedures to connect and disconnect the HPS, and common problems or complications.

The Patients' Understanding of Intestinal Failure

Some of the features of intestinal failure which may include pain, nausea, diarrhoea, the effects of fistulas, difficult stomas, electrolyte imbalance and undernutrition can undermine the patients' dignity and sense of self-worth. There may be frequent, prolonged hospital admissions and numerous operations, each one being more difficult to face as the patients' experience of perioperative problems increase.

During acute illness feelings of helplessness are common and realistic. There is little the patient can control and events appear as an assault on the body and mind challenging the patients' belief in themselves as autonomous adults. For example, an inability to control the bowel and possibly seeing, and smelling, faeces draining from an abdominal wound may evoke primitive feelings about bowel function and being controlled by others in early life. Open wounds are often in a position where the patient can look into the body and see physical evidence of degeneration.

For the patient who develops chronic IF there is the daunting task of learning how to manage the condition at home, of becoming re-integrated into the family and society, and adapting expectations of daily life to one which may be different from that of other people and from their premorbid life. Until discharge the patient may not have got dressed and the transition from being in a hospital gown to putting on clothes should not be underestimated. The patient has entered an unfamiliar arena where jargon and medical abbreviations are widely, used and the nurse is well placed to provide information in a simple to understand format. It is important that the patient understand their new anatomy, how it has altered, and the length of residual bowel they have.

The patient being discharged on HPS will need to use, and find space for, numerous pieces of medical equipment. The role of the nurse is to help the patient identify where equipment will be stored in the home, alongside facilitating their understanding of the medical devices they now require, for example their central venous catheter, stoma/fistula appliances or enteral tubes.

Central Venous Catheter

Reliable venous access is required for home parenteral support. To reduce irritation to the vein it is given via a central venous catheter (CVC)—CVC or "line"—that has been inserted into a large vein with good blood flow. In most people this will be the superior vena cava. Occasionally, if this vein is not suitable/accessible the inferior vena cava is used. To reduce the risk of thrombosis the catheter tip should be at the vena cava/right atrial junction [1]. Although popular in some countries, the use of an arterio-venous fistula for parenteral support is not widely used.

Ensuring the catheter is accessible to the patient and in a position where it will not be visible when clothing is worn is of equal importance to selecting a device suitable for long-term use. The choice between a PICC, Hickman™ type catheter with an external segment and a totally implanted port should be made following discussions with the patient, although choice of device may be limited to what is available at the hospital and who holds the budget for vascular access devices. Factors affecting the choice of catheter used include how long it is needed, the condition of the veins, and lifestyle considerations. As patients with IF may require lifelong vascular access it is imperative that measures are taken to preserve the viability of the patient's veins—peripheral and central, and it is suggested that a validated assessment guide such as the UK Vessel Health and Preservation (VHP) Framework is used [2]. In addition, vein lumen size should be measured using an ultrasound as the size of catheter within the vein can result in a reduction in flow and increased rate of catheter related thrombosis [3, 4]. To reduce the risk of thrombosis a catheter vein ratio of 45% or less [3–5] is recommended. While these studies have been on PICCs the same principle can be applied to Hickman™ type catheters and totally implanted ports.

Catheters can have one, two or three lumens. To reduce the incidence of catheter associated complications—most notably infection—the minimum number of lumen to meet the patient's vascular access requirements should be selected [6–8]. Figure 1 shows a single and double lumen catheter.

The design of a triple lumen catheter is the same as a double lumen but with an extra lumen.

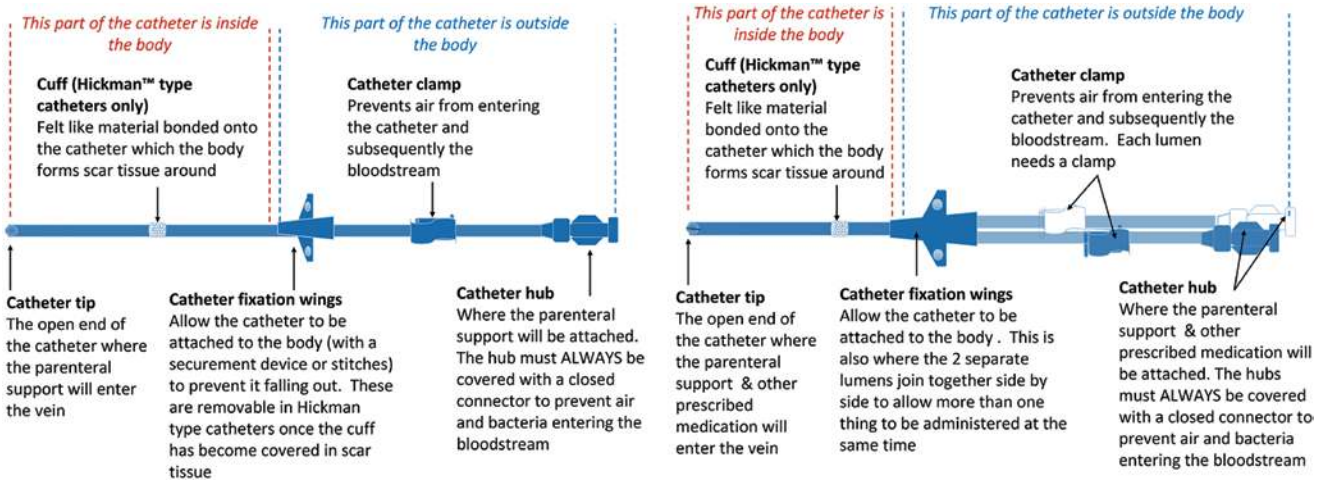


Fig. 1 Single and double lumen catheter

Peripherally Inserted Central Catheter

Peripherally inserted central catheters (PICC) are inserted via one of the veins in the upper arm with the tip lying in the superior vena cava. See Fig. 2. Single, double and triple lumen PICC are available.

Due to their ease of insertion and removal PICC are often chosen for individuals who only require home parenteral support for a few months. They can however remain in place for years. The device with the minimum number of lumen to meet the patient's vascular access requirements should be selected, and it must be appreciated that the double and triple lumen PICC will be a larger Fr gauge than single lumen devices so as to accommodate the multiple lumen (1 Fr = 1/3). This can increase the risk of catheter related thrombosis [9]. In the UK PICC are inserted directly into the vein however, some overseas centres tunnel the PICC with the intention of reducing the risk of infection and thrombosis [10]. While their study established that the tunnelling technique was successful, they conclude that the extent to which tunnelling a PICC reduces complications warrants further study.

PICCs need to be secured and covered with a sterile dressing. Careful consideration needs to be given to the method used as inadequate securement could lead to a number of complications for example; outward PICC migration, infection, vessel trauma from the catheter being able to move in and out of the vein ("pistoning"), and medical adhesive-related skin injury (MARSI) [11–13]. Broadly speaking methods can be classed as adhesive or mechanical. See Table 1.

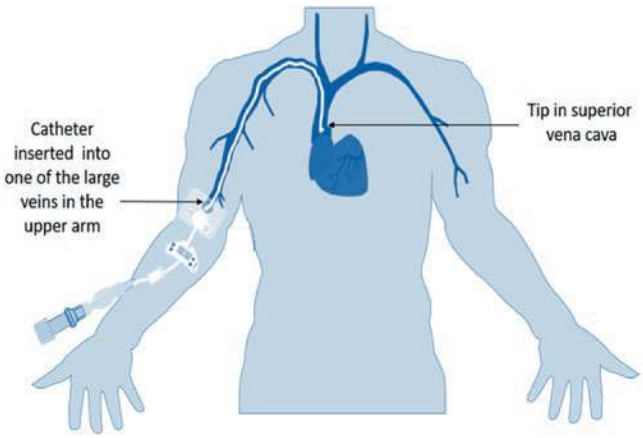


Fig. 2 Peripherally inserted central catheter (PICC)

Table 1 Types of adhesive and mechanical securement

Securement type	Examples
Adhesive	Gauze and surgical tape
	Steri-strips and semi-permeable transparent dressing
	Combination dressing and securement, for example SorbaView® SHIELD
	Manufactured sutureless device, for example Statlock®, or Griplok®
	Tissue adhesive
Mechanical	Subcutaneous metal skin anchor - SecurAcath®

Adhesive securement devices need (Fig. 3) to be changed weekly, or at any time they become loose or soiled. To reduce skin damage the manufacturers advice about removal should be followed (e.g. some must be removed with alcohol containing products).

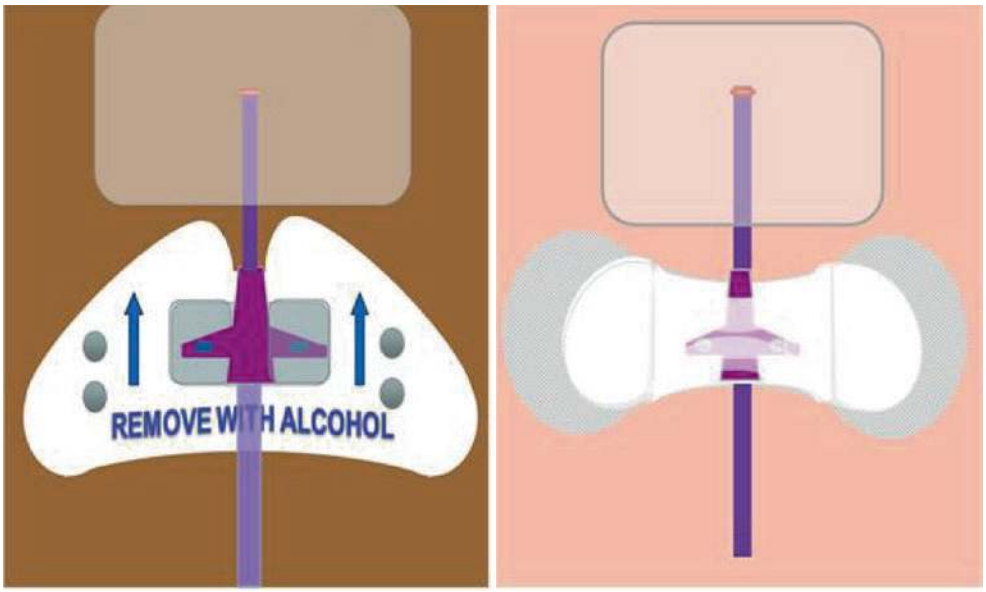


Fig. 3 Commonly used adhesive securement devices

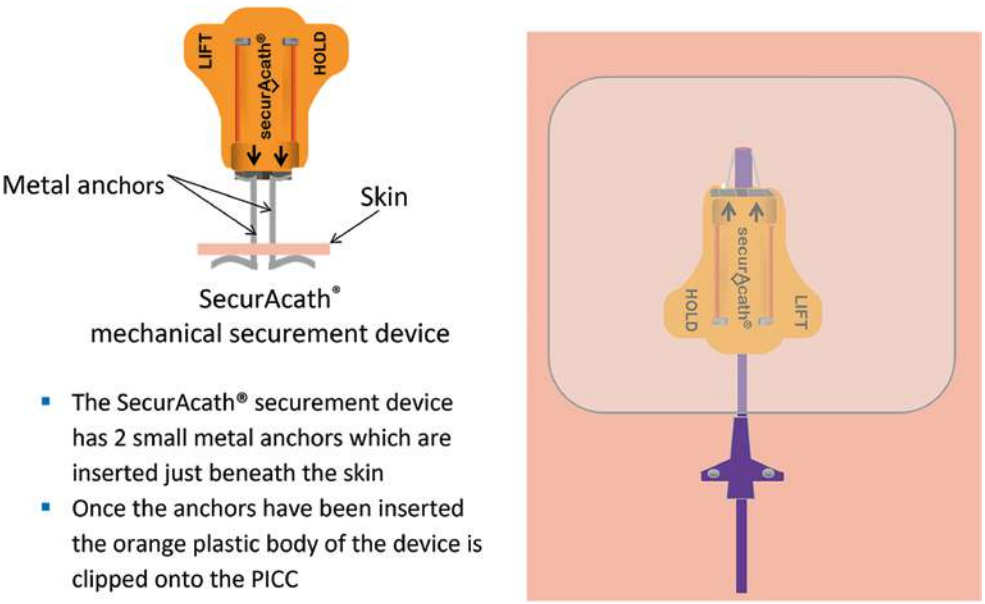


Fig. 4 Mechanical securement device—SecurAcath®

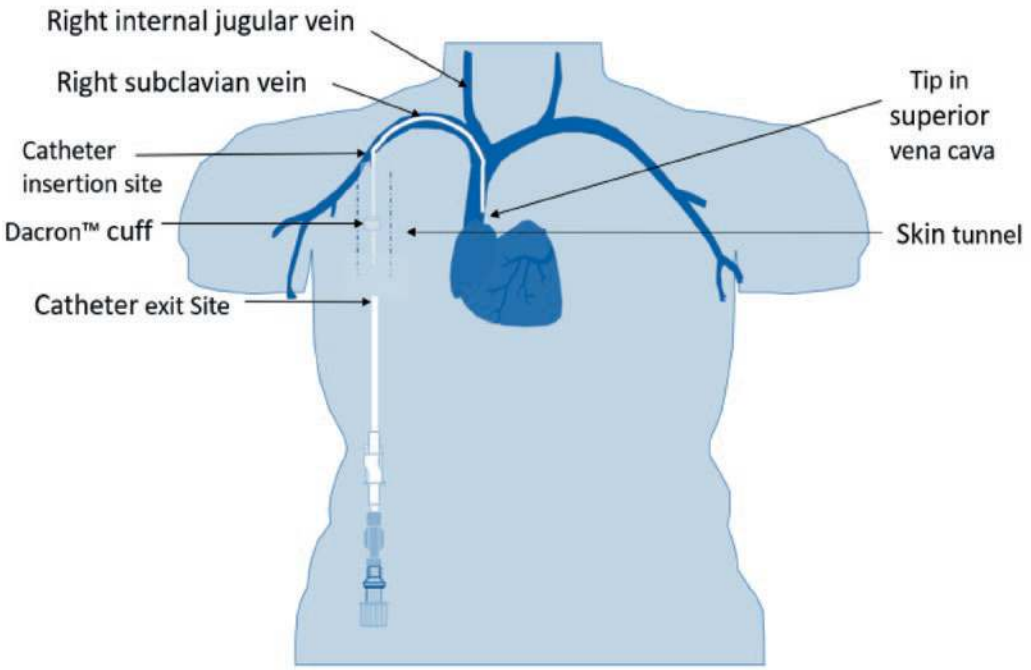
SecurAcath® has been the subject of a National Institute of Clinical Excellence (NICE) Medical Technology Assessment [12, 13]. They concluded that there was evidence to support the use of the device in reducing unintentional catheter migration especially when the PICC would be in-situ for more than 15 days (Fig. 4).

Cyanoacrylate glue has been used successfully by a number of centres to stabilise a PICC, however a review of the evidence supports its use primarily as a means to reduce post insertion site bleeding and extra-luminal catheter contamination [11].

Tunnelled Cuffed Hickman™ Type Catheter

This type of device is the one most commonly used for HPS as they can remain in place for many years (Fig. 5). It is named after Dr Robert Hickman who led the group of surgeons that developed it [14]. The catheter is tunneled under the skin to exit the body on the chest wall. It is held in place underneath the skin by a small cuff made from a felt-like material called Dacron™ that the body forms scar tissue around. The term Hickman is a trademark and refers to a tunneled catheter of a particular size made by one company;

a The catheter in situ



b The skin tunnel and cuff

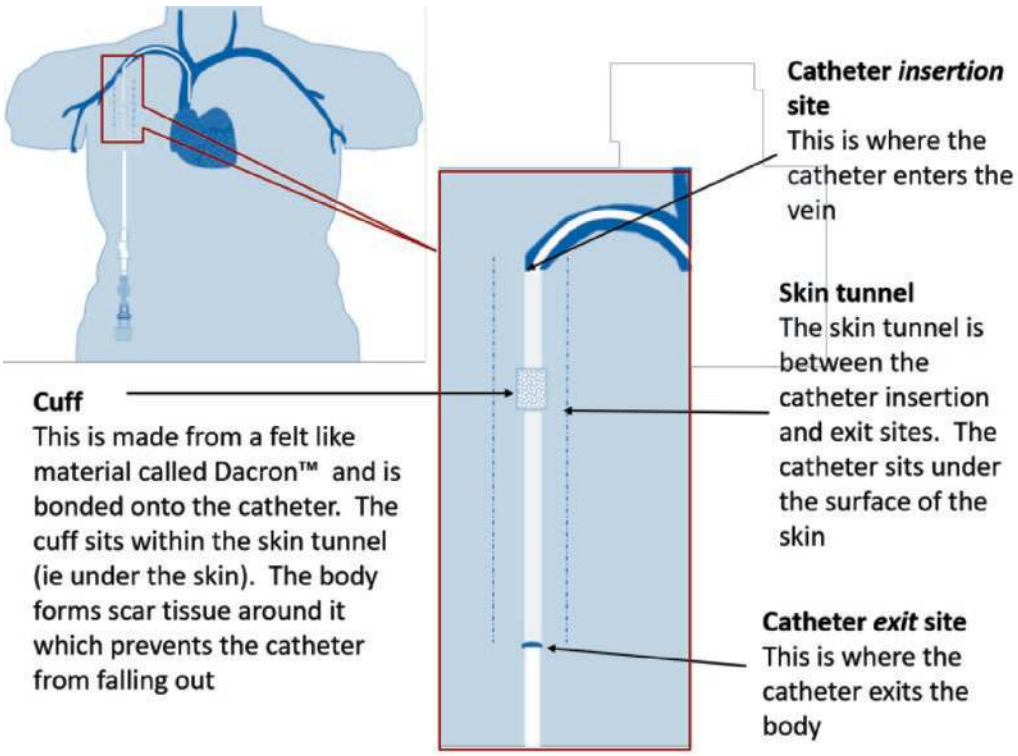


Fig. 5 Hickman™ type catheter. (**a**) The catheter in situ. (**b**) The skin tunnel and cuff

however it tends to be used to refer to any make or size of tunneled cuffed catheter. Nutrition teams often use a Broviac™ catheter, which is narrower (6.6Fr) than a Hickman™ (9.6 Fr). The smaller size is believed to reduce the risk and incidence of thrombosis as there is a better catheter : vessel ratio with the smaller sized device taking up less vessel space than the larger [3–5]. Single, double and triple lumen devices are available.

Hickman™ type catheters need to be secured until the cuff becomes embedded (Fig. 6). This is achieved by either suturing around the line or using a removable stitch fixation device which can either be sutured in place or attached with an adhesive securement device. One make of Hickman™ catheter has two suture rings bonded onto the catheter which allows sutures to be placed.

The sutures/devices only need to be in place until the cuff has become embedded—typically 3–6 weeks.

Totally Implanted Port ("Port-a-cath™")

A totally implanted port is a small metal reservoir filled with a self-sealing silicone disc. The port is inserted under the skin on the chest wall. The port has an attached catheter which is inserted into the superior vena cava via the subclavian or internal jugular vein. Totally implanted ports are often called "ports" or "Port-a-Cath™ which was the name of the first manufactured device (Fig. 7a).

The implanted port is accessed by inserting a removable infusion set with a non-coring (Huber) needle through the skin and silicone disc (Fig. 7b). Using a hypodermic needle will remove small sections of the silicone disc on removal thereby reducing the lifespan of the device. The needle needs to be long enough to go through the silicone septum and reach the back of the port. Failure to reach the back of the port can result in sluggish flow or occlusion.

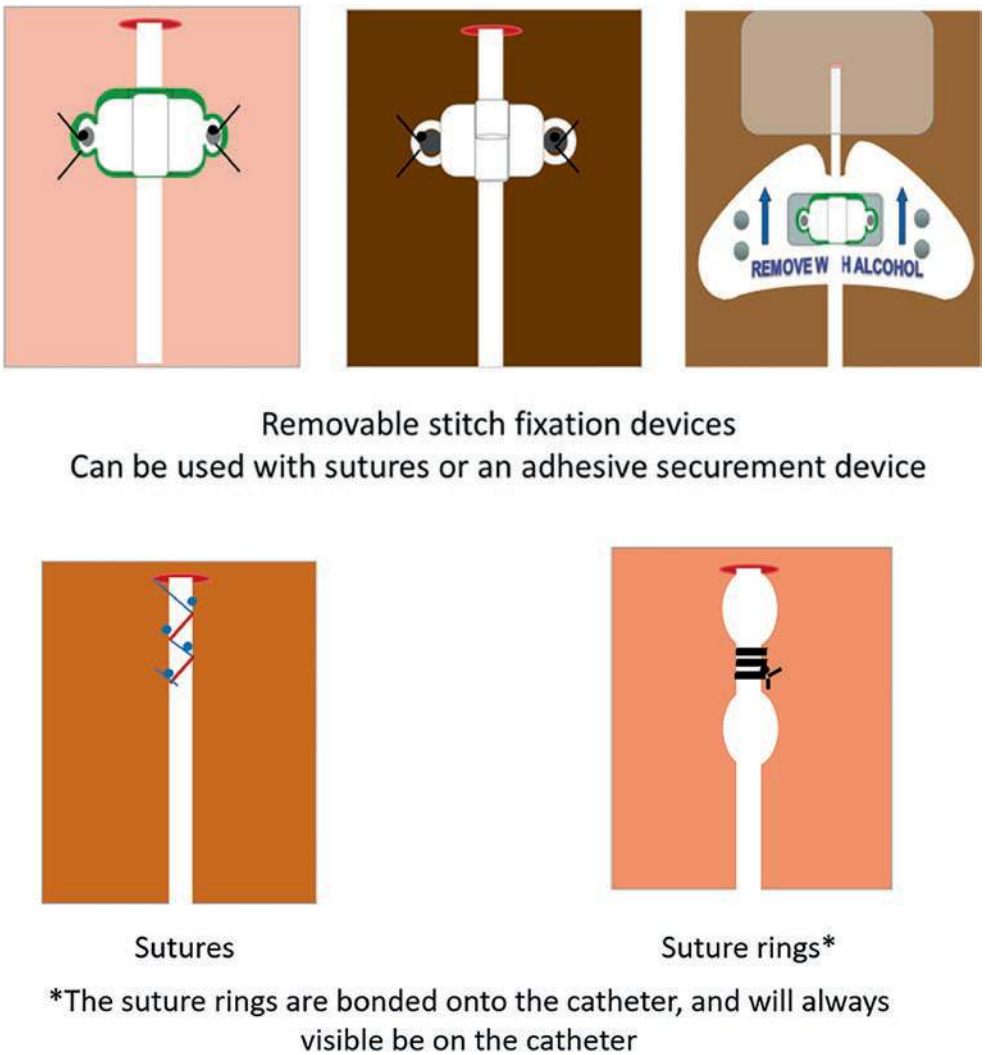
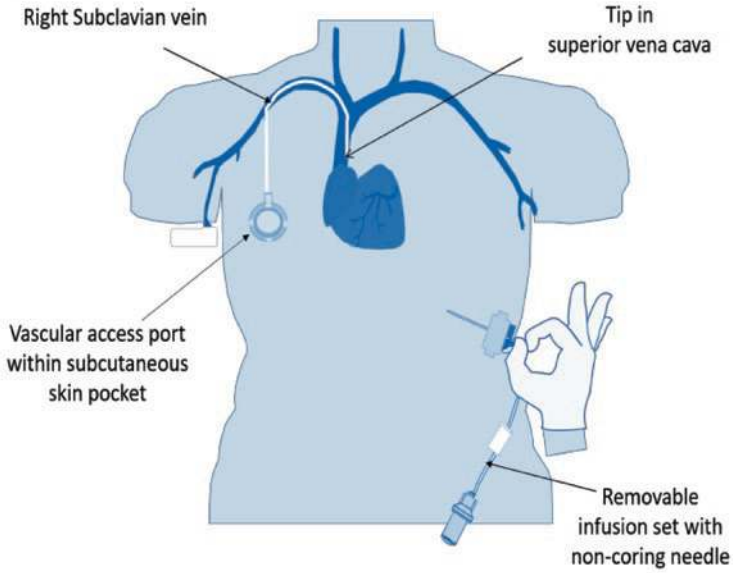


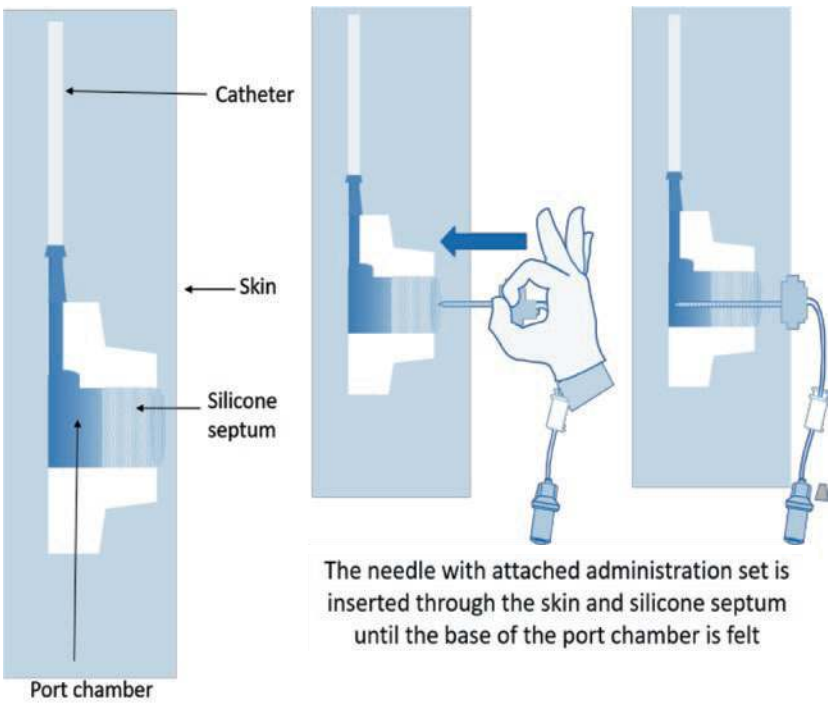
Fig. 6 Hickman™ catheter securement methods

Fig. 7 Totally implanted port. (**a**) Front view. (**b**) Lateral view with the needle in the port

a Front view



b Lateral view with the needle in the port



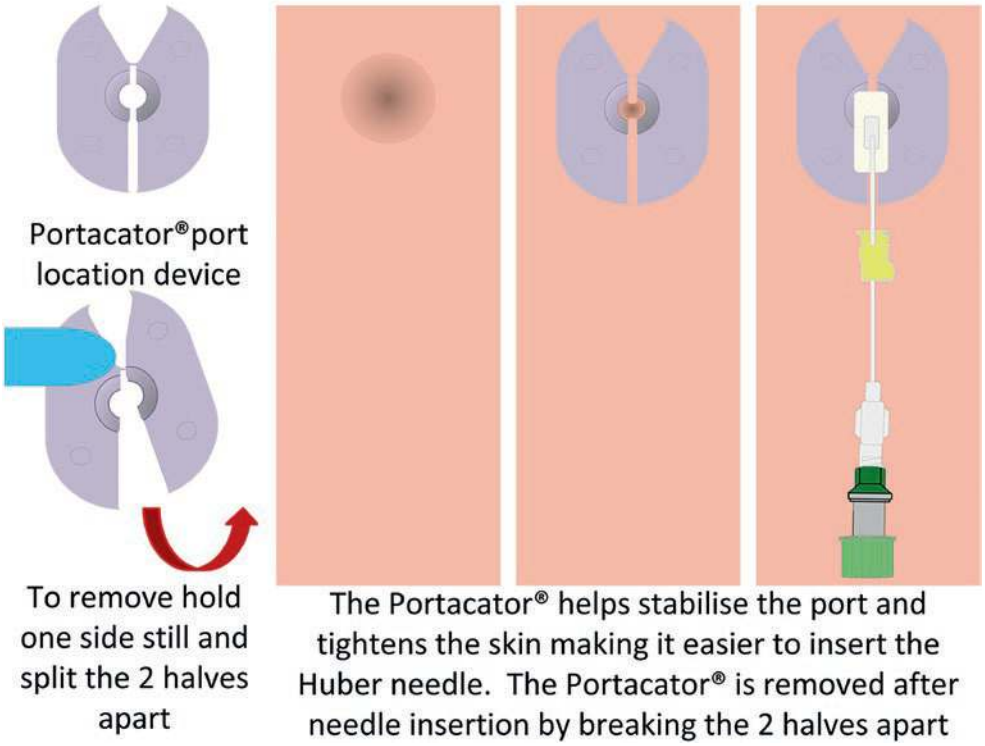


Fig. 8 Portacator® port location device

At the end of the infusion the infusion set can be removed leaving the patient with no visible device during infusion free periods. The infusion set can be left in situ for up to 7 days, however, there is no definitive data to support this [7, 15]. Further study is needed to determine how long it is safe to leave an infusion set in-situ and if this guidance would vary depending on the nature of the infusate, for example parenteral nutrition or chemotherapy.

Using an implanted port for home parenteral support relies on successful insertion of an infusion set with Huber needle. As such their use is not suitable for patients with a needle phobia.

Fluctuation in weight and how mobile the port is within the skin pocket can make insertion difficult, which can lead to missed infusions and/or the possibility of insertion in the subcutaneous tissue. Multiple attempts at insertion can not only be painful, but increase the risk of infection particularly if the same needle is used for successive attempts Using a port location device (Portacator®, PFM Medical), can help overcome this by stabilizing the port and isolating the silicone septum [15]. See Fig. 8.

Valved Catheters

Valved catheters have a pressure sensitive bi-directional valve at either the distal or proximal end of the catheter. The valve is believed to reduce the risk of blood backflow and subsequent catheter occlusion. As the valve prevents air from entering the catheter they do not have a clamp. The pressure sensitive valve is closed unless a syringe or giving set is attached and fluid injected. The valve will also open if the plunger on an attached syringe is pulled back thereby allowing blood sampling. Some patients prefer valved catheters as the absence of the clamp makes the catheter more discreet and comfortable (Fig. 9).

There is mixed evidence surrounding the benefit of a valved device vs. a non-valved one, a summary of which can be found in Table 2.

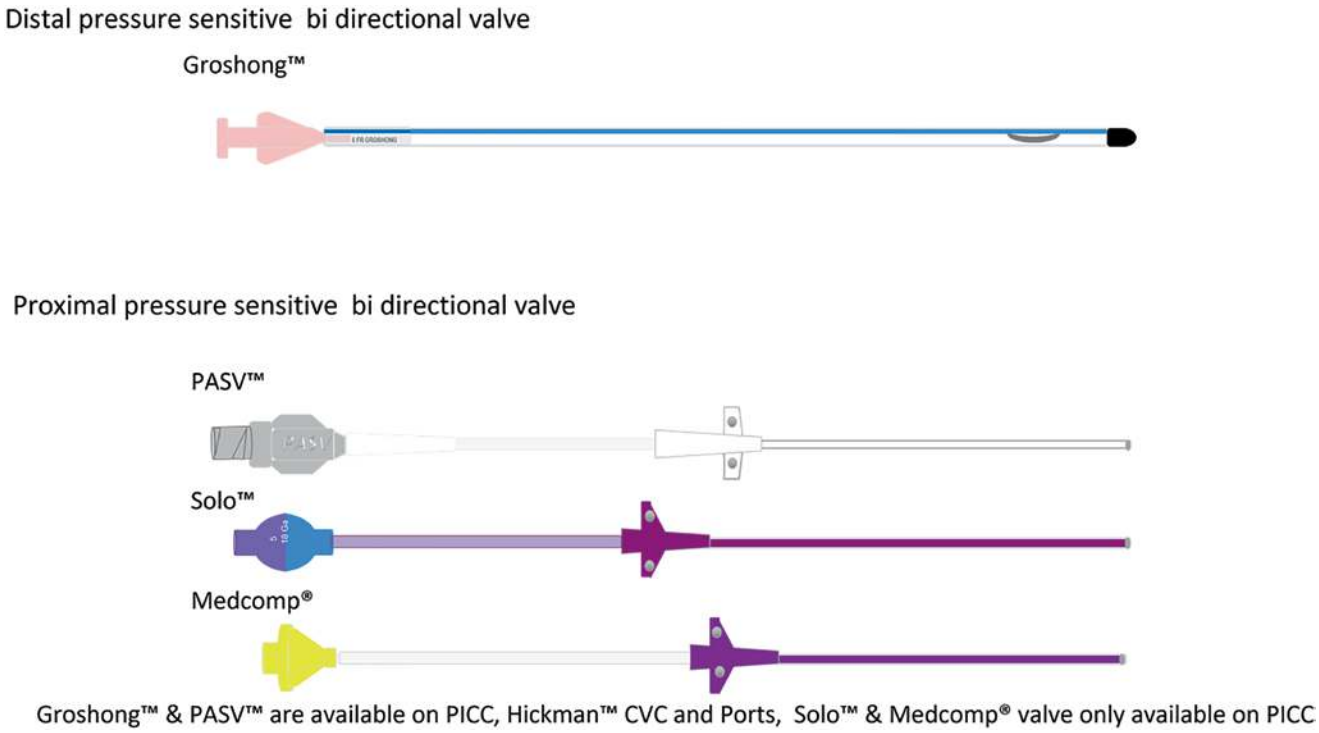


Fig. 9 Common valved catheters

Table 2 Comparison of valved vs. non valved catheters

PICC	Tunneled	Port
PASV less occlusions than Groshong, n = 100 p = 0.06 [16]	PASV easier to aspirate than non valved, n = 54, p = 0.004 [17]	More catheter malfunction valved vs non valved p < 0.05 [18]
Solo vs PASV vs unvalved, n = 180, no difference [19]	PASV easier to aspirate vs non valved, n = 73, p = 0.02 [20]	Increased ball valve effect → risk of thrombosis n = 356 p < 0.01 [21]
		n = 35 no difference in infective or mechanical comps [22]

Power Injectable Catheters

Power injectable catheters are designed to withstand power injection of CT contrast. They are available in PICC, Hickman™ type catheters and totally implanted ports. To distinguish them from non-power injectable devices they are usually purple and/or have purple hubs. This could potentially lead to wrong route administration as the purple has been adopted by most enteral tube and syringe manufacturers. Due to them being made from stronger polyurethane there is concern that their use is associated with a higher risk of catheter related thrombosis than in non-power injectable devices [9].

There are many considerations in selecting a central catheter for an individual patient (Table 3).

Table 3 Central venous catheter selection

Catheter type	Advantages	Disadvantages
PICC	• Easy to insert at bedside	• Require addition of extension set to be able to self access
	• Non invasive easy removal at the bedside	• Requires constant use of dressing and securement device
	• Waterproof covers available to allow bathing and swimming	• Visible if short sleeved clothing worn
		• Increased risk of thrombosis
		• Not all PICC can be repaired
Hickman™ type	• Longevity. Can remain in place for many years	• Requires surgical cut down to remove
	• Infected devices can often be salvaged	
	• Not visible under clothes	
	• Can be repaired	
	• Minimal scarring left on removal	
	• Waterproof covers and dressings available to allow bathing and swimming[a]	

(continued)

Table 3 (continued)

Catheter type	Advantages	Disadvantages
Totally implanted port	• Not visible when not being accessed	• Shorter lifespan than Hickman™ type device due to the eventual failure of the silicone septum to seal after needle removal
	• No need for a covering dressing when not in use	• Need to insert needle to access, so not suitable for anyone with needle phobia
	• No restriction with bathing and swimming	• Removal either under local or general anaesthetic
		• Noticeable scarring on removal
		• Salvage of infected devices difficult due to surface area of the port chamber and silicone disc, and the inability to target antibiotic therapy to all of the puncture sites a needle has been inserted
Valved	• More discreet as do not need a clamp	• Risk of air entry if valve fails
	• Valve *might* help reduce risk of occlusion	
Power injectable	• Allow power injection of CT contrast	• Increased risk of thrombosis
		• Potential for wrong route administration as purple is commonly used to denote enteral devices and syringes

[a]Several waterproof options for patients with Hickman™ are now available; Independence Activity Pouch (Independence Direct), Cath Dry™ pouch and Secuderm® dressing (Vygon UK). Within England, the Independence Activity Pouch and Cath Dry™ pouch are available via NHS Prescription, while Secuderm® can be supplied via the national framework

Needle Free Connector

A Needle Free Connector (NFC) is a removable device which permits the connection of administration sets and syringes to the hub of an intravenous catheter without the use of needles. When in situ they create a closed system which prevents air entry and minimises bacterial ingress (Fig. 10). Their use in patients on HPS is recommended to help reduce bacterial contamination of the catheter [7].

There are many different connectors available, but they all work in a similar way. The connector has an internal 2-way valve which is depressed when a syringe or intravenous giving set is applied allowing fluid to flow into the catheter. Depressing the valve also permits blood to be drawn from the catheter. The individual specification of devices varies in several ways;

- Connection surface (flat or slightly recessed)
- Dead space
- Fluid pathway
- Frequency of change
- Intricacy of valve mechanism
- Amount of fluid displacement on insertion or removal of a syringe
  - Positive connector—a small amount of infusion fluid is forced into the catheter end
  - Negative connector—a small amount of blood moves back into the catheter end
  - Neutral connector—no movement of fluid in either direction
- Clamping sequence
  - Positive connector—apply clamp after removing syringe
  - Negative connector—apply clamp before removing syringe
  - Neutral connector—apply clamp before removing syringe
- Ease of application/access

The extent to which these features *may*, or may *not*, influence catheter related complications such as infection and occlusion has yet to be determined [7, 23]. For the patient being discharged on HPS the two most important considerations are the connection surface and how easy it is for it to be effectively disinfected, and the ease of application and access. Some connectors have a smaller profile and as such can be difficult for some individuals to apply, connectors with an irregular surface may not always be adequately disinfected, while some connectors require more force to depress the valve with a syringe. Logistically, which connector is used in the home will depend on what is available locally. Under the national HPN framework for England any make of connector can be requested which means that the individual needs of the patient can be met. Manufacturer's guidance should be followed regarding the frequency of change as this can vary.

It is important that the patient knows the name of the connector they have, and that there are different brands available, so that if they are admitted to a hospital that uses a different brand they understand that this is an acceptable difference. This is particularly relevant on discharge so that the patient knows to remove the connector used in hospital and apply the one they are supplied with at home.

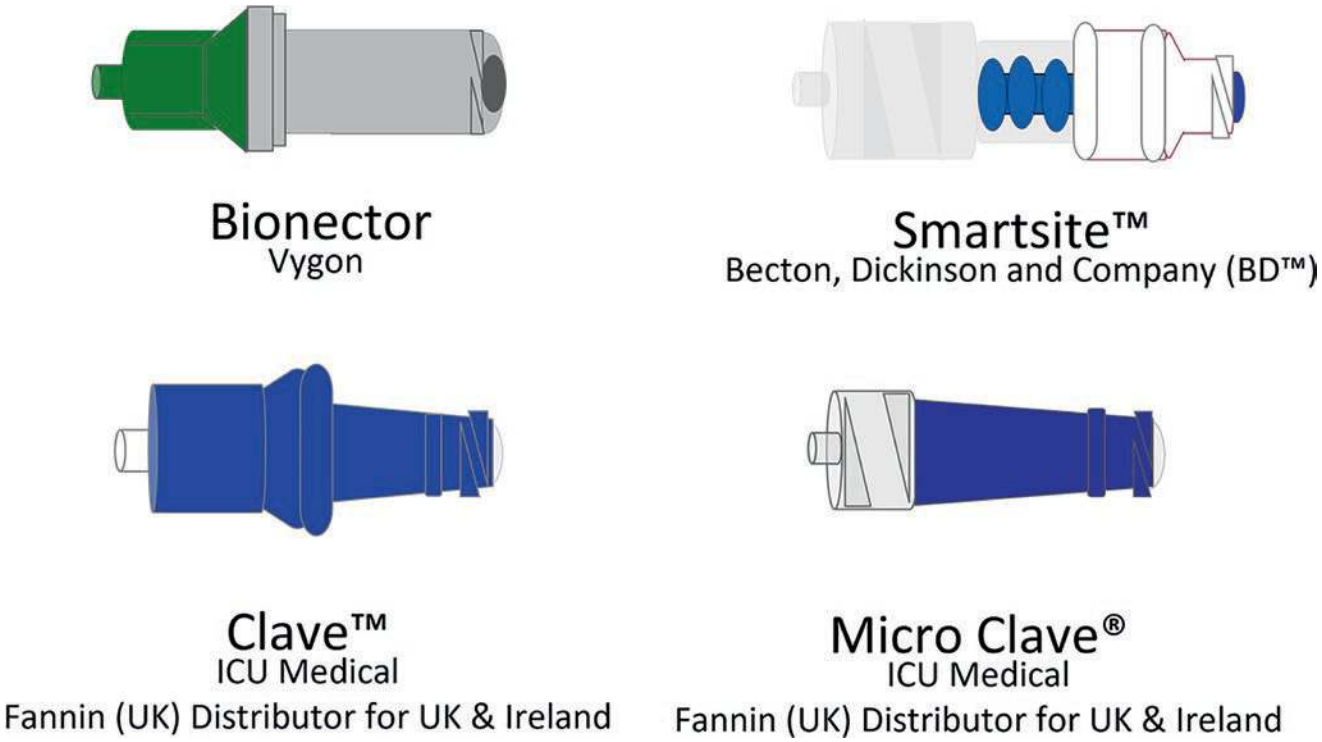
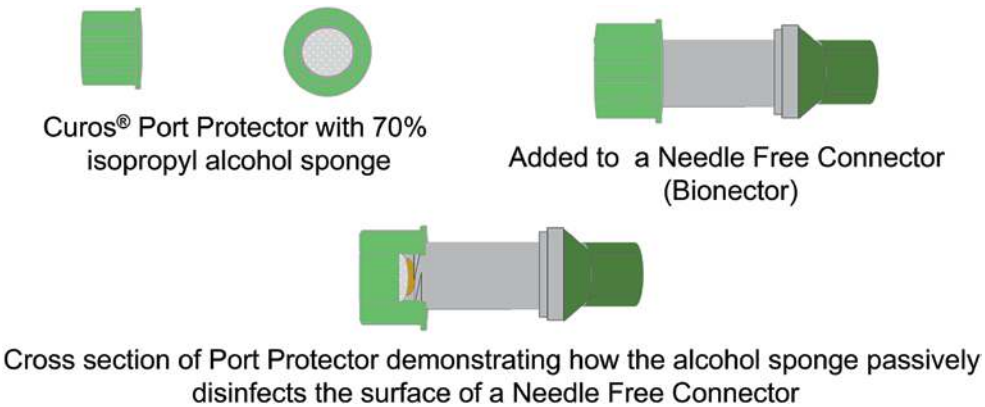


Fig. 10 Commonly used Needle Free Connectors

Fig. 11 Port protector cap



Port Protector Cap

A port protector cap is a single use protective cover, similar to a bottle cap in design, containing a 70% isopropyl alcohol foam disc (Fig. 11). When applied to a needle free connector during infusion free periods it provides continuous passive disinfection *plus* a physical barrier to cross contamination. There are a number of different caps available but they all work in the same way by providing direct contact with the surface of a needle free connector with 70% isopropyl alcohol.

Initial studies have shown promising results in reducing catheter related bloodstream infection [24, 25], and these have been followed by other prospective studies [26, 27], in-vitro evaluation [28] and abstract presentations also showing a reduction in infection rates As the success of passive disinfection relies on full contact of the alcohol impregnated sponge with the surface of the needle free connector knowing which brand of port protector and needle free connector was evaluated is essential. It is also important to note that to date there have not been any comparative studies evaluating each available protector on each available needle free connector. Muslim patients need to be reassured that there are no restrictions on them using any medical devices containing alcohol [29].

In-Line Filters

Although intravenous solutions may appear clear to the naked eye, they contain particles of 1–25 μm, which can induce sterile inflammation and cause granulomas elsewhere such as lungs and brain [30]. The particles consist of glass, cotton fibres, precipitated proteins, microcrystalline drug particles, degenerative products of interactions between fluids and glass, plastic and even rubber stoppers. Some arise from glass ampoules [31] and some from syringes themselves [32]. Consequently, the use of in line filtration is common practice for patients on home parenteral support, and the importance of using a 1.2 μm filter is reiterated in an American Society for Parenteral and Enteral (ASPEN) Position Paper [33]. As well as filtering out particulate matter, in line filters can also filter some harmful bacteria. It is for this attribute that The European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) (ESPEN) recommend their use [7].

In line filters are integrated into all ambulatory pump giving sets primarily to filter out air as the giving set does not have a drip chamber. A separate in line filter should be used if patients are using a static pump. If patients are receiving any long term IV medication the use of a filter straw or needle to draw these up and reconstitute will provide additional protection against particulate matter.

Infusion Pumps

Infusion pumps and accessories used for home parenteral support have evolved over the years, with advances in the size and weight of the pump, battery life, running noise and backpack design. In England ambulatory pumps are now standard practice for all patients which is in stark contrast to 20+ years ago when only 7% of patients had them [34]. The freedom of movement with an ambulatory pump has been associated with an increased quality of life [35]. Pump selection will depend on what is available locally, but if there is a choice then consideration should be made including the parameters listed in Table 4. One pump may be more suitable for a patient than another, especially with respect to ease of inserting the giving set into the bag of parenteral support, inserting the giving set into the pump, and programming the pump.

Table 4 Pump parameters

Parameter	Comments
Pump weight and size	• Noise level increases with increase in flow rate
	• Pump weight needs to factor in weight of parenteral support bags
Battery	• Can the patient receive their full infusion on a single battery charge?
Giving set	• How easy is it to grip and insert?
	• Is the giving set kink resistant so as to reduce occlusion alarms?
	• How easy is it to place in the pump?
Backpack	• How easy is it to secure the pump and infusion fluid?
	• What carrying options, handle(s), wheels, carrying straps are available
Programming the pump and alarms	• How easy is it to programme?
	• Are keys intuitive to use and easy to depress?
	• Are pump alarms easy to understand and correct?

Adapted with permission from LITRE (Looking into the Requirements for Equipment) [36]

Central Venous Catheter Care

Reducing the risk and incidence of central venous catheter related infection is paramount in the care of patients receiving parenteral support. To reduce the risk of infection it is important to understand *how* infection occurs, and *where* infection comes from. There are a number of ways in which infection can occur. The skin surrounding the exit site is the major source of local infections, whereas the catheter hub is the major source of blood stream infections [37].

Local infections can occur if the skin becomes over colonized by micro-organisms. This could be from the environment (for example if the area is not kept covered with a sterile dressing), from the hands during dressing changes if they have not been adequately washed, from using contaminated (unclean) equipment, or contact with body fluids, for example stoma or fistula content.

Catheter hub contamination can occur from the hands, from any contact with non-sterile equipment, from using contaminated equipment, or contact with body fluids, for example stoma or fistula content.

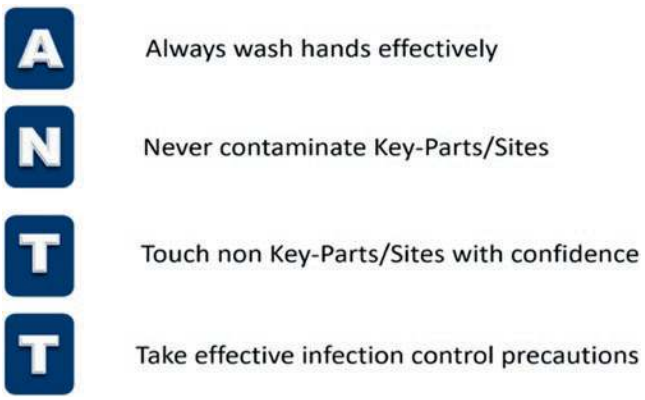


Fig. 12 General principles of ANTT®

Aseptic Technique

The risk and incidence of local and systemic infection can be significantly reduced if there are strictly adhered to procedures for the care of the catheter and administration of parenteral support. The aim of these procedures is to reduce both skin colonization *and* catheter hub contamination.

This can be achieved by using an aseptic technique. Asepsis is the **absence of** bacteria, viruses, and other micro-organisms [8]. An aseptic *technique* therefore aims to prevent bacteria, viruses, and other micro-organisms being introduced onto the skin, or into the catheter and subsequently the bloodstream. An aseptic technique is used widely in healthcare—essentially for all clinical procedures from basic wound care to surgery. There are numerous ways of effectively performing an aseptic technique, consequently there are differences between hospitals in the way it has been taught and performed, which will inevitably result in differences in how patients and carers are trained.

The acknowledged differences with how aseptic technique has been taught and undertaken led to the development of a technique known as Aseptic Non Touch Technique® (ANTT®). This was introduced with the aim of improving the efficacy of and standardizing the technique [38–40]. ANTT® has been adopted by many hospitals within the UK *and* internationally. It is a theory and practice framework using standardized principles and terminology [41]. The general principles of ANTT® can be found in Fig. 12.

Standard vs. Surgical-ANTT®

The ANTT framework describes two types of technique, Standard-ANTT® or Surgical-ANTT®, based on the complexity of the procedure and the number of Key-Sites and Key-Parts. What isn't clear from these definitions is how many Key-Parts/Sites count as numerous, which can lead to confusion and debate between health care professionals as to which technique is the correct one to use. It is important to remember that the principles are the same for each approach, so both are acceptable for central venous catheter care for home parenteral support. The most important thing is that the key principles—**"A" "N" "T" "T"** are followed as described below.

A: Always Wash Hands Effectively

Hands are the most common vehicle by which micro-organisms are transmitted; therefore effective hand hygiene is essential to remove them and reduce the risk of infection. Hand hygiene is a general term that covers both handwashing *and* hand decontamination. This can be achieved by using an antibacterial hand wash solution, or a combination of non-antibacterial hand wash solution followed by antimicrobial hand rub.

There are two types of micro-organisms present on the skin which effective hand hygiene will address;

- transient skin flora
  - These micro-organisms are acquired on the skin through contact with other people, objects, or the environment. These can be easily removed by handwashing.
- resident skin flora
  - These are micro-organisms, which have adapted to the natural condition of the skin. They live in deep skin crevices, hair follicles, sweat glands, and moist areas, such as beneath rings. These are harder to remove.

The hand washing procedure involves three stages—preparation, washing and rinsing, and drying [8].

Preparation

Forearms should ideally be free of any clothing which could impede effective hand washing or potential contamination of equipment, and rings and bracelets should be removed. If jewellery cannot be removed, the washing (and drying) of items into the handwashing technique should be incorporated. In particular, rings should be rotated to allow washing of the skin underneath them. The largest concentration of micro-organisms is found under the fingernails; therefore, nails should not be so long as to interfere with the handwashing process. There have been numerous reports linking the use of artificial nails with an increased risk of line infections [42–45]. Consequently, their use is not recommended. This may prove restrictive for some patients, and also difficult to enforce. Patients/carers should be made aware of the risk so they can make an informed decision. Although not men-

tioned in the literature, bitten nails could also be an infection risk due to the ridges and open areas present on the fingers. Nailbrushes are also not recommended as they will harbour micro-organisms, and could also damage the skin, making it more susceptible to infection

The hands should be moistened with running water before applying the liquid soap. This ensures complete coverage of the hands with soap, and also reduces the drying effect of the soap on the skin. It is important to use running water rather than standing water, for example water in a bowl or basin, as hands could become re-contaminated. The temperature of the water does not matter as it does not affect how many micro-organisms are physically removed and having the temperature too hot can lead to skin irritation.

Washing and Rinsing

Hands must be washed thoroughly to ensure micro-organisms are removed, but should not damage the skin, as this will increase the risk of infection. The procedure should take a minimum of 20 s. Liquid soap is advised rather than bar soap as this can easily become contaminated. Micro-organisms will remain on areas of the hand not exposed to soap and water therefore, the handwashing technique needs to consider *all* aspects of the hands and wrists. Hands and wrists should be rinsed thoroughly before drying so as to remove all soap debris, as this will contain micro-organisms and residual soap could lead to skin irritation.

Drying

Hands should be dried with good disposable quality paper towels. Paper towels are advised to be used as they are disposable. Cloth towels can rapidly become damp and can quickly become contaminated [8]. Some patients may want a more environmentally friendly option than using disposable paper towels. In this instance, the use of muslin cloths or cotton face flannels could be substituted. They would need to be used once only and bulk washed on their own in the washing machine at 60 °C.

The use of a clean paper towel/muslin cloth/cotton face flannel to switch off the tap, carry the rucksack or manouevre the drip stand should also be employed to protect the newly cleaned hand from re-contamination.

Hand Decontamination

In addition to handwashing, hands can be effectively decontaminated by applying alcohol hand rub. The hand rub will rapidly destroy any micro-organisms on the skin surface. Alcohol hand rub should be applied to clean, dry hands, and the hands rubbed together, following the steps in the handwashing technique, until they are completely dry.

Skin Care

Damaged or sore skin can make washing hands uncomfortable, and increases the risk of infection; therefore it is important to keep your skin healthy. In order to protect the skin warm, not hot water, should be used to wash the hands. Water that is too hot or too cold can crack the skin and allow micro-organisms to enter.

The regular use of hand lotion can help prevent chapped hands—in particular the cuticles—which can increase the risk micro-organisms entering the skin. Even skin that does not look dry to the naked eye may have small cracks in it. Hand lotion should be applied at the end of each procedure to help keep hands well moisturized. Assessing efficacy of hand washing using UV disclosing lotion is common in hospital settings and it seems reasonable to include in patient/carer teaching.

N: Never Contaminate Key-Parts/Sites

Key-Part

A Key-Part refers to the part, or parts, of a piece of equipment which if contaminated with micro-organisms could introduce infection. For example, touching, exposure to the environment, or using non-sterile equipment all have the potential for the transmission of micro-organisms. When trying to identify the Key-Parts/Sites for any procedure ask the following question *"Could touching this with unwashed hands lead to infection?"* If the answer is yes, then it is definitely a Key-Part. The number of Key-Parts will vary depending on the procedure being undertaken and also the equipment used. Figure 13 demonstrates the difference in the number of Key-Parts when accessing a Needle Free Connector with a prefilled syringe vs. a manually drawn up syringe.

Key-Site

Key-Sites are open wounds or breaks in skin integrity (such as where the catheter exits the body) which that need to be protected from contamination with micro-organisms. See Fig. 14.

Key-Parts and Key-Sites are protected during an aseptic procedure by using a non-touch technique, which as the name suggests, means not directly touching them with anything that is not sterile, or allowing them to come into contact with any non-sterile items.

In addition, the Key-Parts and Key-Sites are protected by creating an aseptic field. An aseptic field is an area created to maintain asepsis during a clinical procedure. This is achieved by using a sterile towel or sterile packaging, either to place equipment or Key-Parts on. The aseptic field needs to be large enough to protect the Key-Parts. See Fig. 15.

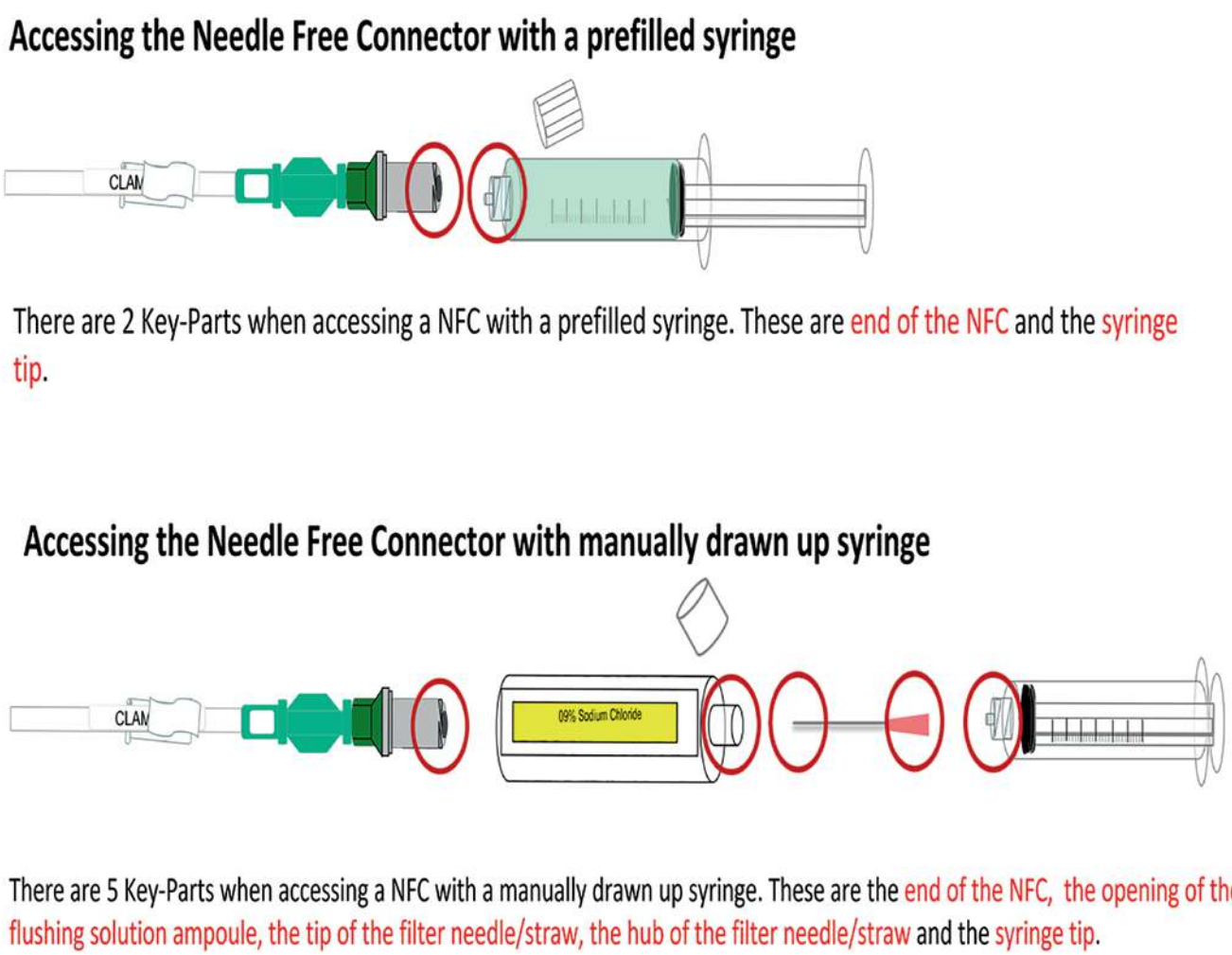


Fig. 13 Key-Parts when accessing a Needle Free Connector (NFC) with a prefilled syringe vs. a manually drawn up syringe

T: Touch Non Key-Parts/Sites with Confidence

Non Key-Parts/Sites can be touched with confidence as there is no risk of transmitting micro-organisms by doing so. Essentially, non-Key-Parts are *any* part of the equipment which is *not* a Key-Part. When trying to identify the non Key-Parts/Sites for any procedure ask the following question *"Could touching this with unwashed hands lead to infection?"* If the answer is no, then it is a non-Key-Part. Using the example outlined in Fig. 14 of Key-Parts when accessing a Needle Free Connector(NFC) with a prefilled syringe vs. a manually drawn up syringe, Fig. 16 illustrates the non Key-Parts.

T: Take Effective Infection Control Precautions

Infection control precautions include the use of personal protective equipment (PPE), and the appropriate preparation and use of any equipment (sterile or unsterile), used during the care of the catheter and administration of home parenteral support.

As more knowledge is gained around the control of infection it is possible that new products may be introduced and/or changes made to how the procedures are undertaken. There may also be temporary changes, for example, during a national pandemic.

Gloves

Gloves are worn to reduce the risk of infection during the aseptic procedures. The wearing of gloves is not a substitute for handwashing, but in addition to it [8]. Microscopic punctures can develop in the gloves, which are not visible to the naked eye, and if the hands have not been thoroughly washed this could result in contamination with micro-organisms and subsequent infection.

It has been standard practice for many years to use sterile gloves for any procedures involving central venous catheters, however, as a non-touch technique is used clean non-sterile gloves may be safely used [8, 46]. If recommending the use

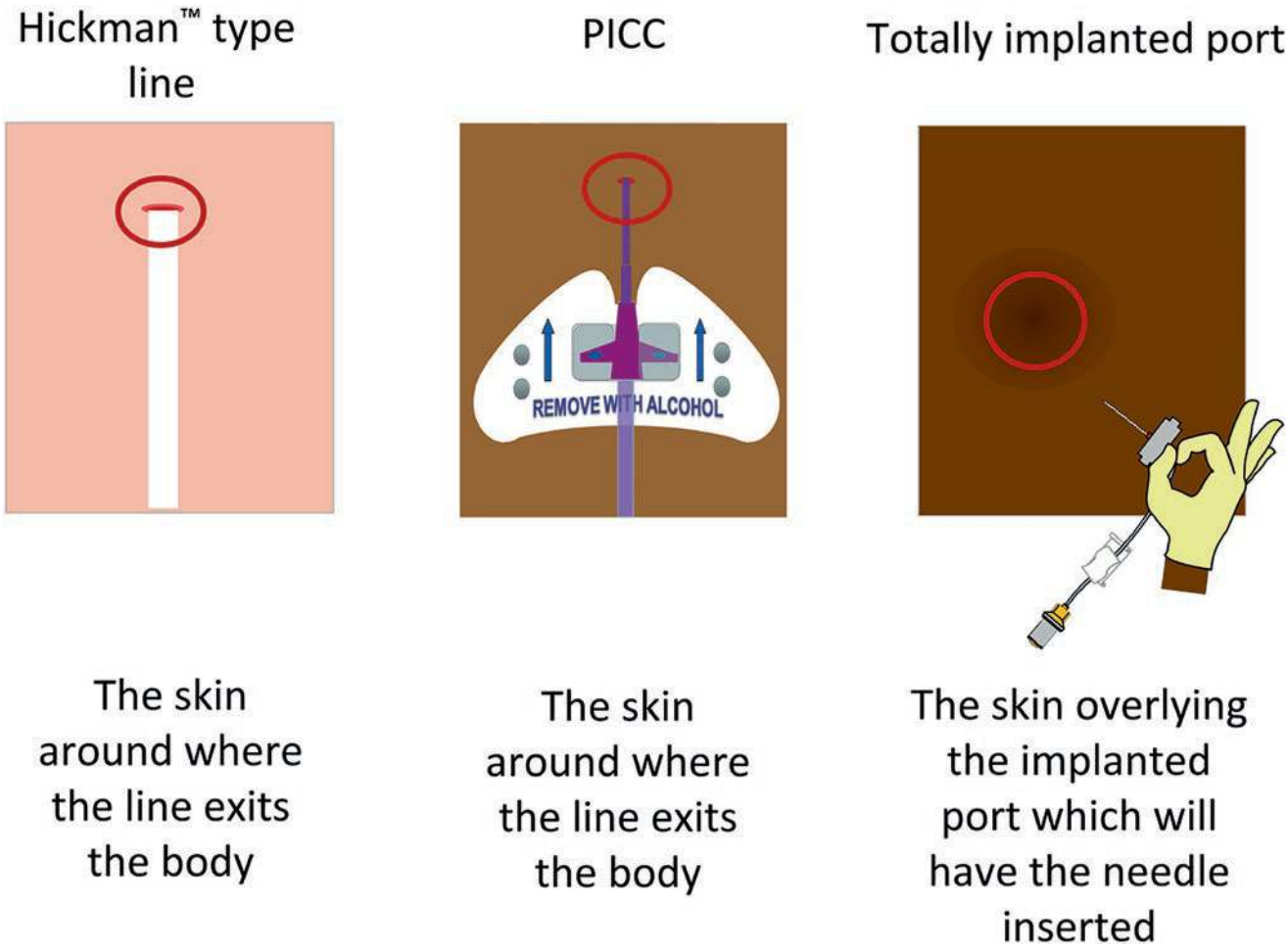


Fig. 14 Key-Sites in central venous catheter care

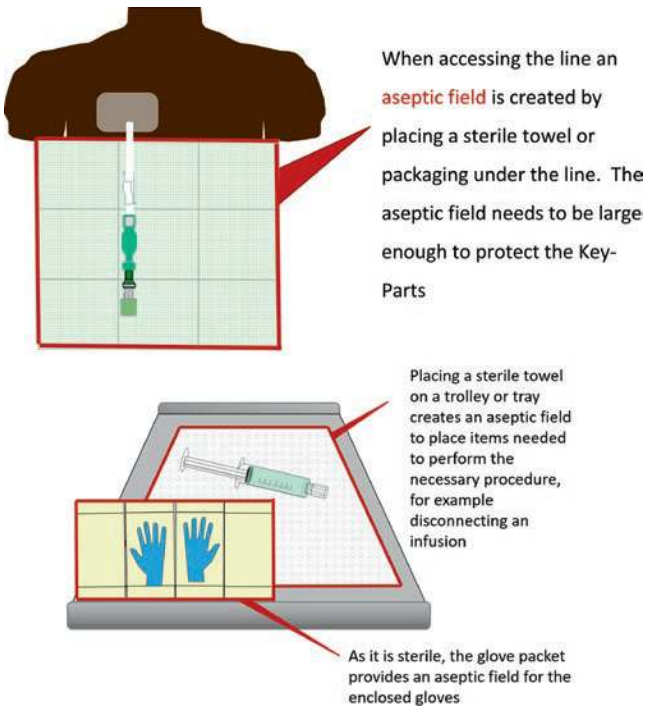


Fig. 15 Creating an aseptic field

of clean non-sterile gloves it is important to consider how they are stored prior to use and assess the potential for cross contamination. Assessment criteria should include ease of removing gloves from the box, and if it is possible to do this without contaminating the glove fingers. Patients should be advised not to replace any surplus gloves that are removed along with the ones they will be using as this could result in contamination.

Trolley/Procedure Tray

Selecting equipment for patients on parenteral support to use at home will depend on what is available locally, but it isn't always necessary to replicate what the patient has been used to seeing in hospital. An example of this is what is used to place the sterile items on in order to undertake the procedures. In hospital this will either be a trolley or a procedure tray(s), however, any flat surface that can be effectively cleaned and disinfected is suitable. Patients should be encouraged to think of what will work for them in their home environment, especially if space is limited. Whatever surface is used it needs to be cleaned and then disinfected. Cleaning

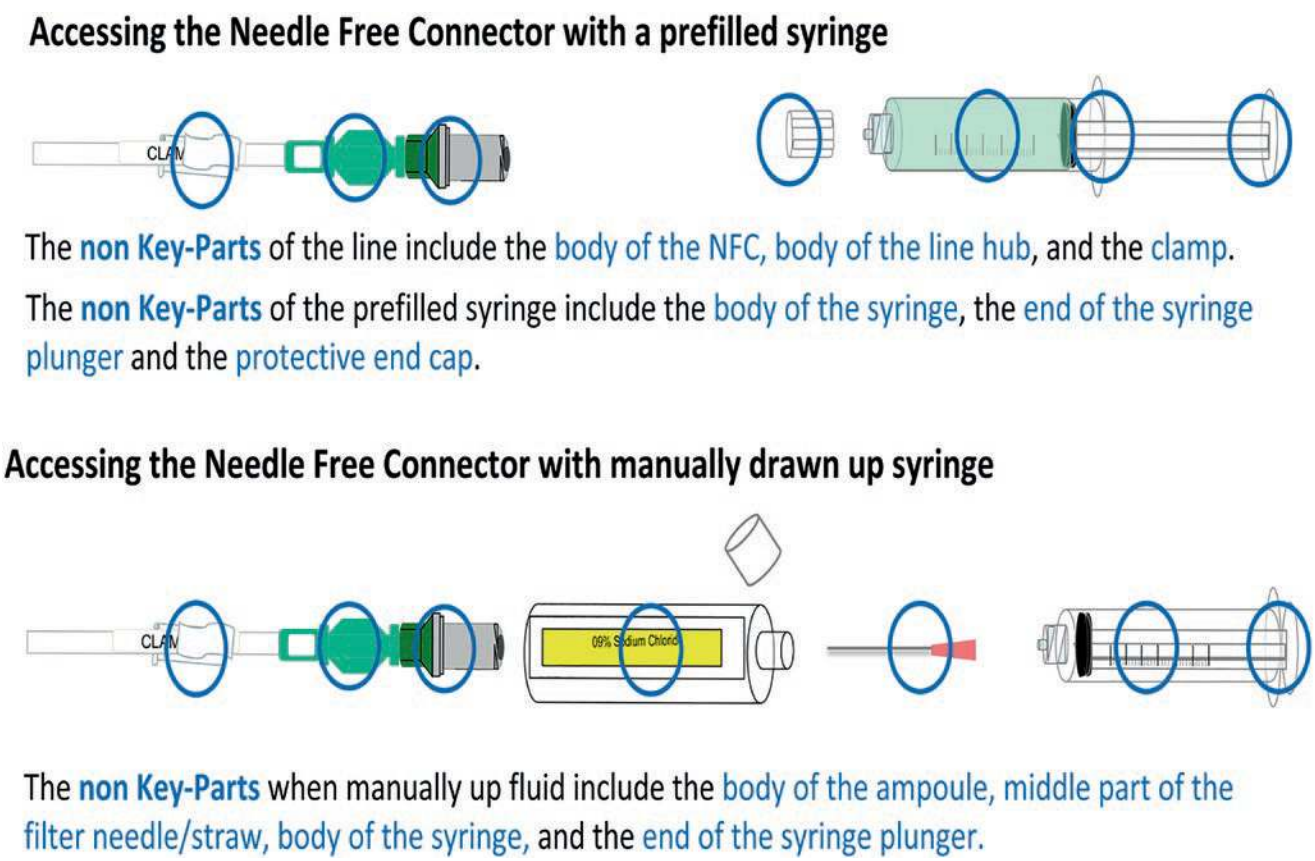


Fig. 16 Non-Key-Parts when accessing a Needle Free Connector (NFC) with a prefilled syringe vs. a manually drawn up syringe

with soap and water or a detergent wipe will remove any dust which contains micro-organisms, and visible dirt. Once this has dried the surface needs to be disinfected with either a disinfection wipe or spray. A lot of emphasis is often placed on this activity, especially whether or not it is acceptable to use a back and forth motion or to only wipe in one direction. The topic can cause a difference of opinion between nurses and often reflects the way they were first taught how to do an aseptic technique. The crucial thing is that the entire surface comes into contact with the products being used.

Needle Free Connector

The membrane of the needle free connector needs to be effectively disinfected prior to connecting a syringe or giving set to it, to avoid the transfer of micro-organisms into the line. This is probably the most important step in any procedure during which the line is accessed. See Fig. 17.

A single use sterile wipe impregnated with Chlorhexidine 2% and 70% Isopropyl Alcohol should be used for a minimum of 15 s using pressure and friction in a twisting action as if juicing an orange [8, 47]. This is often referred to as "scrub the hub". The connector should then be allowed to dry for 30 s before accessing [8]. When teaching patients/carers emphasis needs to be placed on that the membrane of the sterile end connector is the Key-Part and where the disinfection should concentrate. As the length of the catheter and clamp are non Key-Parts it is not necessary to disinfect them. Repeatedly exposing the catheter material to 70% Isopropyl Alcohol (one of the ingredients of the disinfection wipes) *could* lead to it becoming brittle over time. If it gives patients/carers peace of mind to disinfect the clamp this is fine, but it should to be disinfected *after* the membrane of the needle free connector. See Fig. 18.

Due to the importance associated with this part of any procedure where the line is accessed it seems reasonable to assess the patient/carer's efficacy in disinfecting the needle free connector membrane. This can be achieved by using dummy lines and connectors and UV disclosing lotion. The membrane is covered in UV disclosing lotion which is invisible to the naked eye. Following disinfection the patient/carer can be shown how much of the disclosing lotion they have removed by using a UV black light detector. This assessment would also be applicable for reassessing established home parenteral support patients who have developed catheter related bloodstream infection.

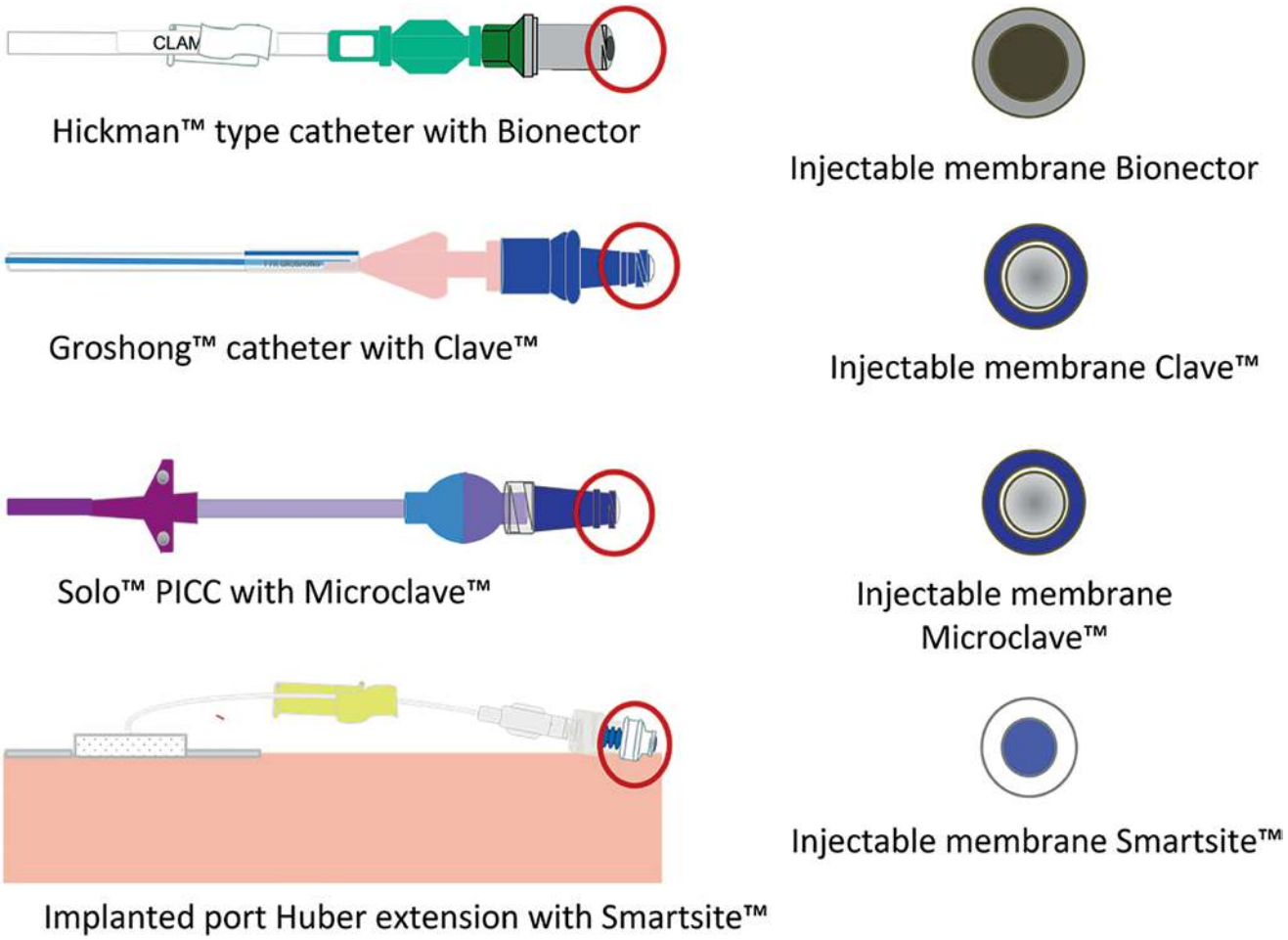


Fig. 17 Commonly used NFC showing the wipeable membrane

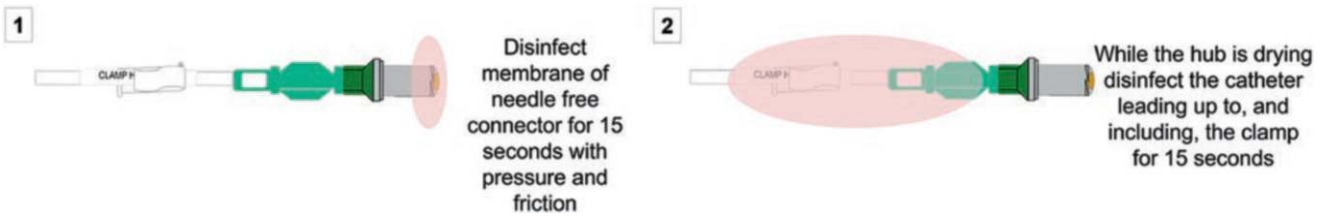


Fig. 18 Order of disinfection—membrane *then* clamp

Sterile Dressing

To protect the skin surrounding where the line exits the body from contamination that could lead to a local infection, the site needs to be covered with a sterile dressing (Fig. 19). Dressings should be vapour permeable, which means they prevent the build-up of moisture under the dressing, as this could increase the risk of infection [8]. Transparent dressings allow the exit site to be continually inspected, not just at dressing changes, however, a dressing with an absorbent pad is recommended if there is any discharge from the exit site. It is still unclear however, if there is a difference in infection rates between different dressing and securement devices [48]. When appraising the literature it is important to note the following;

- Catheter type
  - Direct venous access, PICC or tunneled Hickman™
- Dressing details including the Moisture Vapour Transmission Rate (MVTR)
  - The higher the MVTR greater the ability of the dressing to allow skin moisture to evaporate
- What type of infection
  - Local and/or systemic?

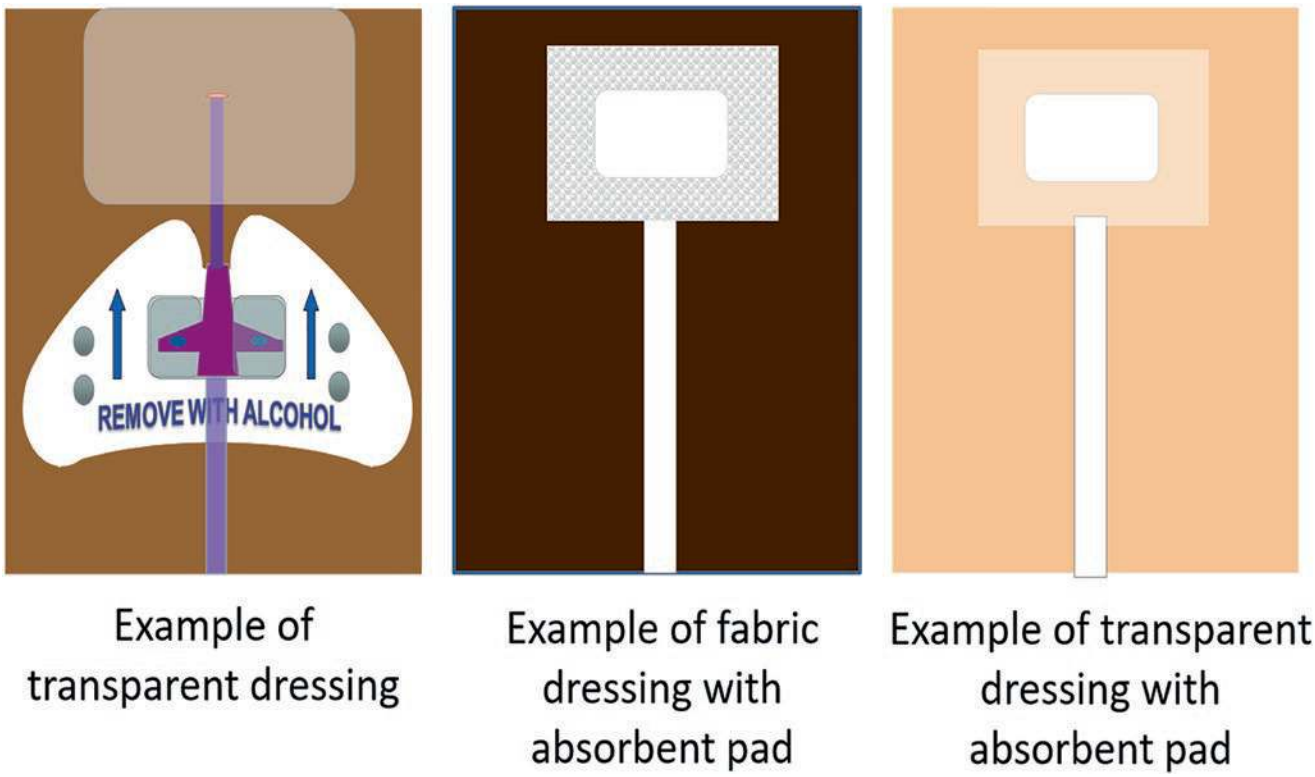


Fig. 19 Examples of sterile exit site dressings

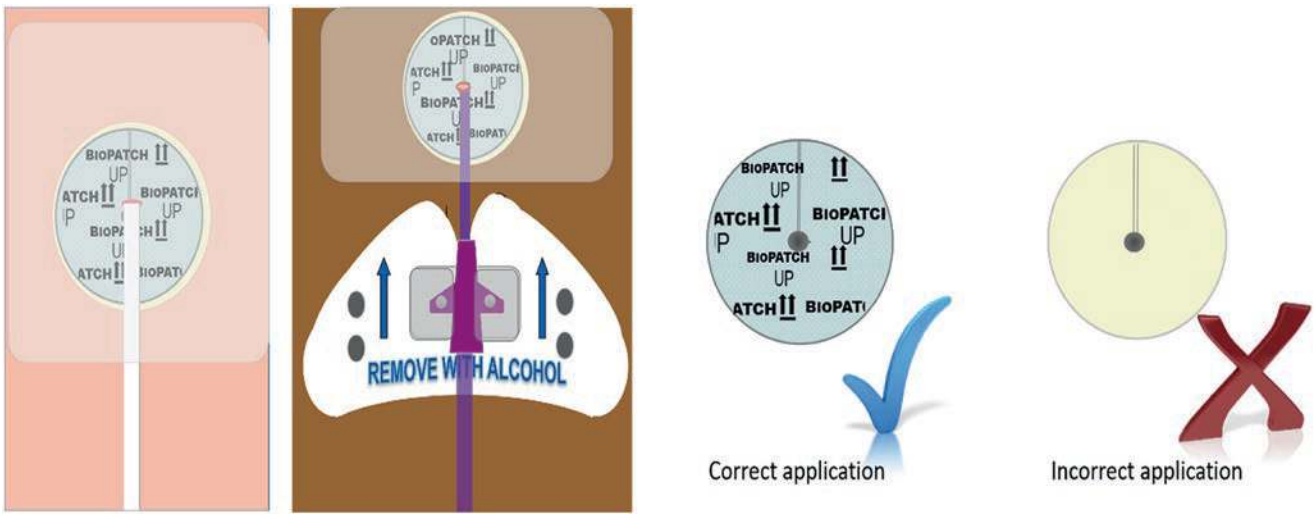


Fig. 20 Biopatch® dressing

An important consideration for the patient/carer is the ease of dressing application. There are some "1 hand" dressings available which as the name suggests can be applied with 1 as opposed to both hands.

Dressings should be changed every 7 days, or at any time they become loose or soiled [7, 8]. The dressing only needs to be large enough to cover the exit site and a few cm of surrounding skin, however, not all suitable dressings are available this small, so a larger dressings may need to be used. Sometimes it may be clinically indicated to use an chlorhexidine impregnated dressing, for example Ethicon Biopatch® or 3M™ Tegaderm™ CHG [8, 48, 49]. While these dressings do not treat infection, they may be helpful in reducing the risk of infection in individuals who have had a history of line site infections. The active ingredient is slowly released into the skin over a period of days. They should be changed every 7 days, or at any time it becomes saturated with fluid. See Fig. 20.

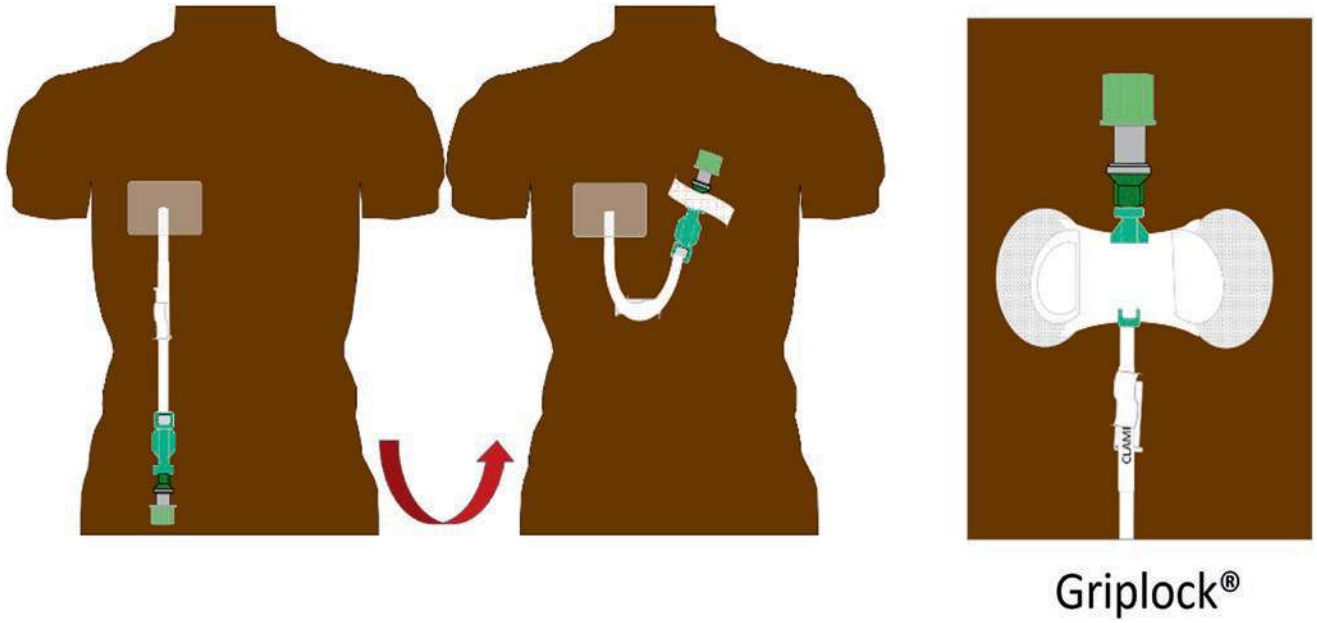


Fig. 21 Securing the catheter hub

Securing the Catheter Hub

Even if the catheter hub is protected with a port protector, for example Curos™, during infusion free periods, keeping it secured away from a stoma or fistula site is an important, but sometimes, overlooked, infection control precaution. This is particularly relevant with Hickman™ type catheters. The hub can be secured with surgical tape or a special dressing, for example Griplok® that can stay on the skin for a number of days. See Fig. 21.

It has been common practice to recommend the catheter hub is wrapped in gauze when not in use. There are a number of proposed benefits to this namely; acting as a deterrent to non-qualified staff accessing the catheter, patient comfort, and reducing the risk of infection. There is no evidence to suggest that wrapping the catheter end in gauze is an effective infection control strategy, as gauze has an open weave design which will not repel micro-organisms, and if wet *could* actually increase the risk of infection. If wrapping is done to reduce discomfort from the catheter hub and clamp from digging into the skin then this is acceptable. For catheter safety any wrapping needs to be easy to remove without the use of scissors.

BIFA Unified Protocol: Standardised Parenteral Support Catheter Guidelines

Despite the popularity of ANNT® a Royal College of Nursing investigation on the understanding of aseptic technique concluded there was still disparity in definition and standardisation [50]. As any procedure should be based on the evidence-based elements of central venous catheter care the reason behind such variation is hard to comprehend. Aware of differences in catheter care NHS England requested a standardised set of procedures so as to reduce any confusion for patients, service users and health care professionals. The unified protocol was developed by the IF units at St Marks and Salford Royal Hospitals and was supported by the National Nurses Nutrition Group (NNNG), British Association for Parenteral and Enteral Nutrition (BAPEN), and the patient support group Patients on Intravenous and Naso-gastric Nutrition Treatment (PINNT). The unified protocol outlines key principles during connection, disconnection and changing the dressing [51]. See Appendix 1 at the end of this chapter.

Catheter Related Complications

Catheter related complications can impact on morbidity and mortality therefore prompt identification and initiation of appropriate treatment is vital.

Catheter Related Infection

Catheter related infection is an umbrella term covering both systemic infection and local infection [8]. Local infections can be categorized according to the amount of skin affected

Table 5 Localised catheter related infections

Type of infection	Signs and symptoms	Suggested treatment
Exit site infection	Erythema and/or induration within 2 cm of the catheter exit site in the absence of systemic infection [37]. A purulent discharge may also be present	Targeted oral antibiotic therapy. IV antibiotics may be required if absorption is severely limited. Once resolved the use of a Chlorhexidine Gluconate dressing is recommended [8, 48, 49]
Tunnel infection	Tenderness, erythema and/or induration >2 cm from the exit site along the subcutaneous tunnel in the absence of systemic infection [37]. A purulent discharge may also be present	As the infection is more widespread targeted IV antibiotic therapy is required, although removal may be required if the infection does not respond to treatment Once resolved the use of a Chlorhexidine Gluconate dressing is recommended [8, 48, 49]
Descending tunnel infection (suggested definition in the absence of any formal definition)	Tenderness, erythema and/or induration >2 cm from the catheter vein insertion site along the subcutaneous tunnel in the absence of systemic infection. A purulent discharge may also be present	As the infection is more widespread targeted IV antibiotic therapy is required, although removal may be required if the infection does not respond to treatment Once resolved the use of a Chlorhexidine Gluconate dressing is recommended [8, 48, 49]
Complete tunnel infection (suggested definition in the absence of any formal definition)	Tenderness, erythema and/or induration along the entire length of the subcutaneous tunnel in the absence of systemic infection. A purulent discharge may also be present	As the infection is more widespread targeted IV antibiotic therapy is required, although removal may be required if the infection does not respond to treatment Once resolved the use of a Chlorhexidine Gluconate dressing is recommended [8, 48, 49]
Cuff infection (suggested definition in the absence of any formal definition)	Tenderness, erythema and/or induration localised over the cuff of a tunneled catheter in the absence of an exit site, tunnel or systemic infection. A purulent discharge may also be present	Targeted IV antibiotic therapy as the infection is likely to be deeper than in an exit site infection. The catheter may need to be removed or it may spontaneously fall out if the infection disrupts the tissue anchoring the cuff in place
Port pocket infection	Purulent fluid in the subcutaneous pocket of a totally implanted port in the absence of a systemic infection [37]	Targeted IV antibiotics

and type of device they can occur with [37]. The definitions have not been revised since 2002, and do not distinguish an isolated cuff infection, or that a tunnel infection can be ascending (from exit site up the skin tunnel), descending (from insertion site down the skin tunnel), or complete (affecting the entire tunnel). Localised infections along with signs and symptoms and suggested treatment are shown in Table 5.

Medical Adhesive Related Skin Injury ("MARSI")

While not an infection, Medical Adhesive Related Skin Injury (MARSI) can be mistaken for one, and could lead to infection if not appropriately treated. MARSI refers to skin damage from prolonged and/or frequent contact with medical adhesive. If left untreated it can lead to infection and loss of skin integrity [52]. Patients on home parenteral support may use a number of products with different types of medical adhesive; for example dressings, securement devices, surgical tape and stoma appliances. The adhesive products will need to be repeatedly applied and removed to the same areas of skin making maintaining skin integrity an important nursing consideration.

The risk of MARSI increases with inappropriate adhesive selection, application, or removal. The skin damage may not be immediately noticeable. MARSI can take the form of redness, skin tears, or blisters and be painful and very itchy. It is often mistaken for an allergy to the dressing or an infection. Secondary infection can occur if MARSI results in breaks in the skin as bacteria are able to enter.

It is thought that MARSI is largely avoidable. Things which can help minimize the risk of developing MARSI include using medical adhesive remover when removing the dressing and protecting the skin with a silicone barrier wipe prior to dressing application [53].

Other strategies include alternating the size of dressing used and/or using dressings with an absorbent pad. This helps by not having the same area of skin constantly in contact with the medical adhesive. Alternatively, a dressing with a low tack adhesive can be used.

Care should be taken not to stretch a dressing when applying it as this can cause microscopic skin tears as the skin contracts once the dressing is in place (Fig. 22). In addition, dressings should be removed as per manufacturer's

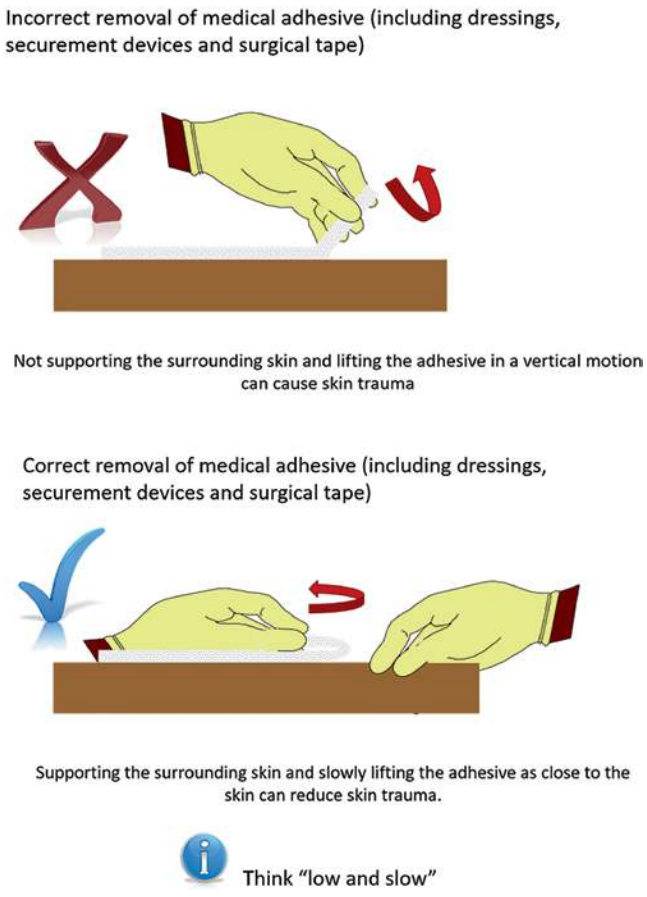


Fig. 22 Removing medical adhesive from the skin

guidelines. For example, some dressings need to be removed using alcohol-based products, or by being stretched outward to remove the contact with the adhesive, as opposed to lifting them off. When lifting off a dressing the surrounding skin should be supported, and the dressing peeled back slowly and as close to the skin as possible. This has been termed the "low and slow" method [54].

Systemic Infection: Catheter Related Blood Stream Infection

Of all of the potential complications of home parenteral support, catheter related bloodstream infection (CRBSI) is arguably the one which patients fear the most. Patients/carers need to be aware of how systemic infection can occur, alongside how it can present and the implications of not seeking urgent medical attention. Information needs to be given in simple language the patient understands without causing undue anxiety, however does need to include some medical terms, such as bloodstream infection or sepsis, so that patients are able to accurately convey their concerns to healthcare professionals. Patients with signs and symptoms of CRBSI often say they think they have a "line infection" which to health care professionals not used to caring for patients with long term CVC suggests a local skin infection rather than a systemic infection. This misunderstanding could lead to ineffective treatment, or even no treatment, being initiated. Providing patients with pre printed proforma letters for common complications can aid in them accessing appropriate treatment if they attend the emergency department.

Not everyone with CRBSI present with the same symptoms, and it is important to help the patient recognize symptoms which may be subtle, for example, general malaise or thinking they have a cold, or overt such as a temperature of 38 °C or more and rigors. It is also important to note that a temperature of less than 36 °C or less can indicate systemic infection, which may not seem obvious to patients. Patients should be advised that while symptoms are often experienced during an infusion or post flushing the catheter, they *can* also occur during infusion free periods.

To be able to benchmark outcome measures it is suggested that IF centres aim for an inpatient catheter related bloodstream rate of less than 3/1000 catheter days and an outpatient one of less than 1/1000 catheter days [55]. To date, there has been no recommendation to report infection rates per type of device. As the risk of catheter related infection varies between PICC, Hickman™ type and implanted ports it seems reasonable to suggest reporting individual device infection rates in addition to the overall rate. The identification and treatment of CRBSI is covered in chapter "Prevention, Diagnosis and Management of Catheter-Related Blood Stream Infections".

Catheter Occlusion

Reduction in central venous catheter patency can result in missed infusions and if not resolved will require insertion of a new device. Central venous catheter occlusion may be thrombotic or non-thrombotic in nature. Thrombotic occlusions arise from the formation of a thrombus either within, surrounding, or at the line tip. They can also arise from backflow into the catheter during infusion free periods, or failing to adequately flush the catheter post blood sampling [56].

Non-thrombotic occlusions can occur from particulate debris or lipid particles [57]. There are also numerous mechanical causes of occlusion and it is important to exclude any of these before considering pharmaceutical intervention. See Table 6.

Occlusion can be complete where it is not possible to instill or aspirate anything, partial where there is resistance on instillation, or a persistent withdrawal occlusion (PWO) where fluids may be infused but it is not possible to withdraw

Table 6 Mechanical causes and interventions of occluded central venous catheters

Possible cause	Intervention
Kinked/clamped line	1. Straighten line
	2. Ensure line clamp is open
	3. Examine reinforcement sleeve for indentations & massage line between thumb and index finger to remove any kinks
Faulty Needle Free Connector	Remove connector and reassess patency by flushing with 0.9% sodium chloride for injection directly via line hub
Faulty pre filled syringe	Try flushing with a new prefilled 0.9% sodium chloride for injection syringe in case the seal on the one used previously wasn't completely released
Obstruction within line hub	1. Direct observation inside the catheter hub to check no obvious obstruction, for example a sponge from Curos™ Port Protector
	2. If connection between hub & line is obscured consider manual extraction of debris. Manual extraction of debris should not be attempted in catheters with proximal valves, for example PASV™ or Solo™ valves as this could damage the valve
Constriction of sutures/dressing	Remove any potentially constricting sutures/dressings. (re-suture if catheter in-situ <3 weeks)
Catheter tip against vessel wall	1. Change patients position (supine/upright or vice-versa)
	2. Try the Valsalva manoeuvre and reassess patency
Catheter tip migration or malposition	1. Check notes and/or CXR for initial tip placement
	2. Perform repeat CXR to assess current tip position
	3. Measure external length of catheter (PICC) and compare against length on insertion
"Pinch-off" syndrome (subclavian vein catheters only)	1. Check patient's notes for verification of venous access route
	2. Assess if the occlusion is intermittent or positional (relieved by rolling shoulder forward or raising arm on ipsilateral side). If the occlusion is relieved by rolling the shoulder or raising the arm the CVC will need to be removed and replaced as there is no treatment for pinch-off syndrome
Implanted ports: needle displacement	1. Insert new Huber™ needle and reassess patency
	2. Consider inserting longer needle if the back of the port is not felt
Displacement/ misalignment of catheter repair segment	1. If the metal spike from the catheter repair segment has dislodged then the segment may no longer be in alignment with the native catheter. This will restrict flow
	2. If a patient has a repaired catheter consider removing the repair segment and performing a new repair

blood [58]. Simple strategies to resolve a PWO include changing the patient's position (e.g. raising their arms above their heads or asking them to cough). While thrombus, lipid and precipitate (protein or drug deposits) can all cause PWO, the commonest cause is a fibrin sheath formed around the catheter [59, 60].

A fibrin sheath is a collection of fibrin and platelets that can be demonstrated in 40% of all catheters with radiological screening after radio-opaque dye has been injected down the catheter [61]. It starts from where the catheter enters the vein and spreads towards the tip. It does not generally cause a problem until it surrounds the catheter tip when it may classically act as a one-way valve such that a solution can be infused down the catheter but not withdrawn.

Treatment of Catheter Occlusion

Simple strategies should be tried first, such as asking the patient to raise their arms and cough, and massaging out any kinks within the clamping reinforcement area. Having atraumatic clamps to hand is essential to be able to clamp the catheter should any attempt to restore patency results in catheter rupture. Gaining a history of the occlusion will help guide treatment options, for example;

- Was it sudden onset?
- Has the catheter been getting sluggish over a period of time?
- Has the catheter been used for blood sampling and not flushed afterward?
- Have they noticed any blood leaking from the needle free connector?
- Is the catheter used for any medication?
- Does their parenteral support regimen include lipid containing bags?

It is also important to rule out catheter related thrombosis as a cause.

Possible signs of thrombosis include;

- Ipsilateral swelling of the arm, neck, head or face
- distended collatoral circulation over chest wall
- Jaw and shoulder pain
- Headaches and/or a feeling of head fullness
- Localised pain and or numbness [62]

Catheter Related Thrombosis Is Covered in Chapter "Central Vein Thrombosis"

Any attempts to unblock CVC should only be attempted by healthcare professionals who are experienced with the management of such devices and have demonstrated competency in the procedures and management of any potential complications for example catheter rupture.

As part of the initial assessment of a blocked catheter to determine the nature of the occlusion it is recommended that the catheter hub is directly observed to identify if the opening between the catheter hub and catheter has become obstructed with any debris or foreign body, for example a sponge from a port protector. There should be a clear pin prick opening visible when the inside of the catheter hub is viewed. Any visible debris can be removed by using a green (21G) safety needle. The technique should not be attempted on catheters with a proximal valve, for example PASV™ or Solo™. While this may seem an unorthodox method, it must be appreciated that only the external catheter hub is being manipulated. In some cases this method is the only intervention required to restore patency. In a case series of 39 (30 total, 9 partial) occlusions hub clearout with a green (21G) needle was used successfully in 5 (17%) episodes of total occlusion. In 2(7%) episodes this was the only method used. Of the 9 partial occlusions, hub clear out alone was used on 7 (78%) occasions [63].

Before instilling a pharmaceutical agent it is also suggested that manipulation with 0.9% Sodium Chloride for Injection is attempted. During this method a 10 mL Luer lock syringe with 5 mL 9% Sodium Chloride for Injection is attached directly to the catheter hub. A gentle back and forth motion on the syringe plunger is then employed to see if this will dissolve the obstruction. The plunger should only be depressed up to the level of resistance, as forcing the plunger all of the way in could result in catheter rupture. If this process is successful debris from the catheter will become visible in the syringe. Patience is required as it can take up to 30 min plus to dissolve all of the intraluminal debris. Although this method is not cited in the literature, it has been standard practice at St Mark's Hospital UK for more than 20 years.

If these methods do not restore patency then instillation of an appropriate pharmaceutical agent can be considered. During instillation the catheter needs to be monitored catheter closely for signs of "ballooning" or traumatic fracture, and it is essential to have atraumatic clamps close to hand in case of catheter rupture. If the instillation of the selected pharmaceutical agent actually resolves the occlusion, the patient should be observed for at least 30 min. Although uncommon, patients may develop systemic sepsis following restoration of patency and so should be advised of this potential risk, and the need to seek urgent medical treatment if they become unwell. If the pharmaceutical agent is being left in situ for a set time period it is advisable that the patient return for removal of the drug and reassessment of patency by an experienced healthcare professional as opposed to the patient doing this themselves at home.

The evidence supporting the use of different pharmaceutical agents is mixed with studies using different doses, mode of instillation (bolus or infusion) and different dwell times. The type of occlusion (full, partial or complete) is not always mentioned, or the catheter type (PICC, tunneled or implanted port), number of lumens (single, double or triple), catheter material (silicone or polyurethane) valved or non-valved devices and size of syringe used. All of these variables could impact on the results. A review of thrombolytic treatment of catheter occlusion concluded that further randomized comparative studies were needed to determine the most effective management for catheter occlusion [64]. Table 7 outlines commonly used pharmaceutical agents for unblocking central venous catheters. From this it can be appreciated that there is the most evidence supporting thrombotic occlusions, and very scant evidence for occlusions resulting from lipid or drug deposits. There may be restrictions on use in some countries, for example Urokinase is not licensed for use in the United States [64] and Hydrochloric Acid [71] which was used to dissolve drug precipitate is no longer available in the UK.

Table 7 Commonly used pharmaceutical agents for unblocking central venous catheters

Urokinase	Alteplase (t-PA)	Ethanol	Sodium hydroxide
n = 19. 5000 units Urokinase, 5–10 minutes dwell time followed by attempted aspiration, repeated every 5–10 min for a maximum of 30–60 min or successful clearance. Successful restoration in 6 of 19 (32%) cases [65]	n = 25. t-PA 6 occlusions failed to clear with 10,000 units Urokinase 4 h dwell time, 5 of these successfully cleared with 2 mg/2 mL t-PA 4 h dwell time [66]	n = 5. 3 mL Ethanol 70%, 1 h dwell time, patency restored in 4/5 (80%) cases [67]	n = 13 totally implanted port. Partially occluded. 10 mL 0.1 Sodium Hydroxide solution at a rate of 1 mL per hour followed by a 2 h lock. Increase in patency determined by formal assessment of gravity flow rate pre and post intervention. All 13 cases demonstrated an improvement in flow rate [68]
n = 19. 6 h Urokinase 40,000 units per hour. Patency restored in 15/19 (79%) cases [69]	COOL 1 trial. n = 995. Single lumen 26%, double lumen 39%, triple lumen 6% and totally implanted ports 29%. 2 mg t-PA, dwell time 30–120 min. Single dose-restoration of patency in 52% devices at 30 min and 78% devices at 120 min. Second dose—restoration of patency in 84% devices at 30 min and 87% at 120 min. Restoration of patency 86% single lumen devices, 93% double lumen devices, 90% triple lumen devices and 79% totally implanted ports [70]	n = 9. 70% Ethanol up to 3 mL, patency restored in 7/12 (58%) cases. 0.1 Hydrochloric acid up to 3 mL bolus with second dose if unsuccessful left for up to 1 h. Patency restored in 2/3 (67%) cases [71]	
PASSPORT 1 trial. n = 200. Bolus with 12,500–50,000 units Urokinase, or catheter infusion with 100,000–250,000 units of Urokinase. The cumulative success rate for thrombolysis was 90.5% after first intervention, 97% after second intervention, and 99% after three [72]			
PASSPORT 2 trial. n = 117. 53% withdrawal occlusion, 47% total occlusion, Withdrawal occlusion patency restored in 80% cases, total occlusion patency restored in 88% cases. Success dose dependent, 83% success with 5000 units Urokinase, 92% with 25,000 units Urokinase [73]			

Syringe Techniques

Applying a specific syringe technique, on its own or in combination, with 0.9% Sodium Chloride for Injection or pharmaceutical agent, can aid in the restoration of patency. A Luer lock, rather than a Luer slip, syringe must always be used so as to prevent the syringe being expelled during the unblocking procedure. A 10 mL syringe should be used to avoid catheter damage, however only part filling this can be beneficial as it makes it easier to assess the level of blockage. The amount of "give" within the catheter can be determined by pressing the syringe plunger with the thumb. If there is total resistance this suggests that the occlusion affects most of the catheter, whereas if it is possible to depress the plunger with some back and forth motion this suggests that the occlusion does not affect the entire catheter and instillation of any pharmaceutical agent will be possible.

Negative Pressure Technique

This is achieved by using 3 way tap, although it can be undertaken without. The aim is to create a vacuum within the catheter which will then automatically draw whatever fluid is being used to restore patency, i.e. 0.9% Sodium Chloride for Injection, Urokinase, Alteplase or Ethanol [74]. Figure 23 illustrates the negative pressure technique using a 3 way tap or with a single syringe.

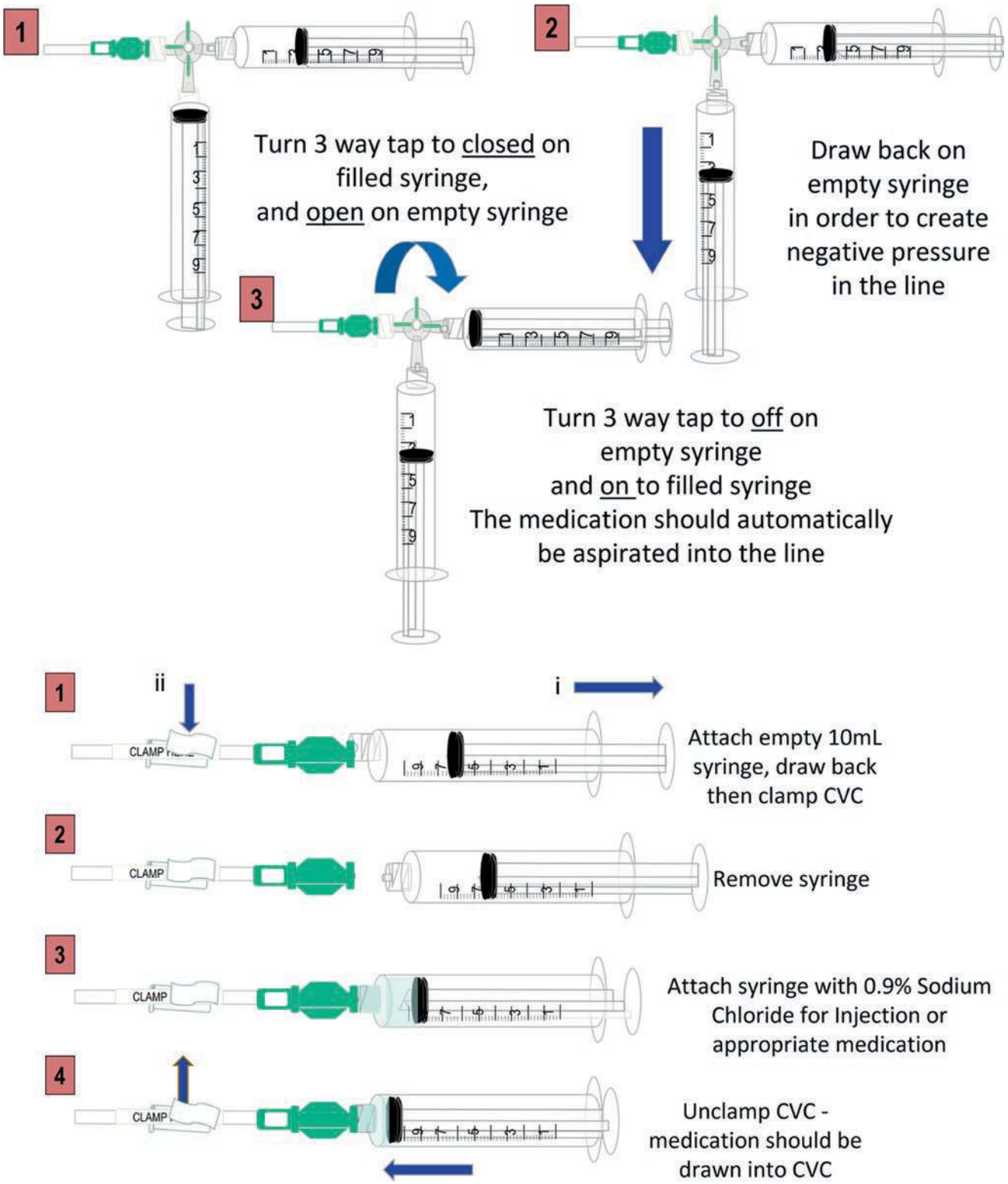


Fig. 23 Negative pressure technique for restoring patency

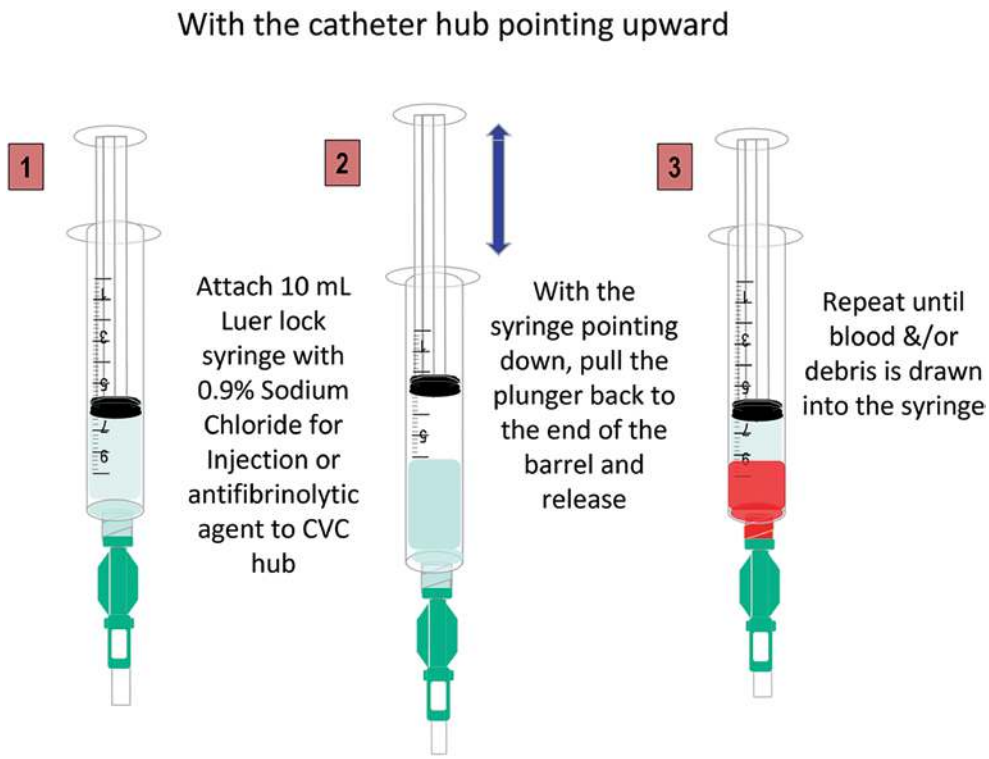


Fig. 24 Percussive POP technique

Percussive POP Technique

The percussive POP technique generates shock waves through the CVC thereby loosening the obstruction and allowing it to be extracted, rather than introduced, into the patient. There is limited evidence to support this technique, however two in-vivo evaluations demonstrated no catheter damage and/or adverse patient outcomes [63, 75]. The first study reported a 94% success rate in 50 catheters with no complications, and the second had a 93% success rate in 39 catheters also with no complications. A further in-vitro evaluation [76] in 30 PICC had a 86% success rate and no catheter damage. As an in-vitro assessment permits the entire catheter length to be occluded with blood this gives valuable information regarding the safety associated with this method. In addition, the POP technique is simple and inexpensive. See Fig. 24.

Maintaining Patency

To maintain patency it important that any infusion fluid is not allowed to sit within the catheter. The catheter should be flushed promptly with 0.9% Sodium Chloride for Injection at the end of an infusion to clear any residue adhering to the inner surface of the catheter [8]. The catheter also needs to be flushed prior to commencing an infusion, and in between any medication. Using effective techniques to flush and minimise the risk of blood backflow into the device should be incorporated into catheter care guidelines. Two established measures are the use of push pause flushing and positive pressure clamping.

Push Pause Flushing

Flushing with a stop start—"push-pause"—motion causes turbulence of flow, thus preventing the build-up of blood and/or infusion deposits within the catheter, which could lead to occlusion [77]. A review of the literature found that pulsatile (push pause) flushing is most efficient when undertaken briskly with only a 0.4 s pause between each push [78]. See Fig. 25.

Syringe size is important when flushing a CVC due to the pressure that is generated. Syringes of 10 mL or greater should be used as smaller syringes generate more pressure which could rupture the CVC [46].

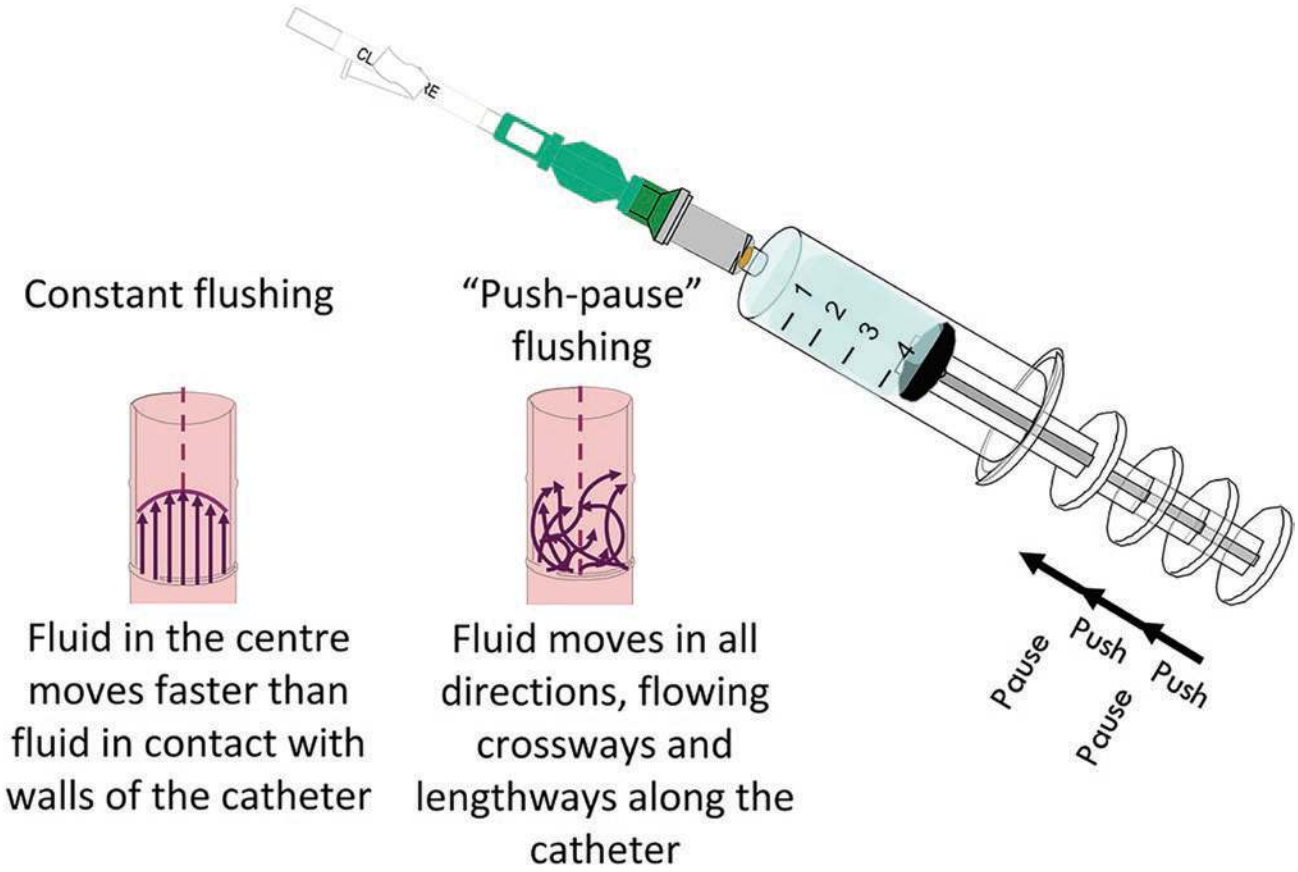


Fig. 25 Push pause flushing

Positive Pressure Clamping

Maintaining a positive pressure within the catheter lumen may reduce the risk of occlusion resulting from blood backflow into the catheter tip. Clamping the catheter while injecting the last few millilitres of fluid seals a column of fluid in the catheter and this may limit the amount of blood that refluxes back up the catheter [46]. For valved catheters with no integral clamp, positive pressure can be achieved by keeping the thumb on the syringe plunger while removing the syringe. See Fig. 26.

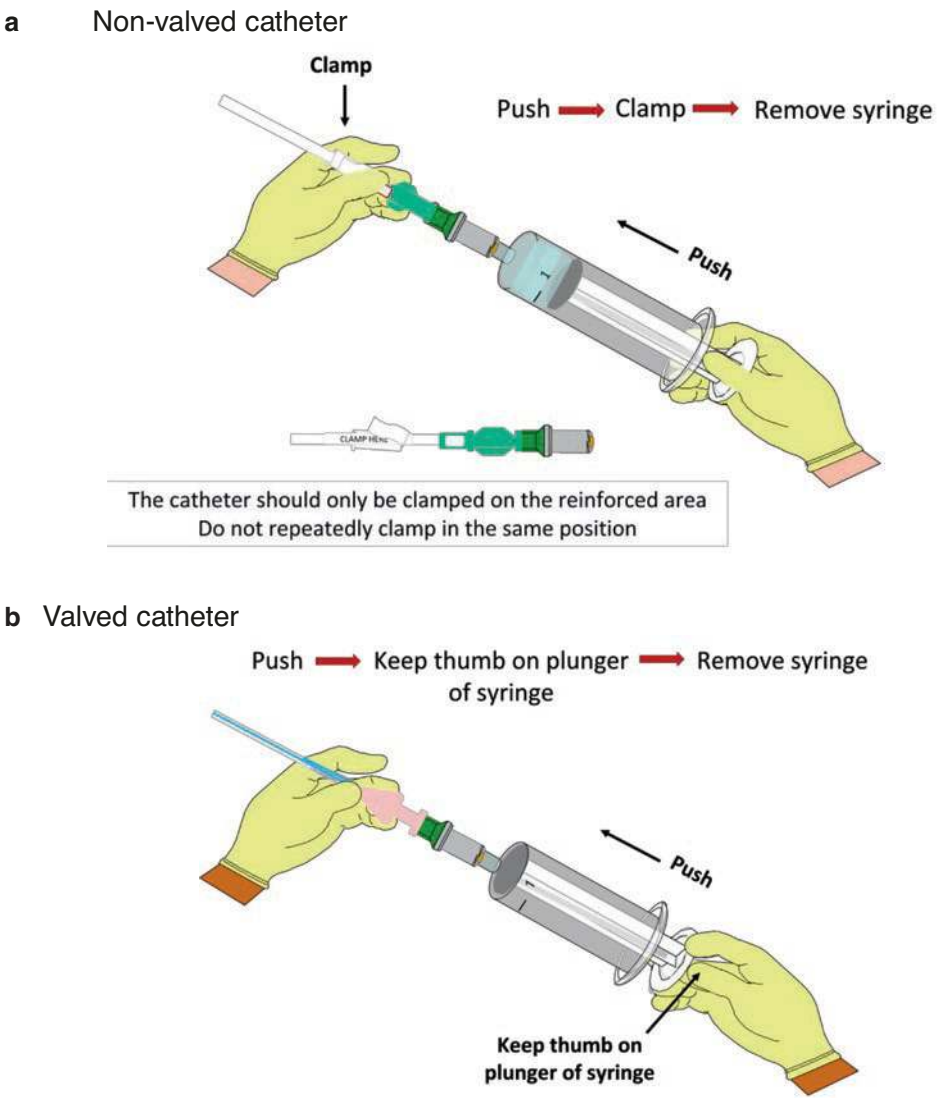


Fig. 26 Positive pressure clamping in non-valved and valved catheters. (**a**) Non-valved catheter. (**b**) Valved catheter

Positive Pressure and Anti-reflux Needle Free Connectors

Positive pressure can also be obtained with the use of either a positive pressure Needle Free Connector, or an anti-reflux Needle Free Connector. Positive pressure connectors, for example CLC2000® (ICU Medical), will expel a small amount of flushing solution from the catheter tip thereby preventing or minimising the amount of blood backflow. To achieve this they require a different clamping sequence than standard needle free connectors (NFC). The syringe should be removed *before* the line is clamped—as opposed to after.

There is conflicting data on their ability to reduce occlusion when compared to other types of connector [79]. This may be due to the variation in design making it hard to draw definitive conclusions. If considering the introduction of positive pressure valves it is recommended that individual manufacturers safety and efficacy data, alongside any restrictions of use, for example valved catheters, is reviewed.

An anti-reflux connector, for example TKO® valve bonded onto a needle free connector, may also help reduce blood backflow. The TKO® 3 way pressure sensitive valve is closed unless a syringe or giving set is attached and fluid injected. The valve will also open if the plunger on an attached syringe is pulled back thereby allowing blood sampling. Jasinsky and Wurster demonstrated a statistically significant reduction in occlusion rates, from 30% to 12.5% of catheters ($p < 0.01$) over a 3 month period when using a TKO® valve bonded to a Nexus needle free connector [80]. In the UK the TKO® valve is bonded to a Vygon Bionector. The TKO® valve should not be used with catheters which already have a valve, for example Groshong™, PASV™ and Solo™. See Fig. 27.

Fig. 27 Example of a positive pressure valve and anti-reflux connector

Catheter Damage and Repair

The ability to be able to repair damaged devices is of clinical benefit as it can mitigate the need to change the catheter. There are a number of ways a catheter can become damaged, for example;

- Flushing against resistance
- Use of small syringes (<10 mL)
- Power injection of contrast material in non-power injectable devices
- Use of scissors/sharp objects near CVC
- Repeatedly clamping in the same place
- Getting catheter caught in a door
- Contact with pets

Prevention strategies include;

- Routine movement of clamp along reinforcement area
- Securing end of the CVC to prevent contact with sharp objects

It is possible to repair Hickman™ CVC with manufacturer specific repair kits. There are different ones available for single and double lumen catheters, and whether a single lumen pigtail or both lumens are affected. There needs to be sufficient undamaged native line available—approximately 5 cm from the exit site—as the damaged section will be removed to allow a new catheter segment with clamp and hub to be applied. While a formal repair kit with new catheter segment and hub is available for Groshong™ catheters, replacement hubs are also available, meaning that a repair can also be more simply achieved by removing the damaged section and inserting a new Groshong™ hub.

Catheter repair kits should be available and staff familiar with their application. A skillful repair to a damaged/split line prevents the trauma and risk of a fresh insertion and can maintain the integrity of a line for several years. Catheter repair has not been associated with an increase of infection [81–83].

Discharge Planning

Discharging a patient on home parenteral support is complex and will inevitably vary from country to country depending on funding arrangements, availability of equipment, and provision of any specialist nursing support. Within England there is a national framework agreement which covers compounding and delivery of the parenteral support, ancillaries, equipment and specialist nursing support if clinically indicated. Key documents from this framework are included as examples, as it is recognised service specifications will vary according to what is available locally.

Discharge planning needs to consider the following criteria;

- Is the patient suitable for homecare?
- Who will fund, prescribe and provide the parenteral support?
- What are the specific nutrient and/or fluid requirements?
- Who will fund and provide the necessary ancillaries and equipment?
- Who will care for the catheter and administer the parenteral support?
- Ongoing support arrangements for patients once discharged

Is the Patient Suitable for Homecare?

This assessment needs to consider where the patient intends to reside on discharge, practical issues such as mobility and dexterity alongside identifying any potential safeguarding concerns, psychological well-being, and the patients' social support network. The English National Framework Patient Needs Assessment form can be found in Appendix 2 at the end of this chapter. A pre-discharge home assessment is recommended to ensure the basic requirements—electricity and running water—are in place. While some patients may want a separate room to undertake their procedures, this isn't clinically necessary, and the nurse is well placed to guide the patient in identifying where equipment and ancillaries will be stored, and also where the procedures will take place.

The challenge arises if it is felt that a patient is *not* suitable for homecare, for example safety concerns regarding the line, as there is no easily identifiable and sustainable alternate way for the infusions to be administered.

Who Will Fund, Prescribe and Provide the Parenteral Support?

Funding streams will vary from country to country. It is recommended that one staff member is allocated the task of securing funding so as to act as a central point of contact

with the relevant commissioning body. It is important to identify who will be prescribing and providing the parenteral support, when the first delivery will be made, how frequent subsequent deliveries will be, and what time of day these will occur. Upon discharge there should be a supply of sufficient Parenteral Support to ensure uninterrupted therapy The Parenteral Support may be provided by a commercial homecare company, hospital pharmacy or community pharmacy depending on what is available locally.

Within England funding is automatically secured by an online high cost management system known as Blueteq. Only hospitals who have been approved to provide a home parenteral support service have access to this, and approval is automatic as long as all of the clinical criteria set out are met.

What Are the Specific Nutrient and/or Fluid Requirements?

When formulating a home parenteral support prescription consideration the needs to be made regarding the practicalities of the regimen being administered at home. For example, while it may be possible to gain stability on a 4 L bag, will the patient be able to lift and carry this around? Although the infusion becomes more manageable as more fluid is infused, sometimes it may be necessary to have two infusions of a manageable size, for example a 3 L bag followed by a litre bag.

How long a patient infuses for can impact on their daily routine so this needs to be considered when sending a patient home on parenteral support. Infusion rates in hospital are usually dictated by the shift pattern of nursing staff, but at home the self-caring patient can have more flexibility. Things to consider when determining flow rates include the hourly content of glucose and certain electrolytes, for example potassium and magnesium. Patients/carers should be informed of the maximal hourly infusion rate they can use, but some may choose to infuse over a longer period so as to not have to wake early to disconnect.

The infusion *mode*—same volume throughout, or variable—also needs to be considered. A variable rate is achieved by programming the infusion pump to taper run the infusion at a slower rate at the beginning and end of the infusion. This can be useful in preventing rebound hypoglycaemia [84].

Who Will Fund and Provide the Necessary Ancillaries and Equipment?

It is easier if the ancillaries and equipment can be provided by the same provider as the Parenteral Support, but it is appreciated that this may not be possible in all countries. Ancillaries and equipment *may* need to be provided by a number of providers depending on the classification of the product, for example dressings may need to be provided from a different source than disinfection wipes or needle free connectors.

When selecting ancillaries there should be consideration of whether or not the patient and/or carer is able to use them, and not just replicate what has been used in hospital. For example, some dressings require both hands to apply which may prove challenging, so "1 hand" dressings which have a rigid frame to keep the dressing material wrinkle free during application may be easier to use. This may seem trivial, however it could mean the difference between a patient being able to undertake their own dressing change or needing to rely on someone else to do this. Other considerations include the use of gloves with textured finger tips to aid with inserting the pump giving set into the bag of parenteral support, or selecting a larger profile needle free connector which is easier to manipulate.

All ancillaries and equipment must meet local medical device related regulations, for example CE/UKCA marking, and it must be determined that the patient and/or carer are not allergic to any of the materials contained within them.

The patient will need to identify suitable storage for ancillaries and equipment and this needs to be discussed with them prior to discharge, so as to prepare them for the volume of items which need to be stored. Ancillaries need to be stored off the floor in a clean and dry environment. Some patients may opt to buy plastic storage units with drawers, but a chest of drawers or cupboard is equally suitable. Fridges may be stored in an outside garage or shed but they may need to be moved inside during the winter months as fridges can only work normally if the temperature of the room in which they are situated is warmer than the temperature inside the fridge. If the patients' regimen includes the use of sharps then they need to be supplied with an approved sharps container which needs to be stored out of reach of children or pets. The patient needs to be aware of how to dispose of filled containers and receive replacements.

Who Will Care for the Catheter and Administer the Parenteral Support?

Where possible the patient should be trained to care for their catheter and administer the parenteral support. Not only does this promote autonomy it also reduces the number of people accessing the catheter. Assessment to determine if a patient will be able to self-care includes visual acuity, manual dexterity and strength. Deficiency in any of these might impact upon the patient's ability to undertake the procedures themselves, but thinking creatively may help resolve the issue(s). For example, patients often struggle to insert the giving set spike into the parenteral support. As well as using gloves with textured fingers, having the bag of parenteral support laid on a flat surface as opposed to hanging on a drip stand might enable the patient to successfully insert the giving set.

Patients with manual dexterity issues may benefit from having prefilled 0.9% Sodium Chloride for Injection syringes as opposed to manually drawing up flush solution. Even if patients cannot undertake all of the required procedures they may be able to undertake *some*, for example they may be able to disconnect and change their dressing, but not be able to connect an infusion.

If a patient is unable to undertake their own procedures then alternative arrangements need to be made. It may be possible to identify a family member/carer who is able *and* willing to be trained. Due to the severity of potential complications, most notably sepsis, both parties need to be happy with this arrangement. Logistics, such as availability for all connection and disconnection visits, also needs to be determined.

Nursing support will need to be secured for patients unable to undertake their own procedures and have no identifiable family member/carer who can learn. This can prove challenging as not all community based nursing services will have experience of central venous catheter management and administration of parenteral support. While community based IV therapy services may exist their remit is usually for short term IV medication administration, and doesn't extend to long term infusion therapies. Within England, the National HPN Framework also includes specialist nursing support. These nurses have to be able to demonstrate competency in the understanding of gastrointestinal function, parenteral support, care of central venous catheters, and recognition of common catheter related complications. These competencies can be found in Appendix 3. While they may seem excessive it serves to illustrate the complexity of care a patient on home parenteral support requires.

Patient/Carer Training

Just as with the nurse competencies there is an English national framework patient competency document outlining what the patient/carer needs to learn. Broadly speaking these cover;

- Understanding how their gastrointestinal function has changed,
- How to safely access the catheter and administer the prescribed parenteral support
- Care for the skin around the catheter
- Troubleshooting common catheter and infusion related complications

The full patient/carer competency document can be found in Appendix 4.

The specific steps needed to undertake these procedures will vary depending upon a number of things;

- The type of catheter, PICC, tunneled Hickman™ type, or implanted port
- Whether the catheter is valved or non-valved
- If the patient is receiving additional medications via the catheter
- Number of lumen the catheter has
- If the patient is receiving one infusion at a time or 2[1]

There are common elements to all procedures, for example hand decontamination and putting on sterile gloves. In addition, all procedures start and end with a social handwash, and can be broadly broken down into the following stages;

- Create an aseptic field with equipment needed to undertake procedure
- Create an aseptic field around the catheter
- Undertake procedure

Creating a Suitable Environment

Patients do not need to make any alterations to their home, but there are some basic "housekeeping" principles to bear in mind when deciding on where the procedures will be undertaken;

1. Where will the procedures take place?

The patient needs to think about how easy it will be for themselves, their carer and/or the nurses to get from where they will wash their hands to where the procedures will take place. Doors should be left open if possible and clean hands protected with a clean paper towel/muslin cloth to minimize the hands becoming contaminated from manoevering the drip stand/back pack. If training is happening in hospital, this should be identified at the outset, so that the patient feels confident to undertake their procedures in a new setting when discharged.

2. Is there anything within the chosen area that could be an infection risk?

There should be no vacuuming during the procedures, or fans in operation, as these will generate dust, and dust contains micro-organisms. It is advisable that any windows are closed and pets kept in a separate room while the procedures are in progress.

In addition to the practical procedures training also needs to consider troubleshooting and lifestyle considerations such as bathing and showering. The full version of the patient training competencies can be found in Appendix 4.

[1]The UK has seen a move from all patients being able to have a compounded regimen to using Multi Chamber Bags with additional IV fluids where clinically possible. This has been due to capacity constraints and product shortages, and has resulted in different ways of administering parenteral support, including separate vitamin/mineral infusions, use of double/triple spike giving sets which allow multiple concurrent infusions (stability permitting), and double lumen extension sets.

Table 8 Catheter and infusion related problems

Problem	Detail
Local infection	Can identify signs and symptoms of
	• Exit site infection
	• Tunnel infection
	• Cuff infection (Hickman™ type catheter only)
	• Port pocket infection (implanted port only)
	• Can identify the correct action to take
Bloodstream infection	• Can identify signs and symptoms of a bloodstream infection and the correct action to take
Blocked catheter	• Can identify signs of a blocked catheter
	• Knows simple first aid measures, for example massaging under the clamp, changing the needle free connector
	• Can identify the correct action to take
Catheter fracture	• Can identify catheter fracture
	• Knows to apply atraumatic clamp above the damaged area
	• Can identify the correct action to take
Catheter related thrombosis	• Can describe signs and symptoms of thrombosis (all catheters)
	• Can describe signs and symptoms of thrombophlebitis (PICC)
	• Can identify the correct action to take
Fluid overload	• Can describe signs and symptoms of fluid overload
	• Can identify the correct action to take
Dehydration	• Can describe signs and symptoms of dehydration and when additional IV fluids are required
Catheter malposition	• Knows function of cuff (Hickman™ type catheter) and approximate location within skin tunnel
	• Knows external length of PICC (If applicable)
	• Understands the implication of catheter malposition and correct action to take

Troubleshooting

Correct and early recognition of catheter and infusion related problems is essential in patients receiving home parenteral support. Patients/carers need to be able to identify the complications listed below *and* the correct action to take (Table 8).

Body Image

It is easy to appreciate how a patient with a stoma or fistula may experience issues with body image, however the impact from a central venous catheter is probably underestimated. While patients may be grateful that there is an effective treatment for their medical condition this doesn't necessarily mean that the presence of a central venous catheter isn't associated with psychological issues [85]. Negative feelings associated with a central venous catheter include the catheter being viewed as the intrusion of a foreign body which can become the focus for neglect, self-harm and abuse. There are reports of patients deliberately damaging their catheter and of injecting faecal matter through it. Patients have described being tethered to the pump during infusions with associated restriction in their daily activities. Rather than being seen positively as a lifeline, patients may describe the catheter tethering them like an umbilical cord to the hospital and healthcare professionals. The catheter has also been associated with disruption in gender identity. This is presumably due to having something hanging from the body, however it may also be experienced by patients with totally implanted ports if the size and shape of the port are clearly visible on the chest wall [85]. For some, having nutrition and/or hydration in liquid form parenteral support may be seen as a return to early childhood where they were reliant on liquid nutrition.

Being aware of the possible psychological issues patients may experience will hopefully facilitate conversation between the nurse and patient, and identify possible measures to alleviate some of these. Examples include suggesting an implanted port, positioning the exit site of a Hickman™ type catheter in a less visible position such as on the side of the body below the armpit and discussing infusion times and how they can be best fitted in around their day.

Ongoing Support Arrangements for Patients Once Discharged

Patients need to know of ad hoc and scheduled support arrangements once they are discharged. It is important to manage patients expectations regarding this, particularly regarding the frequency of scheduled follow up. Before being discharged on Home Parenteral Support patients will have had a lengthy inpatient stay during which they would have been reviewed regularly by the multidisciplinary team, individually, and as a team. They may also have developed friendships with other patients. This stops on discharge which some patients might find daunting.

Once discharged patients need to know *who* and *how* to contact should they have any questions, or think they have developed a line or Parenteral Support related problem. This must include out of normal working hours, weekends and public holiday arrangements. Encourage patients to enter any relevant phone numbers into their mobile phone *before* they are discharged, as paper copies may be lost among the volume of paper information they will receive on discharge.

It must be appreciated that patients may initially feel overwhelmed on discharge when the reality of how Intestinal Failure has changed their pre admission life becomes truly

Table 9 BIFA recommendations for haematological and biochemical monitoring of HPN (Home Parenteral Nutrition) [86]

British Intestinal Failure Alliance (BIFA) Guidance. Haematological and biochemical monitoring of adult patients receiving Home Parenteral Nutrition
1. All haematological and biochemical monitoring of HPN (home parenteral nutrition) patients should be individualised and may change with their clinical condition. The point at which patients become stable post discharge will vary
2. Routine blood tests, including standard electrolytes, chloride, bicarbonate (as a measure of acid-base balance), calcium, magnesium, phosphate, renal and liver function tests, glucose, full blood count, ferritin and CRP should be performed monthly for the first 3 months after discharge. If stable this may then be 3–4 monthly
3. When discharged patients should have their prothrombin time, cholesterol and triglyceride, HbA1c, vitamin D & B12 and folate concentrations checked. These should then be monitored at least 6-monthly
4. Patients who are to receive long-term HPN should have baseline vitamins A&E, zinc, copper, manganese and selenium concentrations checked and then monitored 6-monthly
5. If the CRP is significantly raised (>20 mg/l) iron can be measured with transferrin and transferrin saturation to assist interpretation of iron status. In this situation care must be taken in the interpretation of zinc, copper, selenium and vitamins A, D and E in view of their inflammatory response
6. When measuring zinc, copper, manganese or selenium use a trace element-free collection tube
7. If the triglyceride concentration is elevated a fasting concentration should be repeated
8. Urine sodium concentration is useful for assessing sodium balance in patients with a short bowel and a 24-h urinary oxalate collection for assessing risk of renal stone formation in patients with a short bowel and colon in continuity

apparent. The initial joy of being home may be replaced by anxiety over how to incorporate parenteral support and or stoma/fistula management into their daily life. Patients should be made aware of patient support groups, for example PINNT (Patients on Intravenous and Nasogastric Tube Therapy, www.pinnt.com) who can provide support, education and practical advice about living with parenteral support. Encouraging an activity, within physical capacity, which gives pleasure and expresses individuality, may help to provide continuity with their past life and serve as hope that not all aspects of their pre intestinal failure life are over. It needs to be recognized that patients will have different goals for example one patient may view going on an overseas holiday to be a major achievement, whereas others may view getting dressed and going out for coffee to be of equal achievement.

Patients should be regularly reviewed in a specialized multidisciplinary outpatient clinic with staff experienced in intestinal failure and parenteral support [7]. Frequency and nature of this follow up will depend on how stable the patient is with regard to their prescribed regimen. BIFA (British Intestinal Failure Alliance) statement regarding haematological and biochemical monitoring are listed in Table 9 [86].

In addition to the haematological and biochemical monitoring, outpatient review should also cover appropriateness of current parenteral support regimen, weight, anthropometry, review of the central venous catheter, any issues with deliveries of parenteral support and necessary ancillaries, and quality of life.

Summary

Patients receiving home parenteral support have a lot to incorporate into their daily lives including the administration of parenteral support, maintenance of their central venous catheter and stoma/fistula management. In addition they may also have debilitating symptoms such as nausea/vomiting and chronic pain. Nurses are well placed to help patients integrate back into the community and live as full a life as possible.

Acknowledgments formally of
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Appendix 1. British Intestinal Failure Alliance (BIFA) Guidance

Standardised Parenteral Support Catheter Guidelines

Connecting a Parenteral Support (PS) Infusion

Key Principles of Care and Management of Central Venous Catheters.

- Identify the key parts.
- Ensure no touching of any key parts during the procedure.
- Apply alcohol hand rub directly to hands during the procedure if touching any non-sterile contents and/or if there is any risk of contamination.

Social Handwash

Step 1—Gather & Check Equipment

- Bag of parenteral support (PS) (Check PS prescription, integrity of bag & expiry date)
- Trolley/tray
- Detergent wipes (or paper towel, soap and water)
- 2% CHG & 70% IPA disinfectant wipes • Sterile dressing-pack or dressing towels
- Gloves of choice (as recommended by HPN Centre)
- 10mL pre-filled syringe(s) 0.9% sodium chloride for injection

- Alcohol hand rub
- Sterile intravenous giving set
- Surgical tape
- Infusion pump, stand/rucksack

Step 2—Aseptic Handwash
Step 3—Prepare Equipment

- Clean & disinfect trolley/tray surface
- Attach strips of tape to the edge of the trolley/tray
- Open sterile dressing pack/towel onto trolley/tray surface to create an aseptic field
- Open equipment needed onto aseptic field
- Using gloves (as recommended by HPN Centre) spike bag of PS and prime giving set

Step 4—Prepare Patient & Catheter

- Open sterile towel & place under catheter. Tape in place.
- Remove any outer dressing covering the catheter (if used) & port protector (if used)

Step 5—Access Catheter

- Put on gloves
- Disinfect needle-free device (The order of these first 2 steps can be interchanged depending on HPN Centre recommendation)
- Prime pre-filled syringe(s)
- Attach syringe to needle-free device and flush catheter using push pause flushing and positive pressure clamping technique (as recommended by HPN Centre)
- Attach giving set

Step 6—Start infusion & Secure Catheter

- Ensure giving set & catheter clamps are released
- Start infusion at prescribed rate
- Remove gloves
- Secure catheter (as recommended by HPN Centre)

Step 7—Clear away

- Complete any documentation

Social Handwash

Disconnecting a Parenteral Support (PS) Infusion

Key Principles of Care and Management of Central Venous Catheters.

- Identify the key parts.
- Ensure no touching of any key parts during the procedure.
- Apply alcohol hand rub directly to hands during the procedure if touching any non-sterile contents and/or if there is any risk of contamination.

Social Handwash
Step 1—Gather & Check Equipment

- Trolley/tray
- Detergent wipes (or paper towel, soap and water)
- 2% CHG & 70% IPA disinfectant wipes
- Sterile dressing-pack or dressing towels
- Gloves of choice (as recommended by HPN Centre)
- 10mL pre-filled syringe(s) 0.9% sodium chloride for injection
- Alcohol hand rub
- Port protector (as recommended by HPN Centre)
- Surgical tape

Step 2—Aseptic Handwash
Step 3—Prepare Equipment

- Clean & disinfect trolley/tray surface
- Attach strips of tape to the edge of the trolley/tray
- Open sterile dressing pack/towel onto trolley/tray surface to create an aseptic field
- Open equipment needed onto aseptic field

Step 4—Prepare Patient & Catheter

- Switch off pump and close clamp on giving set
- Open sterile towel & place under catheter. Tape in place.
- Remove outer dressing (if present) to release catheter and clamp catheter (if present and recommended by HPN centre)

Step 5—Access Catheter

- Put on gloves
- Disconnect giving set from needle-free device (The order of these first 2 steps can be interchanged depending on HPN Centre recommendation)
- Disinfect needle free device
- Prime pre-filled syringe(s)
- Attach syringe(s) to needle-free device and flush catheter using push pause flushing and positive pressure clamping technique (as recommended by HPN Centre)
- Attach port protector (as recommended by HPN centre)

Step 6—Secure catheter

- Remove gloves
- Secure catheter (as recommended by HPN Centre)

Step 7—Clear away

- Complete any documentation

Social Handwash

Changing the Parenteral Support (PS) Catheter Dressing

Key Principles of Care and Management of Central Venous Catheters

- Identify the key parts.
- Ensure no touching of any key parts during the procedure.
- Apply alcohol hand rub directly to hands during the procedure if touching any non-sterile contents and/or if there is any risk of contamination.
- This procedure should not be incorporated into any other procedure in which the catheter hub is manipulated so keeping the risk of cross contamination to a minimum.
- Dressings need to be changed every 7 days, if they are soiled or have become loose. A fabric island type dressing is recommended if there is discharge from the exit site.

Social Handwash

Step 1—Gather & Check Expiry Dates of Equipment

- Trolley/tray • Detergent wipes (or paper towel, soap and water)
- 2% CHG & 70% IPA disinfectant wipes
- Sterile dressing-pack or dressing towel
- Gloves of choice (as recommended by HPN Centre)
- Single use 2% CHG & 70% IPA sponge applicator(s)
- Sterile dressing(s) of choice
- Alcohol hand rub
- Suture-less securement device (if required)

Step 2—Aseptic Handwash

Step 3—Prepare Equipment

- Clean & disinfect trolley/tray surface
- Open sterile pack/towel and create an aseptic field
- Open equipment needed onto aseptic field

Step 4—Prepare Patient & Catheter

- Remove existing dressing(s) &/or suture-less securement device
- Attach anchoring strip (if present) from suture-less securement device

Step 5—Access Catheter

- Put on gloves of choice (as recommended by HPN Centre)
- Disinfect skin with single-use 2% CHG & 70% IPA sponge applicator(s)
- Apply dressing(s) &/or suture-less securement device as per manufacturer's recommendation

Step 6—Secure Catheter

- Remove gloves
- Secure catheter (as recommended by HPN Centre)

Step 7—Clear away

- Complete any documentation

Social Handwash

Glossary of Terms

Alcohol hand rub
An alcohol containing product (gel or foam) designed to reduce the number of micro-organisms on the hands. It should be applied to clean, dry hands, and the hands rubbed together, following the steps in the aseptic hand washing technique, until they are completely dry.

Aseptic hand wash
A thorough hand wash procedure concentrating particularly on the areas of the hands where resident bacteria can be found. To be effective the hand wash solution must come into contact with all of the surfaces of the hands and wrists. While there are many different hand washing techniques cited in the literature (with 6–13 steps) the principles are the same, to make sure all surfaces of the hands (including the wrists), are adequately washed, rinsed and dried, especially those areas which may be missed such as finger tips, thumbs and between the fingers.

CVC
A vascular access device whose tip lies in the lower third of the superior vena cava or the upper third of the inferior vena cava (ideally at the vena cava / right atrial junction). They can either be centrally inserted via the subclavian, internal jugular or femoral veins or peripherally inserted via the brachiocephalic veins. The femoral route, which may have a higher risk of infection, is chosen when the upper veins cannot be accessed.

Disinfectant wipes
Single use wipes containing 2% chlorhexidine and 70% isopropyl alcohol (2% CHG & 70% IPA). The combination of both disinfectants is thought to be more effective than when either is used alone.

Key-Part(s)
Things which if touched directly or indirectly could result in the introduction of micro-organisms. They include the catheter hub, the end of the giving set, syringe tip and the skin surrounding the exit site.

Needle Free Connector (NFC)
A device which permits the connection of administration sets, and syringes to the hub of a vascular access device without the use of needles. They were introduced to reduce the incidence of needle stick injuries. They should be disinfected using pressure and friction for a minimum of 15 s prior to, and after, each time they are accessed.

Parenteral Support (PS)
A term which covers both parenteral nutrition and parenteral fluids.

Port Protector Cap
A disposable single use disinfection cap that contains 70% Isopropyl Alcohol (IPA). The port protector twists onto the end of a needle free connector to passively disinfect *and* protect from cross contamination during infusion free periods.

Positive pressure clamping technique
The catheter is clamped while flushing with the last mL of solution so as to seal a column of fluid within the catheter. This may reduce the backflow of blood and thereby the risk of occlusion.

Push-Pause flushing technique
Flushing with a stop/start motion causes turbulence of fluid within the catheter that may help reduce the build-up of any deposits and reduce the risk of occlusion.

2% chlorhexidine gluconate (CHG) & 70% isopropyl alcohol (IPA) sponge applicator
These are single use sponges contain 2% CHG and 70% IPA are designed to disinfect the skin around the exit site. By using gentle, repeated back and forth strokes for 30 s this provides an effective reduction on bacterial load on the skin.

Social hand wash
Also known as a routine hand wash. A general hand wash to remove transient microbes picked up on the hands during daily activities.

Sterile gloves
These have traditionally been advised as best practice for the administration of parenteral support however non sterile gloves can be used. Sterile gloves had been thought to reduce the risk of infection by reducing the transfer of micro-organisms to and from the wearer's hand. The wearing of gloves is not a substitute for hand washing.

Sterile towel
This can be either supplied separately or within a dressing pack. The towel is used to create the aseptic field onto which the sterile items are placed. A second sterile towel is used to lie under the patient's catheter thereby creating an aseptic field when accessing the catheter.

Appendix 2. Patient Needs Assessment Form for HPN, NHS England 2019® (Used with Permission)

The purpose of this document is to assess if the patient is suitable for homecare and HPN. It should be used in conjunction with discharge planning documents used in the Purchasing Authority. It can also be used once the patient is at home if there are any changes in the patient's circumstances and/or to periodically assess a patient's suitability to undertake training for care of their central venous catheter.

Date of Assessment:	**Assessment conducted by:**	
Patient Name	**DOB**	**NHS Number**
Preferred name	**Employment/Education Status**	
Permanent address:	**Secondary address:** (students, initial discharge address (if different from permanent), children living at 2 addresses including temporary foster care placement	
General	**Concerns and Comments**	
Underlying illness leading to intestinal failure		
Does the patient have any co-morbidities that may result them being unsafe at home?		
What is the patient or carers' understanding of the risks and benefits of having a central venous catheter (CVC)? Are there any concerns that the patient may be unsafe with a CVC?		
What medications is the patient on?		
Psychological wellbeing with regards to HPN. Are there any concerns here such as self-harm, neglect or abuse?		
Is there family support for the patient going home on HPN? Are there any concerns? Include details of any hospice/respite facility referrals or details.		

Are there any safeguarding issues? Include Social Worker details and any safeguarding plans.		
Home environment—use RPS standard document for assessment		
Physical	**Comments**	
Mobility:		
Are there any concerns regarding mobility		
Yes/No		
If yes		
Physio assessment/OT		
Yes/No		
Date:		
Dexterity:		
Is dexterity limited		
Yes/No		
Can patient perform activities of daily living?		
(Washing, dressing etc.?)		
Yes/No		
If issues		
OT assessment		
Yes/No		
Vision:		
Does the patient have any visual impairments Yes/No		
If yes—what modifications are needed before discharge?		
Hearing:		
Does the patient have hearing impairments? Yes/No		
If yes—what modifications are needed before discharge?		
Other health concerns:		
Yes/No		
Stoma care, wound care, palliative support, medication, diabetes, respiratory conditions, drug / alcohol intake etc.)		
If yes—please list what extra services are required		
The following 3 questions need to be completed for both the patient and carer(s) who would be undertaking administration of parenteral support and care of central venous catheter	**Patient**	**Carer(s)**
Communication: (Reading and spoken)		
Reading barriers		
Yes/No		
Language barriers		
Yes/No		
If yes—how will this be addressed before discharge		
Cognition:		
Does the patient have a clear understanding of procedures and protocol? Yes/No		

Specific training assessment questions		
These questions are aimed at determining an individual's physical ability to undertake HPN procedures		
Can they use a smartphone/ electronic tablet? Yes/No		
Unscrew/screw on a lid such as on a toothpaste tube?		
Yes/No		
Open a packet, such as a plaster/ packet of crisps		
Yes/No		
Can they lift a weight equivalent to a bag of PN such as 4 litres of milk?		
Yes/No		
Can they raise it as high as a drip stand?		
Yes/No		
Recommendations for administration of HPN and care of CVC		
Train to become independent		
Yes/No		
Re-assess once at home		
Yes/No		
Family member* to train		
Yes/No		
Joint care (patient / family member*/nurse) Yes/No		
Full nursing support		
Yes/No		
Transition training (paed-adult services)		
Yes/No		
*It is recommended that any family member taking on the responsibility is 18 years of age or older		
For patients assessed as being able to train to independence		
Does patient understand the remit of the nursing service and that NHS England expects patients to self-care unless assessed as being unable to learn?		
Yes/No		
General Comments:		
Action plan		**Date achieved**
Signature of healthcare professional undertaking assessment:		**Date**

This record should be made available to the Contractor and the record kept in the patients notes at the Purchasing Authority

Appendix 3. Home Parenteral Nutrition Nurse Competencies NHS England 2019® (used with permission)

Home Parenteral Nutrition Nurse Competencies

Aim: The nurse administering home parenteral nutrition (whether from a homecare company or an NHS nurse undertaking this work) will need to acquire the knowledge and skills listed below.

All nursing staff need to be aware of the following British Intestinal Failure Alliance (BIFA) documents;

- Guidance Standardised Parenteral Support Catheter Guidelines, https://www.bapen.org.uk/pdfs/bifa/standardised-parenteral-support-catheter-guidelines.pdf
- Intestinal Failure Alliance (BIFA) Recommendations for Catheter Related Blood Stream Infections (CRBSI) Diagnosis https://www.bapen.org.uk/pdfs/bifa/recommendations-for-crbsi-diagnosis.pdf
- British Intestinal Failure Alliance (BIFA) Recommendation Management of Catheter Related Blood Stream Infections (CRBSIs) https://www.bapen.org.uk/pdfs/bifa/recommendations-on-management-of-crbsi.pdf

Learning outcome	Achieved (date)	Signature
1. Intestinal failure		
a. Understands principles of normal intestinal function		
b. Can describe how gut function has changed in someone with intestinal failure		
c. Understands common drug therapy used in patients with intestinal failure.		
d. Knows how to minimize effect of GI changes on fluid balance in someone with intestinal failure		
e. Has an understanding of the paediatric specific nursing considerations (where applicable)		
2. Vascular access devices used for home parenteral nutrition		
a. Can identify the following devices; tunneled catheter, PICC, implanted port		
b. Can identify commonly used tunneled catheters, for example Vygon, Bard and Cook		
c. Can identify commonly used valved devices, for example Groshong, PASV and Solo and knows the position of the valve		
2. To understand principles of asepsis		
a. Washes and dries hands effectively		
b. Applies hand rub correctly		
c. Applies gloves correctly		
d. Cleans and disinfects general aseptic field (for example, plastic tray/trolley) correctly		
e. Correctly opens sterile items onto aseptic field		
f. Can identify key parts and non-key parts		
g. Understands the concept of key part and key site management		
h. Disinfects needle free connector for minimum of 15 seconds with pressure and friction, and allows to dry for 30 seconds		
3. To safely disconnect and flush catheter		
a. Deals appropriately with pump and catheter at end of infusion		
b. Prepares syringe with flushing solution correctly		
c. Understands the rationale behind pulsatile flushing and can demonstrate flushing a catheter with push-pause technique		
d. Understands the rationale behind positive pressure clamping and can demonstrate effectively when disconnecting a syringe (open ended catheter)		
e. Understands the rationale behind maintaining positive pressure and can demonstrate effectively when disconnecting a syringe from a valved catheter		
f. Care of unused lumens (if applicable)		
g. Prepares and instills antimicrobial lock correctly (where applicable). Knows the active ingredient(s) within the prescribed lock, indications for use and possible side effects		
h. Removal and safe disposal of Huber needle (port only)		
i. Knows purpose of a port protector and mode of action. Applies 70% isopropyl alcohol port protector correctly and knows frequency of change		
j. Secures catheter as per hospital protocol and can explain to the patient the rationale behind such securement		
4. Administration of any additional prescribed medications (if applicable)		
a. Prepares and administers any additional prescribed medications correctly. Knows the indications for use for these, any contraindications and possible side effects		
b. Knows how to safely dispose of used ampoules/vials/sharps		
c. Knows what to do in case of needlestick injury		
5. Addition(s) to IV fluid (if applicable)		
a. Completes all patient identity checks with the prescription		
b. Can identify additive port on IV fluid container		
c. Prepares any prescribed additions correctly as per manufacturer's instructions using appropriate aseptic technique		

d. Adds any prescribed additions to the IV fluid container correctly using a safety needle, and is aware of the correct order of any additions, using appropriate aseptic technique		
e. Ensures any additions have been dispersed adequately within the IV fluid container		
f. Primes giving set correctly (primary infusion)		
g. Primes any additional administration set for simultaneous secondary infusion, for example Y-site or Octopus double lumen extension set.		
h. Knows how to use Micrel double spike giving set and administration tubing (if used)		
i. Knows how to safely dispose of used ampoules/vials/sharps		
6. To safely set up PN or IV fluids		
a. Checks solution correctly		
b. Can identify if a bag is not safe to administer, ie cracking, creaming, particles		
c. Primes giving set (single, or double spike if used) correctly either manually or via pump. (Note: for manually primed giving sets NHS Improvement have recommended that once primed the giving set is placed into the pump before being connected to the catheter so as to reduce the risk of accidental free flow)		
d. Checks patency of line before connecting infusion (as per hospital protocol)		
e. Has received training on all pumps on the HPN framework		
f. Deals with pump alarms appropriately		
g. Protects bag from light (where applicable)		
h. Insertion of Huber needle (port only). Can identify if needle has been inserted correctly and is the correct length		
i. Knows how to use Portacator (port location device) and when it would be recommended		
j. Can deal appropriately with blood backflow in giving set		
k. Protects giving set/line connection during infusion (if applicable and as per hospital protocols)		
l. Knows what to do or advise if the PN bag is damaged/leaking/contaminated or the delivery is delayed/missing. (note: paeds do not always have a buffer bag)		
m. Knows how to use a gravity giving set and when this would be indicated		
n. For insulin dependent patients. Can measure blood glucose and administer insulin prior to connecting parenteral nutrition. (Only in cases where patient/carer is unable to do)		
7. Calculates infusion rates correctly		
a. Knows maximum hourly infusion rate for prescribed parenteral support		
b. Knows maximum hourly infusion rate for additional IV fluids		
c. Knows how to ramp up and ramp down infusion on each of the pumps on the framework and when this would be indicated		
8. Care of exit site		
a. Can describe appearance of a healthy exit/implanted port site		
b. Assesses exit/implanted port site at each catheter manipulation		
c. Knows when to clean exit site		
d. Knows what to clean exit site with and method of cleaning. Can suggest alternative cleaning solutions in cases of proven allergy		
e. Suitable dressings to use and correct method of application and removal. Can suggest alternative suitable dressings in cases of proven allergy		
f. Knows frequency of sutureless securement device change		
g. Can change commonly used sutureless securement devices and the necessary measures to reduce catheter dislodgement		
h. Knows when and how to remove exit site sutures from all types of devices including how to remove an external stitch fixator		
i. Can identify possible medical adhesive related skin injury (MARSI) and how to treat this		
j. Can identify any skin impairment from a SecurAcath device (if used)		
9. How and when to change needle free connector		
a. Knows how often the following needle free connectors should be routinely changed Vygon Bionector Fanin Clave/Microclave Fanin Neutron Carefusion Smartsite ICU Medical CLC2000 Vygon Bionector TKO		
b. Knows any additional times connector should be changed		
c. Can change connector during disconnection procedure		
d. Can change connector during connection procedure		
e. Knows the difference between specific clamping sequence needed for use with a positive pressure needle free connector, and how this differs from the clamping sequence required for neutral and negative connectors		
f. Knows any incompatible connector/device combinations, for example if anti reflux connector (TKO) can be used with a valved CVC		
10. To detect possible infection		
a. Can identity signs of possible bloodstream infection		
c. Can identify signs of possible exit site/tunnel infection		
d. Can identify signs of possible cuff infection		
e. Can identify overgranulation tissue at exit site		

f. Can identify signs of possible port pocket infection (port only)		
g. Can identify action to take and point of contact for above		
11. To detect possible hypoglycaemia		
a. Can identify the signs of possible hypoglycaemia.		
b. Can identify measures taken to prevent hypoglycaemia.		
c. Knows the at risk periods of hypoglycaemia.		
d. Can identify action to take and point of contact for further advice.		
12. To prevent air embolism		
a. Knows how air can enter bloodstream and infusion		
b. Can describe signs and symptoms of suspected air embolism		
c. Can describe position patient should be placed in if air embolism is suspected		
d. Knows when and how to clamp catheter		
e. Can identity what an approved replacement catheter clamp looks like and can apply to a non valved catheter		
f. Knows how to deal with "air in line" during infusion		
g. Knows what to do in case of catheter falling out		
13. To act appropriately with a blocked catheter		
a. Can identify common reasons catheters can become blocked		
b. Knows signs of catheter blockage		
c. Can identify and perform simple "first aid" measures to try and restore patency		
d. Can identify action to take and point of contact		
14. To act appropriately with catheter fracture		
a. Knows how catheters can become fractured		
b. Can identify signs of catheter fracture		
c. Knows what to do in case of catheter fracture		
d. Can identify when a catheter has been repaired and can assess the integrity of the repair		
e. Can identify point of contact for the above		
15. Can identify possible catheter malposition		
a. Knows the approximate external length of catheter (Cuffed and PICCs)		
b. Knows function of cuff and how to locate approximate location within skin tunnel		
c. Can identify an exposed cuff		
d. Understands function of SecurAcath engineered securement device(if used) and how to identify it is correctly placed		
e. Knows where a catheter tip should be and understands the implication of catheter malposition		
f. Can identify action to take and point of contact for the above		
16. Can recognize signs of possible thrombophlebitis and thrombosis		
a. Can describe and recognize signs of thrombophlebitis in patients with a PICC		
b. Can describe possible signs and symptoms of a central venous catheter related thrombosis		
c. Can identify action to take and point of contact for the above		
17. Correct storage of PN, IV fluids and any other prescribed IV medication		
a. Can describe how to correctly store PN		
b. Can read expiry date correctly		
c. Understands about stock rotation		
d. Understands importance of cleaning fridge		
e. Can describe how to correctly store any IV fluids		
f. Can describe how to safely dispose of any unused prescribed PN/IV fluids or other prescribed medication		
18. Can identify signs of fluid overload		
a. Can recognize signs and causes of possible fluid overload		
b. Can identify action to take and point of contact.		
19. Can identify signs of dehydration		
a. Can recognize signs and causes of possible dehydration		
b. Is aware of the sodium content of the following commonly prescribed prn fluids 1 L 0.9% sodium chloride 1 L 4% dextrose & 0.18% sodium chloride and when it would be clinically appropriate to administer them		
c. Can identify action to take and point of contact		
20. Can take blood from central venous catheter		
a. Knows when a discard volume is necessary and why		
b. Knows how much discard volume to take with different vascular access devices		
c. Can identity measures to facilitate blood return in cases where blood cannot be easily aspirated		
d. Flushes catheter following blood sampling		
21. Safe disposal of healthcare waste		
a. Can describe how to safely dispose on healthcare waste associated with the administration of PN/IV fluids and any other prescribed IV medication		
22. Lifestyle issues		
a. Knows how to advise patient on how to safely care for external surface of the line and clamp		
b. Knows how to advise patient on how protect line during showering/bathing (as per hospital protocols)		

c. Can advise patient re process to follow if they want to go on holiday		
23. Care of venting gastrostomy tube (if applicable)		
a. Understands function of venting gastrostomy tube		
b. Can access tube with appropriate enteral syringe		
c. Can aspirate and flush tube as per hospital protocol		
d. Understands rationale behind, and can demonstrate, rotating and advancing tubes		
e. Can undertake routine balloon care (balloon tubes only)		
f. Knows advice to give and point of contact if tube falls out.		
24. Knows about and informs patients about the patient support group PINNT		
a. Knows about and informs patient about the PINNT Verify tag		
b. Knows about and informs patient about the PINNT restaurant card		
c. Knows about and informs patient about the Patient Safety poster		

Date training completed	
Signature	**Print Name**

Appendix 4. Home Parenteral Nutrition Patient Competencies, NHS 2019® (used with permission)

Home Parenteral Nutrition Patient Competencies

Name _____

_____

Aim: The patient/carer* will acquire the knowledge and skills necessary to safely and effectively administer parenteral support (nutrition and or intravenous fluids) and care for the central venous catheter. *It is recommended that any family members undertaking administration of parenteral support and care of central venous catheters are 18 years of age or above.

Learning outcome	Achieved (date)	Signature
1. To understand why parenteral support is required		
a. Principles of normal intestinal function		
b. How gut function has changed		
c. How to minimize effect of GI changes		
d. How and when to administer additional IV fluids		
2. To understand principles of asepsis		
a. Washes and dries hands effectively		
b. Applies hand rub correctly		
c. Applies gloves (if recommended)correctly		
d. Cleans and disinfects trolley/tray correctly		
e. Correctly opens sterile items onto aseptic field		
f. Can identify key parts and non-key parts		
g. Understands the concept of key part and key site management		
h. Disinfects needle free connector for minimum of 15 seconds with pressure and friction, and allows to dry for 30 seconds		
3. To safely disconnect and flush catheter		
a. Deals appropriately with pump and catheter at end of infusion		
b. Prepares syringe with flushing solution correctly		
c. Flushes catheter with push-pause technique		
d. Uses positive pressure clamping technique when disconnecting syringe (open ended catheters)		
e. Uses positive pressure when disconnecting syringe (valved catheters)		
f. Care of unused lumens (if applicable)		
g. Prepares and instills antimicrobial lock correctly (if applicable)		
h. Removal and safe disposal of Huber needle (port only)		
i. Applies 70% isopropyl alcohol port protector correctly (if recommended)		
j. Secures catheter as per hospital protocol		
4. Administration of any additional prescribed *bolus* medications via central venous catheter (if applicable)		
a. Prepares and administers any additional prescribed bolus medications correctly		
b. Knows how to safely dispose of used ampoules/vials/sharps		
c. Knows what to do in case of needlestick injury (if applicable)		
5. Addition(s) to IV fluids (if applicable)		
a. Can identify additive port on IV fluid container		
b. Prepares any prescribed additions correctly as per manufacturer's instructions using an appropriate aseptic technique		
c. Adds any prescribed additions, using an appropriate aseptic technique to the IV fluid container correctly using a safety needle and is aware of the correct order of any additions		
d. Ensures any additions have been dispersed adequately within the IV fluid container		
e. Primes giving set correctly		
f. Primes any additional administration set for simultaneous secondary infusion, for example Y-site or Octopus double lumen extension set		
g. Knows how to use Micrel double spike giving set and administration tubing (if used)		
h. Knows how to safely dispose of used ampoules/vials/sharps		
6. To safely set up parenteral support (PN or IV fluids)		

a. Checks solution(s) correctly		
b. Can identify if a bag(s) not safe to administer, ie cracking, creaming		
c. Primes giving set (single, or double spike if used) correctly either manually or via pump. (Note: for manually primed giving sets NHS Improvement have recommended that once primed the giving set is placed into the pump before being connected to the catheter so as to reduce the risk of accidental free flow)		
d. Checks patency of catheter before connecting infusion (as per hospital protocol)		
e. Uses pump correctly		
f. Deals with pump alarms appropriately		
g. Protects bag from light (where applicable)		
h. Insertion of Huber needle (implanted port only). Can identify if needle has been inserted correctly and is the correct length		
i. Knows how to use Portactor (port locating device) if recommended (port only)		
j. Can deal appropriately with blood backflow in giving set		
k. Protects giving set/catheter connection during infusion (if applicable as per hospital protocol)		
l. Knows how to use a gravity giving set and when this would be indicated		
7. Calculates infusion rates correctly		
a. Knows maximum hourly infusion rate for prescribed parenteral support		
b. Knows maximum hourly infusion rate for additional IV fluids		
c. Knows how to ramp up and ramp down infusion (where applicable)		
8. How and when to dress exit site		
a. Knows frequency of dressing change and cleaning of exit site		
b. Knows how to remove dressing to minimize skin impairment (+/- medical adhesive remover)		
c. Knows what to clean exit site with and method of cleaning		
d. Knows how to apply silicone skin protection (if recommended)		
e. Suitable dressings to use		
f. Knows frequency of sutureless securement device change (PICC only)		
9. How and when to change needle free connector		
a. Knows name of connector used an how often this should be routinely changed		
b. Knows any additional times connector should be changed		
c. Can change connector during disconnection procedure		
d. Can change connector during connection procedure		
10. To detect possible infection		
a. Can identity signs of possible bloodstream infection		
c. Can identify signs of possible exit site/ tunnel infection		
d. Can identify signs of possible cuff infection		
e. Can identify signs of possible port pocket infection (port only)		
f. Can identify action to take and point of contact for above		
11. To prevent air embolism		
a. Knows how air can enter bloodstream and infusion		
b. Knows when and how to clamp catheter		
c. Knows how to deal with “air in line” during infusion		
d. Knows what to do in case of catheter falling out		
e. Can identify point of contact		
11. To act appropriately with blocked central venous catheter		
a. Knows signs of central venous catheter blockage		
b. Can identify simple “first aid” measures		
c. Can identify action to take and point of contact		
12. To act appropriately with central venous catheter fracture		
a. Knows how catheters can become fractured		
b. Can identify signs of catheter fracture		
c. Knows what to do in case of catheter fracture		
d. Can identify point of contact		
13. Can identify possible catheter malposition		
a. Knows function of cuff (tunneled catheter) and approximate location within skin tunnel		
b. Knows external length of PICC (if applicable)		
c. Understands function of SecurAcath device (if used)		
d. Understands implication of catheter malposition		
e. Can identify action to take and point of contact		
14. Can recognize signs of possible thrombosis		
a. Can describe possible signs and symptoms of a central venous catheter related thrombosis		
b. Can identify action to take and point of contact		
c. Can describe possible signs and symptoms of thrombophlebitis (PICC only)		
d. Can identify action to take and point of contact		
15. Correct storage of PN, IV fluids and any other prescribed IV medication		
a. Can describe how to correctly store parenteral support		
b. Can read expiry date correctly		
c. Understands about stock rotation		

d. Understands importance of cleaning fridge		
e. Can describe how to correctly store any IV fluids		
f. Can describe how to safely dispose of any unused prescribed PN/IV fluids or other prescribed medication		
16. Can identify signs of fluid overload		
a. Can recognize signs of possible fluid overload. b. Can identify action to take and point of contact.		
17. Can identify signs of dehydration		
a. Can recognize signs of possible dehydration		
b. Can identify action to take and point of contact		
18. Safe disposal of healthcare waste		
a. Can describe how to safely dispose on healthcare waste associated with the administration of parenteral support and any other prescribed IV medication		
19. Lifestyle issues		
a. Knows how to safely care for external surface of the catheter and clamp		
b. Knows how to protect catheter during showering/bathing (as per hospital protocol)		
20. To know points of contact at		
a. Discharging hospital		
b. Homecare company		
21. Care of venting gastrostomy tube (if applicable) Training to be carried out by nurses from Purchasing Authority		
a. Understands function of venting gastrostomy tube		
b. Can access tube with appropriate enteral syringe		
c. Can aspirate and flush tube		
d. Understands rationale behind, and can demonstrate, rotating and advancing tubes		
e. Can undertake routine balloon care (balloon tubes only)		
f. Knows what to do and point of contact if tube falls out.		
22. Knows about patient support group PINNT and Half PINNT		
a. Knows how to join		
b. Knows about PINNT Verify tag		
c. Knows about PINNT restaurant card		
d. Knows about PINNT Safety poster		

Date training completed	
Signature	**Print Name**

A copy of this should be kept in the patient's home

References

1. Cadman A, Lawrance JAL, Fitzsimmons L, Spencer-Shaw A, Swindell R. To clot or not to clot? That is the question in central venous catheters. Clin Radiol. 2004;59(4):349–55.
2. Hallam C, Denton A, Weston V, Dunn H, Jackson T, Keeling S, Hill S. UK Vessel Health and Preservation (VHP) Framework: a commentary on the updated VHP 2020. J Infect Prev. 2021;22(4):147–55.
3. Nifong TP, McDevitt TJ. The effect of catheter to vein ratio on blood flow rates in a simulated model of peripherally inserted central venous catheters. Chest. 2011;140(1):48–53.
4. Sharp R, Cummings M, Fielder A, Mikocka-Walus A, Grech C, Esterman A. The catheter to vein ratio and rates of symptomatic venous thromboembolism in patients with a peripherally inserted central catheter (PICC): a prospective cohort study. Int J Nurs Stud. 2015;52(3):677–85.
5. Spencer TR, Mahoney KJ. Reducing catheter-related thrombosis using a risk reduction tool centered on catheter to vessel ratio. J Thromb Thrombolysis. 2017;44(4):427–34.
6. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, Joly F, Kelly D, Lal S, Staun M, Szczepanek K, Van Gossum A, Wanten G, Schneider SM, Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35(2):247–307.
7. Pironi L, Boeykens K, Bozzetti F, Joly F, Klek S, Lal S, Lichota M, Mühlebach S, Van Gossum A, Wanten G, Wheatley C, Bischoff SC. ESPEN guideline on home parenteral nutrition. Clin Nutr. 2020;39(6):1645–66.
8. Loveday HP, Wilson JA, Pratt RJ, Golsorkhi M, Tingle A, Bak A, Browne J, Prieto J, Wilcox M, UK Department of Health. epic3: national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. J Hosp Infect. 2014;86(Suppl 1):S1–70.
9. Baxi SM, Shuman EK, Scipione CA, Chen B, Sharma A, Rasanathan JJ, Chenoweth CE. Impact of postplacement adjustment of peripherally inserted central catheters on the risk of bloodstream infection and venous thrombus formation. Infect Control Hosp Epidemiol. 2013;34(8):785–92.
10. Giustivi D, Gidaro A, Baroni M, Paglia S. Tunneling technique of PICCs and Midline catheters. J Vasc Access. 2021;22:610.
11. Collier M. Minimising pain and medical adhesive related skin injuries in vulnerable patients. Br J Nurs. 2019;28(15):S26–32.
12. Moureau NL. Right securement, dressing and management. In: Moureau N, editor. Vessel health and preservation: the right approach for vascular access. Cham: Springer; 2019. https://doi.org/10.1007/978-3-030-03149-7_9.
13. Macmillan T, Pennington M, Summers JA, et al. SecurAcath for securing peripherally inserted central catheters: a NICE medical technology guidance. Appl Health Econ Health Policy. 2018;16:779–91.
14. Broviac JW, Cole JJ, Scribner BH. A silicone rubber atrial catheter for prolonged parenteral alimentation. Surg Gynecol Obstet. 1973;136(4):602–6.
15. Barton B, Pamment K, Fitzpatrick D. Evaluation of a device to improve non-coring needle insertion into implanted intravenous ports. Br J Nurs. 2018;27(19):S20.

16. Hoffer EK, Bloch RD, Borsa JJ, Santulli P, Fontaine AB, Francoeur N. Peripherally inserted central catheters with distal versus proximal valves: prospective randomized trial. J Vasc Interv Radiol. 2001;12(10):1173–7.
17. Lamont JP, McCarty TM, Stephens JS, Smith BA, Carlo J, Livingston S, Kuhn JA. A randomized trial of valved vs nonvalved implantable ports for vascular access. Proceedigs (Bayl Univ Med Cent). 2003;16(4):384–7.
18. Pasquale MD, Campbell JM, Magnant CM. Groshong versus Hickman catheters. Surg Gynecol Obstet. 1992;174:408–10.
19. Pittiruti M, Emoli A, Porta P, Marche B, DeAngelis R, Scoppettuolo G. A prospective, randomized comparison of three different types of valved and non-valved peripherally inserted central catheters. J Vasc Access. 2014;15(6):519–23.
20. Carlo JT, Lamont JP, McCarty TM, Livingston S, Kuhn JA. A prospective randomized trial demonstrating valved implantable ports have fewer complications and lower overall cost than nonvalved implantable ports. Am J Surg. 2004;188(6):722–7.
21. Tolar B, Gould JR. The prognostic significance of the ball-valve effect in Groshong catheters. Support Care Cancer. 1996;4(1):34–8.
22. Haire WD, Lieberman RP, Lund GB, Edney JA, Kessinger A, Armitage JO. Thrombotic complications of silicone rubber catheters during autologous marrow and peripheral stem cell transplantation: prospective comparison of Hickman and Groshong catheters. Bone Marrow Transplant. 1991;7(1):57–9.
23. Curran E. Needleless connectors: the vascular access catheter's microbial gatekeeper. J Infect Prev. 2016;17(5):234–40.
24. Sweet MA, Cumpston A, Briggs F, Craig M, Hamadani M. Impact of alcohol-impregnated port protectors and needleless neutral pressure connectors on central line-associated bloodstream infections and contamination of blood cultures in an inpatient oncology unit. Am J Infect Control. 2012;40(10):931–4.
25. Wright M-O, Tropp J, Schora DM, Dillon-Grant M, Peterson K, Boehm S, Robicsek A, Peterson LR. Continuous passive disinfection of catheter hubs prevents contamination and bloodstream infection. Am J Infect Control. 2013;41(1):33–8.
26. Kamboj M, Blair R, Bell N, Son C, Huang YT, Dowling M, Lipitz-Snyderman A, Eagan J, Sepkowitz K. Use of disinfection cap to reduce central-line-associated bloodstream infection and blood culture contamination among hematology-oncology patients. Infect Control Hosp Epidemiol. 2015;36(12):1401–8.
27. Taşdelen Y, Çağlar S. Effect of Intravenous infiltration management program on peripheral intravenous catheter success and infiltration in hospitalized infants. J Nurs Care Qual. 2021;36(3):E44–9.
28. Casey AL, Karpanen TJ, Nightingale P, Elliott TSJ. An in vitro comparison of standard cleaning to a continuous passive disinfection cap for the decontamination of needle-free connectors. Antimicrob Resist Infect Control. 2018;7:50.
29. Ahmed QA, Memish ZA, Allegranzi B, Pittet D, on behalf of the WHO Global Patient Safety Challenge. Muslim health-care workers and alcohol-based handrubs. Lancet. 2006;367:1025–7.
30. Garvan JM, Gunner BW. The harmful effects of particles in intravenous fluids. Med J Aust. 1964;II:1–6.
31. Shaw NJ, Lyall EGH. Hazards of glass ampoules. Br Med J. 1985;291:1390.
32. Taylor SA. Particulate contamination of sterile syringes and needles. J Pharm Pharmacol. 1982;34:493–5.
33. Worthington P, Gura KM, Kraft MD, Nishikawa R, Guenter P, Sacks GS, ASPEN PN Safety Committee. Update on the use of filters for parenteral nutrition: an ASPEN position paper. Nutr Clin Pract. 2021;36(1):29–39.
34. Carter D, Wheatley C, Martin R, et al. Nights of bright lights and noisy pumps – home parenteral feeding. Proc Nutr Soc. 1996;55:149A.
35. Saqui O, Fernandes G, Allard JP. Quality of life analysis during transition from stationary to portable infusion pump in home parenteral nutrition patients: a Canadian experience. Nutr Clin Pract. 2014;29(1):131–41.
36. LITRE Assessment of Ambulatory Pumps for Parenteral Nutrition Results of a LITRE Assessment Panel 29 & 30 July 2016. Published February 2017 © PINNT 2017. https://pinnt.com/pdf/LITRE-Report.pdf.
37. O'Grady N. Centers for Disease Control and Prevention. Guidelines for the prevention of intravascular catheter-related infections. MMWR Recomm Rep. 2002;51(RR-10):1–26.
38. Rowley S. Theory to practice: aseptic non touch technique. Nurs Times. 2001;97:VI–VIII.
39. Rowley S, Clare S, Macqueen S, Molyneux R. ANTT® v2: an updated practice framework for aseptic technique. Br J Nurs. 2010;19:S5–S11.
40. Rowley S, Clare S. Standardising the critical clinical competency of aseptic, sterile, and clean techniques with a single international standard: Aseptic Non Touch Technique (ANTT®). J Assoc Vasc Access. 2019;24(4):12.
41. https://www.antt.org/terms-conditions-referencing.html.
42. Saiman L, et al. Banning artificial nails from healthcare settings. Am J Infect Control. 2002;30(4):252–4.
43. Moolenaar RL, et al. A prolonged outbreak of Pseudomonas aeruginosa in a neonatal intensive care unit: did staff fingernails play a role in disease transmission? Infect Control Hosp Epidemiol. 2000;21(2):80–5.
44. Gordin FM, et al. A cluster of hemodialysis-related bacteremia linked to artificial fingernails. Infect Control Hosp Epidemiol. 2007;28:743–4.
45. Gupta A, et al. Outbreak of extended-spectrum betalactamase-producing Klebsiella pneumoniae in a neonatal intensive care unit linked to artificial nails. Infect Control Hosp Epidemiol. 2004;25:210–5.
46. RCN Standards for infusion therapy fourth edition 2016. https://www.rcn.org.uk.
47. The Joint Commission. Preventing central line-associated bloodstream infections: useful tools, an international perspective; 20 Nov 2013. https://www.jointcommission.org. Accessed 20 April 2022.
48. Ullman AJ, Cooke ML, Mitchell M, Lin F, New K, Long DA, Mihala G, Rickard CM. Dressings and securement devices for central venous catheters (CVC) (Review). Cochrane Database Syst Rev. 2015;9:CD010367. https://doi.org/10.1002/14651858. (I)
49. Timsit JF, Mimoz O, Mourvillier B, Souweine B, Garrouste-Orgeas M, Alfandari S, Plantefeve G, Bronchard R, Troche G, Gauzit R, Antona M, Canet E, Bohe J, Lepape A, Vesin A, Arrault X, Schwebel C, Adrie C, Zahar JR, Ruckly S, Tournegros C, Lucet JC. Randomized controlled trial of chlorhexidine dressing and highly adhesive dressing for preventing catheter-related infections in critically ill adults. Am J Respir Crit Care Med. 2012;186(12):1272–8.
50. RCN Understanding Aseptic Technique. An RCN investigation into clinician views to guide the practice of aseptic technique 2020. https://www.rcn.org.uk, publications pub-007928.

51. Cawley C, Lal S, Nightingale J, Small M. British Intestinal Failure Alliance (BIFA) Guidance. Standardised Parenteral Support Catheter Guidelines; April 2018. https://www.bapen.org.uk/pdfs/bifa/standardised-parenteral-support-catheter-guidelines.pdf.
52. Fumarola S, Allaway R, Callaghan R. Overlooked and underestimated: medical adhesive-related skin injuries. J Wound Care. 2020;29:S1–S24. https://doi.org/10.12968/jowc.2020.29.Sup3c.S1.
53. Barton A. Medical adhesive-related skin injuries associated with vascular access: minimising risk with Appeel Sterile. Br J Nurs. 2020;29(8):S20–7. https://doi.org/10.12968/bjon.2020.29.8.S20.
54. Taroc AM. A guide for adhesive removal: Principles, practice and products. Am Nurse Today. 2017;12(10):24–6.
55. Nightingale J, Young A, Hewett R, Stevens P, Rafferty G, Carlson G, Culkin A, Farrer K, Gabe S, Glynn M, Lal S, Newton R, Small M, Smith T, Soop M, Wheatley C, Wong T, Woodward J. British Intestinal Failure Alliance (BIFA) Position Statement Home Parenteral Support (HPS). 2019. https://www.bapen.org.uk/pdfs/bifa/position-statement-home-parenteral-nutrition.
56. Hadaway LC. Reopen the pipeline for IV therapy. Nursing. 2005;35(8):54–61.
57. Gabriel J. Venous access devices part 2: preventing and managing complications of CVADs. Nurs Times. 2013;109(40):20–3.
58. Mayo D, Pearson D. Chemotherapy extravasation: a consequence of fibrin sheath formation around venous access devices. Oncol Nurs Forum. 1995;22:675–80.
59. Hoshal VL Jr, Ause RG, Hoskins PA. Fibrin sleeve formation on indwelling subclavian central venous catheters. Arch Surg. 1971;102:353–8.
60. Stephens LC, Haire WD, Kotulak GD. Are clinical signs accurate indicators of the cause of central venous catheter occlusion? J Parenter Enteral Nutr. 1995;19:75–9.
61. Schneider TC, Krzywda E, Andris D, Quebbeman EJ. The malfunctioning silastic catheter – Radiological assessment and treatment. J Parenter Enteral Nutr. 1986;10:70–3.
62. Wall C, Moore J, Thachil J. Catheter related thrombosis: a practical approach. J Intensive Care Soc. 2016;17(2):160–7.
63. Small M, Patel S, Crowther S. Evaluation of the percussive POP technique to restore patency to long term central venous access in patients on Home Parenteral Nutrition. Gut. 2015;64(Suppl 1):A498–9.
64. Baskin JL, Reiss U, Wilimas JA, Metzger ML, Ribeiro RC, Pui CH, Howard SC. Thrombolytic therapy for central venous catheter occlusion. Haematologica. 2012;97(5):641–50.
65. Monturo CA, Dickerson RN, Mullen JL. Efficacy of thrombolytic therapy for occlusion of long-term catheters. J Parenter Enteral Nutr. 1990;14(3):213–314.
66. Atkinson JB, Bagnall HA, Gomperts E. Investigational use of tissue plasminogen activator (t-PA) for occluded central venous catheters. J Parenter Enteral Nutr. 1990;14:310–1.
67. Pennington CR, Pithie AD. Ethanol lock in the management of catheter occlusion. J Parenter Enteral Nutr. 1987;11(5):507–8.
68. Ter Borg F, Timmer J, De Kam SS, Sauerwein HP. Use of sodium hydroxide solution to clear partially occluded vascular access ports. J Parenter Enteral Nutr. 1993;17(3):289–91.
69. Haire WD, Lieberman RP. Thrombosed central venous catheters: restoring function with 6-hour urokinase infusion after failure of bolus urokinase. J Parenter Enteral Nutr. 1992;16(2):129–32.
70. Deitcher SR, Fesen MR, Kiproff PM, Hill PA, Li X, McCluskey ER, et al. Safety and efficacy of alteplase for restoring function in occluded central venous catheters: results of the Cardiovascular Thrombolytic to Open Occluded Lines Trial. J Clin Oncol. 2002;20(1):317–24.
71. Werlin SL, Lausten T, Jessen S, Toy L, Norton A, Dallman L, Bender J, Sabilan L, Rutkowski D. Treatment of central venous catheter occlusions with ethanol and hydrochloric acid. J Parenter Enteral Nutr. 1995;19(5):416–8.
72. Kumwenda MJ, Mitra S, Khawaja A, Inston N, Nightinale P. Prospective Audit to Study urokinaSe use to restore Patency in Occluded centRal venous caTheters (PASSPORT 1). J Vasc Access. 2019;20(6):752–9.
73. Kumwenda MJ, Dougherty L, Jackson A, Hill S. Prospective audit to study urokinaSe use to restore Patency in Occluded centRal venous caTheters in haematology and oncology patients (PASSPORT 2). J Vasc Access. 2021;22(4):568–74.
74. Hamilton H. Complications associated with venous access devices Part 2. Nurs Standard. 2006;20(27):59–65.
75. Stewart D. The percussion technique for restoring patency to central venous catheters. Care Critic Ill. 2001;17(3):106–7.
76. Fetzer SJ, Manning GPD. Safety and efficacy of the POP technique for restoring patency to occluded PIC catheters. Appl Nurs Res. 2004;17(4):297–300.
77. Goodwin M, Carlson I. The peripherally inserted catheter: a retrospective look at 3 years of insertions. J Intraven Nurs. 1993;12(2):92–103.
78. Boord C. Pulsatile flushing: a review of the literature. J Infus Nurs. 2009;42(1):37–43.
79. Holt D, Lawrence S. The influence of a novel needleless valve on central venous catheter occlusions in pediatric patients. J Assoc Vasc Access. 2015;20(4):2014–220.
80. Jasinsky LM, Wurster JA. Occlusion reduction and heparin elimination trial using an antireflux device on peripheral and central venous catheters. J Infus Nurs. 2009;32(1):33–9.
81. McNiven C, Switzer N, Wood M, Persad R, Hancock M, Forgie S, Dicken BJ. Central venous catheter repair is not associated with an increased risk of central line infection or colonization in intestinal failure pediatric patients. J Pediatr Surg. 2016;51(3):395–7.
82. Chan AP, Baldivia PS, Reyen LE, Lund AN, Marcus EA, Venick RS, Vargas JH, Wozniak LJ. Central venous catheter successful in children with intestinal failure. J Pediatr Surg. 2019;54(3):517–20.
83. Wouters Y, Vissers RK, Groenewoud H, Kievit W, Wanten GJA. Repair of damaged central venous catheters is safe and doubles catheter survival: a home parenteral nutrition patient cohort study. Clin Nutr. 2019;38(4):1692–9.
84. Bielawska B, Allard JP. Parenteral nutrition and intestinal failure. Nutrients. 2017;9(5):466.
85. Stern JM, Jacyna N, Lloyd DA. Review article: psychological aspects of home parenteral nutrition, abnormal illness behaviour and risk of self-harm in patients with central venous catheters. Aliment Pharmacol Ther. 2008;27:910–8.
86. Mercer-Smith G, Kirk C, Gemmell L, Mountford C, Nightingale J, Thompson N and the BIFA Committee. British Intestinal Failure Alliance (BIFA) Position Statement. British Intestinal Failure Alliance (BIFA) Guidance Haematological and Biochemical Monitoring of Adult Patients receiving Home Parenteral Nutrition 2021. www.bapen.org.uk. Accessed 03/05/2022.

Care of Intestinal Stoma and Enterocutaneous Fistula(s)

Louise Williams and Gordon L. Carlson

Key Points

1. Good nursing care of intestinal fistulas and stomas is essential to the effective management of patients with intestinal failure.
2. A stoma should be presited (marked) on flat skin away from bony prominences, skin creases or where clothing may grip, at a site agreed by the patient.
3. An understanding of the relevant intestinal anatomy may be helpful in predicting the short and long-term behaviour of an enterocutaneous fistula (ECF) or stoma.
4. Effective skin care involves avoiding contact between stoma and fistula effluent and the skin, especially in the case of more proximal stomas and fistulas, from which the effluent is highly corrosive.
5. A well-fitting adhesive appliance will protect the skin, remove unpleasant odours, reduce risk of cross-infection, allow assessment of fluid losses, preserve dignity and allow the patient mobility and rest.
6. Fistula and stoma appliances which incorporate negative pressure and drainage devices should be considered in higher output fistulas and stomas, in order to facilitate skin care.
7. In cases where there is uncontrollable and unmanageable leakage from a fistula, early surgery to produce a temporary proximal loop jejunostomy may greatly facilitate nursing care and improve patient wellbeing.
8. Accurate recording of fluid balance (and notably fistula or stoma output) is essential for the effective management of patients with high output fistulas.
9. Measurement and a photographic record of an ECF should be kept.

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Introduction

Patients with acute intestinal failure complicated by the presence of an intestinal stoma or enterocutaneous fistula should be managed by a multidisciplinary team. Suboptimal care of stomas and/or fistulas may result in adverse physical and psychological consequences [1] and may prejudice nutritional support, surgical treatment or spontaneous fistula closure.

This chapter outlines the fundamental principles of management of patients with intestinal stomas and enterocutaneous fistulas in patients with intestinal failure. Distal enteral feeding which may be complete or trophic is increasingly being performed into a distal unobstructed segment of bowel (stoma or fistula) and is discussed in chapter "Distal Feeding and Hydration".

Definitions

Intestinal Stoma

An intestinal stoma is a surgically created opening in the abdominal wall related to a portion of the gastrointestinal tract. Its purpose is to provide a pathway for digested material to leave the body when the normal pathway is obstructed or its function otherwise impaired [2]. An intestinal stoma may involve the stomach (a gastrostomy), part of the small intestine (duodenostomy, jejunostomy, ileostomy) or a part of the large intestine (colostomy). Some stomas may even involve two separate segments of the gastrointestinal tract (for example an ileocolostomy). A stoma is termed an end stoma (in which the bowel at the site selected is divided and brought up to the skin) or a loop/defunctioning stoma when the bowel is not divided but simply opened (Fig. 1). A defunctioning stoma is usually intended for a few months often to defunction an anastomosis distal to it (e.g. in low anterior resection or the rectum or ileoanal pouch). In each case, the bowel is ideally brought out through the rectus

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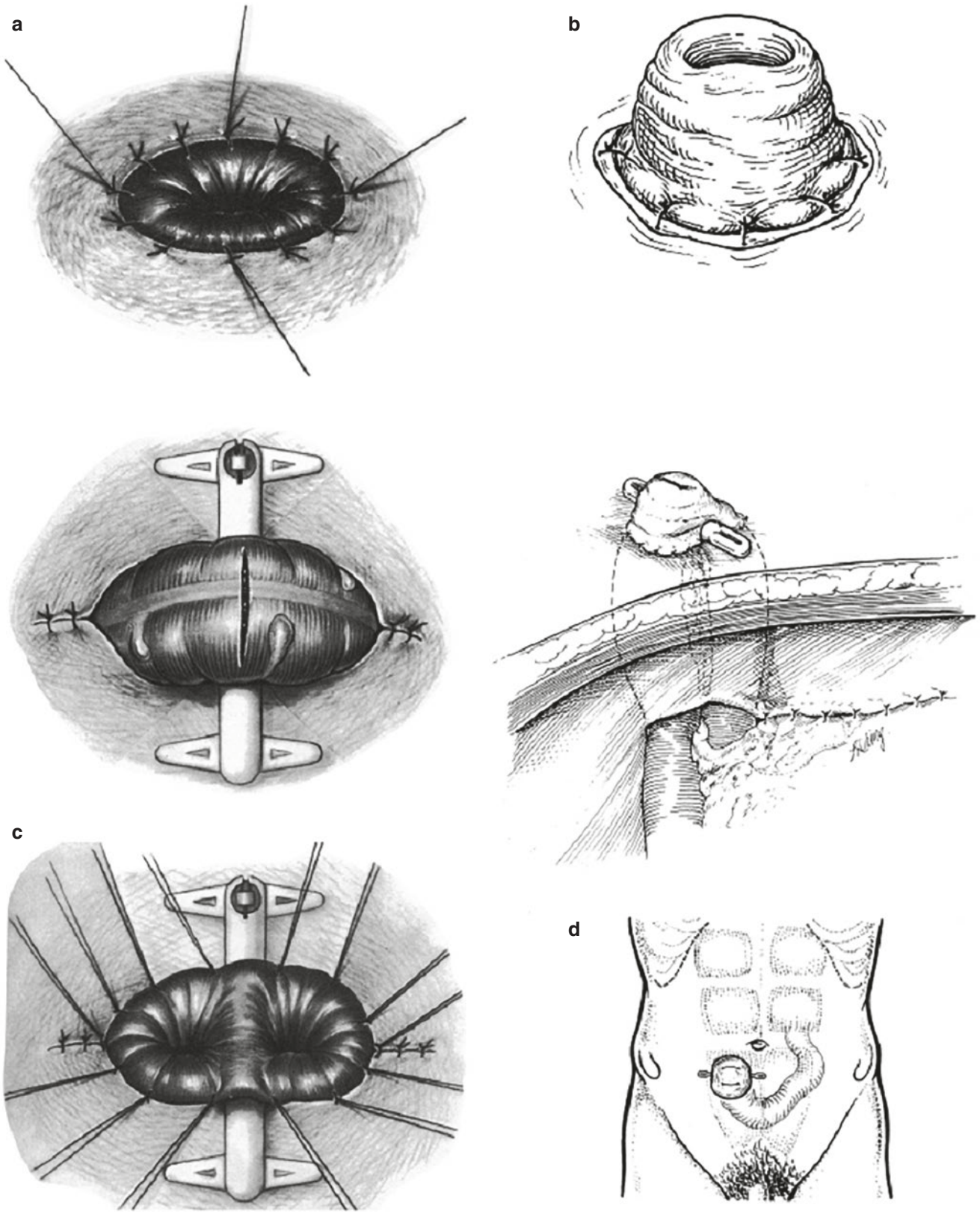


Fig. 1 Types of stoma (**a**) A colostomy, (**b**) A Brooke ileostomy, (**c**) A loop colostomy, (**d**) a loop ileostomy

abdominis muscle to minimize the chance of a parastomal hernia developing [3] and then sutured to the skin after an approximately 2.5 cm circular area of skin has been removed. Large bowel stomas (colostomies) are generally sutured flush with the skin, whereas small bowel stomas (ileostomy, jejunostomy, duodenostomy) usually have an everted 2.5–3.0 cm spout. This modification, devised by Brooke, enables the corrosive effluent to be kept away from the skin and appliances to be kept on with relative ease [4].

Enterocutaneous Fistula

An enterocutaneous fistula is an abnormal communication between the gastrointestinal tract and the skin. Enterocutaneous fistulas may develop as result of complications of surgery or as a result of intrinsic disease of the gastrointestinal tract (e.g. in Crohn's disease, malignancy or diverticular disease of the colon). Enterocutaneous fistulas (Fig. 2) are classified according to the site of origin and attachments, the number of openings, the orientation with respect to the long axis of the intestinal tract and the presence of an associated abscess cavity. When more than one organ system is involved, fistulas are described as complex. For example, a fistula arising from the side of the terminal ileum and passing directly to the skin of the abdomen would be described as a simple lateral ileal fistula (Fig. 2a). A similar track passing from the side of ileum into an abscess cavity, and the bladder then to the skin is described as a complex lateral ileovesicocutaneous fistula (Fig. 2b). Fistulas that arise perpendicular to the long axis of the gut are referred to as end fistulas and may arise following complete anastomotic dehiscence or rectal stump blow out after Hartmann's procedure. They classically develop from the duodenal stump after a Polya gastrectomy. An enteric fistula occurring in the setting of an open abdomen creating a communication between the GI tract and the external atmosphere may be referred to as an enteroatmospheric fistula (EAF). Intestinal fistulas are most commonly caused by an anastomotic or suture line leakage, trauma, inflammatory bowel disease,

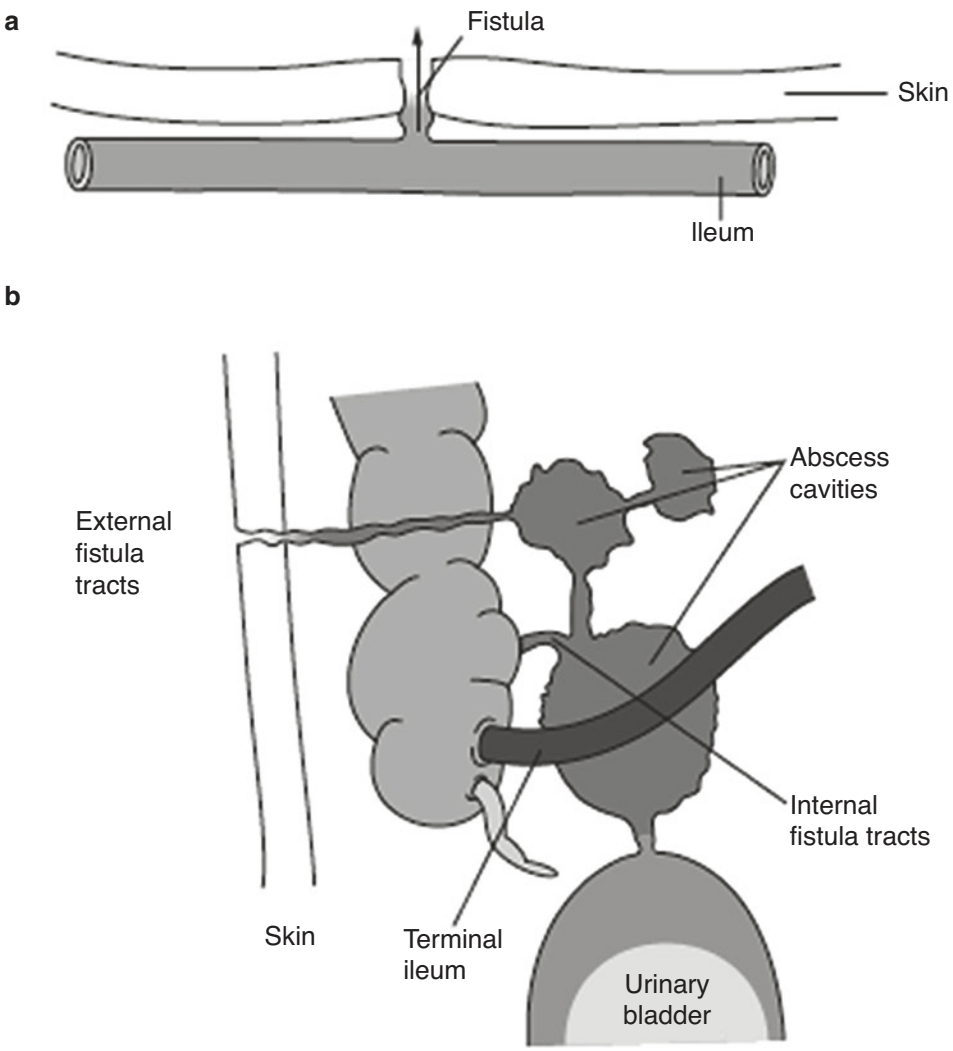


Fig. 2 Classification of intestinal fistulas, showing (**a**) a simple lateral ileocutaneous fistula track and (**b**) a complex track involving skin and bladder with intervening abscess cavities

malignant disease, diverticular disease of the colon, or as a consequence of radiotherapy [5].

The "Normal" Stoma

It is usual for a stoma to be oedematous after surgery and to shrink over the first 1–2 postoperative weeks. This usually results in a requirement for a smaller template.

Choosing the Stoma Site

The Stoma Care Nurse should discuss the planned surgery with the patient, using diagrams to explain what a stoma is, how it will affect their life, how it is managed and how to manage problems. The ideal site for the stoma is selected after careful evaluation of the patient. A flat area of normal skin contour, below the belt or waistline (except for a transverse colostomy) is chosen away from bony prominences (iliac crest or costal margin), surgical scars/skin folds/creases and unobscured by pendulous breasts. The optimal site avoids places where clothing grips the abdomen or where the bag would be conspicuous or easily damaged. The site chosen is marked with indelible ink and should be just medial to the linea semilunaris. The patient is asked to sit, bend, stand and walk to check the suitability of position (it may be useful to apply a bag if difficulties are evident or if the patient requests). A reserve site may also be chosen as type of stoma brought out during surgery may change, some surgeons may ask for patient to be sited on both sides.

Colostomy

A colostomy generally begins to act 2–5 days after surgery. Flatus, followed by watery faeces, will first become apparent but with the introduction of oral fluids and diet the effluent will become solid. The volume of output will be influenced by the diet, the presence of coexisting intestinal disease and the precise location of the stoma with respect to the colon. In general, a colostomy output varies between 200 and 600 mL/24 h.

Ileostomy

An ileostomy generally starts to work within 24 h. During the first week, an output of about 1.2 L of watery stool is expected and this falls for the second week to about 600 mL daily of porridge-like stool. The output initially rises as food is taken. A normal ileostomy may reduce its output over the following few months.

Jejunostomy

The output from a jejunostomy increases dramatically after food/fluid is taken orally and may reach more than 6 L if less than a metre of jejunum remains. Patients with a jejunostomy are likely to require continued intravenous fluid and electrolyte therapy in order to prevent metabolic complications. It should be stressed that excessive thirst due to dehydration should be treated with oral fluid restriction (typically to <1500 mL/day) and the loss replaced intravenously. Allowing such patients unrestricted access to oral fluids results in a vicious cycle in which excessive fluid intake results in increasing fluid output from the stoma and greater thirst. It is important to remember that each litre of jejunostomy effluent contains approximately 100 mmol of sodium and 20–40 mmol of potassium and these electrolytes must be replaced. Maintenance electrolyte fluids are available for intravenous replacement in these circumstances.

In patients with a newly-created jejunostomy, careful attention to monitoring of fluid and electrolyte balance should be undertaken. Although daily plasma measurements are of value, homeostatic mechanisms result in failure of plasma measurements to detect dehydration or electrolyte depletion until late in their evolution. A more useful and more acceptable means of monitoring the patient's fluid and electrolyte status is to weigh the patient and perform measurement of urinary sodium concentration at least twice-weekly. The finding of a urinary sodium of less than 20 mmol/L in such patients implies sodium depletion and a need for further assessment (chapter "Management of a High Output Stoma, Jejunotomy or Uncomplicated Enterocutaneous Fistula").

Diet with a Stoma

Patients with stomas can be reassured that they will not have to make major modifications to their diet. Some foods, however, may cause discomfort or even intestinal obstruction, malodorous flatulence or diarrhoea and may be best avoided, although patients will ultimately determine their dietary preferences on an individual basis.

Nuts and fibrous foods such as dried fruits (e.g. raisins and sultanas) and 'pithy' fruit (e.g. orange) may cause discomfort or even obstruction in patients with an ileostomy. Other foods that may be partly digested include celery, coconut, coleslaw (raw cabbage), sweet-corn, orange, mushroom, nuts, peas, popcorn, pineapple, relishes (e.g. chutney), seeds and skins (e.g. apples/pears). Foods that may cause flatulence/malodour are generally avoided (asparagus, baked beans, cabbage, broccoli, brussel sprouts, fish, cauliflower, eggs, beer, carbonated beverages, onions and parsnips).

Reduction of Odour

Deodorizing drops can be put into a stoma bag if there is perceived to be a major problem of malodour. Neutralizing sprays can also be used. If there is a malodorous wound it may be redressed with a charcoal- or metronidazole-based dressing. Some foods may cause flatulence (e.g. brassicas such as sprouts) and the diet can be restricted if desired.

Training of Patient/Carer

The patient and/or their carer must learn how to empty the stoma bag and change and dispose of a one- or two-piece appliance. They need to know how to look after the peristomal skin and cope with leakage, flatus or malodour. They also need to identify a reliable source of supply of stoma care products.

Irrigation

Some patients try to regulate their colostomy output by irrigation, enabling 'continence'. It is undertaken every 24–48 h, cleansing the colon. One litre of warm water is inserted slowly via a cone on the end of soft tubing sited 5–10 cm into the stoma. Some patients prefer to use a pump to administer the water at a slow pace, their stoma nurse can provide this for them from one of the stoma care company's and trained them how to use it. After a period of time a long drainable pouch is connected over the stoma allowing faeces and water to drain into the toilet. The procedure is time-consuming and some patients prefer to do the procedure at night when the bathroom is not in constant use [6]. Irrigation is **not** suitable for an ileostomy.

Activities

A patient may cover their stoma with a minibag for swimming or sexual intercourse. A bag is usually changed after swimming. Participation in most sports is possible though heavy contact sports (e.g. rugby) should be undertaken with caution and a shield can be provided to wear over the stoma to protect it, weight-lifting may make a stoma more likely to prolapse. When flying, it is helpful and reassuring for the patient to carry spare stoma bags in both the aeroplane hold and in the hand luggage. A journey of any length requires an appropriate supply of spare products in case there is a need to change the appliance whilst travelling [7]. They are advised to do short trips first to gain confidence. The insurance company will need to be informed that the patient has a stoma in case of any complications. During the flight a good fluid and salt intake needs to be ensured as patients with a stoma may be at increased risk of dehydration.

Psychological Care

Psychological care is an integral part of the management of patients with stomas and fistulas. This is especially important in the patient who presents with a fistula after repeated failed surgical procedures. In such cases there may be complete loss of confidence in the carers and a state of profound depression and withdrawal. Interestingly, few, if any, clinical psychologists have specific experience in the problems faced by such patients and are unable to relate to the unique problems associated with complex and repeated surgery, multiple fistulas and stomas and prolonged hospitalization. In general, trained members of nursing staff have proven to be the most effective source of psychological support. The patient should be given sufficient information at all times to be aware and actively engaged in their treatment plan. This may include explanations of investigative procedures, surgical options, intended outcomes and any possible complications. It is necessary to repeat these discussions several times so that uncertainty can be avoided. Family members should also be included whenever this is thought to be appropriate. The availability of the spouse or partner is of vital importance and their support is invaluable in offsetting the initial feelings of shame and mutilation felt by many patients [8]. Education should be given to the relatives so that the sharing relationship is allowed to continue, and the family needs to behave normally and demonstrate continued acceptance of the patient, promoting positive attitudes and dispelling possible feelings of rejection or revulsion [9]. The new body image can be difficult to accept but if there is time for the consideration of change then mental adjustment will be easier. However, sudden developments, as in the occurrence of a fistulae or emergency surgery requiring a stoma can give rise to rejection, denial and the problems of withdrawal. Other factors influencing body image are the visibility of the change and its encroachment on lifestyle [8]. Encouragement and allowing ample opportunities to talk will be much needed for both parties and they should be encouraged to voice concerns and fears. Reassurance regarding the progress or possible outcomes will be constantly required and the nurse must answer honestly but never offer false or premature reassurance [9].

Problem Stomas: Leakage

There are many reasons for leakage (Table 1). While the stoma site and complications relating to it may be respon-

Table 1 Reasons for stomal leakage

1. Badly sited stoma on bony prominence, skin creases, dips or scars
2. Stoma shrinkage, retraction, prolapse, or peristomal herniation
3. Poor technique (can be due to poor vision or manual dexterity)
4. Weight change (gain or loss)
5. Pancaking
6. Peristomal skin allergy or granulation tissue

sible, a poor technique is often the cause. This may be due to poor vision or manual dexterity, an overfull appliance, one that has been left on for too long or alternatively changed too frequently. An uneven skin surface due to sitting in one position for a long time or changing weight (increase, decrease or pregnancy) may affect the way an appliance fits, thus making it liable to leak. Pancaking of solid stool at the top of a stoma can cause leakage. It can be helped by putting baby oil onto the inside top of the appliance, covering the filter or an adhesive bar can be placed on the outside of stoma to form a bridge. This prevents both pancaking and also the stoma bag sticking to the stoma. Peristomal skin irritation can be due to allergy to plaster or the appliance adhesive and a change of these may help. The hairs around an appliance may need to be shaved. Fungal infections frequently occur on moist, warm peristomal skin. Granulation at the stoma edge is harmless but can cause bleeding or prevent bag application. This responds to cautery with a silver nitrate pencil.

The Complicated Stoma

Specific medical and nursing care may be required to manage the stoma when complications occur. The principal general complication associated with creation of a stoma relates to fluid and electrolyte balance in patients with a high output proximal stoma (chapter "Management of a High Output Stoma, Jejunotomy or Uncomplicated Enterocutaneous Fistula"). Local complications associated with stoma formation may be apparent early or late in the postoperative period. Complications of stomas are common and 20–30% of patients will require further surgery within 5 years for a problem with the stoma.

Early

In the first days after surgery, local complications relating to the blood supply of the stoma and its attachment to the skin are common. These include obstruction from torsion or oedema of the stoma (especially in the presence of a loop ileostomy), bleeding, retraction, necrosis and peristomal infection. Infection is surprisingly uncommon in the absence of an element of necrosis at the mucocutaneous junction. These complications may require further surgery. Necrosis of the stoma (Fig. 3) may be managed conservatively, provided that the patient is systemically well, has no signs of spreading peritonitis and viable mucosa is identifiable outside the patients' abdominal wall. This can usually be easily ascertained by gently inserting an endoscope into the stoma or even using a lubricated test-tube and shining a torch along it for illumination. When conservative management is successful, the stoma generally heals with stenosis (Fig. 4) and may require subsequent refashioning.

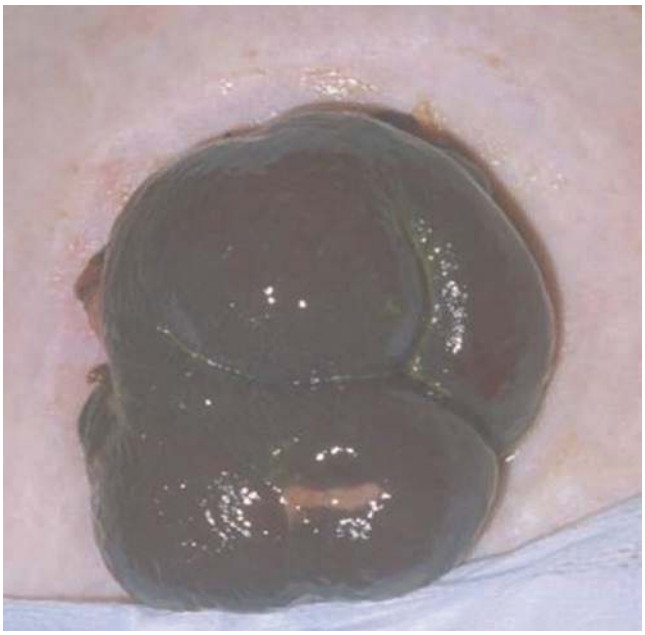


Fig. 3 Superficial necrosis and healthy tissue is seen underneath the covering

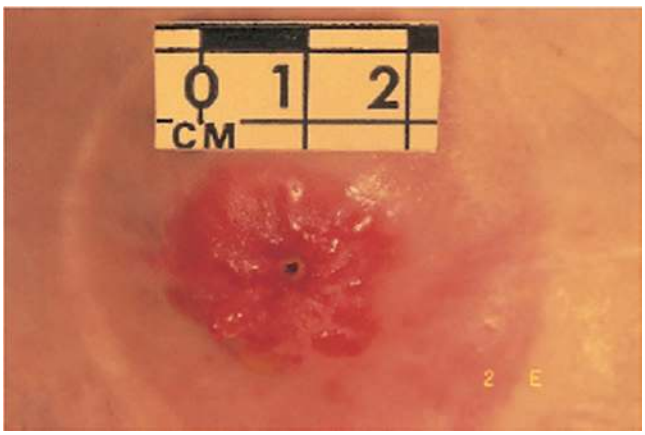


Fig. 4 Stenosis of the stoma following superficial necrosis

Late

Local complications that develop in the weeks or months after fashioning a stoma, generally relate to stoma care itself, the development of a parastomal hernia or intestinal disease.

Skin Damage

Intestinal effluent is a digestive juice and can rapidly digestive the peristomal skin. Skin excoriation will begin to occur within half an hour of exposure to jejunostomy/ileostomy fluid and protective powder or barrier spray should be applied to the area to help healing and to protect the skin. Ulceration around a stoma may be due to a poorly fitting stoma appliance but in patients with inflammatory bowel disease, pyoderma gangrenosum (Fig. 5) should be suspected, with typical 'punched out' ulcers.

Bowel Damage

Ulceration, excessive granulation tissue and bleeding from the mucosa, usually of an ileostomy, are common complaints and may be attributable to a poorly fitting stoma appliance (Fig. 6). In patients with Crohn's disease, recrudescence of disease within the stoma may occur and present with pain, bleeding and visible ulceration. In severe cases, the associated stricturing may lead to intestinal obstruction. A biopsy may be required to establish a definitive diagnosis.

Herniation

Parastomal herniation is very common complication of an end colostomy particularly if a stoma brought out is lateral to the rectal sheath and if the abdominal musculature is very weak as often occurs in the elderly. There is some evidence to suggest that coordinated abdominal wall exercises in the postoperative period may reduce the frequency and/or severity of herniation. The Stoma nurse should offer advice and expertise on the prevention of a parastomal hernia in the form of exercise and wearing a support belt when participating in strenuous activates [10]. A parastomal hernia may predispose to intestinal obstruction and strangulation, is disfiguring for the patient and may make it difficult to fit an appliance.

Parastomal hernias are difficult to correct surgically. A variety of surgical approaches may be adopted, ranging from local suture repair and mesh repair to laparotomy and transposition of the stoma, depending upon the size of the hernia and the age and condition of the patient. The long-term results of repair are poor, however, with up to 50% of patients reporting a recurrence of their hernia. In general, surgical repair of a parastomal hernia is avoided unless the hernia prevents the fitting of a stoma appliance or is narrow-necked and symptomatic.

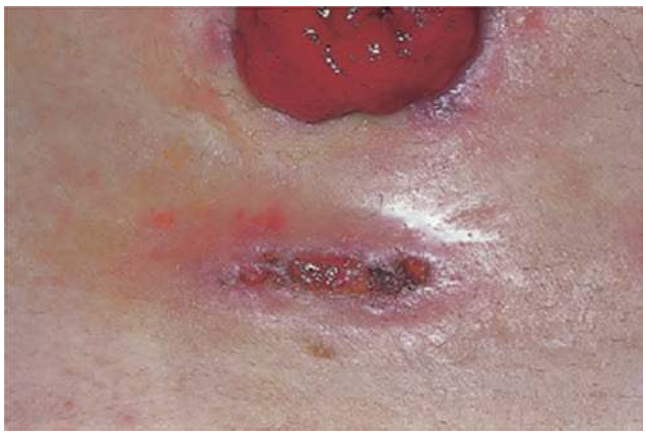


Fig. 5 Pyoderma gangrenosum around an ileostomy

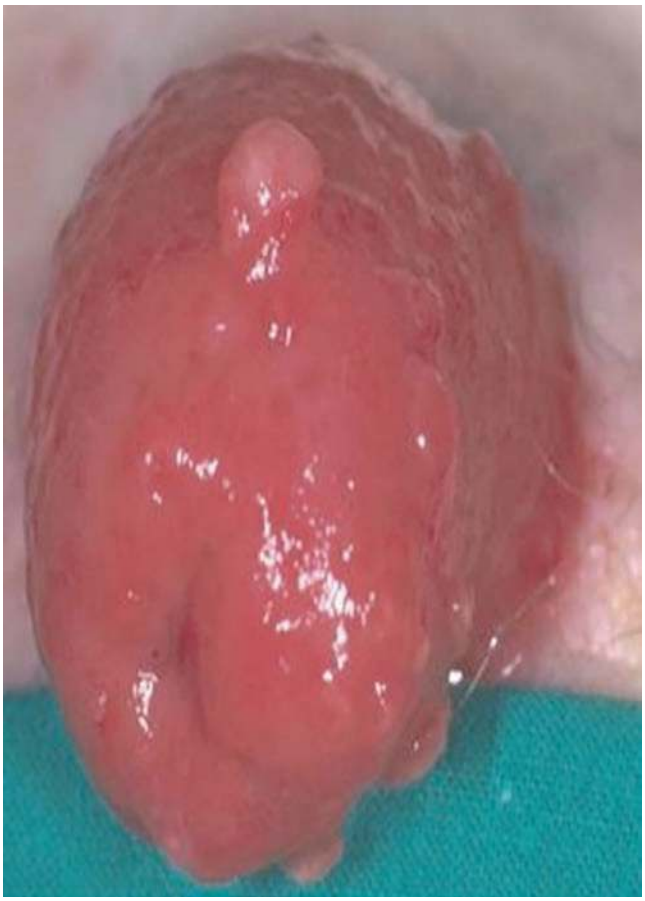


Fig. 6 Granulations and superficial ulceration of an ileostomy, due to a poorly fitting stoma appliance

Prolapse

Prolapse of a stoma is generally associated with the development of a parastomal hernia and is characterized by an 'elephant's trunk-like' everted protrusion of the stoma. This may prevent satisfactory fitting of an appliance and is especially common in patients with a transverse loop colostomy, which should therefore be avoided if at all possible. Surgery may be required to refashion the stoma, especially if prolapse interferes with stoma care.

Emergency surgery may be avoided in some cases by techniques to reduce oedema of prolapsed stomas, for example by application of granulated sugar, which may facilitate reduction of prolapse [11] (Fig. 7). Elective refashioning will usually be required however.

Stenosis and Retraction

These complications both result from defective surgical technique. Stenosis results from circumferential fibrosis at the mucocutaneous junction, most commonly as a secondary consequence of ischaemia and necrosis. If it is too painful to perform a digital examination of the stoma to assess the depth of mucosa stricture then patient may need referring onto a surgeon for dilatation under general anesthetic or refashioning of the stoma [12]. It must be remembered that refashioning an ilesotomy may involve a considerable amount of bowel being resected (>5 cm) and this can be very important if the patient has intestinal failure.

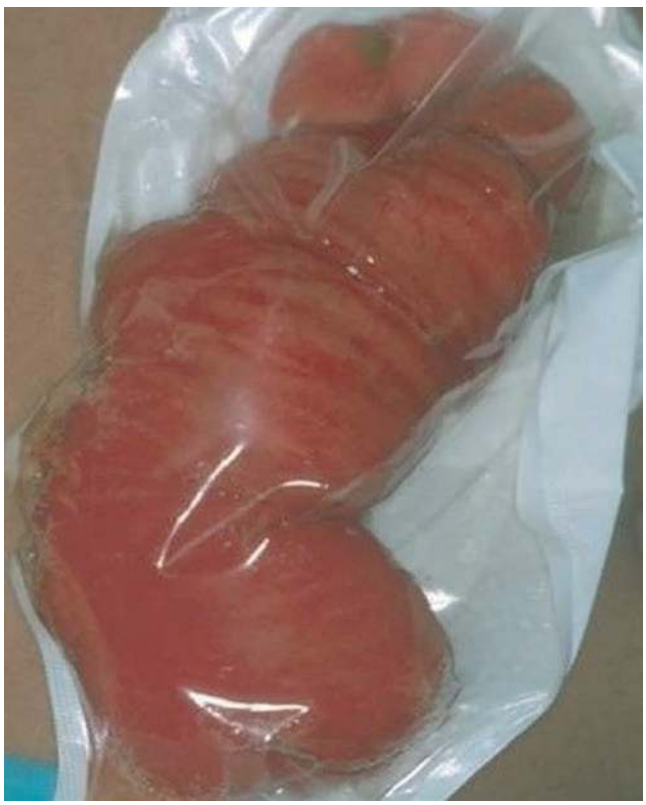


Fig. 7 Prolapsed stoma

Stoma retraction occurs when insufficient bowel has been mobilized to allow the mucosa to be sutured to the skin edge without tension. In the absence of impaired vascularity (as opposed to stenosis) the bowel does not become necrotic but the opening of the stoma lies in a depression. This leads to leakage under the flange, which may then lift off. Persistent leakage, which cannot be compensated for by the use of an appropriate appliance, is an indication for surgical refashioning of the stoma.

Enterocutaneous Fistula Management

The key principles in the management of a patient with an enterocutaneous fistula is the adequate treatment of abdominal sepsis, which is the most common cause of death [13] (chapter "Acute Surgical Intestinal Failure. Sepsis and Enterocutaneous Fistula(s)"). When possible, abdominal sepsis is managed by percutaneous drainage, but in some cases, notably those in which sepsis has arisen due to anastomotic dehiscence, a laparotomy will usually be required for drainage of abscesses and creation of a proximal defunctioning stoma to divert the faecal stream.

Once abdominal sepsis has been treated, attention is given to skin care, nutritional and metabolic support. Many fistulas will heal spontaneously but they will not if there is continuity between the gut mucosa and the skin, disease at the site of the fistula (for example Crohn's disease), distal obstruction and/or an intervening undrained abscess cavity [5]. In such cases enteral nutritional support with a low residue diet is appropriate for low output (<200 mL/day) fistulas in the distal ileum or colon, whereas patients with high output (>500 mL/day) fistulas, which are typically found in the proximal small bowel will usually require parenteral nutrition. It is the authors' preference to restrict such patients to sips of fluid only (some units say "nil by mouth") if contrast radiology suggests that a fistula is likely to close spontaneously. It should be noted that spontaneous closure will not occur when there is exposed bowel mucosa at the fistula opening. Such fistulas eventually mature and behave much like stomas. Where closure is unlikely (as above) and bowel content is not leaking into the abdominal cavity, prevention of oral intake is unnecessary and such patients can be allowed relatively unrestricted access to fluids and diet, provided fluid intake is not excessive and does not make local management of the fistula impossible. The same principles apply to the management of the high output fistula as the high output stoma (e.g. restriction of oral fluid intake and the use of oral glucose–electrolyte solutions, drugs that

reduce motility and intestinal or secretions) (chapter "Management of a High Output Stoma, Jejunotomy or Uncomplicated Enterocutaneous Fistula").

Management of the Patient with an Enterocutaneous Fistula (or Complicated Stoma)

Skin Care

Care of the skin around a stoma or fistula is perhaps the most important component of nursing care. The principal objective is to keep the effluent away from the skin. The more proximal in the gut a fistula, the more likely its output is to discharge corrosive fluid with activated pancreatic enzymes that can cause painful skin destruction (Fig. 8).

Management of the peristomal skin should be pro-active, with the goal being prevention by identifying and managing the causes effectively, thus preventing skin breakdown occurring [14]. An initial assessment of the stoma/fistula and surrounding skin should first be made noting approximate measurements, skin condition/degree of excoriation, description of output and any associated nursing implications (e.g. pain). Skin contours are noted for creases where leakage could occur. It is often helpful to photograph the wounds at this time. This information, together with accurate measurements of stoma output, allows the stomatherapist to select the most appropriate appliance thus enabling collection of the effluent and controlling the problems of leakage and odour. The patient, in turn, gains comfort, confidence and independence. Key aspects of management of the patient with an intestinal stoma or fistula are the selection of appropriate equipment and the adoption of suitable management techniques.

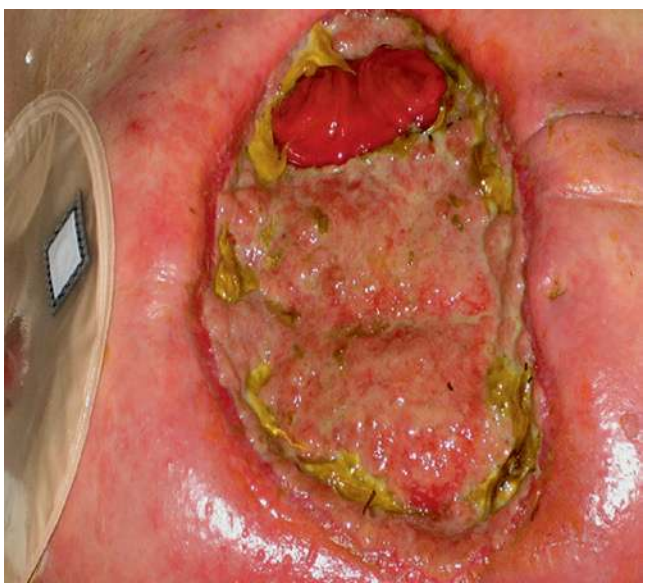


Fig. 8 Extensive skin damage resulting from a high output enteroatmospheric fistula with inadequate skin protection

The Stoma nurse should determine the type and size of appliance and initially the frequency of bag emptying and changing. The aim is to keep the equipment and procedures simple and allow for the patient to choose their preferences. Complex ritualistic procedures must be avoided.

Stoma/Fistula Appliances

A well-fitting adhesive appliance will protect the skin, remove unpleasant odours, reduce risk of cross-infection, allow assessment of fluid losses, preserve dignity and allow the patient mobility and rest [1]. There are many types of stoma and fistula appliances available and the manufacturers also produce accessories to treat damaged skin, produce an even body contour (thus allowing better fitting of a stoma appliance) and deodorize offensive exudates. Immediately postoperatively a clear, unvented, drainable standard bag on which the aperture is cut to fit the stoma is used so that the viability of the stoma can be monitored and stool/air output can be observed. As the stomal output becomes regular and predictable a one- or two-piece bag can be used. The former attaches directly to the skin and may be closed or drainable. A closed bag is often appropriate for a colostomy, which is typically changed 2–3 times a day. A drainable appliance is appropriate for ileostomies/jejunostomies or for colostomies with a fluid output. Flatus valves (vent/charcoal filter), to allow escape of gases, are now present in most appliances. Two-piece appliances have a flange that can stay on the skin for 3–4 days and are fitted with either a drainable or closed bag. Drainable bags should be changed every 24–72 h. Stoma products have changed dramatically over the years and a large selection are now available. Bags for use over an established stoma can have a pre-cut aperture if patient prefers this and come in all different sizes as colors. Most bags hold about 200–300 mL of fluid. Extensive wound areas require a large 'wound manager' (Fig. 9). These can be adapted to the size and shape of any wound and are drained continuously. Planned stomas that are of routine size are more easily catered for, but stomas that have become flush or have retracted, can be successfully managed with the use of convex flanges incorporated within the bags.

Adhesive Flanges

An appliance usually sticks to the skin by a cohesive seal. Clean, warm, dry skin is needed. If the skin is itchy, a barrier spray or wipe can be used and helps both with itching and adhesion.

Filling Pastes/Wafers/Dressings

There are many hydrocolloid pastes that can be used to fill defects in a wound. Wafers may be used to help adherence of

Fig. 9 Fistula appliance attached to a high output collection bag hold 2 L

the appliance and may act as barriers between the bag/skin. The flanges of a stoma bag can safely cover wounds if needed.

Absorbent dressings with associated barrier creams are inadequate for outputs of more than 20 mL/day. Appropriate well-fitting/constructed stoma appliances cut to fit the area and so cover exposed skin enable successful management [15].

Techniques

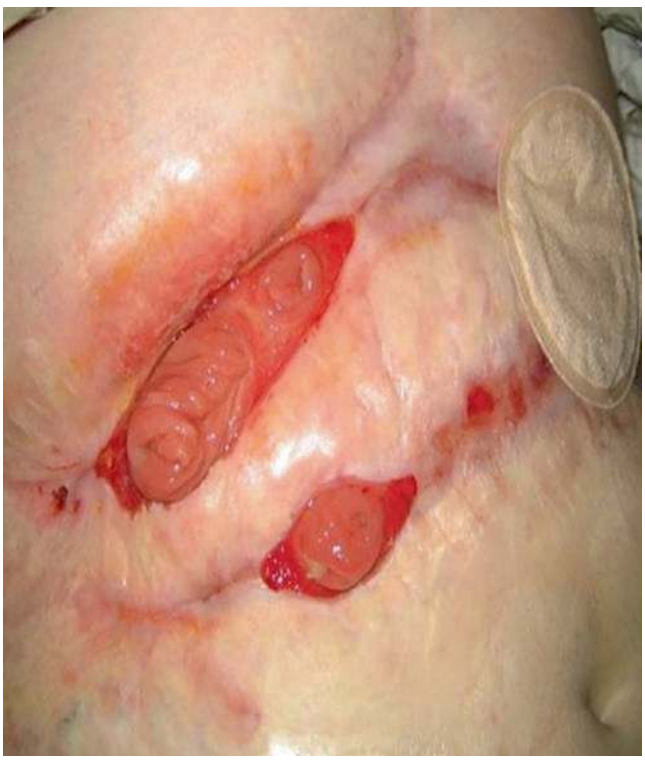
Fitting an Appliance Over a Stoma

The appliance is peeled from the skin gently by easing the skin away and barrier remover spray or wipes can be used to assist this. The surrounding skin is then cleaned using soft wipes and warm water and the area dried well with a dry wipe. Tap water alone is adequate for this purpose. However, if desired, an unperfumed, gentle soap could be used. Direct contact with the intestinal mucosa should be avoided. An appliance of the correct size is selected and cut to size. The backing is peeled off and applied gently to the abdomen over the stoma area.

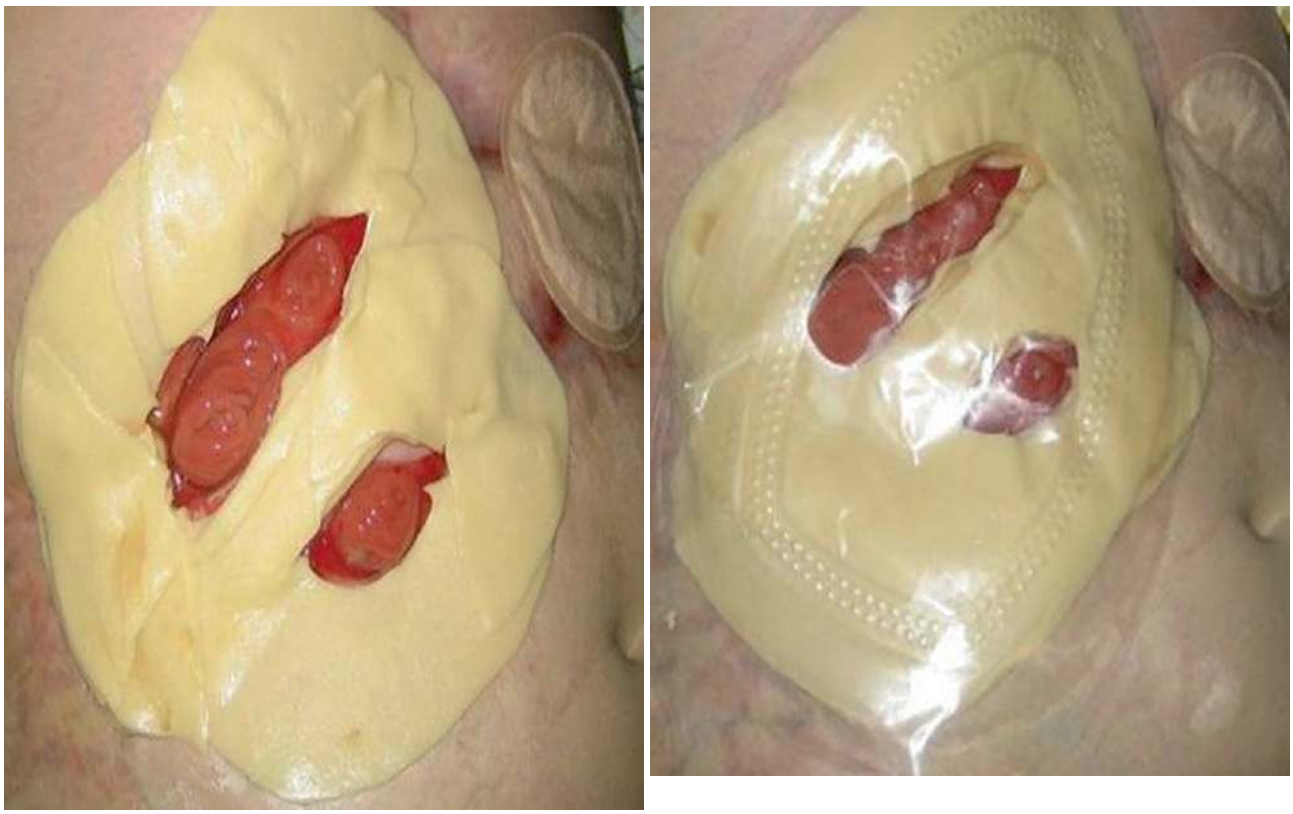
An ileostomy bag is usually emptied 5–6 times/24 h (total volume is about 500–800 mL/24 h) and most patients do this once during the night. If the patient has a high stoma output the flange/bag/dressing change is undertaken when the output is likely to be lowest or when help is available. Following drainage of the bag, the end of the appliance is cleaned with a wipe and rolled up and closed securely. Odour powders/deodorant sprays may be used at this time. The bag is subsequently changed as required. In hot conditions this may need to be undertaken more frequently as the backing can 'melt' or due to the patient's skin sweating and the appliance may therefore leak.

Fitting an Appliance Over a Complex Fistula

The area should be cleaned with warm water and dried thoroughly with soft wipes and a hairdryer can be used on a cool setting. Shaving of body hair may be necessary to optimise adhesion and prevent discomfort. Excoriated skin should have Stomahesive Protective ostomy powder applied sparingly. It is often helpful in caring for large fistula wounds to make a template of the area with a piece of clear plastic material that usually comes in the packaging with the appliance. This assists with cutting the base of the bag and is useful in observing the healing process, as smaller templates will be required probably weekly. Crevices or creases of intact skin can be filled with Stoma paste or pieces of Moldable seals to even the site (Fig. 10). It may be necessary to cover this area with a protective sheet cut to fit, but the base of the wound manager alone is usually quite adequate. The immediate edge around the stoma/fistula should be filled with soft paste to help adhere and prevent leakage of the effluent between the surfaces. The readily prepared appliance should now be applied, firmly moulding it to the surface



Figs. 10–12 Applying a bag to an intestinal fistula



Figs. 10–12 (continued)

and ensuring that no creases occur during the procedure (Figs. 11 and 12). The patient should be encouraged to rest for approximately 30 min to promote adhesion of the appliance.

The technique used should be fully documented with a photographic care plan so that other team members can maintain the prescribed care. The area should be regularly inspected and any evidence of pain, burning of the skin, leakage, odour or detachment of the appliance should be investigated and treated appropriately, appliances should not be patched if leaking appliance will need replacing to prevent sore skin occurring. The plan of nursing care should be evaluated regularly and changes made as required. The patient with extensive fistula formation may not be able to participate in any practical aspects of the skin care until their general condition is improved or surgery to treat the underlying problem is undertaken. However, wherever possible the patient should be encouraged to begin to participate in caring for their stoma and so in turn gain independence, autonomy and sense of well-being. The plan to teach and involve the patient with their care should begin following discussion between the stomatherapist, nurses and, most importantly, the patient.

Some fistulas lie in large irregular cavities, which make them exceptionally difficult to manage. Such fistulas may require a short-term treatment of low suction until the area shrinks to manageable dimensions. This is applied via a catheter incorporated within the bag, through which low-grade continuous suction can be applied. This treatment should not be prolonged because negative pressure at the cutaneous surface of a fistula where there is no exposed mucosa may prevent spontaneous fistula closure and the treatment may also restricts mobilization [16]. However, the application of negative pressure where a fistula cannot, in any event, heal spontaneously (for example where there is already enteroatmospheric fistulation) may greatly facilitate nursing care.

In some cases, the configuration of the fistula may make adequate skin and fistula care almost impossible to achieve—for example where a fistula sits at the base of a deep and/or irregular cavity on a skin crease. Persistent leakage and excoriation may result in ulceration, pain, inability to eat and drink (in order to avoid leakage) and psychological distress and be associated with poor mobility and demoralization. These circumstances may represent an indication for early surgery, if only to explore the (usually relatively untouched) left upper quadrant of the abdomen, in order to establish a proximal stoma to defunction the fistula. A well-spouted proximal loop jejunostomy may have significant implications for fluid and electrolyte balance and

nutritional support, but patients invariably find them easier to tolerate (as a temporary measure) than an uncontrollable fistula.

The ultimate goal of stoma and fistula management is for the patient to be able to care for themselves. This may not always be possible, however. Depending upon the patient's individual circumstances, close relatives may need to undertake patient care or the patient may request they be at least made aware of the needs that may be required. Practical skills should be demonstrated to the patient with careful explanations that can be easily understood. Patients should be reassured that they will not be discharged from hospital until they or their carers can cope with the required stoma care. Following a period of observation, patient participation should be encouraged and this can be gradually increased.

Continuous assessment is required and the nurse must continue to support the patient even when full independence in stoma care is achieved. The patient should be informed of all aspects of stoma care from the obtaining of supplies to the disposal of appliances and should be made aware of the availability of self-help associations who can assist in the rehabilitation or with welfare issues.

Emptying Drainage Bags

Stoma bags and wound managers should be regularly emptied to prevent excessive accumulation of effluent because the weight of the fluid can dislodge the bag. Faecal matter is emptied and the bag is wrapped in a plastic bag for disposal. High output fistulas/stomas (over 500 mL/24 h) may require frequent drainage and this can disturb sleep, thus adding to stress. To prevent this, a secondary drainage container allowing continuous gravity drainage of stoma bags into a high output drainage bag with thick piping that can hold up to 2 L (Fig. 9) can be used.

Discharge

Patients need to be independent with their stoma care to ensure safe discharge from hospital, in the absence then there will need to be adequate support in place at home [17]. When the patient is discharged the stomatherapist and the district nurses will maintain continuity of care, and supportive counselling will still be required. Certain problems only become evident on discharge from hospital, especially relating to difficulties in personal or sexual relationships. These may require expert help from marriage guidance or psychosexual counsellors though the nurse can help assess the situation and make arrangements for referral if appropriate.

References

1. Forbes A, Myers C. Enterocutaneous fistulae and their management. In: Myers C, editor. Stoma care nursing. a patient-centred approach. London: Arnold; 1996. p. 63–77.
2. Fazio V, Church J, Wu J. Atlas of intestinal stomas. New York, NY: Springer; 2012. p. 39–47.
3. Nicholls RJ. Surgical procedures. In: Myers C, editor. Stoma care nursing. a patient-centred approach. London: Arnold; 1996. p. 90–122.
4. Brooke BN. The management of an ileostomy including its complications. Lancet. 1952;2:102–4.
5. Irving MH, Carlson GL. Enterocutaneous fistulas. Surgery. 1998:217–20.
6. McCahon S. Faecal stomas. In: Porrett T, Daniel N, editors. Essential coloproctology for nurses. New York, NY: Wiley; 1999. p. 165–87.
7. Williams L, Varma S. Travel and Holidays: how best to advise ostomist. Gastointest Nurs. 2011;9(7):26–32.
8. Morrall SE. The shock of the new; altered body image after creation of a stoma. Prof Nurse. 1990;5:531–4.
9. Elcoat C. Stoma care, taking an holistic approach. Nurs Times. 1998;84:57–60.
10. North J, Osborne W. ASCN UK guidelines: parastomal hernias. Br J Nurs. 2017;26(22):1262–3, (S6-S13).
11. Theofanis G, Saedon M, Kho S, Mulita F, Germanos S, Leung E. Avoiding emergency stoma surgery with the use of sugar. Br J Nurs. 2017;26(22):1262–3, (S24-S26).
12. Association of Stoma Care Nurses UK. National clinical guidelines. Edinburgh: Association of Stoma Care Nurses UK; 2019.
13. Soeters PB, Ebeid AM, Fischer JE. Review of 404 patients with gastrointestinal fistulas. Impact of parenteral nutrition. Ann Surg. 1979;190:189–202.
14. Metcalf C. Managing moisture associated skin damage in stoma care. Br J Nurs. 2018;27(22):S4–6.
15. Gross E, Irving M. Protection of the skin around intestinal fistulas. Br J Surg. 1977;64:258–63.
16. Blower AL, Irving MH. Enterocutaneous fistulas. Surgery. 1992;12:27–31.
17. Burch J. Promoting enhanced recovery after colorectal surgery. Br J Nurs. 2013;22(5):S4–9. Stoma care supplement.

Management of a High Output Stoma, Jejunotomy or Uncomplicated Enterocutaneous Fistula

Jeremy M.D. Nightingale

Key Points

1. A high output stoma (HOS) or fistula is when the output causes the patient to become water, sodium and magnesium depleted.
2. A HOS tends to occur when the output is more than 1.5–2.0 L/24 h though this varies according to the amount of food/drink taken orally.
3. Management starts with excluding causes other than a short bowel (especially intermittent or partial obstruction). It is helpful to have a measurement of residual small bowel length (at surgery, or by a contrast radiological examination). The stoma and output should be inspected
4. The patient is rehydrated both to relieve excessive thirst and correct electrolyte abnormalities.
5. Oral hypotonic fluids (tea, coffee, fruit juice, alcohol or water etc.) are restricted to a litre or less per 24 h. 1–2 L of a glucose/saline solution (sodium concentration 90–120 mmol/L) (cold, taken through a straw) is sipped throughout the day +/− magnesium supplements.
6. Oral medication to slow transit (loperamide often in high dose or codeine phosphate) is taken before food/drink. For those with a net secretory output (greater than total oral intake) a proton pump inhibitor (omeprazole) may be taken to reduce the volume of gastric acid produced.
7. If hydration cannot be maintained with oral measures subcutaneous saline (usually 1 L with magnesium) given 1–4 times/week may be given before parenteral fluids.
8. In addition to renal function, the urinary sodium concentration and serum magnesium level must be monitored.
9. Consideration should be given to surgically bringing any small or large bowel that is in situ but out of circuit, back into continuity.

Introduction

Most of the classical work published about patients with a short residual length of intestine related to those with jejunum in continuity with colon [1–3]. A number of patients with a jejunostomy are being managed, mainly because the colon is often removed during the surgical treatment of Crohn's disease or it is temporarily out of circuit in the management of ischaemia or a fistula/obstruction. These patients have immediate and serious problems because of large intestinal losses of water, sodium and magnesium. The residual bowel length may not have been measured and such patients are often categorized as having ileostomy diarrhoea. The management of patients with a jejunostomy, ileostomy diarrhoea or a high-output enterocutaneous fistula is the same.

This chapter outlines the medical problems caused by the large volumes of fluid lost from the stoma or fistula and, using data from balance studies, discusses treatments. Information about stoma care is found in chapter "Care of Intestinal Stoma and Enterocutaneous Fistula(s)".

How Common Is a HOS?

A normal ileostomy may function within the first day of surgery depending upon whether an ileus occurs (often due to opiates and excessive intravenous saline). The stomal output from an ileostomy may reduce over several months as adaptation occurs and the normal output when established is 600–1200 mL/24 h. Patients with a jejunostomy (less than 200 cm small bowel remaining) do not generally show any improvement in absorption with time [4].

A high output stoma (HOS) (often called ileostomy diarrhoea) is when the output is enough to cause "dehydration" (water and sodium depletion). In general this occurs with an output of greater than 1.5–2.0 L/24 h. However this depends on the oral intake. A 2 L output for someone taking in 4.0 L will cause no problems but if only an intake of 0.5 L it will result in dehydration [5].

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In one study a HOS occurred early in 16% patients (within 3 weeks of a stoma being formed) and late (more than 3 weeks) in 4% in whom this was a persistent problem [6]. Other studies show similar rates 16–31% following surgery [7–9]. Problems are more common in patients with a loop ileostomy or after an ileal resection. There are rarely any problems of HOS when more than half the colon remains in continuity and there is more than 50 cm functioning small bowel present [6].

Evidence that many patients with an ileostomy are salt and water depleted comes from the observation that plasma renin and aldosterone levels are high in ileostomy patients [10, 11] and 13% have a urine sodium concentration of less than 10 mmol/L [12]. Unrecognised, chronic dehydration in these patients can lead to end stage renal failure. Diuretics given to patients with an ileostomy (especially if they have had problems of HOS) may precipitate renal failure and generally should be avoided. Care must be taken with renal dialysis if needed to not remove additional fluid (indeed more may need to be given).

Presentation of Patients with a Jejunostomy

The problem of fluid loss from a jejunostomy is apparent immediately after the surgery that removes the bowel. The fasting stomal output may be less than a L/24 h but it will rise when food and drink are consumed to as much as 8 or more litres a day. This results in dehydration, sodium depletion and hypomagnesaemia. These patients are dependent on their treatment; if they miss a day of treatment, they rapidly become unwell from dehydration.

Patients with a jejunostomy do have problems of protein–energy undernutrition but these develop slowly over several weeks and are usually attended to at the same time as the fluid balance problems. As jejunal length gets shorter fluid balance problems (less than 200 cm jejunum) occur before nutritional ones (less than 100 cm jejunum). The fluid/nutritional problems should be predicted and treated before the patient becomes dehydrated or undernourished.

Causes of a High Output Other Than a Short Bowel

Causes of a HOS other than a short bowel (jejunostomy <200 cm) should be sought. This is a common group who may have a normal length of small intestine (Table 1). An early HOS is most commonly due to sepsis (a raised WBC on day 1 is a clue [9] and may be why an early HOS is more common in diabetics [7]. The other common causes of an early HOS are medication related; this can be because of a prokinetic drug (e.g. metoclopramide) or the sudden, usually accidental, withdrawal of a medication (e.g. opiates or cortisol). *Clostridium difficile* can affect the small bowel and cause a HOS [9]. A chronically HOS is most commonly due to a short bowel (jejunostomy). However intermittent/partial obstruction due to small bowel strictures is common (with associated bacterial overgrowth); a stenosis is most commonly at the stoma [8] (Fig. 1). Dilation of a stricture and a low fibre/residue diet (Table 2) may prevent the obstructive episodes and the occurrence of a HOS. Recurrent disease (including ischaemia), internal fistula, small bowel diverticula, coeliac disease and thyrotoxicosis can all contribute and if treated the HOS may resolve. If the HOS is due to strictures and there is a low serum albumin it may be

Table 1 Reasons for a high output stoma

Early (<3 weeks of formation)
• Abdominal sepsis/ileus/ischaemia (low albumin)
• Drug-related
– Prokinetic drugs (e.g. metoclopramide)
– Low cortisol
– Opiate withdrawal (e.g. codeine phosphate)
• Enteritis (*Cl difficile*)
Late (chronic more than 3 weeks)
• Short bowel—jejunostomy <200 cm
• Intermittent/partial obstruction (strictures)
• Other less common causes:
– Recurrent disease
– Internal fistula
– Small bowel diverticula
– Coeliac disease
– Thyrotoxicosis

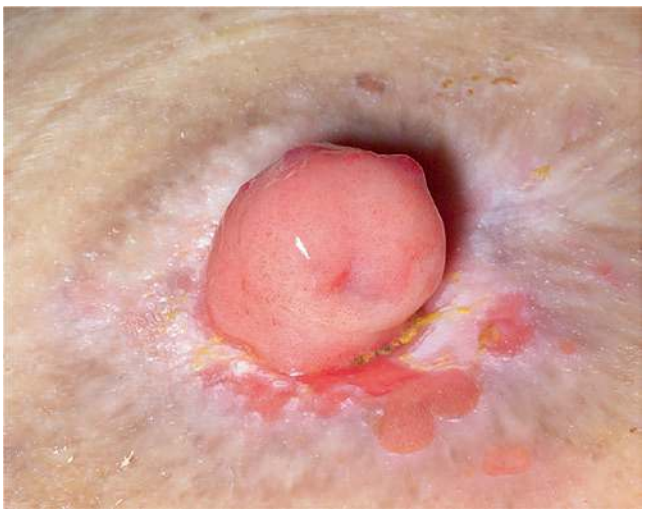

Fig. 1 Narrow stoma causing intermittent high output and renal failure. Resolved after stoma was refashioned

Table 2 Low fibre/low residue diet

Avoid
Vegetables/fruit
Nuts
Wholemeal products
Eat
Meat/Fish/Eggs
Dairy
White Rice/Pasta/Bread
Potato without skin
Jelly

NB: Good teeth/dentures, chew well (often not done well at times of stress)

that a section of chronically/critically ischaemic bowel remains in situ and the problem will only resolve with a surgical resection.

Balance Studies for Patients with a Short Bowel: Jejunostomy

Balance studies have provided the most useful information about the problems and the management of patients with a jejunostomy. They are easier to perform in patients with a jejunostomy than in patients with a short bowel and a preserved colon as a 1–3-day run-in period is not required, and the stomal bag allows for easier collection.

Patients with a short bowel may not feel hungry, and those with a jejunostomy are often just in positive water and sodium balance, so cannot abruptly stop treatments that are maintaining their equilibrium. Patients who suddenly stop taking codeine phosphate when they have been taking it for several months or years are likely to develop the symptoms and signs of opiate withdrawal, which include diarrhoea, manifested as a rise in stomal output. Balance studies are rarely done in the ideal experimental setting with the patient taking no medications.

There are three possible ways to study intestinal balance in patients with a short bowel. With each, a duplicate oral intake is made and assayed.

Test Meal

A standardized meal containing a non-absorbable marker (e.g. polyethylene glycol) is given and the stool or stomal output is collected for a fixed period while nothing else is taken orally. Rodrigues et al. showed that over 90% of a non-absorbable marker in a liquid test meal was recovered from jejunostomy fluid in the 6 h after the meal [13, 14]. This technique is not appropriate for patients with a retained colon as the time taken for the food residue to be passed in the stool may be 2–3 days.

Investigator-Selected Diet

For each 24-h period, the investigator specifies the exact composition and amount and the time at which food and drink are to be consumed by the patient. This is an experimental ideal but patients with a short bowel are fastidious eaters who often feel full very quickly, and such a study is difficult to perform in practice. Studies have been done, however, in which the proportion and total amount of macronutrients and fluid are fixed [15]. A 2-day collection is adequate for patients with a jejunostomy, but if the colon has been retained a run-in period of at least 2 days is needed, so that remnants of other meals will have been passed in the stool.

Patient-Selected Diet

Patients select a diet freely on the first study day and eat and drink whatever is normal for them. They keep an accurate record of the food and drink, the amount and the time at which it is consumed. On all subsequent study days they consume exactly the same food and drink in the same amounts and at exactly the same times as on the first day. All studies by Nightingale et al. use this method for 2 paired control days and 2 further paired test days when a therapy is given [16].

The way in which stool, ileostomy or jejunostomy output is analysed is important. When jejunostomy output is centrifuged, three layers are seen: fat at the top, fluid in the middle and solid at the bottom (Fig. 2). In general, the higher the output the larger the middle fluid layer; if the output is low (less than 1 L daily) then it may not be possible to see a fluid layer, and the fatty layer and the solid component merge together. While it is simpler to aspirate the fluid layer, filter it, and assay for electrolytes; this can only be done when there is a large liquid output and when the patient is taking little or no solid food. Not all studies state whether the whole stomal output is analysed or whether it is just the fluid layer. All studies by Newton, McIntyre, Rodrigues and Nightingale assayed the whole stomal sample. This involved diluting stomal samples with concentrated hydrochloric acid before flame emission photometry for sodium and potassium measurements or ashing a sample in a 550 °C furnace for 15 h before dissolving in nitric acid and using atomic absorption spectrophotometry to measure magnesium and calcium concentrations. Energy content can be determined by freeze-drying a sample then performing bomb calorimetry.

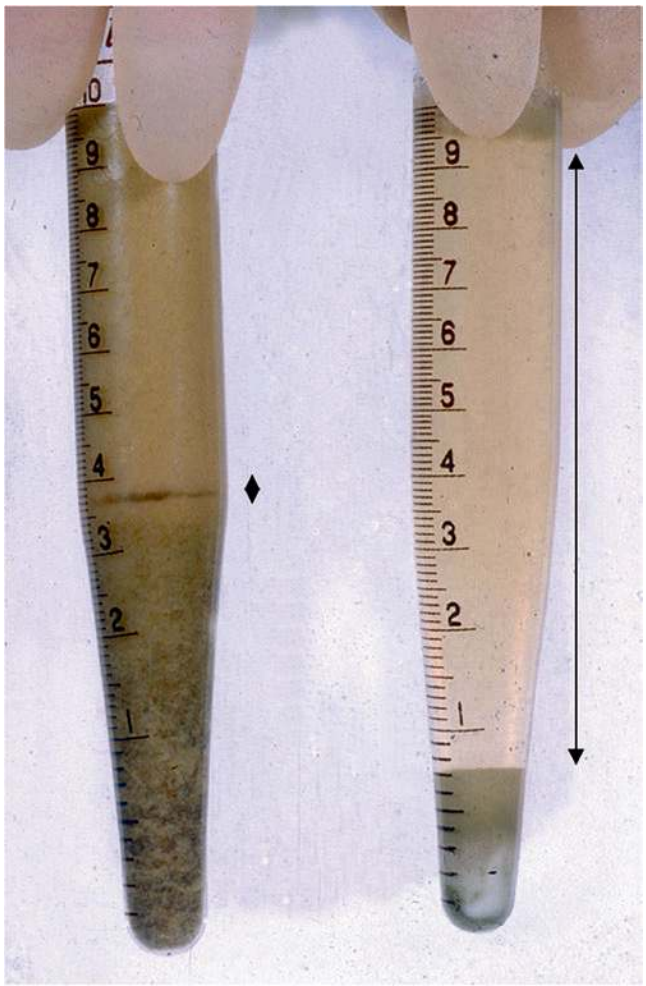

Fig. 2 Centrifuged ileostomy output. Net absorber (150 cm jejunum) on left and net secretor (60 cm jejunum) on right. Note the different size of the middle fluid layer (arrowed). The top layer is fatty and bottom is precipitate/solids

Reasons for a High Output from a Jejunostomy/High Fistula

There are four potential physiological reasons for a HOS in patients with a short bowel and jejunostomy: loss of the normal daily secretions produced in response to food, hypo- or hyper-tonic fluid/food ingestion, gastric acid hypersecretion, and rapid gastrointestinal transit. An excessive thirst may exacerbate the situation.

Loss of Normal Daily Intestinal Secretions

The most important reason for a large volume of stomal output is that the normal daily intestinal secretions produced in response to food and drink (about 4 L/day made up of 0.5 mL saliva. 2 L gastric juice and 1.5 L pancreaticobiliary secretions) cannot be reabsorbed in the short length of bowel

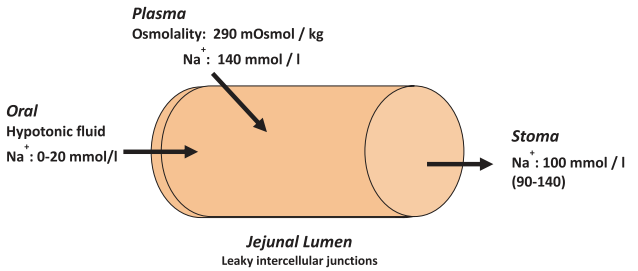

Fig. 3 Diagram to show sodium movement into the jejunal lumen when hypotonic fluid is drunk (upper gastrointestinal secretions not shown)

remaining, so are lost through the stoma. So in most normal subjects, about 6 L of chyme pass the duodeno-jejunal flexure each day and the meal is still just diluted by intestinal secretions 100 cm distal from the duodeno-jejunal flexure [17, 18]. When the small bowel length is less than this, more emerges from the stoma than is taken in by mouth. Even in the fasting state there is an obligatory loss of intestinal secretions produced with the migrating myoelectric complex (MMC) [19].

Hypo- and Hyper-Tonic Fluid Ingestion and Thirst

Jejunal mucosa is 'leaky' and rapid sodium fluxes occur across it. If water or any solution with a sodium concentration of less than 90 mmol/L is drunk there is a net efflux of sodium from the plasma into the bowel lumen [20] until a luminal sodium concentration of 90–100 mmol/L is reached. In a patient with a jejunostomy this fluid is then lost in the stomal output (100 mmol/L sodium) (Fig. 3). Hypertonic fluid (e.g. an elemental diet) will cause a net secretion of water (and sodium) into the lumen till the osmolality nears 300 mOsm/kg. Patients, who are water and sodium depleted, are often very thirsty and so may drink an increasing amount of hypotonic fluid (often containing no sodium) and the effect is to increase the stomal output and increase the sodium losses and so further increasing the thirst [12, 20–23].

Gastric Acid Hypersecretion

There is some evidence to suggest, at least in the short term, that loss of intestinal phase negative feedback inhibition results in hypergastrinaemia [24, 25] and gastric acid hypersecretion, which may all contribute to the high output from a jejunostomy. In man, gastric acid hypersecretion has only been demonstrated in the immediate postoperative period in patients

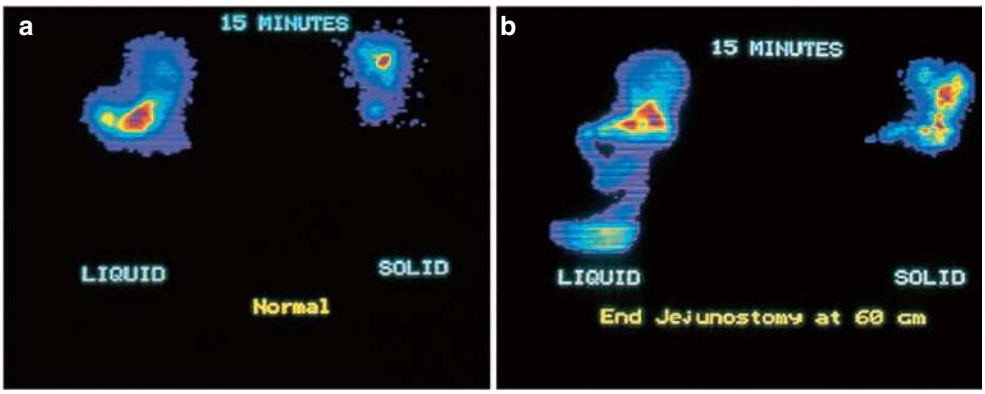

Fig. 4 Gastric emptying of liquid and solid in a normal subject (**a**) and in a patient (**b**) with a jejunostomy 30 cm from the duodeno-jejunal flexure 15 min after starting to eat a meal of a pancake and orange juice

with a retained colon [26]. It is unclear whether this phenomenon persists beyond the first weeks, but a low pH (<6) in the fresh stomal effluent when it exceeds 1 L daily is suggestive.

Rapid Gastrointestinal Transit

Rapid gastric emptying of liquid occurs and may increase the stomal output [27] (Fig. 4). The gastric emptying rate is fastest in those with the shortest lengths of residual jejunum. Small bowel transit time for liquid and solid is also very rapid [28]. Both of these effects may be mainly due to low serum levels of peptide YY [25] and, to a lesser extent, low levels of GLP-2 [28].

The Problem of High-Volume Jejunostomy Output

Water and Sodium Losses

Balance studies in patients with a jejunostomy, using a patient-selected diet, showed that the daily weight of stomal output was about 6–8 kg/d in those on parenteral nutrition with added saline and about 2 kg/d among those receiving oral supplements. The intestinal output is mostly water (mean 92%, range 85–96%) and there is a good correlation between stomal output weight and its sodium content (Fig. 5) [29]. The mean jejunostomy sodium concentration is 88 mmol/L, being lower in patients with a shorter remaining length of jejunum and higher in those with a greater length. The sodium concentration in the terminal ileum may be nearer to that of plasma (140 mmol/L).

Type of Patient with a Jejunostomy (Based Upon Water and Sodium Balance)

Classification of patients with a jejunostomy is based upon balance studies using a patient-selected diet. The weight and sodium content of the diet is compared to the weight and sodium content of the stomal output. The patients can be divided into

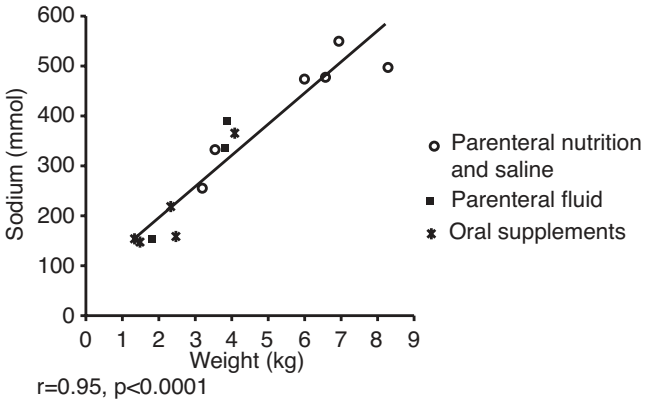

Fig. 5 Wet weight and sodium content of jejunostomy output for 15 patients with less than 200 cm remaining jejunum. ($r = 0.96, p < 0.0001$). The mean sodium concentration was 88 mmol/L (range 60–118 mmol) [29]

one of two groups, either net 'secretors' or net 'absorbers', according to intestinal water and sodium balance. This balance depends upon the degree of dilution of food and drink by digestive juices and the net absorption that has occurred [5] (Fig. 6).

'Absorbers' tend to have more than 100 cm of residual jejunum and can absorb more water and sodium from their diet (which may have been modified to have an increased amount of sodium) than they take orally. Their daily jejunostomy output is usually about 2 kg or less in 24 h, thus they can be managed with oral sodium and water supplements and parenteral fluids are not needed.

'Secretors' tend to have less than 100 cm of residual jejunum and lose more water and sodium from their stoma than they take by mouth. Usual daily stomal output may be 4–8 kg. These patients cannot convert from negative to positive water and sodium balance by taking a modified diet or sodium supplements and they need long-term parenteral supplements [5]. These requirements change very little with time [30]. The jejunostomy output from a net 'secretor' increases during the daytime in response to food and decreases at night, thus any drug therapy that aims to reduce the output must be given prior to food (Fig. 7).

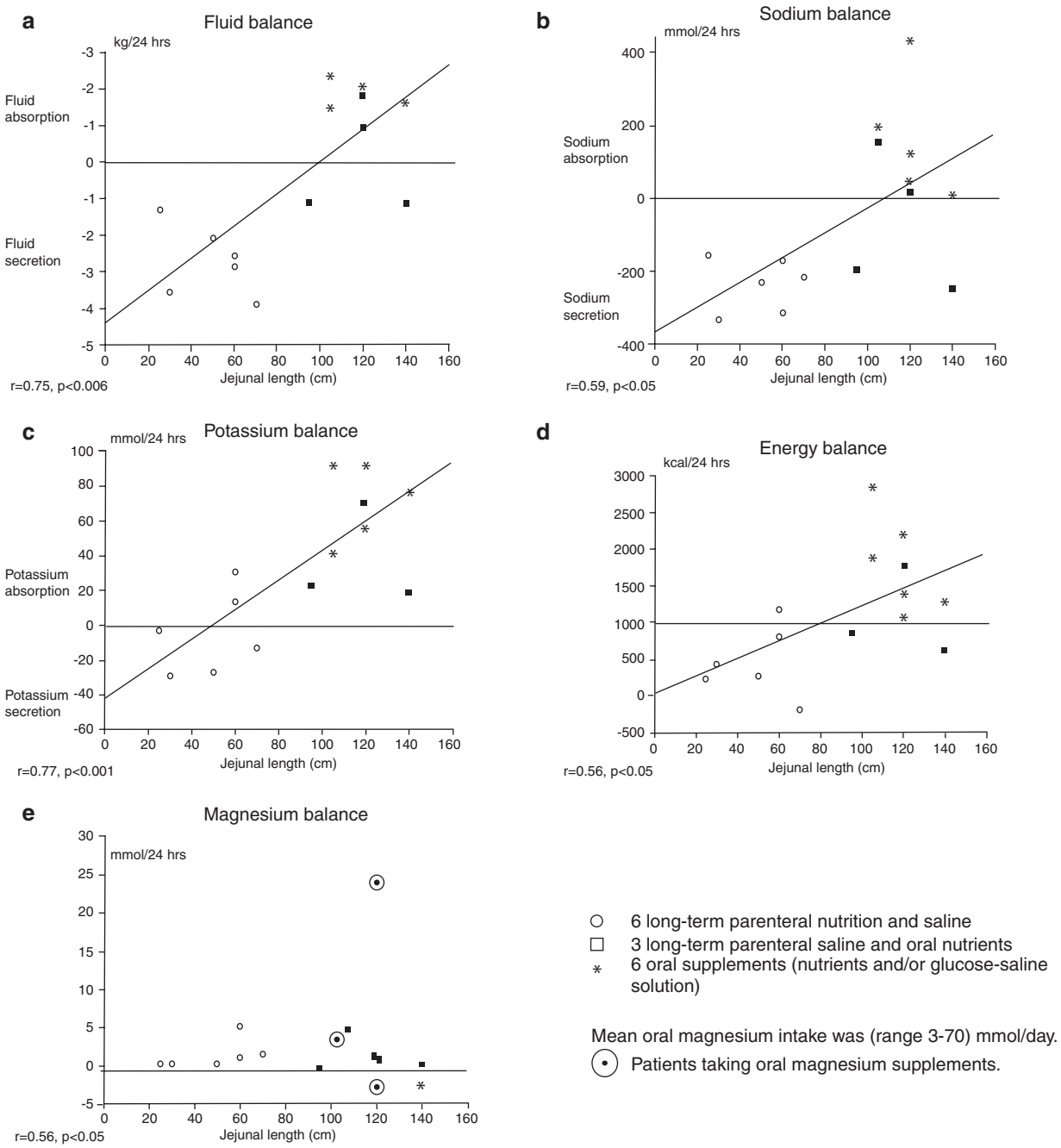

Fig. 6 Balance studies using the patient-selected diet performed for 2 days on 15 patients with a jejunostomy who were all maintaining fluid, electrolyte and nutritional status. Six needed long-term intravenous nutrition, 3 required long-term intravenous fluids but maintained their nutrition with an oral diet, and 6 took oral fluid and nutrient supplements [5]. (**a**) Total weight, (**b**) sodium, (**c**) potassium (**d**) energy and (**e**) magnesium. Note that positive intestinal fluid and sodium balance is achieved at 100 cm jejunum, potassium at 50 cm, and there was no relationship with magnesium balance

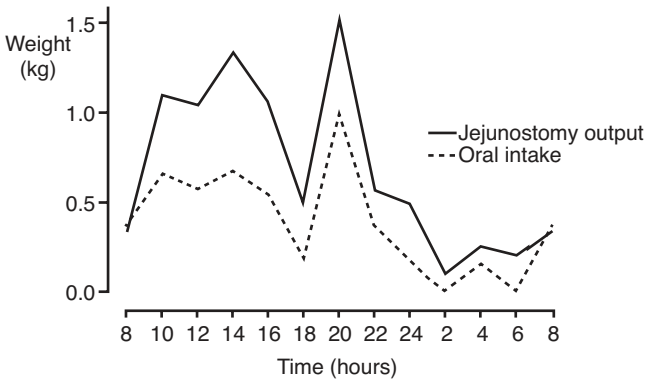

Fig. 7 Oral intake (kg) and stomal output measured every 2 h in a patient who has 30 cm of residual jejunum and shows net secretion [5]

A clinician, unlike a research worker, is unlikely to be able to perform accurate balance studies, in which case the classification can be predicted from knowledge of the residual jejunal length. The change from a net secretory state to a net absorptive state in terms of intestinal water and sodium balance occurs at a jejunal length of about 100 cm.

Potassium Deficiency

The effluent from a jejunostomy or ileostomy contains relatively little potassium (about 15 mmol/L) [5, 11, 31]. Values are higher in patients with a colostomy as the colon secretes potassium. Potassium problems are unusual and the potassium intake rarely needs to be greater than normal. Net loss through the stoma occurs only when less than 50 cm of jejunum remains [5] (Fig. 6c).

Low serum potassium levels do not usually reflect gut losses, but may occur when a patient is sodium depleted and thus has secondary hyperaldosteronism. The high aldosterone levels cause renal conservation of sodium at the expense of potassium, which is excreted in the urine in greater amounts than normal [10, 11, 31].

Hypomagnesaemia causes dysfunction of many of the potassium transport systems (e.g. the Na^+/K^+-ATPase pump) and increases renal excretion of potassium; thus hypomagnesaemia can cause a hypokalaemia, which is resistant to potassium treatment [32].

Before hypokalaemia can be corrected in patients with a high-output stoma, sodium and water depletion must be corrected and the serum magnesium brought into the normal range.

Magnesium Deficiency

Patients with a jejunostomy are often in precarious magnesium balance, and the balance does not correlate with residual jejunal length (Fig. 6e). Hypomagnesaemis is estimated to occur in 78% of patient with a jejunostomy [29]. While it may cause fatigue, depression, irritability, muscle weakness, tremor, tetany if there is associated hypocalcaemia, and, if very severe, convulsions; it is often asymptomatic even at very low serum levels (e.g. 0.2 mmol/L). The reasons for hypomagnesaemia include secondary hyperaldosteronism [33, 34], removal of ileum/colon which are key areas in the gut for absorption, free fatty acid malabsorption (so complexing with Ca and Mg) (especially if taking a high fat diet) [35, 36] and taking proton pump inhibitor drugs [37]. In the long-term hypomagnesaemia will lead to a loss of bone density with a risk of fractures, and chondrocalcinosis [38].

Nutrient Malabsorption

In the long term, parenteral nutrition with additional fluids is always needed if a patient absorbs less than one-third of the oral energy intake [5, 12] and is usually needed when less than 75 cm of jejunum remain. In some young people with high-energy requirements, parenteral nutrition may be needed even when absorption is 35–60%.

Social Problems of a HOS

Patients with a HOS may have problems with the stoma bags becoming detached and so leaking (especially at night), the skin care may be difficult and thus very sore, the frequent emptying of the stomal bag means there will be a need to find a toilet quickly, this can limit going out. The treatment for a HOS cannot be abruptly stopped otherwise dehydration results. The patient may always feel thirsty yet have to avoid quenching their thirst with hypotonic fluid. They may suffer from muscle cramps (helped by taking table salt).

Management of HOS

As stated the management starts with excluding causes of a HOS other than a short bowel and appropriately treating them. A history of colicky abdominal pain, loud bowel sounds (borborygmi); a stoma ceasing to work for a time is suggestive of an obstructive cause. The HOS occurs during recovery from the obstruction and at this time the patient may have no symptoms other than those of dehydration. Such patients often present for medical care episodically (every few months or even years). Radiological contrast examinations do not always show the stricture(s) and a trial of a low fibre/residue diet can be used both as a treatment and as a diagnostic test. If there are strictures bacterial overgrowth may be occurring and a trial of oral antibiotics (e.g.

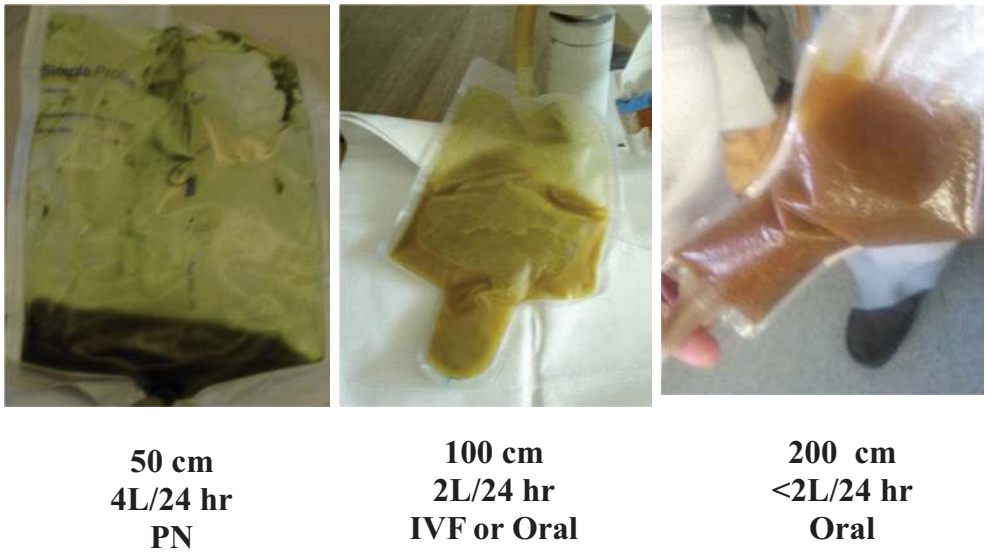

Fig. 8 Stomal output (colour/volume) on normal diet, jejunal length and type of nutritional/fluid support

co-amoxyclav or rifaximin) may be tried and if successful given in rotation (e.g. changing every 6 weeks). If pancreatic malabsorption is thought to contribute to a HOS then a trial of pancreatic enzyme replacement may be tried. A stomal elastase measurement is unlikely to be reliable due to dilution by secretions and oral fluid intake. Other medical conditions may need treatment if found (e.g. low fibre diet, steroids for Addison's, antibiotics for Clostridium, gluten free diet if Coeliac etc).

Table 3 Jejunostomy length and the type of nutritional/fluid support needed

Jejunum (cm)	Nutrition	Fluid
0–50	Parenteral	Saline
51–100	Parenteral[a]	Saline
101–150	Oral/Enteral	OGS
151–200	None	OGS

OGS oral (or enteral) glucose/saline solution
[a]At 85–100 cm may need parenteral saline only

Clinical Assessment

The initial assessment of water and sodium deficiency involves asking the patient about feeling dry, thirsty, lethargic, faint or having muscle weakness and cramps. The physical examination includes looking for dry mucous membranes, reduced skin turgor, rapid weight loss (negative fluid balance), a postural blood pressure fall (>10 mmHg), oliguria (less than 800 mL/24 h) and an assessment of the patient's nutritional status (this is usually good unless the bowel is less than 100 cm). In general, patients who have a stomal output of more than 1.5 L daily when eating are likely to require water and sodium supplements. The stomal should be inspected and the stoma effluent colour, consistency and 24 h volume should be noted (a yellow/green colour in an established stoma suggests a short length of remaining bowel) (Fig. 8). A finger should be inserted gently into the stoma to determine if there is a stenosis. However an obstruction at the stoma may not be felt if it is a functional obstruction, due to oedema or the thickness of the abdominal wall, and a trial of a wide bore catheter placed into the stoma may be tried to determine if the output reduces.

If dehydration is severe, serum creatinine and urea will rise. The creatinine may be low if there is reduced muscle mass Urinary electrolytes are usually more useful than serum measurements because the normal physiological homeostatic mechanisms preserve serum electrolyte concentrations until the late stages of depletion. A low random urinary sodium concentration (<10 mmol/L) is the best indicator of maximal sodium conservation and therefore sodium deficiency, even if serum estimations are normal. When interpreting a urinary sodium result it is important to check that the patient is not receiving diuretics or intravenous/subcutaneous saline or has renal impairment/tubular damage (e.g. from resolving acute kidney injury) when the result may be falsely normal. In addition a urinary sodium concentration can be low if the patient has hypovolaemia due to a low circulating volume secondary to a low plasma oncotic pressure (e.g. due to a low serum albumin).

Bowel Length Measurement

Predictions about the outcome can be made if the residual length of small intestine from the duodenojejunal flexure has been measured at surgery or radiologically from a small bowel meal film using an opisometer (Table 3) [39, 40]. However estimates can be made from CT/MRI enterography providing the total small bowel length is less than 200 cm. A radiological examination will also show the quality of the bowel detecting recurrent disease/obstruction [39]. Despite

this the remaining small bowel length is often unknown. Estimates made from the length of bowel resected are unreliable as the normal small intestinal length is so variable (chapter "Normal Intestinal Anatomy and Physiology").

Citrulline is an amino acid produced by functioning small bowel mucosa, fasting levels do correlate with residual small bowel length. Although clinically used to assess the progress of small bowel function after a small bowel transplant or when the colon is brought into continuity, it has not been widely adopted as a marker of functioning small bowel [41].

Treatment

Total jejunal loss of sodium increases in a linear relationship with volume (at a concentration of about 90 mmol/L) so the clinician can predict with reasonable accuracy that an effluent volume of 3 L contains 270 mmol of sodium (Fig. 5). The concentration of sodium in the output remains constant whatever treatment is given. While there is a small obligatory stomal loss when fasting, the greatest increase in stomal output is after food or drink (Fig. 7). Consideration should be given to attempting to reduce stomal output, even in patients with a jejunostomy requiring parenteral nutrition, as this may well reduce the amount or frequency of intravenous fluid replacement and the social difficulties in managing the stoma.

A patient presenting with a HOS and renal failure will need urgent rehydration and in most cases the progression to irreversible or chronic renal failure can be prevented. The replacement fluid needs to contain 100–150 mmol sodium/L e.g. intravenous normal saline, 2–4 L/day. During this time the patient may be kept "nil by mouth" to reduce the stomal output. In general dialysis is avoided as the removal of any more fluid can worsen the renal failure which may become permanent. Great care must be taken not to give too much fluid as this will readily cause oedema, partly due to the high circulating aldosterone levels [10, 11, 12, 31]. Cramps can be rapidly helped by oral or intravenous sodium chloride, and/or by magnesium supplementation.

Once renal failure has been corrected and thirst relieved, usually over 2–3 days, an attempt is made to reduce stomal output, even in patients with a jejunostomy requiring parenteral nutrition, as this may well reduce the amount or frequency of intravenous fluid replacement and the social difficulties in managing the stoma.

Sometimes, admitting patients with a chronic HOS, giving intravenous saline and keeping them 'nil by mouth' will demonstrate to them that their output is mostly driven by their oral intake. Intravenous fluids are gradually withdrawn over 2–3 days while food and oral fluids are reintroduced. These patients are dependent upon their treatment regimen and if missed/stopped for a day may result in dehydration and a hospital admission for rehydration.

The oral treatment to reduce a HOS and its consequences of dehydration starts with restricting oral hypotonic fluids and giving a glucose saline solution (or in mild cases extra oral salt) to sip. If this alone is not successful then oral medications to reduce gut motility and/or secretions may be tried.

Restrict Oral Fluids

Jejunal mucosa is 'leaky' and rapid sodium fluxes occur across it. If water or any solution with a sodium concentration of less than 90 mmol/L is drunk there is a net efflux of sodium from the plasma into the bowel lumen [19] until a luminal sodium concentration of 90–100 mmol/L is reached (Fig. 3). In a patient with a jejunostomy this fluid is then lost in the stomal output. It is a common mistake for patients to be encouraged to drink oral hypotonic solutions to quench their thirst, but this literally washes sodium out of the body [11, 19–21]. Thus patients must never be advised to "drink as much as possible" either to quench their thirst or keep up with their stomal output as this will increase stomal sodium losses, worsen dehydration and increase thirst.

Treatment for the high output from a jejunostomy, ileostomy or high fistula starts with the patient restricting the total amount of oral hypotonic fluid (water, tea, coffee, fruit juices, alcohol or dilute salt solutions) to 0.5–1.0 L/24 h (Fig. 4). To make up the rest of the fluid requirement the patient is encouraged to drink a glucose–saline rehydration solution. Many patients at home with a marginally high stomal output (1–1.5 L) will be helped by a combination of mild oral fluid restriction (less than 1.5 L per day) and the addition of salt to their diet.

Patients are often advised to take liquids and solids at different times (no liquid for half an hour before and after food), however there is no published evidence that this reduces stomal output or increases absorption of macro- or micronutrients [42].

Drink Oral Glucose–Saline Solution

Patients with stomal losses of less than 1200 mL daily can usually maintain sodium balance by adding extra salt to the limit of palatability at the table and when cooking. When stoma losses are in the range 1200–2000 mL, or sometimes more, it is possible for a patient to maintain sodium balance by taking a glucose–saline solution or salt capsules [22]. In hot weather, patients with a stoma are more likely to have problems of dehydration because of water and sodium loss in sweat.

As the sodium content of jejunostomy (or ileostomy) effluent is relatively constant at about 90 mmol/L and as there is coupled absorption of sodium and glucose in the jejunum [43–45], patients are advised to sip a glucose–saline solution with a sodium concentration of at least 90 mmol/L

Table 4 Oral rehydration solutions

	Modified WHO Cholera solution Dioralyte® strength			
	"St Mark's Solution"[b]	Single	Double[a]	Sodium citrate solution
Volume (L)	1	1	1	1
Na^+ (mmol)	90	60	120	120
K^+ (mmol)	0	20	40	0
Cl^- (mmol)	90	60	120	0
Citrate (mmol)	0	10	20	120
Glucose (mmol)	80	90	180	80

A stronger solution that can be used is is sodium chloride 7 g (120 mmol), glucose (8 g) (44 mmol) and tap water 1 L

[a]10 sachets

[b]Sodium chloride 3.5 g (60 mmol), sodium bicarbonate 2.5 g (30 mmol) or sodium citrate 2.9 g (30 mmol), glucose 20 g (110 mmol) and 1 L tap water

throughout the day. The first World Health Organization (WHO) cholera solution had a sodium concentration of 90 mmol/L [46] and is still commonly used (without the potassium chloride) (sometimes referred to as the St Mark's solution) (Table 4). Patients can prepare this solution at home using simple measuring scoops. There is no evidence that the sodium bicarbonate adds to the effectiveness of this solution [45] and it may be more palatable if sodium bicarbonate is replaced by sodium citrate. Indeed a pure sodium citrate solution (sodium concentration 120 mmol/L) was successful [47]. If the sodium concentration is increased further (e.g. to 136 mmol/L), absorption of sodium and water is improved [48]. Although taste perception changes in patients who are depleted in salt and water, they may find this solution, which tastes like 'sweet seawater', too salty to drink. Double strength Dioralyte ® is often given (Table 4). It does contain potassium and so serum potassium measurements may need to be made more frequently than 3 monthly, especially if renal impairment occurs.

A glucose-polymer (55 g Maxijul®) may be substituted for glucose to increase the energy intake by a mean of 115 kcal/d [22]. The glucose-polymer (or even a rice-based solution) can be especially useful in diabetic patients as it causes less extreme changes in blood glucose than a glucose-based solution.

The patient should be encouraged to sip a total of 1 L or more of one of these solutions in small quantities at intervals throughout the day. They should make up the majority of the oral fluid intake. As compliance is often a major problem, patients need to understand the need for the solution and can make it more palatable by chilling, and/or flavouring with fruit juice and drinking it through a straw. Compliance with the regimen is vital as if one day of fluid restriction/glucose saline solution consumption is omitted the patient may be admitted to hospital dehydrated. It is important to note that solutions with a sodium content of less than 90 mmol/L such as single strength Dioralyte® or commercial preparations used to treat infective or traveler's diarrhoea or in sport's drinks sports are not adequate.

Sodium chloride capsules (500 mg each) are effective when taken in large amounts (14/24 h), but can cause some patients to feel sick and even vomit [22]. If an enteral feed is given, sodium chloride needs to be added to make the total sodium concentration of the feed 100 mmol/L while keeping the osmolality near to 300 mOsm/kg. A hyperosmolar solution/feed (e.g. of amino acids) will cause increase stomal water losses.

Even patients with a jejunostomy receiving long term parenteral support should restrict their intake of oral hypotonic fluid and sip a glucose saline solution to prevent stomal fluid losses.

Subcutaneous or Parenteral Fluids

Some patients cannot be maintained (hydration, sodium and/or magnesium) with an oral regimen (usually if jejunal length is less than 100 cm) and regular subcutaneous or parenteral saline supplements are needed. Subcutaneous saline can be slow to run (e.g. a litre usually containing 4–8 mmol magnesium sulphate that takes 10–12 h to infuse), it may cause swelling of a limb; however it is relatively simple and quick to start with few risks of infection. It is most appropriate if the additional fluid is only needed 1–4 days a week. If more frequent or a higher volume is needed (due to thirst/dehydration) then intravenous normal saline, 2–4 L/day, often with added magnesium sulphate (4–14 mmol/L) may be given.

Patients with less than 100 cm jejunum remaining may need oral or parenteral nutritional supplements, but a few need, no nutritional supplements, only 1 or 2 L of parenteral saline daily, usually with added magnesium sulphate.

Drug Therapy to reduce the High-Volume Output from a Jejunostomy

If restricting oral fluids and giving a glucose– saline solution to drink are not adequate treatment, drugs may be needed. The intestinal output, especially in net 'secretors' rises after meals (Fig. 7), and it is therefore important to give the drugs before food. Drugs used to reduce jejunostomy output act to reduce either intestinal motility or secretions.

Antimotility (Antidiarrhoeal) Drugs

Opiate drugs such as tincture of opium (laudanum) or codeine phosphate have been used for many years to treat diarrhoea but are sedative and, in the long term, addictive. Synthetic drugs were manufactured with the aim that they should be free of opiate-like activity upon the central nervous system. Diphenoxylate (Lomotil®) was the first to be

used in clinical practice but has largely been replaced by loperamide (Imodium®) which has no central nervous system effects. Loperamide is a synthetic piperidine opioid made in 1969 (for diarrhoea), it acts on μ receptor in myenteric plexus to inhibit gut motility and reduce gastrointestinal secretions. It also increases the tone of the anal sphincter. It has peak levels within 4–5 h, a half life of 7–15 h and circulates in the enterohepatic circulation with 30–40% excreted in faeces (1% in urine). It is 97% protein bound.

Loperamide is preferred to codeine phosphate as it does not sedate and is not addictive. Codeine phosphate increases the output of stomal fat [49, 50]; loperamide does not [50, 51] although it reduces the post-prandial pancreatico-biliary secretion of trypsin and bilirubin in patients with a short bowel and preserved colon [52].

Loperamide and codeine phosphate reduce intestinal motility and thus decrease water and sodium output from an ileostomy by about 20–30% [49–51, 53, 54]. Oral loperamide, 4 mg taken four times a day, was more effective in reducing the weight and sodium content of ileostomy fluid than codeine phosphate 60 mg taken four times a day [50], but the effect of both together may be greater [55]. These drugs are effective in most patients with a jejunostomy [13], particularly net 'absorbers'. A combination of both of these drugs, taken before food, a glucose–saline solution and other fluid restriction can liberate some patients from dependence on parenteral saline supplements [55].

Loperamide circulates through the entero-hepatic circulation, but this is severely disrupted in these patients, and small bowel transit may be rapid. Thus high doses of loperamide (e.g. 12–24 mg) at a time) may be needed, as in patients who have had a vagotomy and pyloroplasty [56]. One case series suggested even higher doses (40 mg five times a day, 30 mg three times a day and 100 mg four times a day) were effective [57].

In 2017 the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued an alert about serious cardiovascular events (QT prolongation, torsades de pointes, and cardiac arrest/deaths) associated with high or very high doses of loperamide when used as a drug of abuse or for self-treatment of opioid withdrawal. The British Intestinal Failure Alliance (BIFA) advice about this included performing an ECG in all patients with a high output stoma/fistula before starting high dose loperamide (more than 4 mg four times a day) and the QT interval being measured. It was suggested that the ECG should be repeated after starting the high dose and then every 3 years if the patient remained on high dose loperamide therapy. If the QT interval was prolonged cardiac co-morbidities should be considered, drugs known to prolong the QT interval are rationalised and metabolic causes (e.g. hypomagnesaemia) treated. The total daily dose of loperamide should be below 80 mg, however if this is exceeded serum loperamide levels should be measured (normal therapeutic range 0.24–1.2 mg/mL). Loperamide toxicity should be considered in any patient with fainting episodes not accounted for by dehydration or other drugs and if there is QT prolongation or a serious ventricular arrhythmia including torsades de pointes or cardiac arrest has occurred [58].

Antisecretory Drugs

Food and drink are diluted by digestive juices, thus the volume of stomal effluent can be reduced in 'secretors' by drugs that reduce the secretions from the stomach, liver and pancreas. Drugs that reduce gastric acid secretion, such as the H_2 antagonists or proton pump inhibitors or the somatostatin analogue octreotide, are most commonly used.

H_2 Antagonists/Proton Pump Inhibitors

Cimetidine (400 mg orally or intravenously four times a day) reduced the output from a jejunostomy/ileostomy when the daily output exceeded 2 L daily [59, 60]. This beneficial effect is likely to be due to the reduction in normal daily gastric acid secretion or to a reduction in gastric acid hypersecretion.

Omeprazole, 40 mg orally once a day, reduced the stomal output by a mean of 0.7 kg/24 h in 7 patients with a net secretory output [61] (Fig. 9a). Omeprazole, 40 mg given intravenously twice a day, reduced the jejunostomy output in patients whose output exceeded 2.6 kg/24 h.48 Omeprazole is readily absorbed in the duodenum and upper small bowel, but if less than 50 cm of jejunum remains it may need to be given intravenously. Giving omeprazole orally dissolved in bicarbonate may improve absorption enough for it to be successful. Omeprazole has little beneficial effect in patients who are net absorbers.

Oral omeprazole, 40 mg once daily, gave an equivalent reduction in stomal output to oral ranitidine, 300 mg twice daily, in one patient [5, 61]. Intravenous omeprazole, 40 mg twice daily, was more effective than intravenous ranitidine 150 mg twice daily, probably because the dose of ranitidine was too low [62]. Oral omeprazole, 40 mg once daily, was shown in two patients to be equivalent to intravenous octreotide 50 μg twice daily [5, 61].

Omeprazole, ranitidine and cimetidine reduce jejunostomy output in those with the highest outputs (net 'secretors') while often having no effect on net 'absorbers'. They may need to be given intravenously if less than 50 cm of jejunum remains. They do not change the absorption of energy, carbohydrate, lipid, nitrogen and divalent cations [61, 62] and do not reduce jejunostomy output sufficiently to prevent the need for parenteral fluid and electrolyte replacement.

Other PPI drugs have not been reported to reduce jejunostomy output but are likely to be as effective. The PPIs have been associated with Cl difficile infection, abnormal liver function tests, hypomagnesaemia, osteopenia/osteoporosis and increased risk of fractures (hip, wrist and spine), myo-

cardial infarction (possibly by suppressing NO production) and renal impairment [63]. When used (e.g. omeprazole 40–80 mg daily) the dose can be titrated such that fresh stomal fluid has a pH greater than 5.

Somatostatin and Octreotide

Somatostatin and octreotide reduce salivary, gastric and pancreatico-biliary secretions, slow small bowel transit, and may delay gastric emptying; for these reasons they may be expected to reduce the intestinal output from a jejunostomy in both net 'secretors' and 'absorbers'. Somatostatin has a serum half-life of 3 min so is given by continuous infusion, whereas that of octreotide is 90 min so it is usually given as regular (two or three times daily) subcutaneous injections before food.

Somatostatin

Four patients with more than 100 cm of small intestine remaining (one also had some residual colon) were given a continuous infusion of somatostatin, 4 μg/min for 24 h. Mean daily intestinal output reduced from 1.9 kg to 1.2 kg, however magnesium, nitrogen and fat absorption were unchanged [64].

Octreotide

Effect of octreotide upon water, sodium and magnesium balance. A case report in 1984 first demonstrated that 50 μg of octreotide given subcutaneously twice a day allowed a patient with ileostomy diarrhoea to stop intravenous fluids [65]. Several studies in adults have shown octreotide to reduce ileostomy diarrhoea and large-volume jejunostomy outputs (Table 5) [13, 28, 66–72]. The greatest reductions in intestinal output have occurred in net 'secretors', (Fig. 9) and many patients have been able to reduce the volume of parenteral supplements needed [71, 72]. Although some patients have achieved positive intestinal fluid balance, they have rarely been able to stop parenteral fluids completely [71, 72]. All studies have shown a reduction in sodium output which parallels that of the intestinal output [13, 28, 66–72]. Stomal output has been reported as reduced [70] in 2 and increased [28] in 2 jejunostomy patients classified as net 'absorbers'. However, in one study in which all patients had mild ileostomy diarrhoea (0.8–1.3 kg/24 h) and were thus net absorbers, the output reduced by only 0.3 kg/24 h [67]. Octreotide, 20–100 μg/24 h, has been used successfully to reduce ileostomy diarrhoea in 2 children aged 3 months and 5 years [73]. In 3 patients, an intravenous dose of 50 μg octreotide twice a day was as effective in reducing the intestinal output as 100 μg three times a day [69]. Magnesium balance has not been changed by octreotide [68, 70].

The effect of octreotide is maintained in the long term [66, 68–70, 72]. After a year's continuous therapy with 50 μg intravenous octreotide twice daily, the reduction in stomal output was the same as at the start of treatment [69, 72].

Somatostatin and octreotide both reduce the output from a high fistula and appear to accelerate the rate of spontaneous closure [74, 75].

Effect of Octreotide Upon Nutrient Absorption Although octreotide reduces stimulated gastric acid and pancreatic enzyme secretion and reduces the splanchnic uptake of amino acids [76], it does not significantly change total energy [69, 71, 72] or nitrogen absorption [66, 68, 70–72]. As

Table 5 Octreotide to treat high-volume ileostomy or jejunostomy output

Author	Number	Dose	Days	Stomal output (l or kg/24 h)	
				Control	Octreotide
Ileostomy diarrhoea					
Cooper et al. [66] 1986	5	25 μg/h infusion	3	5.3	4.2
Kusuhara et al. [67]* 1992	12	100 μg t.d.s.	5	1.0	0.7
High-output jejunostomy					
Shaffer et al. [68] 1988	6(?)	50–150 μg/24 h s.c.	3	4.0	2.4
Rodrigues et al. [13] 1989**	4(4)	50 μg s.c.	6 h	0.9/6 h†	0.4/6 h†
Nightingale et al. [28, 69] 1989	6(6)	50 μg b.d. i.v.	2	5.0	2.8
	2(0)	100 μg t.d.s.			
Ladefoged et al. [70] 1989	6(4)	25 μg/h infusion	2	–	1.1 less
	5(4)	50 μg b.d. s.c.	2	–	1.4 less
Lemann et al. [71] 1993	7(7)	100 μg t.d.s. s.c.	10 h	1.6/10 h†	1.0/10 h†
O'Keefe et al. [72] 1994	10(10)	100 μg t.d.s. s.c.	3	8.1†	4.8†

*Defunctioning ileostomy above 'ileoanal anastomosis'
() number of net 'secretors'
s.c. subcutaneous, *i.v.* intravenous, *b.d.* twice daily, *t.d.s.* three times a day
All had normal meals except ** in which a liquid meal was given
Median results except †, where means are presented

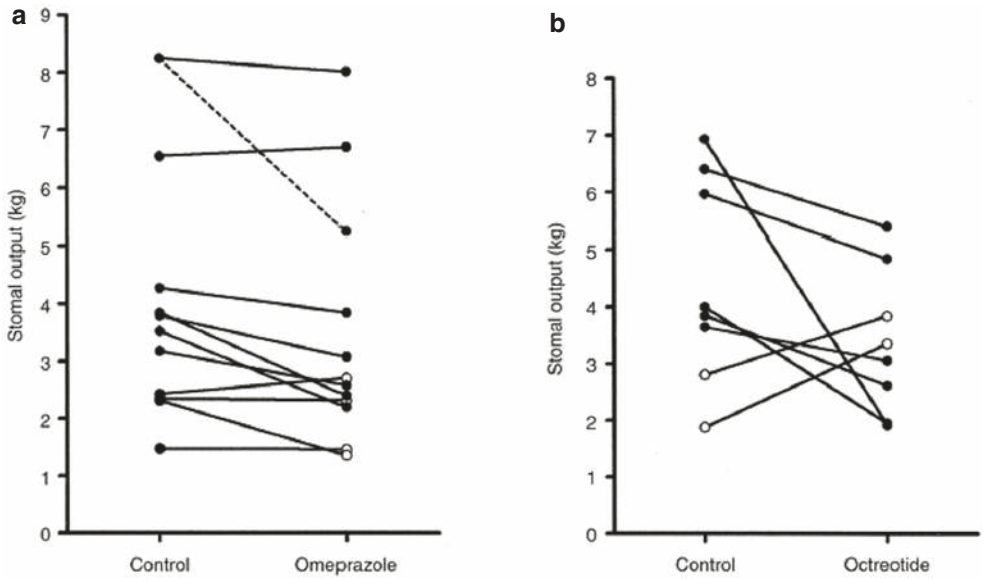

Fig. 9 Mean daily stomal output from 2 day collections. Effect of (**a**) omeprazole (40 mg orally once a day), and (**b**) octreotide (50 µg given intravenously twice a day) except ○ when 100 µg given subcutaneously three times a day into net 'absorbers' upon jejunostomy output. The dotted line shows the effect of intravenous omeprazole given to one patient with 30 cm jejunum after there was no response to an oral dose

pancreatico-biliary secretion is reduced, it would be expected that fat absorption would be reduced [66]. However, it is usually unchanged [69–72].

Problems of Octreotide Therapy A subcutaneous injection of octreotide may be painful, especially in the very thin, while an intravenous injection may cause flushing, nausea and headache [69]. Blood glucose generally remains within the normal range [70]. Patients with a jejunostomy have a very high prevalence of gallstones (45%) [29], and long-term octreotide therapy may further increase this [77]. Although hypoglycaemia may occur [73], there is no evidence that octreotide causes diabetes or hypothyroidism after prolonged usage. Increasing the consistency of the small bowel contents could increase the risk of developing small bowel obstruction if there are adhesions [72].

Mechanism of Action of Octreotide Octreotide increases total intestinal transit time [13, 66, 71, 72]. This probably reflects an increase in small bowel transit time as the rate of gastric emptying remains normal [66, 71]. This slowing of transit may be the mechanism whereby some net 'absorbers' respond to octreotide therapy. In net 'secretors', the reduction in jejunostomy output was similar to that achieved with omeprazole, hence the suggestion that, in these patients, octreotide acts mainly by reducing the volume of gastric acid secreted in response to food [78]. A reduction in pancreaticobiliary secretion may explain why fat malabsorption increases in some patients [66], and it may be this that increases the intestinal output in some net 'absorbers' [78].

Octreotide at a dose of 50 µg twice daily given subcutaneously or intravenously reduces intestinal water and sodium losses in most patients with a jejunostomy, and in some with ileostomy diarrhoea or a high small intestinal fistula. This effect is greatest in patients with the highest net 'secretory' output and is maintained long-term without tolerance developing. The reduction in output may reduce, but rarely avoids, the need for parenteral fluids. Some patients use these preparations, particularly octreotide, before meals to diminish the social inconvenience of a profuse jejunostomy output after food. In these patients octreotide does not affect the absorption of magnesium or nutrients.

Long Acting Somatostatin Analogues Long acting octreotide 20 mg [79] and lanreotide 120 mg [80] have both been used to treat HOS with deep subcutaneous/intramuscular injections every 4 weeks.

Mineralocorticoids

The distal ileum, with its tight intracellular junctions, can concentrate the intraluminal contents. This ability develops from 2 to 16 weeks after the formation of an ileostomy [81, 82]. This capacity for sodium absorption may partly relate to high aldosterone levels [10, 30] and can be induced by mineralocorticoids (e.g. 2 mg oral fludrocortisone or 2 mg intravenous D-aldosterone) [83–85] or high-dose hydrocortisone [86]. Although intraluminal hydrocortisone does increase jejunal water, sodium and glucose absorption in normal subjects [87], mineralocorticoids do not usually reduce ileostomy output. However, studies have only been performed in patients with a relatively normal ileostomy output. Studies of patients with a high-output ileostomy or jejunostomy are

awaited, but it would not be surprising if these were disappointing, as high circulating aldosterone levels may have already maximized sodium absorption.

Desmopressin

Desmopressin, an analogue of antidiuretic hormone, has no effect upon ileal fluid or electrolyte loss in man [88].

Cholylsarcosine

A synthetic bile acid resistant to bacterial deconjugation and dehydroxylation, cholylsarcosine (4 g taken three times a day), was given to 3 patients with a jejunostomy and resulted in an improvement in fat (18%, 37% and 51%) and calcium absorption but did not affect the volume of stomal output [89, 90].

Clonidine

Clonidine is an α_2-adrenergic agonist that prolongs gastrointestinal transit and has been used to treat chronic diarrhoea. A 0.3 mg clonidine patch (as has been used in hypertension [91]) to 8 jejunostomy patients receiving parenteral nutrition resulted in a reduction in stomal output of 0.44 kg/day (39 mmol sodium) without affecting energy, fat or xylose absorption [92]. It is rarely used but may be a treatment for those who are not responding to other conventional treatments.

Peptide Hormones (Including Growth Factors) (Chapter "Pro-Adaptive Hormones in the Rehabilitation of Adult Patients with a Short Bowel")

Patients with a jejunostomy have low circulating levels of PYY (slows transit) and GLP-2 [24, 27]. GLP-2 agonists (e.g. teduglutide, apraglutide and glepaglutide), which stimulates small bowel mucosal growth and increases absorption of salt, water and nutrients, may be used as a treatment (though are expensive and in the UK can only prescribed by specialist IF/HPN centres) [93]. While in studies teduglutide may reduce parenteral requirements by 20% and may occasionally allow a patient to stop parenteral nutrition [94–96]. A GLP-1 agonist (liraglutide) which primarily slows upper gastrointestinal transit has been used with some success [97]. There may be a future role for using combinations of peptide hormone analogues. While peptide YY analogues have been manufactured they have not been used clinically [98].

Magnesium Supplements

There are many therapeutic ways of improving hypomagnesaemia (Table 6). Dehydration and sodium depletion cause secondary hyperaldosteronism, which leads to renal magnesium loss; correction of these conditions may help to treat magnesium depletion. In addition, a diet relatively low in fat reduces stool or stomal magnesium losses [35] (chapter "Dietary Treatment of Patients with a Short Bowel").

Serum magnesium levels can usually be improved by oral supplements, however the data about the magnesium absorption from different preparations are often derived from normal volunteer studies and studies of patients with a short bowel and retained colon. Tablet dissolution and magnesium availability may be very different in patients with a jejunostomy than in normal subjects and patients with a short bowel and retained colon.

Many oral magnesium salts, which are generally poorly absorbed, have been given as a treatment and include magnesium sulphate, chloride, hydroxide, acetate, carbonate, gluconate, lactate, citrate, aspartate, pyroglutamate, oxide and diglycinate [99, 100]. In clinical practice in the UK magnesium oxide, glycerophosphate or aspartate are most commonly given. Magnesium oxide may be given to a total of 12–24 mmol daily. Oral magnesium treatment, such as three gelatine capsules each of 4 mmol (160 mg of MgO), is usually given at night when intestinal transit is assumed to be slowest and hence there is more time for absorption. This regimen increases magnesium absorption and does not appear to increase stomal output.

A topical magnesium chloride spray may help those with magnesium depletion who do not adequately absorb magnesium preparations from their gut [101] and may offer a mode of correcting serum levels and helping symptoms that may be related to hypomagnesaemia. Proton pump inhibitor drugs can reduce serum magnesium levels and a trial of stopping these may be beneficial [37].

If oral magnesium supplements do not bring the magnesium level into the normal range, oral 1α-hydroxycholecalciferol in a gradually increasing dose (every 2–4 weeks) of 1–9 μg daily has been shown to improve magnesium balance in patients with a retained colon [102, 103]. This action occurs by increasing both intestinal and renal magnesium absorption [103]. As hypomagnesaemia will have caused both a failure of parathormone release and a resistance to its action, 1α-hydroxycholecalciferol cannot be made in the kidney in adequate amounts. Thus it is important that the 1α preparation is given.

Magnesium can occasionally be given as: a subcutaneous injection of 4 mmol magnesium sulphate every 2 or more

Table 6 Summary for hypomagnesaemia treatment

Correct dehydration
Oral magnesium (oxide, glycerophosphate, aspartate)
Topical magnesium chloride spray
1-alpha calciferol
Reduce lipid in diet
Stop PPI

days, but this can cause skin ulceration; an intramuscular injection of 10 mmol/L, but this is painful; or a regular intravenous infusion of 4–8 mmol, usually in a litre of saline over 1–2 h, though this can cause a flushing sensation. Occasionally a subcutaneous infusion [104] 4–8 mmol of magnesium sulphate is infused subcutaneously in a litre of saline over 10–12 h 1–3 times a week. Initially there was a worry that this caused hardening of the subcutaneous tissues but was not supported by longer term experience.

Nutrient Absorption

Need for Enteral or Parenteral Nutrition

Most patients with less than 75 cm of jejunum remaining need long-term parenteral nutrition; most in the range 75–100 cm need parenteral saline (sometimes with added magnesium) but manage to maintain nutritional status with an enteral regimen even though they may only absorb about 50–60% of their oral energy intake.

All patients wish to eat food so as to feel normal and to maintain social relationships. In patients maintained on parenteral nutrition, an oral intake is detrimental as it increases jejunostomy losses (Fig. 7). Patients taking an oral regimen need to consume more energy than a normal person to compensate for malabsorption. Most patients can achieve this by eating more high-energy food. Oral sip-feeds may be given in addition to food, preferably taken between meals and at bedtime. By these means, a patient may increase energy intake by at least 1000 kcal/d. If oral sip-feeds during the day fail to achieve weight gain or maintain nutrition, a nasogastric or gastrostomy tube may be inserted and a feed given at night so that the short residual length of intestine is used at a time when it is usually inactive. There are rarely any problems inserting a percutaneous endoscopic gastrostomy (PEG) in patients with Crohn's disease provided that there is no distal obstruction [105].

Once weight is regained, the daily energy requirement may decrease so that a nocturnal feed can be reduced or stopped and sip-feeds during the day may become adequate. Only if these measures fail and the patient continues to lose weight, or fails to regain lost weight, is parenteral nutrition given.

Oral/Enteral Nutrition/Food

Patients with a jejunostomy absorb a constant proportion of the nitrogen, energy and fat from their diet [14, 36, 104]. Increasing fat in the diet raises fat excretion but does not usually increase stomal output, nor make the output offensive [14, 36, 106]. One study showed that increasing fat in the diet increased the loss of the divalent cations Mg and Ca [35], but this was not the case in another [106]. There is no advantage in giving a diet of small molecules (e.g. an elemental diet); this causes a feed to be hyperosmolar [106] and usually contains little sodium, so potentially increasing the losses of water and sodium from the stoma. A peptide diet still has the problem of a relatively high osmolality and thus can increase stomal output [106]. Little advantage comes from taking a diet of water-soluble medium-chain triglycerides in place of normal fat [107]. The addition of glutamine, 15 g, to a litre of rehydration solution in patients with a jejunostomy resulted in no additional benefit in terms of water or sodium absorption [108]. The fibre content of the diet plays only a minor role in determining jejunal output [49].

Thus jejunostomy patients need a large total oral energy intake of a polymeric, iso-osmolar (300 mOsm/kg) diet that is relatively high in fat with added salt (sodium concentration 100 mmol/L). The volume of the stomal output may become so high with a normal diet or with extra feeding that it is a major social disability. If this is the case, parenteral feeding may be needed to enable oral intake to be reduced.

The ideal nutrient solution with an osmolality of 300 mOsm/kg and a sodium concentration of at least 100 mmol/litre has yet to be marketed. A low fibre diet is advised if intermittent/partial obstructions is thought to be occurring and often is first used as these patients have a high probability of having adhesions and an area of bowel narrowing. Liquid diets must be near ro iso-osmolar. A hyperosmolar feed (e.g. amino acids) will cause water secretion into the gut and also if little/no sodium in the feed then sodium excretion will occur.

Monitoring

Accurate daily measurements of body weight, fluid balance (especially stomal effluent) and postural blood pressure are important. Serum electrolyte (creatinine, potassium and magnesium) and urinary sodium estimation may be done every 1–3 days initially but once or twice weekly when the patient is stable in hospital. The aims are to maintain hydration and body weight and a daily urine volume of at least 800 mL with a sodium concentration greater than 20 mmol/L. At home, if stable, measurements of weight, urine sodium concentration and serum magnesium are done every 3 months [109].

Predicting Drug Absorption

Many drugs are incompletely absorbed by patients with a short bowel and may be needed in much higher amounts than usual (e.g. thyroxine, warfarin and digoxin [110] or may

need to be given intravenously. An attempt to predict the absorption of a medication in patients with a short bowel can be made by using the time to peak levels and the biopharmaceutical classification of drugs (see chapter drugs and short bowel). A drug with a short time to peak plasma levels is likely to be absorbed in the upper gut and so be absorbed in patients with a short bowel; this will not be the case if there is a long time to peak plasma levels. The biopharmaceutical classification of drugs is based upon drug aqueous solubility and intestinal permeability [111, 112]. A drug with high solubility and high permeability (class 1) is likely to be well absorbed in a short length of gut but this will not be the case for one with poor solubility and permeability.

Changes in Jejunostomy Output with Time

Patients with a normal terminal ileostomy experience a decrease in stomal output from about day 5 to 16 weeks after its formation [113]. Hill et al. showed, in patients with an 'ileostomy' following an ileal resection, that there was no decrease in ileostomy water, sodium and potassium losses from 11 days after the resection to 6 months [114]. There is no structural change in distal duodenal mucosa in patients with an established jejunostomy [76]. Thus there is no evidence for any structural or functional adaptive changes occurring in patients with a jejunostomy. The fluid and nutrients needed change very little with time and are likely to be the same for as long as the jejunostomy remains [29].

Surgical Options

If there is small or large bowel out of circuit then if this is brought back into continuity absorption may improve and problems of a HOS resolved. This is well shown when patients after a mesenteric infarction have continuity restored and 77% were able to stop parenteral nutrition within 5 years [115]. The reversal of a 10 cm segment of small bowel has been reported to be successful in increasing absorption in some patient s with a short bowel with few complications reported [116]. The Serial Transverse Enteroplasty Procedure (STEP) is being performed if the small bowel is sufficiently dilated and has mainly been performed in children with a colon in continuity [117]. Rarely small bowel transplantation can be required mainly for complications related to intestinal failure/parenteral nutrition (e.g. liver disease or failing venous access)

Patient Support

Patients with a stoma and a high output may need psychosocial support and the help of local stoma nurses and patient support groups (e.g. ileostomy association or PINNT in the UK; Oley foundation in USA) and advice leaflets.

Future Treatments

The ideal nutrient solution with an osmolality of 300 mOsm/kg and a sodium concentration of 100–140 mmol/L has yet to be marketed. A feed of high viscosity (possibly containing non-absorbable carbohydrate) that delays gastric emptying so allowing more time for absorption may be developed.

As the awareness of the physiological changes in patients with a jejunostomy becomes better defined, treatments, especially with peptide hormones, may be more physiologically administered. For example a combination of peptide hormone analogues (e.g. GLP2 and PYY) may be given at or just after a meal.

References

1. Flint JM. The effect of extensive resections of the small intestine. Bull Johns Hopkins Hosp. 1912;23:127–44.
2. Haymond HE. Massive resection of the small intestine: an analysis of 257 collected cases. Surg Gynecol Obstet. 1935;61:693–705.
3. Booth CC. The metabolic effects of intestinal resection in man. Postgrad Med J. 1961;37:725–39.
4. Nightingale JMD. How to manage a high-output stoma. Frontline Gastroenterol. 2021;13:140–51. Epub ahead of print: 23 March. https://doi.org/10.1136/flgastro-2018-101108.
5. Nightingale JMD, Lennard-Jones JE, Walker ER, Farthing MG. Jejunal efflux in short bowel syndrome. Lancet. 1990;336:765–8.
6. Baker ML, Williams RN, Nightingale JM. Causes and management of a high output stoma. Colorectal Dis. 2011;13:191–7.
7. Villafranca JJA, López-Rodríguez C, Abilés J, Rivera R, Adán NG, Navarro PU. Protocol for the detection and nutritional management of high-output stomas. Nutr J. 2015;14:45.
8. Takeda M, Takahashi H, Haraguchi N, Miyoshi N, Hata T, Yamamoto H, Matsuda C, Mizushima T, Doki Y, Mori M. Factors predictive of high-output ileostomy: a retrospective single-center comparative study. Surg Today. 2019;49(6):482–7.
9. Hara Y, Miura T, Sakamoto Y, Morohashi H, Nagase H, Hakamada K. Organ/space infection is a common cause of high output stoma and outlet obstruction in diverting ileostomy. BMC Surg. 2020;20(1):83.
10. Kennedy HJ, Al-Dujaili EAS, Edwards CRW, Truelove SC. Water and electrolyte balance in subjects with a permanent ileostomy. Gut. 1983;24:702–5.
11. Ladefoged K, Ølgaard K. Fluid and electrolyte absorption and renin–angiotensin–aldosterone axis in patients with severe short-bowel syndrome. Scand J Gastroenterol. 1979;14:729–35.
12. Newton CR, Drury P, Gonvers JJ, McIntyre P, Preston DM, Lennard-Jones JE. Incidence and treatment of sodium depletion in ileostomists. Scand J Gastroenterol. 1982;74(suppl):159–60.
13. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJG. Energy absorption as a measure of intestinal failure in the short bowel syndrome. Gut. 1989;30:176–83.
14. Rodrigues CA, Lennard-Jones JE, Walker ER, Thompson DG, Farthing MJG. The effects of octreotide, soy polysaccharide, codeine and loperamide on nutrient, fluid and electrolyte absorption in the short bowel syndrome. Aliment Pharmacol Ther. 1989;3:159–69.
15. Nordgaard I, Hansen BS, Mortensen PB. Colon as a digestive organ in patients with short bowel. Lancet. 1994;343:373–6.
16. Nightingale JMD, Lennard-Jones JE, Walker ER, Farthing MJG. Jejunal efflux in short bowel syndrome. Lancet. 1990;336:765–8.

17. Borgström B, Dahlqvist A, Lundh G, Sjövall J. Studies of intestinal digestion and absorption in the human. J Clin Invest. 1957;36:1521–36.
18. Fordtran JS, Locklear TW. Ionic constituents and osmolality of gastric and small intestinal fluids after eating. Am J Dig Dis. 1966;11:503–21.
19. Vantrappen GR, Peeters RL, Janssens J. The secretory component of the interdigestive migrating motor complex in man. Scand J Gastroenterol. 1979;14:663–7.
20. Newton CR, Gonvers JJ, McIntyre PB, Preston DM, Lennard-Jones JE. Effect of different drinks on fluid and electrolyte losses from a jejunostomy. J Roy Soc Med. 1985;78:27–34.
21. Griffin GE, Fagan EF, Hodgson HJ, Chadwick VS. Enteral therapy in the management of massive gut resection complicated by chronic fluid and electrolyte depletion. Dig Dis Sci. 1982;27:902–8.
22. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJG. What is the ideal sodium concentration of oral rehydration solutions for short bowel patients? Clin Sci. 1988;74(suppl 18):69.
23. Nightingale JMD, Lennard-Jones JE, Walker ER, Farthing MJG. Oral salt supplements to compensate for jejunostomy losses: comparison of sodium chloride capsules, glucose electrolyte solution and glucose polymer electrolyte solution (Maxijul). Gut. 1992;33:759–61.
24. Buxton B. Small bowel resection and gastric acid hypersecretion. Gut. 1974;15:229–38.
25. Nightingale JMD, Kamm MA, van der Sijp JRM, Walker ER, Ghatei MA, Bloom SR, Lennard-Jones JE. Gastrointestinal hormones in the short bowel syndrome. PYY may be the 'colonic brake' to gastric emptying. Gut. 1996;39:267–72.
26. Windsor CWO, Fejfar J, Woodward DAK. Gastric secretion after massive small bowel resection. Gut. 1969;10:779–86.
27. Nightingale JMD, Kamm MA, van der Sijp JRM, et al. Disturbed gastric emptying in the short bowel syndrome. Evidence for a "colonic brake". Gut. 1993;34:1171–6.
28. Jeppesen PB, Hartmann B, Hansen BS, Thulesen J, Holst JJ, Mortensen PB. Impaired stimulated glucagon-like peptide 2 response in ileal resected short bowel patients with intestinal failure. Gut. 1999;45:559–63.
29. Nightingale JMD. The Sir David Cuthbertson Medal Lecture. Clinical problems of a short bowel and their treatment. Proc Nutr Soc. 1994;53:373–91.
30. Nightingale JMD, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces the need for parenteral therapy, increases the incidence of renal stones but does not change the high prevalence of gallstones in patients with a short bowel. Gut. 1992;33:1493–7.
31. Ladefoged K, Ølgaard K. Sodium homeostasis after small-bowel resection. Scand J Gastroenterol. 1985;20:361–9.
32. Whang R, Whang DD, Ryan MP. Refractory potassium repletion. A consequence of magnesium deficiency. Arch Intern Med. 1992;152:40–5.
33. Hanna S, MacIntyre I. The influence of aldosterone on magnesium metabolism. Lancet. 1960;2:348–50.
34. Horton R, Biglieri EG. Effect of aldosterone on the metabolism of magnesium. J Clin Endocrinol Metab. 1962;22:1187–92.
35. Ovesen L, Chu R, Howard L. The influence of dietary fat on jejunostomy output in patients with severe short bowel syndrome. Am J Clin Nutr. 1983;38:270–7.
36. Hessov I, Andersson H, Isaksson B. Effects of a low-fat diet on mineral absorption in small-bowel disease. Scand J Gastroenterol. 1983;18:551–4.
37. Pisani LF, Filippi E, Vavassori S, Munizio N, Vecchi M, Pastorelli L. Effect of proton pump inhibitors on magnesium balance: is there a link to cardiovascular risk? Magnes Res. 2016;29(1):1–10.
38. Richette P, Ayoub G, Lahalle S, Vicaut E, Badran AM, Joly F, Messing B, Bardin T. Hypomagnesemia associated with chondrocalcinosis: a cross-sectional study. Arthritis Rheum. 2007;57(8):1496–501.
39. Nightingale JMD, Bartram CI, Lennard-Jones JE. Length of residual small bowel after partial resection: correlation between radiographic and surgical measurements. Gastrointest Radiol. 1991;16:305–6.
40. Carbonnel F, Cosnes J, Chevret S, et al. The role of anatomic factors in nutritional autonomy after extensive small bowel resection. J Parenter Enteral Nutr. 1996;20:275–80.
41. Fragko KC, Forbes A. Citrulline as a marker of intestinal function and absorption in clinical settings: a systematic review and meta-analysis. United Eur Gastroenterol J. 2018;6(2):181–91.
42. Woolf GM, Miller C, Kurian R, Jeejeebhoy KN. Nutritional absorption in short bowel syndrome. Evaluation of fluid, calorie and divalent cation requirements. Dig Dis Sci. 1987;32:8–15.
43. Olsen WA, Ingelfinger FJ. The role of sodium in intestinal glucose absorption in man. J Clin Invest. 1968;47:1133–42.
44. Sladen GE, Dawson AM. Interrelationships between the absorptions of glucose, sodium and water by the normal human jejunum. Clin Sci. 1969;36:119–32.
45. Fordtran JS. Stimulation of active and passive sodium absorption by sugars in the human jejunum. J Clin Invest. 1975;55:728–37.
46. Avery ME, Snyder JD. Oral therapy for acute diarrhoea. The underused simple solution. N Engl J Med. 1990;323:891–4.
47. Culkin A, Gabe SM, Nightingale JM. A new palatable oral rehydration solution. A randomised controlled crossover study in patients with a high output stoma. J Hum Nutr Diet. 2021;35(1):94–101. Online ahead of print. https://doi.org/10.1111/jhn.12935.
48. Beaugerie L, Cosnes J, Verwaerde F, Dupas H, Lamy P, Gendre J-P, Le Quintrec Y. Isotonic high-sodium oral rehydration solution for increasing sodium absorption in patients with short-bowel syndrome. Am J Clin Nutr. 1991;53:769–72.
49. Newton CR. Effect of codeine phosphate, Lomotil and Isogel on ileostomy function. Gut. 1978;19:377–83.
50. King RFGJ, Norton T, Hill GL. A double-blind crossover study of the effect of loperamide hydrochloride and codeine phosphate on ileostomy output. Aust NZ J Surg. 1982;52:121–4.
51. Tytgat GN, Huibregtse K, Dagevos J, van den Ende A. Effect of loperamide on fecal output and composition in well-established ileostomy and ileorectal anastomosis. Dig Dis. 1977;22:669–76.
52. Remington M, Fleming CR, Malagelada J-R. Inhibition of postprandial pancreatic and biliary secretion by loperamide in patients with short bowel syndrome. Gut. 1982;23:98–101.
53. Tytgat GN, Huibregtse K. Loperamide and ileostomy output—placebo-controlled double-blind crossover study. Br Med J. 1975;2:667–8.
54. Kristensen K, Qvist N. The acute effect of loperamide on ileostomy output: a randomized, double-blinded, placebo-controlled, crossover study. Basic Clin Pharmacol Toxicol. 2017;121(6):493–8.
55. Nightingale JMD, Lennard-Jones JE, Walker ER. A patient with jejunostomy liberated from home intravenous therapy after 14 years; contribution of balance studies. Clin Nutr. 1992;11:101–5.
56. O'Brien JD, Thompson DG, McIntyre A, Burnham WR, Walker ER. Effect of codeine and loperamide on upper intestinal transit and absorption in normal subjects and patients with postvagotomy diarrhoea. Gut. 1988;29:312–8.
57. Mackowski A, Chen HK, Levitt M. Successful management of chronic high-output ileostomy with high dose loperamide. BMJ Case Rep. 2015;2015:bcr2015209411.
58. Nightingale J, Meade U, and The BIFA Committee. British Intestinal Failure Alliance (BIFA) Position Statement The use of high dose loperamide in patients with intestinal failure. 2018. https://www.bapen.org.uk/pdfs/bifa/position-statements/use-of-loperamide-in-patients-with-intestinal-failure.pdf. Accessed 23 Apr 2018.
59. Aly A, Barany F, Kollberg B, Monsen U, Wisen O, Johansson C. Effect of an H_2-receptor blocking agent on diarrhoeas after

extensive small bowel resection in Crohn's disease. Acta Med Scand. 1980;207:119–22.
60. Jacobsen O, Ladefoged K, Stage JG, Jarnum S. Effects of cimetidine on jejunostomy effluents in patients with severe short bowel syndrome. Scand J Gastroenterol. 1986;21:824–8.
61. Nightingale JMD, Walker ER, Farthing MJG, Lennard-Jones JE. Effect of omeprazole on intestinal output in the short bowel syndrome. Aliment Pharmacol Ther. 1991;5:405–12.
62. Jeppesen PB, Staun M, Tjellesen L, Mortensen PB. Effect of intravenous ranitidine and omeprazole on intestinal absorption of water, sodium, macronutrients in patients with intestinal resection. Gut. 1998;43:763–9.
63. British National Formulary (BNF), NICE. https://bnf.nice.org.uk/drug-class/proton-pump-inhibitors-2.html#sideEffects.
64. Dharmsathophorn K, Gorelick FS, Sherwin RS, Cataland S, Dobbins JW. Somatostatin decreases diarrhoea in patients with the short bowel syndrome. J Clin Gastroenterol. 1982;4:521–4.
65. Williams NS, Cooper JC, Axon ATR, King RFGJ, Barker M. Use of a long acting somatostatin analogue in controlling life threatening ileostomy diarrhoea. Br Med J. 1984;289:1027–8.
66. Cooper JC, Williams NS, King RFGJ, Barker MCJ. Effects of a long acting somatostatin analogue in patients with severe ileostomy diarrhoea. Br J Surg. 1986;73:128–31.
67. Kusuhara K, Kusunoki M, Okamoto T, Sakanoue Y, Utsunomiya J. Reduction of the effluent volume in high-output ileostomy patients by a somatostatin analogue, SMS 201–995. Int J Colorectal Dis. 1992;7:202–5.
68. Shaffer JL, O'Hanrahan T, Rowntree S, Shipley K, Irving MH. Does somatostatin analogue (201–995) reduce high output stoma effluent? A controlled trial. Gut. 1988;29:A1432–3.
69. Nightingale JMD, Walker ER, Burnham WR, Farthing MJG, Lennard-Jones JE. Octreotide (a somatostatin analogue) improves the quality of life in some patients with a short intestine. Aliment Pharmacol Ther. 1989;3:367–73.
70. Ladefoged K, Christensen KC, Hegnhoj J, Jarnum S. Effect of a long acting somatostatin analogue SMS 201–995 on jejunostomy effluents in patients with severe short bowel syndrome. Gut. 1989;30:943–9.
71. Lémann M, de Montigny S, Mahé S, et al. Effect of octreotide on water and electrolytes losses, nutrient absorption and transit in short bowel syndrome. Eur J Gastroenterol Hepatol. 1993;5:817–22.
72. O'Keefe SJD, Peterson ME, Fleming R. Octreotide as an adjunct to home parenteral nutrition in the management of permanent end-jejunostomy syndrome. J Parenter Enteral Nutr. 1994;18:26–34.
73. Lamireau T, Galperine RI, Ohlbaum P, Demarquez JL, Vergnes P, Kurzenne Y, Hehunstre JP. Use of a long acting somatostatin analogue in controlling ileostomy diarrhoea in infants. Acta Paediatr Scand. 1990;79:871–2.
74. Nubiola P, Badia JM, Martinez-Rodenas F, Gil MJ, Segura M, Sancho J, Sitges-Serra A. Treatment of 27 postoperative enterocutaneous fistulas with the long half life somatostatin analogue SMS 201–995. Ann Surg. 1989;210:56–8.
75. Scott NA, Finnegan S, Irving MH. Octreotide and postoperative enterocutaneous fistulae: a controlled prospective study. Acta Gastroenterol Belg. 1993;56:266–70.
76. O'Keefe SJD, Haymond MW, Bennet WM, Oswald B, Nelson DK, Shorter RG. Long-acting somatostatin analogue therapy and protein metabolism in patients with jejunostomies. Gastroenterology. 1994;107:379–88.
77. Dowling RH, Hussaini SH, Murphy GM, Wass JAH. Gallstones during octreotide therapy. Digestion. 1993;54(suppl 1):107–20.
78. Nightingale JMD, Walker ER, Burnham WR, Farthing MJG, Lennard-Jones JE. The short bowel syndrome. Digestion. 1990;45(suppl 1):77–83.
79. Nehra V, Camilleri M, Burton D, Oenning L, Kelly DG. An open trial of octreotide long-acting release in the management of short bowel syndrome. Am J Gastroenterol. 2001;96(5):1494–8.
80. Mesli Y, Holterbach L, Delhorme J-B, Lakkis Z, Ortega-Deballon P, Deguelte S, Rohr S, Brigand C, Meyer N, Romain B. Is Lanreotide really useful in high output stoma? Comparison between Lanreotide to conventional antidiarrheal treatment alone. J Invest Surg. 2020;4:1–5. https://doi.org/10.1080/08941939.2020.1800871.
81. Wright HK, Cleveland JC, Tilson MD, Herskovic T. Morphology and absorptive capacity of the ileum after ileostomy in man. Am J Surg. 1969;117:242–5.
82. Ladas SD, Isaacs PET, Murphy GM, Sladen GE. Fasting and postprandial ileal function in adapted ileostomates and normal subjects. Gut. 1986;27:906–12.
83. Goulston K, Harrison DD, Skyring AP. Effect of mineralocorticoids on the sodium/potassium ratio of human ileostomy fluid. Lancet. 1963;ii:541–3.
84. Levitan R, Goulston K. Water and electrolyte content of human ileostomy fluid after D-aldosterone administration. Gastroenterology. 1967;52:510–2.
85. Kramer P, Levitan R. Effect of 9 α-fludrocortisone on the ileal excreta of ileostomized subjects. Gastroenterology. 1972;62:235–41.
86. Feretis CB, Vyssoulis GP, Pararas BN, Nissiotis AS, Calaitzopoulos JD, Apostolidis NS, Golematis BCH. The influence of corticosteroids on ileostomy discharge of patients operated for ulcerative colitis. Am Surg. 1984;50:433–6.
87. Sandle GI, Keir MJ, Record CO. The effect of hydrocortisone on the transport of water, sodium and glucose in the jejunum. Perfusion studies in normal subjects and patients with coeliac disease. Scand J Gastroenterol. 1981;16:667–71.
88. Sutters M, Carmichael DJS, Unwin RJ, et al. 'Low sodium' diuresis and ileal loss in patients with ileostomies: effect of desmopressin. Gut. 1991;32:649–53.
89. Gruy-Kapral C, Little KH, Fortran JS, Meziere TL, Hagey LR, Hofmann AF. Conjugated bile acid replacement therapy for short-bowel syndrome. Gastroenterology. 1999;116:15–21.
90. Weinand I, Hofmann AF, Jordan A. Cholylsarcosine use for bile acid replacement in short bowel syndrome. Gastroenterology. 1999;116:G0441.
91. Sica DA, Grubbs R. Transdermal clonidine: therapeutic considerations. J Clin Hypertens (Greenwich). 2005;7(9):558–62.
92. Buchman AL, Fryer J, Wallin A, Ahn CW, Polensky S, Zaremba K. Clonidine reduces diarrhea and sodium loss in patients with proximal jejunostomy: a controlled study. J Parenter Enteral Nutr. 2006;30(6):487–91.
93. Oke S, Nightingale J, Jeppesen P, and the BIFA Committee. British Intestinal Failure Alliance (BIFA) position statement. Use of peptide growth factors for adult patients with intestinal failure. 2018. www.bapen.org.uk/pdfs/bifa/position-statements/use-of-peptide-growth-factors-for-adult-patients-with-intestinal-failure.pdf.
94. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O 'keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011;60(7):902–14.
95. Jeppesen PB, Pertkiewicz M, Messing B, Iyer K, Seidner DL, Okeefe SJ, Forbes A, Heinze H, Joelsson B. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology. 2012;143(6):1473–81.
96. Schwartz LK, O'Keefe SJ, Fujioka K, Gabe SM, Lamprecht G, Pape UF, Li B, Youssef NN, Jeppesen PB. Long-term Teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. Clin Transl Gastroenterol. 2016;7(2):e142.

97. Hvistendahl M, Brandt CF, Tribler S, Naimi RM, Hartmann B, Holst JJ, Rehfeld JF, Hornum M, Andersen JR, Henriksen BM, Brøbech Mortensen P, Jeppesen PB. Effect of Liraglutide treatment on jejunostomy output in patients with short bowel syndrome: an open-label pilot study. J Parenter Enteral Nutr. 2018;42(1):112–21.
98. Litvak DA, Iseki H, Evers M, et al. Characterization of two novel proabsorptive peptide YY analogs, BIM-43073D and BIM-43004C. Dig Dis Sci. 1999;44:643–8.
99. Kaufman SS, Loseke CA, Anderson JB, Murray ND, Vanderhoof JA, Young RJ. Magnesium acetate vs magnesium gluconate supplementation in short bowel syndrome. J Pediatr Gastroenterol. 1993;16:104–5.
100. Schuette SA, Lashner BA, Janghorbani M. Bioavailability of magnesium diglycinate vs magnesium oxide in patients with ileal resection. J Parenter Enteral Nutr. 1994;18:430–5.
101. Kass L, Rosanoff A, Tanner A, Sullivan K, McAuley W, Plesset M. Effect of transdermal magnesium cream on serum and urinary magnesium levels in humans: a pilot study. PloS One. 2017;12(4):e0174817. https://doi.org/10.1371/journal.pone.0174817.
102. Selby PL, Peacock M, Bambach CP. Hypomagnesaemia after small bowel resection: treatment with 1 alpha-hydroxylated vitamin D metabolites. Br J Surg. 1984;71:334–7.
103. Fukumoto S, Matsumoto T, Tanaka Y, Harada S, Ogata E. Renal magnesium wasting in a patient with short bowel syndrome with magnesium deficiency: effect of 1 α-hydroxyvitamin D_3 treatment. J Clin Endocrinol Metab. 1987;65:1301–4.
104. Makowsky MJ, Bell P, Gramlich L. Subcutaneous magnesium sulfate to correct high-output ileostomy-induced hypomagnesemia. Case Rep Gastroenterol. 2019;13(2):280–93.
105. Nightingale JMD. Gastrostomy placement in patients with Crohn's disease. Eur J Gastroenterol Hepatol. 2000;12:1073–5.
106. McIntyre PB, Fitchew M, Lennard-Jones JE. Patients with a jejunostomy do not need a special diet. Gastroenterology. 1986;91:25–33.
107. Jeppesen PB, Mortensen PB. The influence of a preserved colon on the absorption of medium-chain fat in patients with small bowel resection. Gut. 1998;43:478–83.
108. Beaugererie L, Carbonnel F, Hecketsweiler B, Dechelotte P, Gendre J-P, Cosnes J. Effects of an isotonic oral rehydration solution, enriched with glutamine, on fluid and sodium absorption in patients with a short bowel. Aliment Pharmacol Ther. 1997;11:741–6.
109. Mercer-Smith G, Kirk C, Gemmell L, Mountford C, Nightingale J, Thompson N and the BIFA Committee. British Intestinal Failure Alliance (BIFA) Guidance. Haematological and Biochemical Monitoring of Adult Patients receiving Home Parenteral Nutrition. 2021. www.bapen.org.uk/pdfs/bifa/position-statements/position-statement-haematological-biochemical-monitoring-adult-hpn.pdf.
110. Ehrenpreis ED, Guerriero S, Nogueras JJ, Carroll MA. Malabsorption of digoxin tablets, gel caps, and elixir in a patient with an end jejunostomy. Ann Pharmacother. 1994;28:1239–40.
111. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutics drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12:413–20.
112. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm. 2004;58(2):265–78.
113. Crawford N, Brooke BN. Ileostomy chemistry. Lancet. 1957;i:864–7.
114. Hill GL, Mair WSJ, Goligher JC. Impairment of 'ileostomy adaptation' in patients after ileal resection. Gut. 1974;15:982–7.
115. Adaba F, Rajendran A, Patel A, Cheung YK, Grant K, Vaizey CJ, Gabe SM, Warusavitarne J, Nightingale JM. Mesenteric infarction: clinical outcomes after restoration of bowel continuity. Ann Surg. 2015;262:1059–64.
116. Beyer-Berjot L, Joly F, Maggiori L, Corcos O, Bouhnik Y, Bretagnol F, Panis Y. Segmental reversal of the small bowel can end permanent parenteral nutrition dependency: an experience of 38 adults with short bowel syndrome. Ann Surg. 2012;256(5):739–44; discussion 744–5.
117. Yannam GR, Sudan DL, Grant W, Botha J, Langnas A, Thompson JS. Intestinal lengthening in adult patients with short bowel syndrome. J Gastrointest Surg. 2010;14(12):1931–6.

Dietary Treatment of Patients with a Short Bowel

Morag Pearson and Jeremy M.D. Nightingale

Key Points

1. A patient with a short bowel taking an oral diet requires a malabsorption factor to be taken into account. Adaptive hyperphagia will help compensate for this.
2. Adhesions are common and so the diet may need to be low in fibre to reduce the chance of obstruction.
3. Jejunostomy patients, whose intestine does not adapt with time, need a high energy iso-osmolar (high lipid) oral/enteral intake with added sodium (and cation supplements). They should restrict oral hypotonic fluids and take an oral rehydration solution.
4. Jejunum-colon patients, whose absorption (adaptation) may improve for up to 2 years after the anastomosis, need a high carbohydrate diet (for colonic fermentation), with no excess lipid (worsens diarrhoea), that is low in oxalate with calcium supplementation (to prevent calcium oxalate renal stones).
5. D-lactic acidosis may occur in jejunum-colon patients. It causes confusion, a high anion gap acidosis and may be helped by antibiotics ideally targeted at specific faecal microbes.

Introduction

Intestinal rehabilitation aims to optimise residual intestinal function through medical, pharmacological, dietary and surgical strategies and to provide the nutrition, fluid and electrolytes required to maintain health (with a normal body weight) and growth in children. It also aims to promote nutritional autonomy and enable a reduction or weaning of parenteral nutrition (PN), so reducing associated complications and improving the quality of life.

Short bowel is categorised according to residual anatomy [1, 2]:

Jejunostomy: following jejuno-ileal resection, colectomy and formation of a jejunostomy, patients will immediately become dehydrated due to large stomal water and sodium losses, which are greatest after food and drink consumption, and rapidly develop malnutrition.

Jejunum-colon: following a jejuno-ileal resection with jejuno-colic anastomosis, patients appear well apart from diarrhoea/steatorrhoea, but in the following months may lose weight and become severely undernourished.

Jejunum-ileum: following a predominantly jejunal resection leaving more than 10 cm of terminal ileum in continuity with colon, patients rarely develop nutritional problems, but if undernutrition or severe diarrhoea arise, then they are treated as per jejunum-colon guidance so will not be discussed separately in this chapter.

Patients with short bowel and taking an oral diet only may have difficulty maintaining nutritional status, fluid and electrolyte balance. This is due to malabsorption and fluid losses which may result in malnutrition and/or dehydration if there is not adequate nutritional support and fluid replacement.

In the immediate postoperative period, many patients may require PN, but its long-term use has been associated with life-threatening metabolic, hepatic and catheter related complications [3, 4] and a reduced quality of life [5, 6]. Over time, intestinal absorption in those with a colon in continuity may improve with adaptation of the residual bowel, a process that is stimulated by intraluminal nutrients and gastrointestinal (especially pancreatico-biliary) secretions. When the gut is functional, patients are encouraged to eat, with advice on modifying oral intake to reduce stoma or stool losses. When the gut has the potential to absorb water, electrolytes and nutrients then nutritional intake should be optimised through dietary counselling, use of oral rehydration solution,

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anti-secretory and anti-motility medications, overnight enteral nutrition (EN), distal feeding or other rehabilitative strategies such as surgical restoration of continuity or intestinotrophic hormones. In this way some patients may be able to reduce or withdraw their need for parenteral support [2].

Dietary aspects of intestinal rehabilitation include understanding the anatomical and physiological changes that affect nutrient, fluid and electrolyte absorption; assessing and monitoring patients, promoting adaptation (including hyperphagia) and dietary strategies to optimise absorption, reduce stoma/stool losses and short bowel related complications. The practical aspects of dietary care should be integrated within the multidisciplinary team management. This chapter focuses on the dietary aspects of intestinal rehabilitation, especially the dietary treatment to maximise absorption of nutrients, fluid and electrolytes and reduce short bowel related complications. It outlines most of the key studies on which dietetic advice is based and it gives a full practical dietetic account about D-lactic acidosis and calcium oxalate renal stones.

Remaining Bowel Length and Energy/Fluid Absorption

Balance studies, performed in short bowel patients eating their usual diet, provide an objective measure of nutrient absorption and thus residual intestinal absorptive capacity [7] (Table 1). They involve the 24-h collection of duplicate oral food and fluid intake plus all stoma/stool and urinary losses, each of which are homogenized and frozen or freeze-dried for analysis. Fluid (wet weight) absorption is calculated from the difference between the weight of oral intake and faecal losses, whilst energy content is analysed by bomb calorimetry and absorption calculated from the difference between dietary intake and stool losses.

Rodrigues et al. [8] measured energy absorption from a polymeric test drink, following an overnight fast, in 12 short bowel patients including seven with jejunostomies stable on an oral diet/enteral feed (median 110 cm small bowel) and five (three jejunostomies, one jejunocolic anastomosis to colostomy, one ileo-rectal anastomosis) on home parenteral nutrition (HPN) (median 50 cm small bowel) who remained nil by mouth during the 6-h collection of intestinal output. Median energy absorption was 67% (range 59–78%) in patients stable on diet compared with 27% (range 2–63%), ($p < 0.01$) in those dependent on PN. Energy absorption correlated with residual jejunal length ($r = 0.73$, $p < 0.01$), wet weight ($r = -0.83$, $p < 0.001$) and dry weight ($r = -0.99$, $p < 0.001$) of the stoma/stool output.

Balance studies in 15 patients (six PN, three intravenous fluid (IVF) and six diet/oral nutrient supplements (ONS)) with <150 cm jejunum to stoma, who ate their usual diet also found that jejunal length was inversely correlated with energy absorption ($r = 0.64$, $p < 0.02$) [9]. Patients who required PN had <80 cm jejunum and absorbed <35% of their oral energy intake (mean 8646 kJ (2066 kcal)/day), whereas those stable on diet had >100 cm jejunum and absorbed 58% of their oral energy intake (mean 12,782 kJ (3055 kcal)/day, suggesting an increased oral intake to compensate for malabsorption. Jejunal length was also inversely correlated with net intestinal fluid ($r = 0.75$, $p < 0.01$) and sodium losses ($r = 0.59$, $p < 0.05$), such that patients could be classified as either net 'secretors' or 'absorbers' depending on the relative weight of their oral intake and stomal output and corresponding sodium content. 'Secretors' had less than 100 cm residual jejunum and lost more water and sodium from their stoma than they took by mouth (daily jejunostomy output 2–8 kg, containing 154–551 mmol sodium). They could not convert from negative to positive water and sodium balance by taking more orally and so required long-term parenteral supplements. Their stoma output increased during the day in response to food and decreased at night, highlighting the need to take anti-motility medication prior to food. The 'absorbers' had more than 100 cm of residual jejunum and absorbed more water and sodium from their diet than they took orally (daily jejunostomy output 1–3 kg containing 149–368 mmol sodium). They were able to avoid parenteral support by taking a high salt diet with an oral rehydration solution to maintain fluid and sodium balance.

Jeppesen et al. [10] investigated energy and wet weight absorption by 48-h balance studies in 44 non-HPN patients with intestinal insufficiency (<200 cm small bowel or malabsorption exceeding 2 MJ/day) and 45 HPN patients with intestinal failure. Non-HPN patients had a higher median energy intake (11.69 MJ (2794 kcal)/day) compared with HPN patients (7.56 MJ (1807 kcal)/day), ($p < 0.001$), corresponding respectively to 178% and 134% of basal metabolic rate (BMR) as calculated by Harris-Benedict and a twofold higher energy absorption (7.92 MJ (1893 kcal)/day) compared with HPN patients (3.96 MJ (946 kcal)/day), ($p < 0.001$), corresponding respectively to 130% and 71% of BMR ($p < 0.001$). Intestinal wet weight absorption was threefold higher in non-HPN patients (2.48 kg/day) compared with HPN patients (0.84 kg/day), $p < 0.001$). Non-HPN patients, who absorbed less than half of their intake, avoided HPN through hyperphagia with energy intakes of 10–24 MJ (2390–5736 kcal)/day, equivalent to 200–400% of BMR. Non-HPN patients who maintained intestinal autonomy, tended to have an energy absorption that exceeded 84% of BMR and wet weight absorption of more than 1.4 kg/day, whereas those dependent on HPN absorbed less of either or both.

Whilst balance techniques remain the optimal way to quantify intestinal insufficiency or failure in individual patients [10], very few centres have the facilities to under-

Table 1 Studies of energy, fluid and sodium absorption in patients with a short bowel

Reference	Subjects	Mean residual small bowel length (cm) (range)	Mean residual colon (range)	Method	Diet composition Mean daily energy (MJ) (kcal) (range) Mean daily wet weight (kg) (range) Mean daily sodium (mmol) (range)	Mean daily % energy absorption (range)	Mean daily stoma or stool wet weight (kg) (range)	Mean daily stoma or stool sodium output (mmol) (range)
Rodrigues et al. 1989 [8]	**7 Oral** 7 jejunostomy (1ONS, 2NG, 1NGE, 3 IVF)	Median 110 (60–140)	–	Balance 6 h	300 mL polymeric drink containing 337 kcal and 10.5 mmol Na	Median 67% (59–78)	Median 0.4 (0.3–0.6)	Median 53 (31–80)
	5 HPN 3 jejunostomy 1 JCA 1 JRA	Median 50 (20–100)	50% colon (n = 1); Rectum (n = 1))	Balance 6 h	300 mL polymeric drink containing 337 kcal and 10.5 mmol Na	Median 27% (2–63)	Median 0.7 (0.3–1.5)	Median 77 (29–144)
Nightingale et al. 1990 [9]	**6 Oral** 6 jejunostomy	105–140	–	Balance 1 day	Usual diet 12.78MJ (3043kcal) (8.13–20.03) 3.5 kg (2.7–5.2) 361 mmol Na (157–800)	58%	1.9 (1.2–3.5)	200 (148–368)
	3 IVF 3 jejunostomy	95–140	–	Balance 1 day	Usual diet 9.72MJ (2322kcal) (6.6–13.98) 2.2 kg (2–2.4) 151 mmol Na (140–172)	46%	2.9 (1.5–3.7)	294 (154–392)
	6 HPN 5 jejunostomy, 1JRA	25–70	Rectum (n = 1)	Balance 1 day	Usual diet 8.65MJ (2066kcal) (3.75–14.43) 2.7 kg (1.3–4.6) 195 mmol Na (100–335)	35%	5.4 (3.0–7.8)	431 (256–551)
Jeppesen et al. 2000 [10]	**44 Oral** 21 jejuno-ileostomy 23 JCA	180 (165–195) 140 (89–158)	57% (57–100) (n = 23)	Balance 2 days	Usual diet 11.69MJ[a] (2794kcal) (9.28–13.56) 3.6kg[a] (3.01–4.4) 135 mmol Na[a] (104–180)	71% (58–78)	1.25 (0.7–1.8) % Fluid absorption 63% (55–80)	105 (19–159) % Na absorption 30% (−13 to 89)
	45 HPN 27 jejuno-ileostomy 18 JCA	100 (49–140) 90 (45–131)	64% (28–100) (n = 18)	Balance 2 days	Usual diet 7.56 MJ[a] (1807 kcal) (5.7–9.38) 2.8 kg[a] (2.2–3.7) 134 mmol Na[a] (67–159)	49% (40–76)	2.2 (1.2–3.0) % Fluid absorption 31% (0–51)	129 (69–218) % Na absorption −16% (−67 to 46)

HPN home parenteral nutrition, *IVF* intravenous fluids, *ONS* oral nutritional supplement, *NG* nasogastric, *NGE* nasogastric electrolytes, *JCA* jejunum-colon, *JRA* jejuno-rectal anastomosis, *cm* centimetre, *n* number, *kcal* kilocalorie, *kg* kilogram, *mmol* millimole, *Na* sodium, *kJ* kilojoule, *MJ* megajoule, *%* percentage

[a]Median

take these meticulous metabolic studies, so clinicians use knowledge of type and length of residual bowel to predict long-term nutritional support requirements [11]. Large cohort studies in short bowel patients with <200 cm healthy jejunum report that the minimum small bowel length required to avoid long-term PN is 60–115 cm in jejunostomy and 30–65 cm in jejunum-colon patients [12–15] (Table 2). In the latter group, conservation of colon is beneficial because it absorbs water, sodium, calcium, some nutrients, maintains a normal rate of gastric emptying of liquids and may stimulate

Table 2 Guide to predicting long-term nutritional support/fluid requirements from residual bowel length in short bowel patients [12–15]

Jejunal length (cm)	Jejunum-colon	Jejunostomy
0–50	PN	PN ± PS; restrict hypotonic fluids
51–100	ON[a]	PN ± PS[b]; ORS
101–150	ON[a]	ON (added salt); if stoma losses >1.5 L, ORS
151–200	ON	ON (added salt) ± ORS

cm centimetre, *PN* parenteral nutrition, *PS* parenteral saline (±magnesium), *ON* oral nutrition (± oral or enteral nutritional support), *ORS* oral (or enteral) rehydration solution in combination with hypotonic fluid restriction

[a]If colon length reduced, may require added salt ± ORS

[b]At 85–100 cm may need parenteral fluid/electrolytes only

intestinal hyperplasia [13]. Preservation of more than 50% of colon in patients with less than 100 cm small bowel reduced parenteral sodium and energy requirements by half, compared with those without colon [16] and is equivalent to about 50 cm of small intestine in terms of the need for parenteral supplements [13], which explains the importance of restoration of colonic continuity where ever possible.

However, long-term nutritional support needs may be affected by both the integrity and degree of adaptation within the remaining bowel as well as patient specific factors, so each patient should be assessed and monitored on an individual basis.

Integrity of Remaining Bowel

If the remaining small bowel is affected by active Crohn's disease [16], radiation enteritis [16] or radiological proven lesions [14, 15], then its absorptive capacity may be reduced and longer than predicted lengths of small bowel may be required to achieve independence from PN [2].

Adaptation of Residual Bowel

Post-resection intestinal adaptation is a spontaneous process that attempts to increase nutrient and fluid absorption from the remaining bowel through intestinal mucosa hyperplasia to increase the absorptive area (structural adaptation) and/or by slowing of gastrointestinal transit to increase nutrient and fluid absorption (functional adaptation) [11, 17]. It is promoted by intraluminal nutrients and pancreatico-biliary secretions, the development of hyperphagia, modified gastrointestinal hormonal secretion (glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) and plasma peptide YY (PYY)), alteration of the gut microbiota and accumulation of faecal D/L-lactate in some patients and is highly variable and unique to each patient [2] (chapter "Intestinal Adaptation").

Residual Anatomy

In jejunum-colon patients, no definite structural intestinal adaptation has been demonstrated, [18, 19], but functional adaptation with slowing of gastric emptying and small bowel transit may occur [20], probably due to high PYY [21] and GLP-2 [22] concentrations. There is increased jejunal absorption of macronutrients, water, sodium and calcium with time [23–26] that allows a gradual reduction in parenteral requirements with an increased chance of the patient being able to reduce or stop PN [1, 12–15]. Although most adaptation is thought to occur within the first 2–3 years post-resection [15, 27], improved intestinal absorption with reduced dependence on PN has been observed many years later [13, 28, 29] and late adaptation has been enhanced by intestinotrophic therapies [30], highlighting the importance of ongoing monitoring and optimisation of dietary and pharmaceutical management.

In contrast, there is no evidence of structural [31] or functional [13, 32] adaptation at any time in jejunostomy patients, likely due to low plasma concentrations of PYY [21] and GLP-2 [33] and leading to rapid gastric emptying and small bowel transit with reduced absorption. Thus, their parenteral nutrition and fluid needs are unlikely to change with time [1].

Enteral Nutrients

Luminal stimulation with enteral nutrients is required to maintain the structure of the intestinal mucosa [17]. Lack of enteral nutrition induces mucosal atrophy and decreases digestive enzyme and nutrient transporter activity in animals and humans, even when adequate calories are provided via PN [17]. PN-induced mucosal atrophy is reversed by reintroduction of enteral nutrition [34, 35], so it is important that food or EN are reintroduced as soon as possible after resection, even in those likely to require long-term PN. Animal studies suggest that post-resection adaptation is enhanced by nutrient complexity, fats particularly long-chain triglycerides (LCTs) and short-chain fatty acids (SCFAs), but the optimum diet to stimulate human intestinal adaptation is not yet known [17]. SCFAs are trophic [36] and make a significant contribution to energy balance in jejunum-colon patients [37]. However, in six jejunum-colon patients, 2-week dietary supplementation with 4 g daily of pectin, a starch that acts a substrate for bacterial SCFA production, increased colonic levels of SCFAs but failed to demonstrate improvements in macronutrient or fluid absorption [38].

Hyperphagia

Many patients compensate for significantly reduced energy absorption by spontaneously increasing their oral intake in a behavioural adaptation known as hyperphagia. In a study of 90 patients with <200 cm small bowel, with or without colonic resection (39 oral diet; 51 HPN), 14 of whom were studied in early (<6 months) and late (>6 months) periods after digestive continuity, 81% had hyperphagia (a spontaneous oral intake >1.5 times resting energy expenditure), which was independently and negatively related to fat absorption ($p < 0.01$) and body mass index ($p < 0.001$) but not braked by the presence of PN. There was an increase in hyperphagia over time highlighting the importance of promoting oral intake in patients receiving long-term PN to maximize residual absorptive capacity [39].

Intestinal Growth Factors

Growth hormone (GH) receptors are located throughout the intestine and GH induces growth and proliferation in many different tissues plus the production of the intestinotrophic hormone, insulin-like growth factor-1 [40]. In addition to regulating gastrointestinal motility, the hormones GLP-1, GLP-2 and PYY exert a trophic effect on the mucosa by enhancing intestinal villus and crypt cell growth [2]. These intestinal growth factors have the potential to hasten or exceed the normal intestinal adaptation response, leading to investigation of the efficacy of GH, its recombinant somatotropin and the GLP-2 analogue, teduglutide, in maximizing absorption from the remnant bowel, decreasing intestinal losses and reducing the requirement for parenteral nutrition or fluids [41] (chapter "Pro-Adaptive Hormones in the Rehabilitation of ADULT patients with a Short Bowel").

Patient Specific Factors

Patient specific factors that may delay adaptation and/or influence long-term PN requirements include the ability to restore oral feeding or develop a post-resection adaptive hyperphagia and to adapt dietary intake to decrease intestinal losses; reduced oral or enteral intake due to symptoms such as nausea, vomiting, bloating or pain, food aversion, aging, chronic narcotic use, psychological factors, underlying comorbidities and social factors [11, 28]. Occasionally PN may be required if increasing the oral or enteral nutrient intake causes a socially unacceptably high stomal output, severe diarrhoea or fails to meet nutritional needs when energy requirements are high and absorption is 30–60% [42].

Nutritional Assessment and Monitoring

Short bowel syndrome (SBS) is a complex condition that requires a multidisciplinary evaluation to determine the most appropriate therapy. Patients may rapidly become dehydrated, electrolyte depleted and malnourished, so require a comprehensive nutrition assessment at baseline (chapter "Assessment of Nutritional and Fluid Status"), which should be repeated regularly to assess the effectiveness of nutrition intervention [43], particularly during HPN weaning when close monitoring is required (chapter "Monitoring of Parenteral Nutrition at Home").

Nutritional Status

The assessment of nutritional status should include weight, body mass index (BMI) and percentage weight loss over 3–6 months. If the patient is dehydrated or overhydrated then their weight may be several kilograms below or above their actual weight and this should be taken in to account when assessing nutritional status and calculating requirements [43]. Rapid changes in body weight are likely to reflect the significant fluid shifts that may be experienced by these patients, so it is best practice to measure mid arm circumference and triceps skinfold thickness (TST) to calculate mid arm muscle circumference (MAMC) in order to monitor changes in body composition in response to nutrition support [43] (chapter "Assessment of Nutritional and Fluid Status"). Handgrip is also valuable in determining functional capacity. MAMC and handgrip should be repeated monthly in hospital [43] and at least annually in stable outpatients to detect any changes in nutritional status to inform amendments in nutritional support.

Micronutrient Status

Short bowel patients are at high risk of developing micronutrient deficiencies due to fat malabsorption and high stoma/fistula losses or diarrhoea/steatorrhoea. A serum micronutrient screen, which depending on laboratory availability, may include folate, iron, ferritin, selenium, zinc, copper, vitamins B12, A, D and E, should be performed in conjunction with the assessment of clinical signs and symptoms of deficiency at the onset of HPN and then at least once per year [4, 44] (chapter "Monitoring of Parenteral Nutrition at Home"), although frequency may vary with changes in clinical status or micronutrient prescription during PN weaning [45]. Whilst laboratory tests play an important role in determining individual requirements, it is unclear to what extent serum concentrations reflect tissue status and true requirements, especially during acute illness [46]. Serum concentrations

lack diagnostic sensitivity as they are maintained within the reference range until severe deficiency or excess develops [46]. Most plasma micronutrients fall as part of the systemic inflammatory response (with the exception of copper, which rises in association with caeruloplasmin synthesis [47]), due to redistribution between tissues and blood, making them unreliable measures of nutritional status when C-reactive protein (CRP) >10 mg/L [45]. In the absence of functional or intracellular measurements, it may be helpful to review serial measurements in relation to CRP changes [48], in the context of clinical features and potential risk factors for deficiency [46]. Micronutrient concentrations may also be affected by other factors for example recent intake (folate) [49], lipid levels (vitamin E) [50], hypoalbuminaemia (zinc) [45], oestrogens (copper) [47] as well as specimen contamination or analytical problems.

Fluid and Electrolyte Status

Fluid and sodium deficiency result in loss of extracellular fluid volume leading to thirst, hypotension and pre-renal failure. Hydration status may be assessed from clinical appearance, fluid balance charts, routine haematology and biochemistry including random urinary sodium. Dehydration is indicated by a low urine output (<1 L/24 h), rapid weight loss (1 kg in 24 h indicates fluid depletion by 1 L) and in the absence of renal disease by a raised urea and creatinine [1]. However, creatinine may be low in patients with reduced muscle mass and urea may be low if protein/nitrogen intake is reduced so making dehydration difficult to identify [51]. Because of the influence of the renin-angiotensin mechanism, the plasma sodium concentration remains normal until body stores are severely depleted [52], so a random urinary sodium provides a better indicator of sodium status (<20 mmol/L indicates maximal renal conservation in response to sodium depletion). Physical signs of depletion become apparent before major changes in blood chemistry, providing important warning signs and include thirst, dry mouth, loss of appetite, nausea, lethargy, muscle cramps, sunken dark-ringed eyes, reduced skin tone, rapid low volume pulse and dizziness on standing due to postural hypotension (confirmed by a lying to standing decrease in blood pressure >20 mmHg systolic and >10 mmHg diastolic) [53]. Inpatient hydration status should be reviewed daily (weight, clinical symptoms, fluid charts and biochemistry) until stable [4] when biochemistry may be reduced to twice per week and post-discharge at each outpatient review.

Magnesium depletion is common, especially in patients with a high stomal output and a serum value of <0.6 mmol/L may give rise to symptoms (fatigue, depression, irritability, muscle cramps and if severe, cardiac arrhythmias and convulsions; tetany may indicate a concomitant hypocalceamia) [42]. Magnesium should be monitored daily during the refeeding risk period until stable when it may be reduced to twice per week and post-discharge at each outpatient review.

Clinical Assessment

Information about underlying illness, co-morbidities and anatomy, residual bowel length and quality (from surgical records and bowel mapping studies using radiology, endoscopic or colonoscopic imaging), enable predictions to be made about absorption, long term fluid/nutrition support needs, including the potential for PN weaning and are crucial to the provision of appropriate advice on diet and fluid intake.

In addition to hydration, clinical assessment should review mobility, signs and symptoms of weight loss, muscle wasting, micronutrient and essential fatty acid deficiencies, intestinal function (nausea, vomiting, bloating, stoma/fistula losses, bowel frequency/stool type and losses from naso-enteric or venting gastrostomy/enterostomy catheters or abdominal drains), temperature, inflammatory markers and signs of sepsis, inflammation or acute disease which may increase nutritional requirements, urinalysis to monitor for ketones and glucose and review of medication including over the counter or herbal preparations which may cause side effects such as nausea, taste changes, increased intestinal losses or abnormal electrolytes [43].

Nutritional Intake

The relative contributions from parenteral, enteral or dietary intake are assessed in conjunction with factors affecting oral intake, an estimate of likely dietary absorption and review of optimisation in relation to short bowel management to inform decisions about the most appropriate form of long-term nutrition support, scope for dietary optimisation and PN weaning.

Oral nutritional intake may be assessed from a detailed food diary or diet history to establish the type and amounts of food consumed, eating patterns, food and fluid preferences, cooking methods, any previous trials of dietary modification or nutrition support, including route, rate, formula and outcome [43] as well as appetite, degree of adaptive hyperphagia and clinical (e.g. dentition, nausea, vomiting, bloating, stoma/fistula output or leakages, stool frequency, incontinence, pain, medication side effects), cultural, behavioral, social or psychological factors [54] that may affect food intake.

Dietary energy and protein intake may be compared with requirements estimated from predictive equations, adjusted for age, sex, weight, disease activity, physical activity and requirement for weight gain/loss or lean tissue gain [55]. In

short bowel patients who are malnourished, ideal body weight has been shown to be a better predictor of resting energy expenditure than actual body weight [56]. Estimated requirements should also be adjusted to compensate for nutrient malabsorption using evidence from balance studies.

Nutritional Management of Short Bowel

The nutritional management of short bowel is a dynamic process that involves overlap or transition between diet, EN and PN in response to changes in the patient's condition and intestinal adaptation [57]. Post-operatively, patients generally receive PN to maintain fluid, electrolyte and nutritional status, until their gastrointestinal function allows re-introduction of oral or EN. If the patient's residual bowel length, anatomy, quality and adaptive potential predict the need for long term PN, then dietary treatment aims to balance eating for pleasure with avoiding high intestinal losses, whereas if there is potential to reduce PN dependence, then oral intake is optimised to maximise absorption. Nutritional goals include the maintenance of a healthy weight (BMI), normal body composition (triceps skin fold thickness and mid-arm circumference measurements used to calculate mid arm muscle circumference), acceptable functional status (activities of daily living, mobility, handgrip), adequate fluid and electrolyte balance (stable weight, a daily urinary volume of at least 1000 mL with random urine sodium concentration of greater than 20 mmol/L, normal serum creatinine and urea with magnesium >0.6 mmol/L) [42], micronutrients within the normal range with no clinical signs of deficiency or toxicity and an acceptable quality of life. Whilst the ultimate goal is enteral independence, this takes time and may not be achievable, highlighting the importance of regular monitoring and individualised management by the multidisciplinary team.

Macronutrient Absorption

Balance studies show that the absorption of dietary macronutrients varies with type, length and quality of remaining bowel (Table 3).

Woolf et al. 1987 [58] investigated macronutrient absorption during a 10-day balance study in eight stable short bowel patients (five jejunostomy, three jejunum-colon, remaining small bowel length 107 cm to all, one receiving HPN), who received isocaloric diets (mean 1869 kcal (31.4 kcal/kg) per day), that matched their usual intake with constant protein, carbohydrate, fat (22%, 32% and 46% of energy respectively) and fluid (2196 mL/day) content. They absorbed 62% of dietary energy and 81%, 61% and 54% respectively from protein, carbohydrate and fat. It was concluded that short bowel patients should increase their oral intake to 35–40 kcal/kg/day of ideal body weight and 80–100 g protein/day to counteract increased losses.

Messing et al. 1991 [59] measured macronutrient absorption during a 3-day balance study in ten short bowel patients (one jejunostomy, nine jejunum-colon, mean small bowel length 75 cm, five receiving HPN) who ate a constant diet that replicated their usual intake and provided mean 3103 kcal (57.9 kcal/kg) per day) and 23%, 46% and 31% of energy from protein, carbohydrate and fat respectively. HPN provided a mean 1120 kcal/day and there was no significant difference in oral intake between parenteral and non-parenteral groups. They absorbed 67% of dietary energy and 61%, 79% and 52% respectively from protein, carbohydrate and fat, with the higher proportion from carbohydrate thought to reflect colonic fermentation. The five patients stable on diet maintained their weight by spontaneously increasing their energy intake to 2.5 times their estimated basal energy expenditure (Harris-Benedict) to compensate for malabsorption.

Crenn et al. 2004 [39] investigated oral intake by dietary questionnaire and macronutrient absorption in a 3-day balance study in 90 patients with <200 cm small bowel, with or without colonic resection (39 oral and 51 HPN), 14 of whom were studied in the early (<6 months) and late (>6 months) periods after digestive continuity. Both groups spontaneously ate a high energy diet (oral group: mean 2667 kcal (45.6 kcal/kg) per day and HPN group: 2507 kcal (48.1 kcal/kg) per day) that provided twice their estimated resting energy expenditure (Harris Benedict) and contained similar proportions of energy from protein (20%), carbohydrate (45–47%) and fat (33–35%). During the balance study they received a constant diet that replicated their usual intake and net dietary absorption was higher in the oral diet group (68% energy, 70% protein, 73% carbohydrate and 61% fat) compared with the PN group (57% energy, 52% protein, 65% carbohydrate, 47% fat). In the subgroup, re-establishment of digestive continuity improved fat and protein absorption in the first 6 months by 30% and 37% respectively with a further 15% increase in protein absorption after this period. It was concluded that macronutrient absorption may be improved by restoration of colonic continuity and promotion of spontaneous adaptive hyperphagia as an oral nutritional strategy.

Estívariz et al. 2008 [60] investigated the habitual home oral diet (7-day food diary plus dietetic review) and macronutrient absorption during a 4-day balance study in 19 short bowel patients (five jejuno- or jejuno-ileostomies, 14 jejunum-colon, mean small bowel length 118 cm), who had received HPN but no dietary instruction for 31 months prior to starting a bowel rehabilitation programme. Mean spontaneous energy and protein intakes were respectively 2656 kcal (39 kcal/kg) and 17 g N_2 (0.22 g N_2/kg) per day, with 15%, 53% and 31% of energy from protein, carbohydrate and fat.

Table 3 Studies of macronutrient absorption in patients with a short bowel

Reference	Subjects	Mean residual small bowel length (cm) ± SD (range)	% Mean residual colon ±SD (range)	Method	Diet composition Mean daily energy (kcal) ± SD (range) % Protein, CHO and fat	% Daily nutrient absorption			
						Energy Mean ± SD (range)	Protein Mean ± SD (range)	CHO Mean ± SD (range)	Fat Mean ± SD (range)
Woolf et al. 1987 [58]	**7 Oral, 1 HPN** 5 Jejunostomy 3 JCA	107—all jejunum[b]	TDR (n = 3)	Balance 10 days	Usual diet 1869 ± 174 kcal (1165–2708) 22% protein 32% CHO 46% fat	62 ± 3 (52–76)	81 ± 5 (71–90)	61 ± 7 (24–81)	54 ± 4 (35–71)
Messing et al. 1991 [59]	**4 Oral, 5 HPN** 1 Jejunostomy 9 JCA	75 (0–200)	67 ± 37 (n = 9)	Balance 3 days	Usual diet 3103 ± 754 kcal[a] 23% protein 46% CHO 31% fat	67 ± 12[a]	61 ± 19[a]	79 ± 15[a]	52 ± 16[a]
Crenn et al. 2004 [39]	**39 Oral** 5 Jejunostomy 34 JCA	105 ± 37 (25–190)	69 ± 30 (0–100) (n = 34)	Balance 3 days	Usual diet 2667 ± 817 kcal (1425–4854) 20% protein 47% CHO 33% fat	68 ± 15 (51–91)	70 ± 17 (37–94)	73 ± 19 (40–93)	61 ± 24 (17–97)
	51 HPN 7 Jejunostomy 44 JCA	61 ± 47 (0–200)	62 ± 32 (0–100) (n = 44)	Balance 3 days	Usual diet 2507 ± 844 kcal (1345–4642) 20% protein 45% CHO 35% fat	57 ± 18 (15–90)	52 ± 21 (0–89)	65 ± 21 (18–100)	47 ± 23 (0–89)
Estívaritz et al. 2008 [60]	**19 HPN** 5 Jejunostomy 14 JCA	118 ± 25 (Duodenum −350)	Left to entire (n = 14)	Balance 4 days	Usual diet 2656 ± 242 kcal[a] 15% protein 53% CHO 31% fat	59 ± 3[a]	42 ± 5[a]	76 ± 3[a]	41 ± 5[a]

HPN home parenteral nutrition, *JCA* jejunum-colon, *cm* centimetre, *SD* standard deviation, *TDR* transverse descending colon plus rectum, *n* number, *kcal* kilocalorie, % percentage, *CHO* carbohydrate

[a]Range not available

[b]mean not available

There was no difference in fat and carbohydrate consumption, whether the colon was present or absent. Simple sugars comprised 43% of oral carbohydrate intake, whilst oral fluid intake averaged 2712 mL/day, primarily from water, coffee, sodas, fruit juices and sports drinks. During the balance study they received a constant diet that replicated their usual intake and mean dietary absorption was 59% energy, 42% nitrogen, 76% carbohydrate and 41% fat. It was concluded that patients were consuming types of foods and fluids that were incorrect for their residual intestinal anatomy and function, which may worsen malabsorption and thus increase HPN requirements. This highlights the importance of individualised nutritional assessment and counselling to facilitate intestinal rehabilitation.

Studies of macronutrient absorption include patients with varying lengths of small bowel, with or without colon in continuity, which makes comparisons difficult, but on average, patients who achieved enteral autonomy, absorbed two-thirds of their oral energy and protein intake [8–10, 39, 58–60]. They compensated for significantly reduced energy absorption by spontaneously increasing oral energy intake to >1.5 times resting energy expenditure through hyperphagia [39]. One study found that patients, who absorbed less than half of their intake, avoided HPN by increasing energy intake to 200–400% of basal metabolic rate equivalent to 10–24 MJ (2380–5714 kcal)/day [10]. Thus, short bowel patients are recommended to compensate for malabsorption by taking a hyperphagic diet containing 30–60 kcal/kg and 0.2–0.25 gN_2 (1.25–1.5 g protein)/kg/day [57] from regular meals, snacks, food fortification, ONS or overnight EN. However, balance studies demonstrated differences in response to dietary manipulation depending on the presence or absence of colon, leading to the recognition that dietary advice should be tailored to the residual bowel anatomy to optimise absorption and minimise complications [4] (Table 4).

Table 4 Dietary recommendations in short bowel patients according to intestinal anatomy [57]

Dietary content	Jejunostomy or ileostomy	Jejuno-ileal or jejunocolic anastomosis
Energy	30–60 kcal/kg/day	30–60 kcal/kg/day
Nitrogen	0.2–0.25 g/kg/day	0.2–0.25 g/kg/day
Protein	1.25–1.5 g/kg/day	1.25–1.5 g/kg/day
Fat	30–40% of total energy	20–30% of total energy
Medium-chain triglycerides (MCT)	No proven benefit	up to 50% of total fat
Carbohydrate	40–50% of total energy[a]	50–60% of total energy[b]
Lactose	No need to restrict	No need to restrict
Oxalate	Normal	Low
Sodium chloride	Extra required from salty foods, addition of salt in cooking or to food on serving	Normal
Oral nutritional supplements or enteral nutrition	Polymeric	Polymeric or semi-elemental with high MCT content
Oral fluid	Restriction of hypotonic fluids with substitution of oral rehydration solution	No restriction usually required

kcal kilocalorie, *kg* kilogram, *g* gram, *%* percentage
[a]Polysaccharides in preference to mono/disaccharides to keep osmolality low
[b]Polysaccharides in preference to mono/disaccharides to reduce the extremely rare occurrence of D-lactic acidosis

Dietary Treatment for Patients with Jejunum in Continuity with a Functioning Colon

Carbohydrate (Table 5)

The recognition of the colon, not only as an organ for fluid and electrolyte absorption, but as a potential energy-salvaging organ has altered dietary recommendations for jejunum-colon patients [61].

Energy salvage from bacterial fermentation of unabsorbed carbohydrate was demonstrated by Royall et al. 1992 [62], who measured hourly breath hydrogen and blood acetate concentrations in twelve short bowel patients (seven with and five without colon) and six normal volunteers after consumption of a 50 g carbohydrate bread meal following an overnight fast. Breath hydrogen levels were significantly higher in jejunum-colon than jejunostomy or normal volunteers ($p < 0.01$), indicating capacity for fermentation and blood acetate levels were also significantly higher ($p < 0.05$), reaching a peak at 4 h suggesting their production from colonic fermentation. It was proposed that colonic carbohydrate fermentation could provide unrealised clinical benefits in terms of energy balance.

The effect of colon on energy absorption was also demonstrated indirectly in two large cohort reviews, which noted that preservation of at least half the colon was equivalent to about 50 cm of small intestine in terms of the need for parenteral supplements [13], and in patients with <100 cm small bowel, it reduced parenteral energy requirements by 50% compared with stoma patients with the same small bowel length [16].

Nordgaard et al. 1994 [61] investigated the effect of manipulating carbohydrate and fat intake on nutrient and fluid absorption in eight patients with 50–245 cm small bowel to colon, who were maintained on isocaloric diets (10.7 MJ (2557 kcal)/day, 20% protein) and randomised to receive either a low carbohydrate, high fat (20:60% of energy) or a high carbohydrate, low fat (60:20%) diet, each over 4 days. The high carbohydrate low fat diet reduced faecal energy loss by 2.0 MJ (478 kcal)/day ($p < 0.00001$) and significantly increased energy absorption from 49 to 69% ($p < 0.001$) compared with the low carbohydrate, high fat diet. Faecal excretions of carbohydrates were low and not affected by change in carbohydrate intake whereas faecal fat increased from 44 to 75% as dietary fat intake increased. There was no change in the faecal volume between the two diets, but the amount of water consumed with the high carbohydrate diet was one litre more than with the high fat diet, suggesting that the colon is capable of reabsorbing additional fluid or that the high carbohydrate diet may improve fluid absorption.

A second study in 82 patients with varying lengths of small bowel in continuity with colon, who consumed their habitual diet (mean 9.9 MJ (2366 kcal)/day), which was high in carbohydrate (55% total energy) found that colonic digestion can supply up to 4.2 MJ (1000 kcal) per day as small bowel failure proceeds, highlighting the importance of encouraging patients with <200 cm to take a high carbohydrate diet [37]. However, high carbohydrate diets increase the volume of food to be eaten (Fig. 1), which may reduce energy intake and colonic fermentation produces gases, which may increase bloating and flatulence [4], so patients should be supported to find a balance between maximising carbohydrate intake for energy and avoiding unwanted side effects.

Pectin is water soluble, non-cellulose fibre, which may prolong gastrointestinal transit time and is fermented by the colonic bacterial flora to produce SCFAs, which may enhance energy absorption. Atia et al. 2011 [38] investigated the effect of giving a pectin supplement (4 g three times per day for 2 weeks) on intestinal absorption and transit in six short bowel patients with 50 cm small bowel anastomosed to colon

Table 5 Studies of the effect of diet composition on nutrient absorption in patients with a short bowel

Reference	Subjects	Mean residual small bowel length (cm), (range)	Method	Diet composition	Effect on energy absorption	Effect on water and sodium absorption	Effect on divalent cation absorption
Jejunostomy							
McIntyre et al. 1986 [202]	4 Jejunostomy (2 oral, 2 HPN)	103 (0–150)	RCT, crossover, each patient acted as own control	Three diets containing equivalent amounts of calories, nitrogen, electrolytes and minerals, but varying fat and fibre • HF (68–106 g)/ Hfibre (26–29 g) • LF (42–50 g)/Hfibre (24–29 g) • LF (39–46 g)/Nfibre (14–15 g) Each over 2–3 days	None	None	None for Ca and Mg
Nordgaard et al. 1994 [61]	6 Jejunostomy (4 oral, 1HPN, 1HPF)	168 (100–250)	RCT, crossover	Two isocaloric diets based on habitual intake (mean 10. 6 MJ (2533 kcal)/d), 20% protein) with varying CHO and fat • HCHO/LF (60% CHO, 20% fat) • LCHO/HF (20% CHO, 60% fat) Each over 4 days (last 3 days test period)	None % Energy absorption HCHO/LF: LCHO/HF 55: 48% p = 0.21	None stoma vol HCHO/LF: LCHO/HF 2691:1959 mL/day p = 0.10	–
Ovesen et al. 1983 [199]	5 Jejunostomy (5 HPN)	83 (35–125)	RCT, crossover	Three isocaloric, isonitogenous diets with varying fat, CHO, P/S ratio • 30% fat, 55% CHO • 60% fat, 25% CHO, P/S 1:1 • 60% fat, 25% CHO, P/S 1:4 Each over 9 days (last 2 days test period)	–	None	HF (60%) diet ↑ stoma losses of Ca, Mg, Cu and Zn
Jeppesen et al. 1998 [79]	6 Jejunostomy 3 Ileostomy (5 oral, 4 HPN)	203 (125–300)	RCT, crossover	Two isocaloric diets based on habitual intake (mean 10.8 MJ (2581 kcal)/d), with varying LCT or LCT/MCT content • HF (50% LCT) • HF (25% MCT + 25% LCT) Each over 4 days (last 3 days test period)	None % Energy absorption LCT: MCT/LCT 47:49%, P = 0.63	MCT ↑ stoma vol LCT: MCT/LCT 2177: 2729 g/day (p = 0.07)	–
Woolf et al. 1983 [201]	5 Jejunostomy 3 Jejunum-transverse colon (5 oral, 3 HPN)	31 (n = 2) 51 (n = 1) All (n = 5)	RCT, crossover, each patient acted as own control	Two isocaloric, isonitogenous diets, based on habitual intake with constant fluid and fibre but varying CHO and fat • HF 60% fat, 20% CHO • LF 20% fat: 60% CHO Each over 5 days (last 4 days test period)	None	None	None for Ca, Mg and Zn

Table 5 (continued)

Reference	Subjects	Mean residual small bowel length (cm), (range)	Method	Diet composition	Effect on energy absorption	Effect on water and sodium absorption	Effect on divalent cation absorption
Jejunum-colon							
Nordgaard et al. 1994 [61]	6 Jejunum-ileum-colon 2 Jejunum-colon (7 oral, 1 HPN)	114 (50–245)	RCT, crossover	Two isocaloric diets based on habitual intake (mean 10. 7 MJ (2557 kcal)/d), 20% protein) with varying CHO and fat • HCHO/LF (60% CHO, 20% fat) • LCHO/HF (20% CHO, 60% fat) Each over 4 days (last 3 days test period)	HCHO ↑ % energy absorption HCHO/LF: LCHO/HF 69: 49% ($p < 0.001$)	None Faecal vol HCHO/LF: LCHO/HF 809:766 mL/day NS	–
Andersson et al. 1974 [67]	10 Ileal-colon 1 Ileostomy 2 active Crohn's without resection (13 oral)	110 (0–195) small bowel resected	Balance	Two isocaloric diets with varying fat, protein and CHO • HF: 100 g/d (2450 kcal, 16% protein, 37% fat, 47% CHO), over 8–16 days • LF: 40 g/d (2420 kcal, 20% protein, 15% fat, 65% CHO) over 16–24 days	–	LF ↓ faecal water by 36% and Na by 11%	–
Hessov et al. 1983 [68]	7 Ileal-colon 2 active Crohn's without resection (9 oral)	145 (35–195) ileum resected	Balance	Two isocaloric diets with varying fat, protein and CHO • HF: 100 g/d (2660 kcal, 16% protein, 33% fat, 51% CHO), 3 × 4 day periods • LF: 40 g/d (2460 kcal (22% protein, 15% fat, 63% CHO) over 4 × 4 day periods	–	–	LF ↑ % absorption of Ca (−25 to 4%; $p < 0.01$) Zn (5–30%; $p < 0.01$) Mg (4–20%; NS)
Jeppesen et al. 1998 [79]	10 JCA (8 oral, 2 HPN)	143 (50–250)	RCT, crossover	Two isocaloric diets based on habitual intake (mean 9.6 MJ (2294 kcal)/d), with varying LCT or LCT/MCT content • HF 50% LCT • HF 25% MCT + 25% LCT Each over 4 days (last 3 days test period)	MCT ↑% energy absorption LCT: MCT/LCT 46:58% $p = 0.02$	None faecal vol LCT: MCT/LCT 981:1114 g/day $p = 0.32$	–
Atia et al. 2011 [38]	6 Jejunum-colon (2 oral, 4 HPN)	50.3 ± 36.5	Balance	Standard diet (30 kcal/kg, 1 g protein/kg, 100 g fat and 16 g mixed fibre per day) • Pre pectin supplementation • Post 2 weeks supplementation with 3 × 4 g pectin/day Each over 5 days (last 3 days test period)	None % Energy absorption pre: post pectin 68.3:62.1% ($p = 0.44$)	None Faecal wet weight pre: post pectin 1582:1689 g/day ($p = 1$)	–

HPN home parenteral nutrition, *HPF* home parenteral fluid, *cm* centimetre, *n* number, *RCT* randomized controlled trial, *HF* high fat, *LF* low fat, *Hfibre* high fibre, *Nfibre* normal fibre, *kcal* kilocalorie, *d* day, *CHO* carbohydrate, *HCHO* high carbohydrate, *LCHO* low carbohydrate, *P/S* poly-unsaturated/saturated fatty acid ratio, *MJ* megajoule, *LCT* long chain fatty acid, *MCT* medium chain fatty acid, *g* gramme, *kg* kilogrammes, ↑ increase, ↓ decrease, *vol* volume, *mL* millilitre, *Na* sodium, *Ca* calcium, *Mg* magnesium, *Cu* copper, *Zn* zinc, *NS* not significant

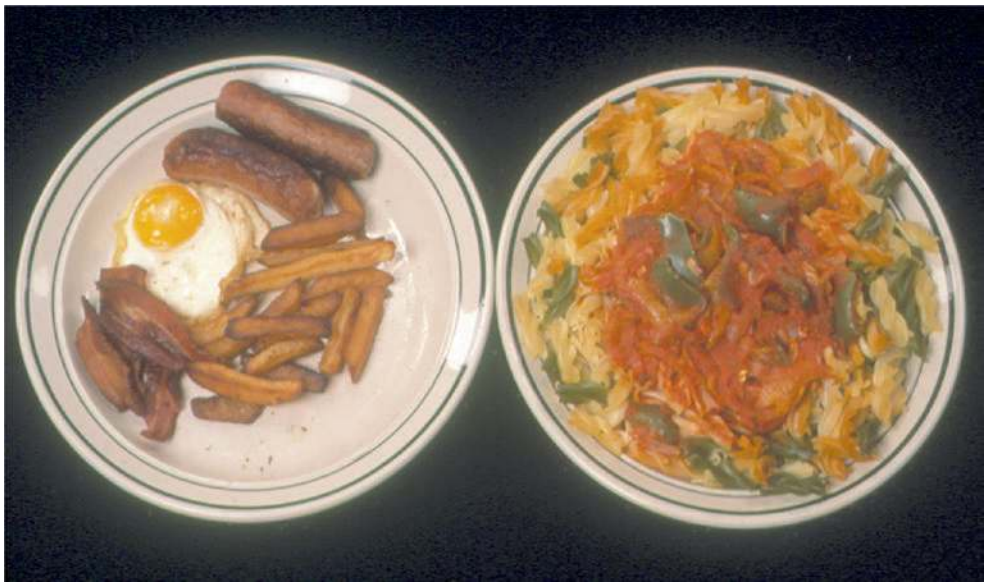

Fig. 1 Two 700 kcal meals. A high fat fried meal and a pasta meal. While the pasta meal is ideal for jejunum-colon patient it is a much larger volume so can be hard to consume

(four HPN). Whilst there was an increase in short chain fatty acid production ($p = 0.02$), there was no change in percentage energy ($p = 0.438$), carbohydrate ($p = 0.56$) or fat ($p = 0.22$) absorption, faecal wet weight ($p = 1.00$) or urine production ($p = 1.00$). There was a non-significant increase in gastric emptying and oro-colonic transit time. As the addition of soluble fibre did not enhance overall intestinal absorption, supplementation is not recommended in short bowel [4].

Lactose

Small bowel resection may cause secondary lactose intolerance due to reduced absorptive surface and shortened transit. Arrigoni et al. 1994 [63] randomised 17 patients with <150 cm small bowel (six jejunostomy, 11 jejunum-colon) to receive a 20 g lactose load from milk or yogurt after a 12 h fast, then measured faecal weight and carbohydrate excretion from lactose and hexose flow rates (stoma) or breath hydrogen excretion (colon) over the next 8 h. There were no clinical signs of intolerance or increase in faecal weight, but lactose was better absorbed from yogurt than milk (76% versus 50%, $p < 0.05$) in the stoma patients with no significant difference in colon patients.

In a follow-up study, Marteau et al. 1997 [64] studied a single 20 g lactose load in 14 fasted patients with <150 cm small bowel (six jejunostomy, eight jejunum-colon) and then randomised them to receive their usual diet plus either 20 g/d lactose or no lactose, each over 3 days, with an interval of 7 days in between. Lactose absorption from the single load was 61% and 53% in the stoma and colon patients respectively. There were no symptoms of intolerance and no differences in faecal weight between the lactose rich or lactose free diets in the stoma ($p = 0.36$) or colon ($p = 0.19$) patients. Since foods containing lactose provide a valuable source of energy, protein and calcium, they should not be restricted unless there is a clear association between lactose ingestion and increased diarrhoea [4].

Fat (Table 5)

Unlike carbohydrate and protein, long chain fatty acids (LCFAs) are only absorbed from the small bowel and their malabsorption in to colon results in steatorrhoea and a concomitant diarrhoea [65], that led to the use of a low-fat diet for symptomatic treatment after ileal resection [66].

Balance studies compared the effect of a high fat (100 g/day over two to four 4-day periods) versus low fat intake (40 g/day over 16–24 days) on stool output in 13 patients with diarrhoea post-ileal resection (ten ileal-colonic anastomosis, two active Crohn's disease and one ileostomy), who ate a constant energy and protein diet [67]. The low-fat diet reduced mean faecal fat excretion from 23 to 9 g/day with a marked reduction in faecal water and sodium excretion by 36% and 11% respectively, such that ten patients passed formed stool. There was a mean weight gain of 1.5 kg despite a lower energy intake during the study (mean 2420 kcal) compared with usual intake (mean 3290 kcal). However, it is not known whether these patients had a true short bowel and the reduction in fat was accompanied by an increase in protein and carbohydrate intake, which may have influenced colonic absorption.

A follow-up study in nine of these patients found that the low-fat diet increased absorption of magnesium (not significant), calcium ($p < 0.01$) and zinc ($p < 0.01$), although interpretation is limited by the higher mineral content of the

low-fat diet, which occurred as a consequence of its increased protein content [68].

In their comparison of a low fat (20%), high-carbohydrate (60%) versus high-fat (60%) low-carbohydrate (20%) diet in eight patients with 50–245 cm small bowel to colon Nordgaard et al. 1994 [61] found that fecal fat excretion increased from 44 to 75% as dietary fat intake increased and this accounted for differences in faecal loss of energy.

Whilst a low-fat diet decreases steatorrhoea/diarrhoea, calcium, magnesium and zinc losses and oxalate absorption [69], it may have the adverse effect of reducing food palatability and oral energy intake as it is less energy dense than comparable weights of carbohydrate. In practice, patients should be supported to find a balance between including fat for energy and avoiding steatorrhoea. Symptomatic patients who report pale, oily stools that float and are difficult to flush, may benefit from reducing intake of high fat foods and changing to lower fat products and cooking methods. The combination of severe fat malabsorption (>25–50% of dietary fat intake) [70] and a low-fat diet [71] may increase the risk of essential fatty acid deficiency, so these patients should consume fats that are rich in essential fatty acids [71]. They should be monitored for clinical signs of deficiency (dry flaky skin), which may be prevented or treated by cutaneous application of sunflower oil [72] or safflower oil [73]. These patients are also at risk of developing fat soluble vitamin deficiency [71, 74] so require oral supplementation, often at above recommended doses to compensate for malabsorption, with regular monitoring for clinical signs of deficiency and trends in serum concentrations [4, 27].

Medium-Chain Triglycerides (MCTs) (Table 5)

MCTs are rapidly absorbed by passive diffusion from the small bowel into the portal system, without the need for cholecystokinin, pancreatic enzymes or bile [75], so may be beneficial in patients with a short bowel. Early case reports noted that the substitution of long chain fatty acids (LCT) with MCT reduced steatorrhoea and supported weight gain [76–78], whilst colonic absorption of MCT was reported in animal studies [79].

Jeppesen et al. 1998 [79] investigated colonic absorption of MCT in 19 small bowel resected patients (six jejunostomy and three ileostomies, mean small bowel length 203 cm; ten jejunum-colon, mean small bowel length 143 cm), who were randomised and crossed over between two isocaloric (10 MJ (2390 kcal)) high fat diets containing 50% of energy from LCT or a 50% substitution of LCT with MCT, each over 3 days. Jejunum-colon patients absorbed MCTs considerably better than those with a stoma. In jejunum-colon patients, faecal excretion of MCT was negligible suggesting almost complete (>90%) absorption of MCT even when LCT was malabsorbed. The replacement of half LCT with MCT increased fat (MCT + LCT) absorption from 23 to 58% ($p < 0.001$) and increased bomb calorimetric energy absorption from 46 to 58% of dietary intake ($p = 0.02$) corresponding to 1.308 MJ (313 kcal)/day, with no significant increase in faecal volume. In stoma patients, MCT increased fat absorption from 37 to 46% ($p = 0.05$), but did not improve overall energy absorption because there was a concomitant decrease in protein and carbohydrate absorption, possibly related to increased stoma volume (2177 to 2729 g/day; $p = 0.07$). It was postulated that MCTs are water-soluble so may be absorbed from the colon in a similar way to short chain fatty acids (SCFAs) and may therefore provide an alternative energy source for jejunum-colon patients, particularly in those struggling with satiety or wind on a high carbohydrate diet or who are at the borderline of requiring PN [4].

MCTs are unsuitable as the sole source of fat as they do not contain essential fatty acids or fat-soluble vitamins, but may be used to partially replace LCTs through the inclusion of natural food sources like coconut or palm kernel oil, commercial MCT oil preparations or ONS with a high MCT content. MCT containing products should be introduced slowly in divided doses to prevent gastrointestinal symptoms like abdominal discomfort, bloating or diarrhoea [75].

Management or Prevention of Complications in Jejunum- Colon Patients

D-Lactic Acidosis

Although conservation of colon is beneficial, its presence is associated with the extremely rare occurrence of D-lactic acidosis (DLA). A systematic review identified 98 original case reports published between 1977 and 2017 in patients aged 7 months to 86 years [80]. It is associated with the rapid degradation of large quantities of unabsorbed carbohydrate in individuals with an altered colonic microbiota that increases D-lactate production, leading to faecal accumulation, increased concentrations in blood and urine, metabolic acidosis and neurological symptoms.

Lactic acid has two optical isomers, L- and D-lactate, which are metabolized to or produced from pyruvate by isomer specific enzymes, L-lactate dehydrogenase (L-LDH) and D-lactate dehydrogenase (D-LDH). Human cells lack D-LDH but do contain L-LDH so the primary isomer formed during anaerobic glycolysis is L-lactate, although small quantities of D-lactate are produced via the methylglyoxal pathway [81], which are metabolized to pyruvate by the enzyme D-2-hydroxyacid-dehydrogenase (D-2-HDH) [82, 83] located mainly in liver and kidney or excreted in urine [84] so blood concentrations normally remain low. However, colonic bacteria can produce both L- and/or D-lactate depending on the L-LDH and D-LDH content of bacterial species [85] and the

presence of DL-lactate racemase, which converts one lactate isomer to the other [85]. Both isomers may be degraded to SCFAs [85, 86], absorbed in to the circulation [87] or excreted in the stool so do not usually accumulate as their production does not exceed metabolism [88].

In jejunum-colon patients, the bacterial degradation of large amounts of unabsorbed carbohydrate increases organic acid production, which leads to a progressive decrease in intraluminal pH, favouring the growth of acid-resistant, lactate generating bacteria [85, 89] with increased numbers of the Lactobacillus/Leuconostoc group and reduced numbers and diversity of Clostridium and Bacteroides [90, 91]. If D-lactate producing bacteria become predominant, then degradation of large amounts of carbohydrate, particularly readily fermentable simple sugars, increase D-lactate production, leading to accumulation and raised concentrations in blood and urine [92]. Other contributory factors include the use of antibiotics [90, 93, 94] or probiotics [95, 96] that alter the intestinal flora to promote D-lactate-producing bacteria [80], a reduction in intestinal bacteria able to convert D-lactate to SCFAs [92], decreased metabolism due to inhibition of D-2-HDH by reduced pH [83] or hyperoxaluria [83] and reduced renal excretion due to impaired renal function or hypoperfusion secondary dehydration [97, 98].

The occurrence of DLA is unpredictable and may reflect an imbalance between microbial formation and the individual's ability to metabolise D-lactic acid [85, 97, 98]. Mayeur et al. 2013 [99] investigated the microbiota imbalance in 16 short bowel patients (<150 cm jejunum in continuity with colon) who had been stable for 2 years and found two subtypes: those who had no detectable lactate (44%) and those who accumulated D- and L-lactate in faeces (56%). Patients who did not accumulate lactate or who preferentially accumulated L-lactate had never developed DLA, whereas those with a high faecal D/L-lactate ratio and low plasma bicarbonate values had an increased risk of developing DLA. It was concluded that the D/L faecal lactate ratio may provide a better index of imbalanced microbiota and higher DLA risk than D- and L-lactate faecal concentrations per se.

DLA presents with neurological symptoms including impaired alertness, ataxia, gait disturbances, weakness, slurred speech, deep rapid breathing (Kussmal breathing), confusion, nausea or vomiting, blurred vision, nystagmus, aggressive or inappropriate behavior and stupor that may progress to coma [80, 98, 100] and a metabolic acidosis with an increased serum anion gap that is confirmed by increased concentrations of D-lactate in blood and urine, while L-lactate is often normal [97, 98].

Whilst neurological symptoms are attributed to elevated D-lactate concentrations, there is poor correlation between the onset or severity of symptoms and plasma concentrations [101, 102]. In normal subjects, the infusion of D-lactate to produce comparable plasma concentrations to those found in DLA did not cause neurological symptoms [87, 97, 103] and other types of acidosis of comparable or greater severity do not cause such symptoms [98]. It has been hypothesized that noxious substances produced during colonic fermentation like aldehydes, alcohols, mercaptans and amines may act as false neurotransmitters to cause neurological symptoms [88] or that inhibition of pyruvate dehydrogenase (PDH) by thiamine deficiency [104] or low intraneuronal pH from D-lactate accumulation may affect pyruvate metabolism by altering neurotransmitter production and neurological functioning [105].

Acute episodes of DLA are treated with parenteral bicarbonate to correct acidosis [89, 106], rehydration with lactate free crystalloids [100] to optimize renal excretion of D-lactate [92], carbohydrate restriction to decrease the substrate available for further D-lactate production [106, 107], non-absorbable broad-spectrum oral antibiotics to reduce D-lactate producing bacteria [1], thiamine repletion to increase PDH availability for pyruvate metabolism [92] or haemodialysis to clear both isomers in severe D-lactate toxicity [108]. Temporary fasting is associated with a rise in serum bicarbonate and fall in serum and urine D-lactate levels within 72 h [109] that allows rapid improvement in encephalopathy. Malnourished patients may be given short-term PN during fasting, as calories derived primarily from carbohydrate or lipid had no significant effect on either acid or D-lactate concentrations [110].

However, the prevention of repeated episodes is more challenging. Simple sugars should be restricted with substitution of modest amounts of slowly digestible, less easily fermentable polysaccharides to limit the substrate available for bacterial fermentation [85, 106, 109]. Serum D-lactate concentrations rise through the day to peak after the last evening meal and then fall during the night to their lowest concentration just before the first morning meal, so consuming modest amounts of carbohydrate over 4–6 small meals will lower peak serum concentrations [111]. Overnight EN should be used with caution as it will prevent the usual decline in serum D-lactate concentrations and thereby increase acidosis risk [111].

Maintaining adequate hydration supports renal clearance of D-lactate, so the usual dietary and pharmacological measures to reduce stool output should be emphasized [92]. The inhibition of D-2-HDH activity by hyperoxaluria may be reduced by consumption of a low oxalate, moderate fat diet in conjunction with calcium supplements to bind dietary oxalate [92].

Recurrent DLA symptoms may be prevented by a rotating course of oral antibiotics, although efficacy varies widely. Alternatively, some patients may take antibiotics when they recognize early neurological disturbances to prevent the development of encephalopathy [92]. However, antibiotic therapy can induce DLA by promoting overgrowth of D-

lactate producing organisms, which may be prevented though selection of appropriately targeted therapy using stool culture antimicrobial sensitivities [93, 94]. Long-term use may promote antibiotic resistance, so probiotics have been tried as an alternative therapeutic option [112]. Depending on the supplemented strains, there are reports of DLA being induced [95, 96] or prevented by probiotics [112–115] or synbiotics [116, 117]. More recently the microbiological analysis of stool facilitated the selection of a strain-specific non-D-lactate producing daily probiotic that prevented further episodes of DLA in a 4-year-old boy with short bowel [112]. There is a need for randomized controlled trials to test strain-specific effects and to determine the duration and frequency of probiotic use [118]. If dietary and medical therapies fail, then surgical strategies such as intestinal lengthening [85] or colonic resection may be considered whilst promising results from fecal transplantation have been reported [119, 120].

Calcium Oxalate Renal Stones

In contrast to short bowel patients with a jejunostomy, those with less than 200 cm jejunum in continuity with colon have a 25% increased risk of developing symptomatic calcium oxalate renal stones, which develop at a median of 30 months (range 2–67) post-surgery due to increased colonic oxalate absorption leading to hyperoxaluria [13] (chapter "Nephrolithiasis and Nephrocalcinosis").

Urinary oxalate is derived from the diet, endogenous production (metabolism of glycine, glycolate, hydroxyproline and synthesis from glyoxylate) and breakdown of ascorbic acid [121]. Normally less than 10% is derived from diet [122] but this may increase up to 50% depending on oxalate intake, its bioavailability, the presence of oxalate-binding cations and oxalate-degrading bacteria and gastrointestinal absorption [123, 124]. Oxalic acid is present in plant foods including nuts, fruits, vegetables, grains and legumes as soluble (sodium or potassium oxalate) or insoluble (calcium or magnesium oxalate) salts that may be absorbed throughout the gastrointestinal tract by active or passive mechanisms [125]. Since oxalate cannot be further metabolised, it is excreted in urine with a peak 2–4 h after ingestion, suggesting that small intestine is a key absorptive site and that oxalate rich foods can induce transient hyperoxaluria that may not be noticed in 24-h urine samples [126, 127].

In health, urinary supersaturation is affected by solute concentration, ionic strength, pH value and the presence of promotors (calcium, sodium, oxalate, low urine volume and low urine pH) or inhibitors (citrate, magnesium, phosphonates and other organic substances) of stone formation, which may vary during the day depending on fluid intake, dietary intake and body metabolism [128, 129]. Urine is often supersaturated with respect to calcium oxalate in a metastable solution that is prone to precipitate upon small increases in oxalate concentration [128] and higher oxalate concentrations substantially increase the risk of nucleation, growth and aggregation of kidney stones [130]. Nephrolithiasis results in renal colic, obstructive uropathy (which may cause irreversible renal damage), urinary tract infection, (which in the presence of obstruction may cause pyonephrosis) and rarely nephrocalcinosis with progressive renal impairment [131].

The association between hyperoxaluria, ileal resection and increased oxalate absorption was first demonstrated by Chadwick et al. 1973 [132] who measured urinary excretion of the isotope ^{14}C oxalate taken with food. Ileal-resected patients absorbed up to five times more oxalate than control subjects but oxalate excretion returned to normal with a low oxalate semi-synthetic diet (<4 mg oxalate per 24 h). Extensive ileal resection (≥100 cm compared with <50 cm) was associated with increased urinary oxalate excretion and there was a direct correlation between fat malabsorption and urinary oxalate excretion such that increasing dietary fat further increased urinary oxalate excretion [133].

Steatorrhoea was associated with increased colonic absorption of dietary oxalate [134–136], especially in the distal colon [137]. Calcium and oxalate normally form an insoluble complex that is passed in the stool, but ileal resection results in malabsorption of free fatty acids in to the colon, where they bind with calcium to release soluble oxalate for absorption [138]. Both free fatty acids and unabsorbed bile acids increase colonic permeability to oxalate, thereby facilitating its absorption [139]. An infusion of chenodeoxycholate in to the colon increased oxalate absorption fivefold [140], whilst cholestyramine (a bile-salt binding drug) taken orally reduced oxalate absorption [132, 141]. Colonic oxalate absorption is increased by low dietary calcium, hyperparathyroidism and vitamin D administration, all of which reduce calcium concentration in the colon and thus the extent to which oxalate is bound to calcium in the gut lumen [131, 135, 142–145].

Oxalate absorption may be reduced by the presence of intestinal bacteria able to metabolise oxalate including 'generalist oxalotrophs' like bifidobacterium and lactobacillus that degrade other carbon sources as well as oxalate and 'specialist oxalotrophs' like Oxalobacter formigenes which is a commensal anaerobe that metabolises only oxalate [146]. Treatment with antibiotics markedly reduces colonisation with Oxalobacter formigenes [147–149]; it is cultured less frequently from the stools of patients with Crohn's disease or steatorrhoea [150] and its growth is inhibited by low bile acid concentrations [151], all of which may contribute to increased oxalate absorption and nephrolithiasis in jejunum-colon patients. A study of 37 idiopathic calcium oxalate stone formers (excluding enteric hyperoxaluria) found that colonisation with oxalobacter formigenes was associated

with a reduced risk of calcium oxalate stone formation and a significantly lower urinary oxalate excretion compared with non-colonised patients whilst on a controlled diet [152].

The concentration of lithogenic substances in urine is determined by the excretion rate of calcium and oxalate and independently by the excretion of water [131]. Jejunum-colon patients who experience bowel frequency may become dehydrated with a reduced urinary volume, which increases calcium and oxalate concentrations and makes nucleation more likely to occur.

Prevention of Calcium-Oxalate Stones from Enteric Hyperoxaluria

The incidence of calcium-oxalate stones may be reduced by restriction of dietary oxalate and fat in conjunction with adequate oral calcium to reduce oxalate absorption and maintenance of hydration to achieve adequate urine volume.

Reduction of Dietary Oxalate and Fat

The restriction of dietary oxalate and fat intake in metabolic studies of enteric hyperoxaluria [69, 132, 134, 153] reduced urinary oxalate excretion but this has never been confirmed by randomised controlled trial [131, 154]. Holmes et al. 2016 [155] cited that loading studies in normal subjects consuming controlled oxalate and calcium diets found that increasing oral oxalate from 100 to 750 mg/day increased urinary oxalate by 2 mg per 100 mg of oxalate consumed [123, 156]. Calcium-oxalate stone formers with hyperoxaluria had a 36% reduction in urinary oxalate excretion when they consumed a low oxalate (80–100 mg/day) and normal calcium (1000 mg/day) diet [157].

Both clinical investigation and dietary advice have been hampered by inadequate or inaccurate data on the oxalate content of foods and variations in its bioavailability and gastrointestinal absorption [123]. Differences in oxalate values for a single food may reflect the analytical technique, with methods utilising colorimetric [158, 159] or enzymatic [160] assays reported to be less specific or reproducible than high performance capillary electrophoresis and ion chromatography [161, 162].

Accuracy is further limited by variation in amount of oxalate synthesized by the plant due to cultivar, growing conditions and time of harvest [163]. The amount of oxalate absorbed from a food is affected by its salt form (oxalate absorption is proportional to the amount of soluble oxalate [164]), food processing and cooking methods (boiling vegetables reduced oxalate content by 30% due to loss of soluble oxalate [165]) and meal composition (simultaneous consumption of calcium and magnesium reduced oxalate absorption by formation of insoluble salts [124, 166]), gastrointestinal transit time, the presence of oxalate degrading bacteria in the large bowel [161, 162] and inherited capacity to absorb oxalate [167].

As there is no definitive information on the oxalate content of foods or their effect on urinary excretion and oxalate rich meals may cause a transient rise in renal oxalate load that is amplified by increased intestinal absorption [123, 168], it is reasonable to advise jejunum-colon patients to reduce hyperoxaluria by avoiding foods that are high in oxalate [124, 154] including spinach, rhubarb, beetroot, wholemeal bread, bran-containing cereals, black tea, chocolate, cocoa, nuts, beans, soybeans and soy products. If individual patients require more specific dietary advice, then dietitians should select food analyses based on reliable methods and use averages for the food concerned [124, 169]. Regular dietary counselling at clinic visits significantly reduced urinary oxalate by 55.5% in 137 patients with urolithiasis risk, managed initially with only dietary intervention [170].

Whilst fat restriction is theoretically helpful, it may not be desirable for nutritional reasons, so patients should be supported to moderate their fat intake to reduce steatorrhoea and thus limit hyperoxaluria. Substitution with MCTs may be helpful in reducing oxalate absorption [138].

Adequate Dietary Calcium

Studies in patients with ileal disease or resection and jejuno-ileal bypass found that the degree of hyperoxaluria correlated directly with severity of steatorrhoea and inversely with dietary calcium content [135, 138]. High calcium diets [135] and oral calcium supplements [143–145] reduced oxalate absorption and urinary oxalate excretion, although this has never been confirmed by randomised controlled trial [131, 154].

A loading study in twelve healthy volunteers consuming a controlled oxalate diet (250 mg oxalate/day) found that reducing calcium from 1002 to 391 mg increased urinary oxalate excretion by a mean of 28.2% [123]. Another study in eight healthy volunteers consuming a controlled diet (2500 kcal, 83 g protein, 63 mg oxalate) found oxalate absorption depended linearly on calcium intake with mean oxalate absorption decreasing from 17 to 2.6% as calcium intake increased from 200 to 1200 mg/day. Within this range, an increase in calcium supply by 70 mg decreased oxalate absorption by 1% and vice versa. Calcium addition beyond 1200 mg/day reduced oxalate absorption only one-tenth as effectively [171].

The American Urological Association guidelines [154] note that large prospective epidemiological studies found an increased risk of stone formation with lower calcium diets [172–174] whilst higher calcium diets were associated with reduced oxalate excretion [175]. When the recommended daily quantity of dietary calcium was consumed, calcium oxalate stone risk was not significantly affected despite a relatively high dietary oxalate intake [176]. However, supplemental calcium was associated with an increased risk of stone formation in older women [172], but not younger

women and men [174]. The discrepancy between risks associated with dietary calcium and supplemental calcium may be due to the timing of calcium supplement intake and/or overzealous supplementation resulting in excessive total calcium [177].

A randomized controlled trial in recurrent hypercalciuric calcium oxalate stone formers, not known to have enteric hyperoxaluria or bowel resection, reported a 51% reduction in stone recurrence in men consuming a normal calcium (1200 mg/day), lower sodium (1200 mg/day) and animal protein (52 g/day) diet compared with a low calcium diet (400 mg/day) at 5 years [178]. Oxalate consumption was thought to be similar in both groups as they were advised to restrict intake of oxalate-rich foods. Although urinary calcium declined in both groups, urinary oxalate increased in the lower calcium group and decreased in the normal calcium group. However, it is not possible to determine the independent effect of calcium due to the use of a multicomponent diet [154, 179].

Consequently jejunum-colon patients should be advised to consume calcium in line with dietary recommendations [154, 179] from either dairy or non-dairy sources [180]. If dietary intake is inadequate, then calcium supplements in doses not exceeding 1000–1200 mg daily [154] may be taken with meals to enhance gastrointestinal binding of oxalate [135, 144, 145, 181].

Prevention of Dehydration

In health, fluid intake is the main determinant of urine volume and as such a high fluid intake is a critical component of stone prevention. Observational studies found that higher fluid intake reduces the risk of stone formation [172, 174, 182], whilst a randomized controlled trial found reduced stone recurrence rates among recurrent calcium oxalate stone formers randomized to a high fluid intake compared with a comparable group given no specific recommendations (12% versus 27%, respectively at 5 years) [183]. Although there is no definitive threshold for urine volume and increased risk, stone formers are generally recommended to take a fluid intake that will achieve a urine volume of at least 2.5 L daily [154, 179]. However, a high fluid intake may increase stool frequency in jejunum-colon patients, so their hydration and urine output should be optimised through dietary and pharmacological measures to reduce stool output although some may require parenteral fluid support.

Probiotics

Small studies have assessed the use of oral probiotics containing oxalobacter in primary hyperoxaluria [184–186] or different combinations of lactobacillus, bifidobacterium, enterococcus and other oxalate degraders [157, 187–192]. They found promising but mixed results, in part due to transient reductions in urinary oxalate excretion that were reversed when probiotic treatment was stopped; the use of different probiotic preparations containing multiple bacterial strains that varied in their administration with meals and variations in the control of dietary factors that might confound probiotic-induced effects [193]. Research in this field is still in its early stages and more work is required to determine the exact strain and dose and validate oxalate-targeting probiotics.

Vitamin C

Ingested vitamin C is partly converted to oxalate and excreted in urine, which may increase the risk of calcium oxalate stone formation and a metabolic study in 47 stone formers found that supplementation with 1- or 2-g vitamin C increased mean urinary oxalate by 61% and 41% respectively [194]. In a large epidemiological study, total and supplemental intake of ≥1000 mg/day vitamin C was significantly associated with a higher risk of incident kidney stones in men, but not among women [195], but there was no association with dietary vitamin C in any cohort. Whilst it may not be generalizable to women, it is prudent to advise avoidance of vitamin C supplements [154].

Dietary Treatment for Patients with a Jejunostomy

Macronutrient Absorption

Carbohydrate Versus Fat (Table 5)

Since protein and carbohydrate are mostly absorbed from the first 200 cm of jejunum [196] and fat malabsorption is increased by ileal resection and bile salt deficiency [197], jejunostomy patients were historically advised to take a low fat, high carbohydrate diet to improve absorption [66]. However, reducing fat intake may compromise energy intake and increasing carbohydrate, particularly from simple sugars, may increase intestinal luminal osmolality and thus stomal fluid losses [198, 199].

The potential for a higher fat intake to improve energy absorption without increasing jejunal losses was first suggested by Simko et al. 1980 [200] who measured fat absorption from three isocaloric, isonitrogenous liquid formula diets (3850 kcal/24 h) with varying proportions of fat and carbohydrate in a patient with a jejunostomy at 137 cm. Although fat losses increased proportionately with increasing intake, the percentage fat absorption remained remarkably constant irrespective of dietary intake. Increasing dietary fat from 64 to 200 g/day, with a reciprocal decrease in carbohydrate from 759 to 453 g/day, led to a linear increase in fat absorption from 44 to 133 g/day ($r = 0.99$) without shortening intestinal transit time, increasing stool weight or causing undesirable side effects. Continuation of the high fat

diet led to 16 kg weight gain over 12 months and discontinuation of parenteral fluids and electrolytes.

Woolf et al. 1983 [201] investigated absorption in eight patients (five jejunostomy, three jejuno-transverse colon), who were maintained on isocaloric, isonitrogenous diets with constant fluid and fibre content, but randomised and crossed over between a high fat, low carbohydrate diet (60:20% energy) or a low fat, high carbohydrate diet (20:60% energy), each over 5 days. There were no significant differences in total energy, percentage fat or protein plus carbohydrate absorption, stool weight or absorption of calcium, magnesium and zinc between the two diets. Faecal fat excretion was three times higher on high fat than low fat diet, but there was no difference in the proportion of ingested fat that was absorbed. As the low-fat diet conferred no benefits in calorie, fluid or divalent cation absorption, it was concluded that dietary fat should not be restricted. However, these results were reported as a mean of the two anatomical types of short bowel, which may limit their application.

Ovesen et al. 1983 [199] evaluated the effect of fat versus carbohydrate as an energy source and the effect of substituting saturated with polyunsaturated fat on the absorption of fat, fluid, sodium, potassium, calcium, magnesium, zinc and copper in five jejunostomy patients (35–125 cm jejunum), stable on HPN. They were randomised to receive three isocaloric, isonitrogenous diets: one low fat (30% kcal), high complex carbohydrate (55% kcal), and two high fat (60% kcal), low carbohydrate (25% kcal) diets with differing polyunsaturated: saturated fatty acid ratios of 1:4 or 1:1, each over 9 days, with collection of excreta on the last two. Although the high fat diet increased steatorrhoea, neither the type nor amount of dietary fat had any consistent effect on jejunostomy volume or fat absorption (40–45%), raising the possibility of greater net energy absorption from high fat, but this could not be confirmed as carbohydrate absorption was not measured. The sodium and potassium concentration of the jejunostomy fluid stayed constant, suggesting that losses reflected jejunostomy volume rather than the fat or carbohydrate content of the diet. However, the high fat diet did increase stomal losses of calcium, magnesium, zinc and copper, which in most cases were converted to net absorption by the low fat, high carbohydrate diet. Altering the polyunsaturated/saturated fatty acid ratio had no effect on divalent cation losses. It was concluded that patients should be advised to either reduce their fat intake or receive supplementation to achieve adequate cation status.

McIntyre et al. 1986 [202] measured absorption in four patients with a jejunostomy (60–150 cm jejunum), who were randomised and crossed-over between three diets, which contained equivalent quantities of nitrogen, calories, electrolytes and minerals but varying amounts of fat and fibre to provide high fat/high fibre, reduced fat/high fibre or reduced fat/normal fibre intakes, each over 2–3 days. There were no significant differences in energy, nitrogen or fat absorption or weight of stoma effluent between the three diets. The high fat diet led to a non-significant increase in faecal fat excretion, but did not increase jejunostomy effluent or sodium, potassium, calcium or magnesium losses. There was no detriment with a high fibre diet compared with a normal fibre diet. It was concluded that a liberal attitude towards fat and fibre intake was acceptable in patients with a high jejunostomy.

In their comparison of a high carbohydrate, low fat (60:20% of energy) versus low carbohydrate, high fat (20:60%) diet in six patients with 100–250 cm small bowel to a jejunostomy maintained on isocaloric diets (10.6 MJ (2533 kcal)/day, 20% protein), Nordgaard et al. 1994 [61] found no significant difference in energy excretion between high carbohydrate (4.8 MJ/day) and high fat diets (5.9 MJ/day; $p = 0.08$) with carbohydrate and fat excretions proportional to the amounts ingested. Energy absorption was similar between the high carbohydrate (55%) and high fat (48%) diets ($p = 0.21$). However, the high carbohydrate diet increased stomal effluents by mean 732 mL/day ($p = 0.10$) compared with the high fat diet. Beverage intakes were similar (3154 versus 2880 mL for high carbohydrate and high fat respectively) but the higher water content of the high carbohydrate (1420 mL/day) compared with the high fat diet (717 mL/day; $p = 0.0003$) resulted in a higher fluid intake of about 1000 mL/day, which may have implications for fluid management.

In a 3-day balance study of macronutrient absorption in 90 patients with <200 cm small bowel who received a constant diet that replicated their usual intake (Table 3), Crenn et al. 2004 [39] reported that fat absorption was significantly related to jejunal length ($p < 0.01$). In the twelve jejunostomy patients, the amount of fat absorbed was dependent on fat intake ($p < 0.001$) without an upper threshold, supporting the promotion of a non-limited fat intake for these patients

Thus, fat restriction did not improve energy, fluid or monovalent electrolyte absorption in jejunostomy patients [61, 199, 202]. Since a constant proportion of dietary fat is absorbed [39, 61, 199, 202], jejunostomy patients should be encouraged to take a higher fat diet to increase energy absorption, reduce dietary osmolality and provide essential fatty acids. Whilst this does raise fat excretion, it does not usually increase stomal output nor make it more offensive [61, 199, 202]. However, a high fat diet may reduce absorption of divalent cations such as calcium, magnesium, zinc and copper [199] and malabsorption increases the risk of essential fatty acid [70] and fat-soluble vitamin deficiencies [71, 74] so these should also be monitored and supplemented as required [4, 27].

MCTs (Table 5)

In contrast to patients with a retained colon, the 50% substitution of LCT with MCT in jejunostomy patients [79] increased fat absorption from 37 to 46% ($p = 0.05$), but did not improve overall energy absorption because MCT significantly decreased absorption of protein from 63 to 51% ($p < 0.05$); carbohydrate from 71 to 63% ($p < 0.05$), LCT from 35 to 27% ($p < 0.05$) and increased stoma volumes from 2177 to 2729 g/day ($p = 0.07$) and is therefore not recommended.

Fluid and Electrolyte Management

Jejunostomy patients lose large volumes of fluid from their stoma, which increase after eating and drinking due to loss of digestive secretions secondary gastric hypersecretion, rapid gastric emptying and accelerated small bowel transit. Each 1 L of jejunostomy fluid contains approximately 100 mmol/L of sodium [9] so sodium losses rise with stoma volume, increasing the risk of dehydration and electrolyte disturbances. Patients with less than 100 cm jejunum to a stoma usually have intestinal fluid and sodium losses that exceed oral intake, leading to a constant negative balance that requires correction with long term parenteral replacement, whilst those with more than 100 cm residual jejunum may have lower intestinal losses but still lose considerable amounts of fluid and sodium, which require replacement [9]. Dietary management with a high salt diet, restriction of oral hypotonic fluids and substitution of an oral rehydration solution to decrease stoma losses in conjunction with anti-secretory medication to decrease gastric secretions and anti-motility medications to slow transit and improve absorption may secure intestinal autonomy in those with intestinal insufficiency or reduce parenteral dependency in those with intestinal failure.

High Salt Diet

Patients with intestinal outputs of <1200 mL/day can usually maintain fluid and sodium balance by taking high salt foods, adding salt in cooking or to food after serving, to utilise the coupled absorption of sodium with glucose and amino acids in the jejunum [1, 203].

Restrict Oral Hypotonic Fluids

The jejunal mucosa is very permeable to water and sodium fluxes, which maintain intra-luminal contents iso-osmolar with plasma at approximately 300 mOsm/L with a sodium concentration of about 100 mmol/L [9]. Consumption of hyperosmolar fluids such as fruit juices, fizzy or energy drinks, alcoholic beverages [204] and some ONS supplements increase intraluminal osmolality, leading to movement of water from plasma into the intestinal lumen to restore iso-osmolality [4, 205]. Hypotonic fluids with a sodium concentration of <90 mmol/L like water, tea, coffee, squash, milk, juice, fizzy and alcoholic beverages dilute intraluminal sodium concentration leading to secretion of sodium to maintain luminal concentration at 100 mmol/L [206–208]. The loss of this sodium rich fluid in jejunostomy effluent results in dehydration and sodium depletion [9]. Patients often describe an 'insatiable thirst' and their natural response is to drink more fluid [4], which may mistakenly be reinforced by health professionals, but this literally washes sodium out of the body creating a vicious cycle of chronic dehydration and excessive beverage intake [207–211].

Absorption of sodium from the jejunum can only take place against a small concentration gradient, when the luminal concentration is 90–120 mmol/L [206, 210, 212] and depends on water movement and the presence of glucose and amino acids to promote absorption by solvent drag [203]. A study of fluid and electrolyte absorption in seven patients with <150 cm small bowel to a stoma found that ingestion of 500 mL of water or tea resulted in negative sodium and fluid balance whereas 500 mL of an oral rehydration solution containing 90 mmol/L of sodium led to positive sodium and fluid balance [208]. Patients with marginally high stoma losses in the range of 1200–2000 mL can maintain hydration by restricting oral hypotonic fluids to 1 L to decrease net secretion with substitution of 1 L of an oral rehydration solution containing 90–120 mmol/L sodium to meet fluid requirements and promote jejunal absorption [1, 208, 211]. They should avoid hyperosmolar fluids [213] and adherence with hypotonic fluid restriction may be encouraged by use of smaller cups or glasses, sucking sweets, ice cubes or lollies, self-monitoring of intake and strategies that distract from thirst.

If patients are struggling with severe thirst and marked sodium/water depletion, it may be difficult to replace previous losses with an oral regimen, but equilibrium can be re-established by placing them 'nil by mouth' whilst giving intravenous normal saline for 48 h [1]. This also helps to demonstrate that output is being driven by oral intake. Intravenous saline can then be gradually reduced as oral food and fluids are reintroduced.

Drink an Oral Rehydration Solution

Oral rehydration solutions have been formulated to provide optimal amounts of sodium in combination with glucose to facilitate absorption [1, 4]. A modification of the World Health Organisation's original cholera solution, which contains 90 mmol/L sodium, is made from 20 g glucose, 3.5 g sodium chloride and 2.5 g sodium bicarbonate made up to 1 L with water [214]. Although taste perception changes in patients who are salt and water deplete, some still find this

solution too salty but acceptance can be improved by chilling, sipping through a straw or flavouring with the addition of a small amount of squash or cordial as part of the fluid used to make up the solution. Patients should be discouraged from adding ice or flavouring to each glass as this dilutes the sodium concentration, making it less effective [215, 216]. Alternate solutions include replacing sodium bicarbonate with sodium citrate to increase palatability [211] or giving Dioralyte®, made at double the normal strength (10 sachets made up to 1 L), which contains 120 mmol/L sodium and 40 mmol/L potassium and therefore requires monitoring to prevent hyperkalaemia [217]. Patients should sip 1 L in small quantities throughout the day, perhaps with medications in order to preserve their hypotonic fluid allowance for more pleasurable drinking. It should be noted that many sports drinks have suboptimal sodium-glucose composition so do not provide an effective alternative to oral rehydration solutions [215, 218]. Alternatively, sodium chloride capsules (500 mg) are effective when taken in large amounts (7 g/day) but can cause patients to feel sick and even vomit [211].

It is vital to give individualised and consistent advice to aid patient understanding, motivation and compliance. Chronic dehydration may result in renal impairment so patients should be taught to monitor their urine colour in conjunction with signs and symptoms of dehydration and given management strategies together with health professional contact details for advice. It is equally important to educate health professionals about oral fluid and electrolyte management so that they can give consistent advice and provide appropriate rapid intravenous fluid and electrolyte replacement when required.

Timing of Antimotility Medications

Loperamide and codeine phosphate reduce intestinal motility and thus decrease water and sodium output by approximately 20–30% [1]. Since the intestinal output rises after meals, it is important that these medications are taken 30–60 min before food and at bedtime. If they emerge unchanged in the stoma effluent, then capsules can be opened or tablets crushed and mixed with water, yogurt or put on food [1].

Separation of Food and Fluids

Loss of the ileal and colonic braking mechanisms results in rapid gastric emptying of liquid [20] so taking fluids separately from food may improve absorption. However, a balance study in eight short bowel patients (five jejunostomy; three jejunum-colon) who received isocaloric diets with a constant fluid content and were randomized and crossed over between taking fluid with meals or restricting fluid intake from 1 h before to 1 h after meals, each over 5 days, found no difference in energy, divalent cation, fluid or electrolyte absorption [58]. Whilst some patients anecdotally report a benefit, the advice to restrict fluid intake with meals is not recommended as a general rule [4].

Fibre

Reducing fibre intake may slow transit to allow more time for absorption, but a randomized crossover study in four jejunostomy patients receiving isocaloric diets with variable amounts of fat and fibre, each over 2–3 days found no significant improvement in absorption and a liberal approach to fibre intake was recommended [202]. However, rapid transit does lead to the appearance of undigested foods in stoma effluent and patients anecdotally report a reduction in intestinal output with reduced fibre [217] from bread, pasta, crackers, biscuits or cakes made with white flour, white rice, refined breakfast cereals, small portions of well cooked, mashed or stewed fruit and vegetables with skins, seeds, pips and stalks removed, small portions of pulses if vegetarian and avoidance of nuts and dried fruits. A low fibre diet is recommended to prevent obstructive symptoms in patients with strictures or adhesions [217].

Oral Nutritional Support Supplements

Protein: Polymeric, Peptide or Elemental?

Patients who find it difficult to maintain adequate nutritional intake from diet may increase their energy and protein intake from orak nutritional support (ONS) taken in between meals (Table 6). It was postulated that partially digested proteins in the form of peptides (semi-elemental) or amino acids (elemental) may be more completely absorbed across a reduced absorptive surface than whole protein (polymeric) diets.

In a randomised controlled study, McIntyre et al. 1986 [202] compared absorption of energy, nitrogen, fat and electrolytes from equal volumes of isocaloric, isonitrogenous semi-elemental versus polymeric liquid diet in seven patients with <150 cm jejunum to a jejunostomy. Each diet was taken over 12–14 h, either as a sip feed (five patients) or by slow continuous nasogastric infusion (two patients). Two patients were unable to tolerate full quantities of either diet and their measurements were conducted using 50% of the recommended intake. There were no significant differences in nitrogen, fat or energy absorption and neither diet significantly reduced stoma effluent weight nor consistently affected sodium, potassium, magnesium or calcium losses, suggesting that semi-elemental provides no nutritional advantage over polymeric diet.

Cosnes et al. 1992 [219] investigated the effect of protein hydrolysis on absorption in six patients with a jejunostomy (90–150 cm jejunum), who had been stable on polymeric EN for at least 2 weeks, prior to being randomized and crossed

Table 6 Studies of the effect of ONS/enteral formula protein composition on nutrient absorption in patients with a short bowel

Reference	Subjects	Mean residual small bowel length (cm), (range)	Method	Diet composition	Effect on energy absorption	Effect on nitrogen absorption	Effect on water and sodium absorption	Effect on divalent cation absorption
Jejunostomy								
McIntyre et al. 1986 [202]	7 Jejunostomy (2HPN 1HPF 2NG 2oral)	101 (60–150)	RCT, crossover, each patient acted as own control	Two liquid diets based on body weight and standardized to contain equal amounts of nitrogen, fluid and sodium (constant 100 mmol/d) in each test period • Polymeric (6 g Nitrogen, 1060 kcal, 37 g fat (LCT) and 146 g CHO/L) • Semi-elemental (6.4 g Nitrogen, 1000 kcal, 10 g fat (LCT: MCT 50:50%) and 183 g CHO/L) Each over 12–14 h by sip feed (5) or NG (2) Due to poor tolerance, tests completed on consumption of half quantities in two patients	None	None	None	None for Ca and Mg
Cosnes et al. 1992 [219]	6 Jejunostomy (6 NG)	110 (90–150)	RCT, crossover double blind	Three liquid diets (3325 kcal, 146 g protein, 130 g fat, 395–470 g CHO, 2500 mL and 300 mmol sodium per day) with varying protein hydrolysis • Polymeric (osmolality 580 mOsmol/L) • Mixed polymeric: semi-elemental 50:50% (osmolality 610 mOsmol/L) • Semi-elemental (osmolality 667 mOsmol/L) Each over 22 h/d by NG for 3 days (last 2 days test period). Nil orally except approximately 1 L water. 5 patients received 1–2 L ileocolonic infusion of saline to maintain Na balance	None % Energy absorption Polymeric: semi-elemental 56.8: 57% (NS)	↑ Nitrogen absorption from semi-elemental compared with polymeric 14.3:10.9 g/day P = 0.012	None	None for Ca and Mg

HPN home parenteral nutrition, *HPF* home parenteral fluid, *NG* nasogastric, *cm* centimetre, *RCT* randomized controlled trial, *mmol* millimole, *d* day, *g* gramme, *kcal* kilocalorie, *LCT* long chain fatty acid, *MCT* medium chain fatty acid, *CHO* carbohydrate, *L* litre, *%* percentage, *mL* millilitre, *mOsm/L* milliosmole/litre, *NS* not significant, *Ca* calcium, *Mg* magnesium

over between exclusive polymeric, semi-elemental or a 50:50 mixture of polymeric and semi-elemental. Nitrogen was significantly better absorbed from peptide (14.3 g/day) than whole protein diet (10.9 g/day), (p = 0.012), but there were no differences in absorption of fat or calories, stool weight or faecal excretions of sodium, potassium, calcium and magnesium. The osmolality of the peptide diet was high (667 mOsm/L) but stool output was increased in only one patient. It was concluded that a semi-elemental diet may be beneficial when nitrogen requirements are high.

Since polymeric ONS are more palatable, lower in osmolality and have a higher energy density than elemental formulae, they are less likely to increase stoma losses and therefore recommended in jejunostomy patients who require nutrition support [4].

Fibre

Rodrigues et al. 1989 [220] investigated the effect of fibre containing ONS on 6-h intestinal transit, energy, water and sodium absorption in six patients with 30–120 cm jejunum (four jejunostomy, one jejunum-colon to colostomy, one jejunal-rectal anastomosis) who fasted overnight and were randomized to drink either 300 mL polymeric diet or 300 mL polymeric diet containing 6 g soy polysaccharide (40% soluble fibre). Soy polysaccharide decreased percentage energy absorption from 20 to 6% in the four patients measured. It delayed transit time in three of four patients from 66 to 166 min (postulated to be due to a delay in gastric emptying, although this was not measured), but increased 6-h wet weight (895 to 917 g) and sodium output (89 to 136 mmol) in four of five patients. Thus, fibre enriched ONS are not recommended [4].

Osmolality

Although ONS provide a ready source of energy, protein and micronutrients, they are hypotonic and many are hyperosmolar, which will increase sodium and fluid movement into the bowel and increase stoma losses. Osmolality is a measure of millimoles of solutes per kg of solvent [221]. ONS osmolality is influenced by particle size and increased by electrolyte, amino acid/peptide or sugar but not fat content. Rud et al. 2019 [222] investigated the effect of ONS osmolality on stoma output, urine production and natriuresis in eight patients with an ileostomy (150–350 cm residual small bowel) who ate their habitual diet and were advised to maintain a constant fluid intake. They were randomised and crossed over to replace 800 mL of their daily fluid intake with 200 mL four times per day of either an iso-osmolar (279 mOsm/kg) or hyperosmolar (681 mOsm/kg) oral supplement, each over 48 h in two study periods. There were no significant changes in stoma output, despite increased fluid intake, but in comparison with the hyperosmolar supplement, the iso-osmolar supplement induced a significant increase in urine volume (470 mL/day, $p = 0.02$) and natriuresis (36 mmol/day, $p = 0.02$), suggesting improved intestinal water and sodium absorption. Whilst iso-osmolar ONS may benefit hydration, their lower energy density will compromise energy intake. In practice, patients may be offered a 1.5 kcal/mL polymeric, fibre free supplement to maximise nutritional intake within a lower volume, but if the higher osmolality increases intestinal losses, then a 1 kcal/mL supplement with a lower osmolality (approximately 300 mOsm/kg) or a lower volume, modular energy/protein supplement may be offered. ONS should be sipped slowly in between meals and their low sodium content necessitates their inclusion within any hypotonic fluid restriction.

Role of Education and Individualised Dietary Advice

Patient education and motivation are important factors in determining the success of the PN weaning [223]. A lack of understanding may lead to sub-optimal management with potential clinical consequences [224] and a study in short bowel patients on HPN, who had not received dietary education, found dietary patterns that were likely to worsen diarrhoea, cause malnutrition (or prevent repletion) and increase parenteral fluid and nutrient requirements [60]. It is recommended that short bowel patients receive education from an experienced multidisciplinary team, using a combination of written information and verbal education to improve understanding of the physiological changes associated with short bowel, the rationale for dietary and pharmacological therapies [223] and intensive dietary guidance on suitable types and quantities of food/beverages, tailored to individual gastrointestinal anatomy, lifestyle, requirements and preferences to aid compliance, which is adjusted in response to changing needs [225].

The effectiveness of personalised nutrition advice supported by a booklet (containing information about the condition, eating/drinking advice, medication use and long-term monitoring), on knowledge and clinical outcomes was evaluated over 3–6 months in 48 patients with intestinal failure [224]. Patient knowledge improved significantly after dietetic intervention with verbal and written advice ($p < 0.001$). There was an increase in oral energy ($p = 0.04$) and fat ($p = 0.003$) intake with an improvement in BMI ($p = 0.02$). Patients on HPN showed a reduction in parenteral energy ($p = 0.02$), nitrogen ($p = 0.003$), volume ($p = 0.02$) and frequency of infusions ($p = 0.003$). This study demonstrated that personalised nutritional advice in conjunction with an information booklet, tailored to individual requirements, significantly improved knowledge and clinical outcomes, highlighting the positive effect of on-going education in stable intestinal failure patients.

Micronutrients

Parenteral multivitamin and multi-trace element preparations are formulated to meet the requirements of most patients receiving PN [45, 226], but abnormal serum micronutrients concentrations continue to be reported [227], highlighting the potential variation in individual requirements with oral intake, nutritional status, underlying illness, sepsis, inflammation, oxidative stress, absorptive capacity and abnormal losses [45]. Patients with short bowel have an increased risk of developing micronutrient deficiencies due to their underlying condition, fat malabsorption, high stoma/fistula or stool losses or inadequate intake. Optimising diet, fluid intake and medications may permit adequate macronutrient absorption to allow PN weaning, but it cannot be assumed that micronutrient intake or intestinal absorption will be sufficient to maintain adequate body stores or function [228].

A study in short bowel patients on HPN found low micronutrient consumption in association with avoidance of foods that may increase stool losses (dairy products, vegetables) and reduced dietary variety [60].

Short bowel patients receiving intermittent PN with a prescribed oral multivitamin and mineral supplement were deficient in vitamin D [74] and had serum concentrations below the reference range for vitamins E [74, 229], A, C [229] and copper [230], although interpretation is difficult as clinical deficiency symptoms were not reported.

A study of 44 patients with intestinal insufficiency and varying degrees of fat malabsorption not requiring HPN (160–250 cm residual small bowel; 17 no colon), found reduced plasma retinol, α- and γ-tocopherol concentrations in 7%, 61% and 32% of patients, which were rarely associated with clinical symptoms, so it was difficult to interpret their significance, but the authors concluded that supplementation may be required [71].

Vitamin D status and bone mineral density (BMD) were measured in 60 short bowel patients (residual small bowel length 89.6 cm) after weaning off PN (80% oral diet, 20% enteral nutrition) [231]. All patients had suboptimal vitamin D status (5% vitamin D insufficiency and 95% vitamin D deficiency), which was significantly correlated with residual small bowel length (B, 0.072, $p = 0.001$) and duration of short bowel (B, −0.066, $p = 0.020$). Only 2 patients had a normal BMD with osteopenia and osteoporosis present in 68.3% and 28.3% respectively. Despite routine oral vitamin D supplementation (1200 IU/day), 86.7% of patients did not achieve satisfactory status, emphasizing the importance of regular vitamin D monitoring, annual BMD measurements [4], advice on diet and sunlight exposure and consideration of alternative methods of supplementation such as intramuscular administration of vitamin D after PN weaning.

A 9-day balance study in five jejunostomy patients (35–125 cm jejunum), stable on HPN found that a high fat (60% kcal), low carbohydrate (25% kcal) diet increased stomal losses of calcium, magnesium, zinc and copper, which in most cases were converted to net absorption by a low fat (30% kcal), high carbohydrate (55% kcal) highlighting the importance of monitoring and supplementation in patients with fat malabsorption [199].

A 5-day balance study in seven short bowel patients (mean 64 (40–110) cm healthy small bowel in continuity with colon) who had been stable on diet mean 2.7 years found normal serum concentrations and positive balance for iron, zinc and copper suggesting that satisfactory status can be achieved from oral diet [232].

In short bowel, guidelines for micronutrient prescription and monitoring are based on expert opinion [4, 226], necessitating the development of local protocols until more robust evidence becomes available. Micronutrient deficiencies may be prevented by regular monitoring during PN weaning and in those stable on diet, with or without intravenous fluid/electrolyte infusions. Key aspects of management include (1) the promotion of a balanced diet, guided by individual tolerance, which may require periodic adjustment as the bowel adapts (2) optimisation of absorption through dietary, fluid and pharmaceutical management (3) the provision of an oral general multivitamin and mineral supplement during PN weaning, which may need to be given in doses above those recommended for healthy individuals to compensate for malabsorption [223] (4) if a deficiency arises, then the route of delivery, dose and duration of supplementation should be guided by the patient's bowel anatomy and individual characteristics [4] in conjunction with manufacturer's guidance.

Conclusion

Nutritional management is a dynamic process that involves overlap or transition between PN, EN and diet, in response to changes in the patient's condition and intestinal adaptation. The consequences of dietary manipulations, not only on nutrient, electrolyte and fluid absorption, but also on overall quality of life and patient autonomy should be taken in to consideration. Dietary manipulations may affect diet palatability, satiety, abdominal discomfort or bloating and passing of wind, faecal consistency and incontinence. Some patients cope with the hyperphagia, large stool volumes, fatigue and chronic dehydration in order to avoid a life dominated by having a central line and the need for parenteral supplements.

Others see parenteral supplements as a place of refuge escaping the demands of constant hyperphagia, large stool volumes and abdominal discomfort.

References

1. Nightingale J, Woodward JM, on behalf of the Small Bowel and Nutrition Committee of the British Society of Gastroenterology. Guidelines for management of patients with a short bowel. Gut. 2006;55(Suppl 4):iv1–12.
2. Pironi L, Corcos O, Forbes A, Holst M, Joly F, Jonkers C, et al. Intestinal failure in adults: recommendations from the ESPEN expert groups. Clin Nutr. 2018;37:1798–809.
3. National Confidential Enquiry into Patient Outcome and Death (NCEPOD). A mixed bag: an enquiry into the care of hospital patients receiving parenteral nutrition. 2010. https://www.ncepod.org.uk/2010report1/downloads/PN_report.pdf. Accessed 7 Apr 2018.
4. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35:247–307.
5. Jeppesen PB, Langholz E, Mortensen PB. Quality of life in patients receiving home parenteral nutrition. Gut. 1999;44:844–52.
6. Huisman-de Waal G, Schoonhoven L, Jansen J, Wanten G, van Achterberg T. The impact of home parenteral nutrition on daily life—a review. Clin Nutr. 2007;26:275–88.
7. Jeppesen PB. Spectrum of short bowel syndrome in adults: intestinal insufficiency to intestinal failure. J Parenter Enteral Nutr. 2014;38(Suppl 1):8S–13S.
8. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJG. Energy absorption as a measure of intestinal failure in the short bowel syndrome. Gut. 1989;30:176–83.
9. Nightingale JM, Lennard Jones JE, Walker ER, Farthing MJ. Jejunal efflux in short bowel syndrome. Lancet. 1990;336:765–8.
10. Jeppesen PB, Mortensen PB. Intestinal failure defined by measurements of intestinal energy and wet weight absorption. Gut. 2000;46:701–6.
11. Pironi L, Arends J, Baxter J, Bozzeti F, Peláez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34:171–80.
12. Gouttebel MC, Saint-Aubert B, Astre C, Joyeux H. Total parenteral nutrition needs in different types of short bowel syndrome. Dig Dis Sci. 1986;31:718–23.
13. Nightingale JM, Lennard Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces need for parenteral therapy, increases incidence of renal stones, but does not change high prevalence of gall stones in patients with a short bowel. Gut. 1992;33:1493–7.
14. Carbonnel F, Cosnes J, Chevret S, Beaugerie L, Ngô Y, Malafosse M, et al. The role of anatomic factors in nutritional autonomy after extensive small bowel resection. J Parenter Enteral Nutr. 1996;20:275–80.
15. Messing B, Crenn P, Beau P, Boutron-Rualt M, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology. 1999;117:1043–50.
16. Jeppesen PB, Mortensen PB. Significance of a preserved colon for parenteral energy requirements in patients receiving home parenteral nutrition. Scand J Gastroenterol. 1998;33:1175–9.
17. Tappenden KA. Intestinal adaptation following resection. J Parenter Enteral Nutr. 2014;38(Suppl 1):23S–31S.
18. Porus RL. Epithelial hyperplasia following massive small bowel resection in man. Gastroenterology. 1965;48:753–9.
19. De Francesco A, Malfi G, Delsedime L, David E, Pera A, Serra R, et al. Histological findings regarding jejunal mucosa in short bowel syndrome. Transplant Proc. 1994;26:1455–6.
20. Nightingale JMD, Kamm MA, van der Slip JRM, Morris GP, Walker ER, Mather SJ, et al. Disturbed gastric emptying in the short bowel. Evidence for a 'colonic brake'. Gut. 1993;34:1171–6.
21. Nightingale JM, Kamm MA, van der Sijp JR, Ghatei MA, Bloom SR, Lennard-Jones JE. Gastrointestinal hormones in short bowel syndrome. PYY may be the 'colonic brake' to gastric emptying. Gut. 1996;39:267–72.
22. Jeppesen PB, Hartmann B, Thulesen J, Hansen BS, Holst JJ, Poulsen SS, Mortensen PB. Elevated plasma glucagon-like peptide 1 and 2 concentrations in ileum resected short bowel patients with a preserved colon. Gut. 2000;47:370–6.
23. Althausen TL, Doig RK, Uyeyama K, Weiden S. Digestion and absorption after massive resection of the small intestine. II. Recovery of the absorptive function as shown by intestinal absorption tests in two patients and a consideration of compensatory mechanisms. Gastroenterology. 1950;16:126–39.
24. Dowling RH, Booth CC. Functional compensation after small-bowel resection in man. Demonstration by direct measurement. Lancet. 1966;2:146–7.
25. Cosnes J, Carbonnel F, Beaugerie L, Ollivier JM, Parc R, Gendre JP, et al. Functional adaptation after extensive small bowel resection in humans. Eur J Gastroenterol Hepatol. 1994;6:197–202.
26. Gouttebel MC, Saint Aubert B, Colette C, Astre C, Monnier LH, Joyeux H. Intestinal adaptation in patients with short bowel syndrome. Measurement by calcium absorption. Dig Dis Sci. 1989;34:709–15.
27. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel and intestinal transplantation. Gastroenterology. 2003;124:1111–34.
28. Amiot A, Messing B, Corcos O, Panis Y, Joly F. Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel. Clin Nutr. 2013;32:368–74.
29. Pironi L, Forbes A, Joly F, Colomb V, Lyszkowska M, Van Gossum A, et al. Survival of patients identified as candidates for intestinal transplantation: a 3-year prospective follow-up. Gastroenterology. 2008;135:61–71.
30. O'Keefe SJ, Jeppesen PB, Gilroy R, Perkiewicz M, Allard JP, Messing B. Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel syndrome-intestinal failure. Clin Gastroenterol Hepatol. 2013;11:815–23.
31. O'Keefe SJ, Haymond MW, Bennet WM, Oswald B, Nelson DK, Shorter RG. Long-acting somatostatin analogue therapy and protein metabolism in patients with jejunostomies. Gastroenterology. 1994;107:379–88.
32. Hill GL, Mair WSJ, Goligher JC. Impairment of 'ileostomy adaptation' in patients after ileal resection. Gut. 1974;15:982–7.
33. Jeppesen PB, Hartmann B, Hansen BS, Thulesen J, Holst JJ, Mortensen PB. Impaired meal stimulated glucagon-like peptide 2 response in ileal resected short bowel patients with intestinal failure. Gut. 1999;45:559–63.
34. Buchman AL, Moukarzel AA, Bhuta S, Belle M, Ament ME, Eckhert CD, et al. Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. J Parenter Enteral Nutr. 1995;19:453–60.
35. Guedon C, Schmitz J, Lerebours E, Metayer J, Audran E, Hemet J, et al. Decreased brush border hydrolase activities without gross morphologic changes in human intestinal mucosa after prolonged total parenteral nutrition of adults. Gastroenterology. 1986;90:373–8.
36. Kripke SA, Fox AD, Berman JM, Settle RG, Rombeau JL. Stimulation of intestinal mucosal growth with intracolonic infusion of short-chain fatty acids. J Parenter Enteral Nutr. 1989;13:109–16.

37. Nordgaard I, Hansen BS, Mortensen PB. Importance of colonic support for energy absorption as small-bowel failure proceeds. Am J Clin Nutr. 1996;64:222–31.
38. Atia A, Girard-Pipau F, Hébuterne X, Spies WG, Guardiola A, Ahn CW, et al. Macronutrient absorption characteristics in humans with short bowel syndrome and jejunocolonic anastomosis: starch is the most important carbohydrate substrate, although pectin supplementation may modestly enhance short chain fatty acid production and fluid absorption. J Parenter Enteral Nutr. 2011;35:229–40.
39. Crenn P, Morin MC, Joly F, Penven S, Thuillier F, Messing B. Net digestive absorption and adaptive hyperphagia in adult short bowel patients. Gut. 2004;53:1279–86.
40. Warner BW. The pathogenesis of resection-associated intestinal adaptation. Cell Mol Gastroenterol Hepatol. 2016;2:429–38.
41. Jeppesen PB. The use of hormonal factors to promote intestinal function in short bowel syndrome. In: Bozzetti F, Staun M, van Gossum A, editors. Home parenteral nutrition. 2nd ed. Oxfordshire: CABI; 2015. p. 419–33.
42. Nightingale JMD. The short bowel. In: Nightingale JMD, editor. Intestinal failure. London: Greenwich Medical Media; 2001. p. 179–98.
43. Culkin A. Nutrition support in intestinal failure. In: Hickson M, Smith S, editors. Advanced nutrition and dietetics in nutrition support. 1st ed. Chichester: Wiley Blackwell; 2018. p. 302–12.
44. Mercer-Smith G, Kirk C, Gemmell L, Mountford C, Nightingale J, Thompson N and the BIFA Committee. British Intestinal Failure Alliance (BIFA) Position Statement. Guidance on haematological and biochemical monitoring of adult patients receiving home parenteral nutrition. 2021. https://www.bapen.org.uk/pdfs/bifa/position-statements/position-statement-haematological-biochemical-monitoring-adult-hpn.pdf. Accessed 14 Mar 2021.
45. Blaauw R, Osland E, Sriram K, Ali A, Aard JP, Ball P, et al. Parenteral provision of micronutrients to adult patients: an expert consensus paper. J Parenter Enteral Nutr. 2019;43(Suppl 1):S5–S23.
46. Livingstone C. Fat-soluble vitamins in nutrition support. In: Hickson M, Smith S, editors. Advanced nutrition and dietetics in nutrition support. 1st ed. Chichester: Wiley Blackwell; 2018. p. 144–54.
47. Scottish Trace Element and Micronutrient Diagnostic and Research Laboratory. Copper. https://www.trace-elements.co.uk/copper.asp. Accessed 4 May 2021.
48. McMillan DC, Maguire D, Talwar D. Relationship between nutritional status and the systemic inflammatory response: micronutrients. Proc Nutr Soc. 2019;78:56–67.
49. Howard L. Folate and parenteral nutrition. Nutr Clin Pract. 2012;27(appendix 8):482–4.
50. Ford I, Farr J, Morris P, Berg J. The value of measuring serum cholesterol-adjusted vitamin E in routine practice. Ann Clin Biochem. 2006;43:130–4.
51. Maroulis J, Kalfarentzos F. Complications of parenteral nutrition at the end of the century. Clin Nutr. 2000;19:295–304.
52. Ladefoged K, ØLgaard K. Fluid and electrolyte absorption and renin-angiotensin-aldosterone axis in patients with severe short-bowel syndrome. Scand J Gastroenterol. 1979;14:729–35.
53. Nightingale JMD. The medical management of intestinal failure: methods to reduce the severity. Proc Nutr Soc. 2003;62:703–10.
54. Jonkers-Schuitema CF. Dietary care in home parenteral nutrition and intestinal failure. In: Bozzetti F, Staun M, Van Gossam A, editors. Home parenteral nutrition. 2nd ed. Oxfordshire: CABI; 2015. p. 349–60.
55. Cope J, Culkin A, Judges D, Marfrici B, Soulsby C, Weekes E. Estimating nutritional requirements for adults. In: Todorovic VE, Mafrici B, editors. A pocket guide to clinical nutrition. 5th ed. BDA: Birmingham; 2018. p. 3.1–3.98.
56. Araújo ECF, Suen VMM, Marchini JS, Vannucchi H. Ideal body weight better predicts resting energy expenditure than does actual body weight in patients with short bowel syndrome. Nutrition. 2007;23:778–81.
57. Culkin A. Intestinal failure and nutrition. In: Lomer M, editor. Advanced nutrition and dietetics in gastroenterology. Chichester: Wiley-Blackwell; 2014. p. 210–7.
58. Woolf GM, Miller C, Kurian R, Jeejeebhoy KN. Nutritional absorption in short bowel syndrome. Evaluation of fluid, calorie, and divalent cation requirements. Dig Dis Sci. 1987;32:8–15.
59. Messing B, Pigot F, Rongier M, Morin MC, Ndeïndoum U, Rambaud JC. Intestinal absorption of free oral hyperalimentation in the very short bowel syndrome. Gastroenterology. 1991;100:1502–8.
60. Estívariz CF, Luo M, Umeakunne K, Bazargan N, Galloway JR, Leader LM, Ziegler TR. Nutrient intake from habitual oral diet in patients with severe short bowel syndrome living in the Southeastern United States. Nutrition. 2008;24:330–9.
61. Nordgaard I, Hansen BS, Mortensen PB. Colon as a digestive organ in patients with short bowel. Lancet. 1994;343:373–6.
62. Royall D, Wolever TM, Jeejeebhoy KN. Evidence for colonic conservation of malabsorbed carbohydrate in short bowel syndrome. Am J Gastroenterol. 1992;87:751–6.
63. Arrigoni E, Marteau P, Briet F, Pochart P, Rambaud JC, Messing B. Tolerance and absorption of lactose from milk and yogurt during short-bowel syndrome in humans. Am J Clin Nutr. 1994;60:926–9.
64. Marteau P, Messing B, Arrigoni E, Breit F, Flourié B, Morin MC, Rambaud JC. Do patients with short-bowel syndrome need a lactose-free diet? Nutrition. 1997;13:13–6.
65. Kellock TD, Pearson JR, Russell RI, Walker JG, Wiggins HS. The incidence and clinical significance of faecal hydroxy fatty acids. Gut. 1969;10:1055.
66. Andersson H. The use of a low-fat diet in the symptomatic treatment of ileopathia. World Rev Nutr Diet. 1982;40:1–18.
67. Andersson H, Isaksson B, Sjögren B. Fat-reduced diet in the symptomatic treatment of small bowel disease. Gut. 1974;15:351–9.
68. Hessov I, Andersson H, Isaksson B. Effects of a low-fat diet on mineral absorption in small-bowel disease. Scand J Gastroenterol. 1983;18:551–4.
69. Andersson H, Jagenburg R. Fat-reduced diet in the treatment of hyperoxaluria in patients with ileopathy. Gut. 1974;15:360–6.
70. Jeppesen PB, Christensen MS, Høy CE, Mortensen PB. Essential fatty acid deficiency in patients with severe fat malabsorption. Am J Clin Nutr. 1997;65:837–43.
71. Jeppesen PB, Høy CE, Mortensen PB. Deficiencies of essential fatty acids, vitamin A and E and changes in plasma lipoproteins in patients with reduced fat absorption or intestinal failure. Eur J Clin Nutr. 2000;54:632–42.
72. Press M, Hartop PJ, Prottey C. Correction of essential fatty-acid deficiency in man by the cutaneous application of sunflower-seed oil. Lancet. 1974;1:597–8.
73. Miller DG, Williams SK, Palombo JD, Griffin RE, Bistrian BR, Blackburn GL. Cutaneous application of safflower oil in preventing essential fatty acid deficiency in patients on home parenteral nutrition. Am J Clin Nutr. 1987;46:419–23.
74. Braga CB, Vannucchi H, Freire CM, Marchini JS, Jordão AA Jr, da Cunha SF. Serum vitamins in adult patients with short bowel receiving intermittent parenteral nutrition. J Parenter Enteral Nutr. 2011;35:493–8.
75. Shah ND, Limketkai BN. The use of medium-chain triglycerides in gastrointestinal disorders. Pract Gastroenterol. 2017;XL1(2):20–8. https://med.virginia.edu/ginutrition/wp-content/uploads/sites/199/2014/06/Parrish-February-17.pdf. Accessed 18 Mar 2019.

76. Zurier RB, Campbell RG, Hashim SA, Van Itallie TB. Use of medium-chain triglyceride in management of patients with massive resection of the small intestine. N Engl J Med. 1966;274:490–3.
77. Bochenek W, Rodgers JB Jr, Balint JA. Effects of changes in dietary lipids on intestinal fluid loss in the short-bowel syndrome. Ann Intern Med. 1970;72:205–13.
78. Tandon RK, Rodgers JB Jr, Balint JA. The effects of medium-chain triglycerides in the short bowel syndrome. Increased glucose and water transport. Am J Dig Dis. 1972;17:233–8.
79. Jeppesen PB, Mortensen PB. The influence of a preserved colon on the absorption of medium-chain fat in patients with small bowel resection. Gut. 1998;43:478–83.
80. Bianchetti DGAM, Amelio GS, Lava SAG, Bianchetti MG, Simonetti GD, Agostoni C, et al. D-lactic acidosis in humans: systematic literature review. Pediatr Nephrol. 2018;33:673–81.
81. Thornalley PJ. The glyoxalase system: new developments towards functional characterization of a metabolic pathway fundamental to biological life. Biochem J. 1990;269:1–11.
82. Cammack R. Assay, purification and properties of mammalian d-2-hyroxy acid dehydrogenase. Biochem J. 1969;115:55–63.
83. Tubbs PK. The metabolism of D-alpha-hydroxy acids in animal tissues. Ann N Y Acad Sci. 1965;119:920–6.
84. Judge MA, van Eyes J. Excretion of D-lactic acid in humans. J Nutr. 1962;76:310–3.
85. Hove H, Mortensen PB. Colonic lactate metabolism and D-lactic acidosis. Dig Dis Sci. 1995;40:320–30.
86. Belenguer A, Holtrop G, Duncan SH, Anderson SE, Calder AG, Flint HJ, et al. Rates of production and utilization of lactate by microbial communities from the human colon. FEMS Microbiol Ecol. 2011;77:107–19.
87. De Vrese M, Koppenhoefer B, Barth CA. D-lactic acid metabolism after an oral load of DL-lactate. Clin Nutr. 1990;9:23–8.
88. Halperin ML, Kamel KS. D-lactic acidosis: turning sugar into acids in the gastrointestinal tract. Kidney Int. 1996;49:1–8.
89. Caldarini MI, Pons S, D'Agostino D, DePaula JA, Greco G, Negri G, et al. Abnormal fecal flora in a patient with short bowel syndrome. An in vitro study on effect of pH on D-lactic acid production. Dig Dis Sci. 1996;41:1649–52.
90. Bongaerts GP, Tolboom JJ, Naber AH, Sperl WJ, Severijnen RS, Bakkeren JA, et al. Role of bacteria in the pathogenesis of short bowel syndrome-associated D-lactic acidemia. Microb Pathog. 1997;22:285–93.
91. Joly F, Mayeur C, Bruneau A, Noordine ML, Meylheuc T, Langella P, et al. Drastic changes in fecal and mucosa-associated microbiota in adult patients with short bowel syndrome. Biochimie. 2010;92:753–61.
92. Petersen C. D-lactic acidosis. Nutr Clin Pract. 2005;20:634–45.
93. Flourie B, Messing B, Bismuth E, Etanchaud F, Thuillier F, Rambaud JC. D-lactic acidosis and encephalopathy in short-bowel syndrome occurring during antibiotic treatment. Gastroenterol Clin Biol. 1990;14:596–8.
94. Coronado BE, Opal SM, Yoburn DC. Antibiotic-induced D-lactic acidosis. Ann Intern Med. 1995;122:839–42.
95. Ku WH, Lau DCY, Huen KF. Probiotics provoked D-lactic acidosis in short bowel syndrome: case report and literature review. HK J Paediatr. 2006;11:246–54.
96. Munakata S, Arakawa C, Kohira R, Fujita Y, Fuchigami T, Mugishima H. A case of D-lactic acid encephalopathy associated with use of probiotics. Brain Dev. 2010;32:691–4.
97. Oh MS, Uribarri J, Alveranga D, Lazar I, Bazilinski N, Carroll HJ. Metabolic utilization and renal handling of D-lactate in men. Metabolism. 1985;34:621–5.
98. Uribarri J, Oh MS, Carroll HJ. D-lactic acidosis. A review of clinical presentation, biochemical features, and pathophysiologic mechanisms. Medicine (Baltimore). 1998;77:73–82.
99. Mayeur C, Gratadoux JJ, Bridonneau C, Chegdani F, Larroque B, Kapel N, et al. Faecal D/L lactate ratio is a metabolic signature of microbiota imbalance in patients with short bowel syndrome. PloS One. 2013;8(1):e54335. https://doi.org/10.1371/journal.pone.0054335.
100. Kowlgi NG, Chhabra L. D-lactic acidosis: an underrecognized complication of short bowel syndrome. Gastroenterol Res Pract. 2015;2015:476215. https://doi.org/10.1155/2015/476215.
101. Thurn JR, Pierpont GL, Ludvigsen CW, Eckfeldt JH. D-Lactate encephalopathy. Am J Med. 1985;79:717–21.
102. Bongaerts G, Tolboom J, Naber T, Bakkeren J, Severijnen R, Willems H. D-lactic acidemia and aciduria in pediatric and adult patients with short bowel syndrome. Clin Chem. 1995;41:107–10.
103. Connor H, Woods HF, Ledingham JGG. Comparison of the kinetics and utilisation of D (−)- and L (+)-sodium lactate in normal man. Ann Nutr Metab. 1983;27:481–7.
104. Hudson M, Pocknee R, Mowat NA. D-lactic acidosis in short bowel syndrome-an examination of possible mechanisms. Q J Med. 1990;74:157–63.
105. Vella A, Farrugia G. D-lactic acidosis: pathologic consequence of saprophytism. Mayo Clin Proc. 1998;73:451–6.
106. Mayne AJ, Handy DJ, Preece MA, George RH, Booth I. Dietary management of D-lactic acidosis in short bowel syndrome. Arch Dis Child. 1990;65:229–31.
107. Perlmutter DH, Boyle JT, Campos JM, Egler JM, Watkins JB. D-Lactic acidosis in children: an unusual metabolic complication of small bowel resection. J Pediatr. 1983;102:234–8.
108. Hingorani AD, Macdougall IC, Browne M, Walker RW, Tomson CR. Successful treatment of acute D-lactate encephalopathy by haemodialysis. Nephrol Dial Transplant. 1993;8:1283–5.
109. Ramakrishnan T, Stokes P. Beneficial effects of fasting and low carbohydrate diet in D-lactic acidosis associated with short-bowel syndrome. J Parenter Enteral Nutr. 1985;9:361–3.
110. Karton M, Rettmer RL, Lipkin EW. Effect of parenteral nutrition and enteral feeding on D-lactic acidosis in a patient with short bowel. J Parenter Enteral Nutr. 1987;11:586–9.
111. Bongaerts G, Bakkeren J, Severijnen R, Sperl W, Willems H, Naber T, et al. Lactobacilli and acidosis in children with short small bowel. J Pediatr Gastroenterol Nutr. 2000;30:288–93.
112. Yilmaz B, Schibli S, Macpherson AJ, Sokollik C. D-lactic acidosis: successful suppression of D-lactate-producing lactobacillus by probiotics. Pediatrics. 2018;142(3):e20180337. https://doi.org/10.1542/peds.2018-0337.
113. Vanderhoof JA, Young RJ. Use of probiotics in childhood gastrointestinal disorders. J Pediatr Gastroenterol Nutr. 1998;27:323–32.
114. Gavazzi C, Stacchiotti S, Cavalletti R, Lodi R. Confusion after antibiotics. Lancet. 2001;357:1410.
115. Uchida H, Yamamoto H, Kisaki Y, Fujino J, Ishimaru Y, Ikeda H. D-lactic acidosis in short-bowel syndrome managed with antibiotics and probiotics. J Pediatr Surg. 2004;39:634–6.
116. Kanamori Y, Hashizume K, Sugiyama M, Morotomi M, Yuki N. Combination therapy with Bifidobacterium breve, Lactobacillus casei, and galactooligosaccharides dramatically improved the intestinal function in a girl with short bowel syndrome: a novel synbiotics therapy for intestinal failure. Dig Dis Sci. 2001;46:2010–6.
117. Takahashi K, Terashima H, Kohno K, Ohkohchi N. A stand-alone synbiotic treatment for the prevention of D-lactic acidosis in short bowel syndrome. Int Surg. 2013;98:110–3.
118. Johnson E, Vu L, Matarese LE. Bacteria, bones, and stones: managing complications of short bowel syndrome. Nutr Clin Pract. 2018;33:454–66.
119. Davidovics ZH, Vance K, Etienne N, Hyams JS. Fecal transplantation successfully treats recurrent D-lactic acidosis in a child with short bowel syndrome. J Parenter Enteral Nutr. 2017;41:896–7.

120. Bulik-Sullivan EC, Roy S, Elliott RJ, Kassam Z, Lichtman SN, Carroll IM, et al. Intestinal microbial and metabolic alterations following successful fecal microbiota transplant for D-lactic acidosis. J Pediatr Gastroenterol Nutr. 2018;67:483–7.
121. Robijn S, Hoppe B, Vervaet BA, D'Haese PC, Verhulst A. Hyperoxaluria: a gut-kidney axis? Kidney Int. 2011;80:1146–58.
122. Finch AM, Kasidas GP, Rose GA. Urine composition in normal subjects after oral ingestion of oxalate-rich foods. Clin Sci (Lond). 1981;60:411–8.
123. Holmes RP, Goodman HO, Assimos DG. Contribution of dietary oxalate to urinary oxalate excretion. Kidney Int. 2001;59:270–6.
124. Massey LK. Food oxalate: factors affecting measurement, biological variation, and bioavailability. J Am Diet Assoc. 2007;107:1191–4.
125. Hatch M, Freel RW. Intestinal transport of an obdurate anion: oxalate. Urol Res. 2005;33:1–18.
126. Holmes RP, Ambrosius WT, Assimos DG. Dietary oxalate loads and renal oxalate handling. J Urol. 2005;174:943–7.
127. Knight J, Holmes RP, Assimos DG. Intestinal and renal handling of oxalate loads in normal individuals and stone formers. Urol Res. 2007;35:111–7.
128. Laube N, Berg W, Bernsmann F, Gravius S, Klein F, Latz S, et al. Induced urinary crystal formation as an analytical strategy for the prediction and monitoring of urolithiasis and other metabolism-related disorders. EPMA J. 2014;5:1–13.
129. Thomsett K. Kidney stones. In: Gandy J, editor. Manual of dietetic practice. 6th ed. Wiley Blackwell: Chichester; 2019. p. 545–53.
130. Curhan GC, Taylor EN. 24-h uric acid excretion and the risk of kidney stones. Kidney Int. 2008;73:489–96.
131. Tomson CRV. Nephrocalcinosis and nephrolithiasis. In: Nightingale JMD, editor. Intestinal failure. London: Greenwich Medical Media; 2001. p. 227–42.
132. Chadwick VS, Modha K, Dowling RH. Mechanism for hyperoxaluria in patients with ileal dysfunction. N Engl J Med. 1973;289:172–6.
133. Earnest DL, Johnson G, Williams HE, Admirand WH. Hyperoxaluria in patients with ileal resection: an abnormality in dietary oxalate absorption. Gastroenterology. 1974;66:1114–22.
134. Dobbins JW, Binder HJ. Importance of the colon in enteric hyperoxaluria. N Engl J Med. 1977;296:298–301.
135. Stauffer JQ. Hyperoxaluria and intestinal disease. The role of steatorrhea and dietary calcium in regulating intestinal oxalate absorption. Am J Dig Dis. 1977;22:921–8.
136. Hylander E, Jarnum S, Jensen HJ, Thale M. Enteric hyperoxaluria: dependence on small intestinal resection, colectomy, and steatorrhoea in chronic inflammatory bowel disease. Scand J Gastroenterol. 1978;13:577–88.
137. Modigliani R, Labayle D, Aymes C, Denvil R. Evidence for excessive absorption of oxalate by the colon in enteric hyperoxaluria. Scand J Gastroenterol. 1978;13:187–92.
138. Earnest DL, Williams HE, Admirand WH. A physicochemical basis for treatment of enteric hyperoxaluria. Trans Assoc Am Physicians. 1975;88:224–34.
139. Dobbins JW, Binder HJ. Effect of bile salts and fatty acids on the colonic absorption of oxalate. Gastroenterology. 1976;70:1096–100.
140. Fairclough PD, Feest TG, Chadwick VS, Clark ML. Effect of sodium chenodeoxycholate on oxalate absorption from the excluded human colon—a mechanism for 'enteric' hyperoxaluria. Gut. 1977;18:240–4.
141. Smith LH, Fromm H, Hofmann AF. Acquired hyperoxaluria, nephrolithiasis, and intestinal disease. Description of a syndrome. N Engl J Med. 1972;286:1371–5.
142. Zarembski PM, Hodgkinson A. Some factors influencing the urinary excretion of oxalic acid in man. Clin Chim Acta. 1969;25:1–10.
143. Caspary WF, Tönissen J, Lankisch PG. 'Enteral' hyperoxaluria. Effect of cholestyramine, calcium, neomycin, and bile acids on intestinal oxalate absorption in man. Acta Hepatogastroenterol. 1977;24:193–200.
144. Barilla DE, Notz C, Kennedy D, Pak CY. Renal oxalate excretion following oral oxalate loads in patients with ileal disease and with renal and absorptive hypercalciurias; effect of calcium and magnesium. Am J Med. 1978;64:579–85.
145. Hylander E, Jarnum S, Nielson K. Calcium treatment of enteric hyperoxaluria after jejunoileal bypass for morbid obesity. Scand J Gastroenterol. 1980;15:349–52.
146. Hatch M. Gut microbiota and oxalate homeostasis. Ann Transl Med. 2017;5:36. https://doi.org/10.21037/atm.2016.12.70.
147. Sidhu H, Hoppe B, Hesse A, Tenbrock K, Brömme S, Rietschel E, et al. Absence of Oxalobacter formigenes in cystic fibrosis patients: a risk factor for hyperoxaluria. Lancet. 1998;352:1026–9.
148. Kelly JP, Curhan GC, Cave DR, Anderson TE, Kaufman DW. Factors related to colonization with Oxalobacter formigenes in U.S. adults. J Endourol. 2011;25:673–9.
149. Kharlamb V, Schelker J, Francois F, Jiang J, Holmes RP, Goldfarb DS. Oral antibiotic treatment of Helicobacter pylori leads to persistently reduced intestinal colonization rates with Oxalobacter formigenes. J Endourol. 2011;25:1781–5.
150. Allison MJ, Cook HM, Milne DB, Gallagher S, Clayman RV. Oxalate degradation by gastrointestinal bacteria from humans. J Nutr. 1986;116:455–60.
151. Argenzio RA, Liacos JA, Allison MJ. Intestinal oxalate-degrading bacteria reduce oxalate absorption and toxicity in guinea pigs. J Nutr. 1988;118:787–92.
152. Siener R, Bangen U, Sidhu H, Hönow R, von Unruh G, Hesse A. The role of Oxalobacter formigenes colonization in calcium oxalate stone disease. Kidney Int. 2013;83:1144–9.
153. Hofmann AF, Laker MF, Dharmsathaphorn K, Sherr HP, Lorenzo D. Complex pathogenesis of hyperoxaluria after jejunoileal bypass surgery. Oxalogenic substances in diet contribute to urinary oxalate. Gastroenterology. 1983;84:293–300.
154. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, et al. Medical management of kidney stones: AUA guideline. J Urol. 2014;192:316–24.
155. Holmes RP, Knight J, Assimos DG. Lowering urinary oxalate excretion to decrease calcium oxalate stone disease. Urolithiasis. 2016;44:27–32.
156. Jiang J, Knight J, Easter LH, Neiberg R, Holmes RP, Assimos DG. Impact of dietary calcium and oxalate, and Oxalobacter formigenes colonization on urinary oxalate excretion. J Urol. 2011;186:135–9.
157. Lieske JC, Tremaine WJ, De Simone C, O'Connor HM, Li X, Bergstralh EJ, et al. Diet, but not oral probiotics, effectively reduces urinary oxalate excretion and calcium oxalate supersaturation. Kidney Int. 2010;78:1178–85.
158. Zarembski PM, Hodgkinson A. The oxalic acid content of English diets. Br J Nutr. 1962;16:627–34.
159. Hodgkinson A. Oxalic acid in biology and medicine. London: Academic; 1977. p. 159–211.
160. Kasidas GP, Rose GA. Oxalate content of some common foods: determination by an enzymatic method. J Hum Nutr. 1980;34:255–66.
161. Holmes RP, Goodman HO, Assimos DG. Dietary oxalate and its intestinal absorption. Scanning Microsc. 1995;9:1109–18.
162. Holmes RP, Kennedy M. Estimation of the oxalate content of foods and daily oxalate intake. Kidney Int. 2000;57:1662–7.

163. Libert B, Franceschi VR. Oxalate in crop plants. J Agric Food Chem. 1987;35:926–38.
164. Chai W, Liebman M. Assessment of oxalate absorption from almonds and black beans with and without the use of an extrinsic label. J Urol. 2004;172:953–7.
165. Chai W, Liebman M. Effect of different cooking methods on vegetable oxalate content. J Agric Food Chem. 2005;53:3027–30.
166. Liebman M, Costa G. Effects of calcium and magnesium on urinary oxalate excretion after oxalate loads. J Urol. 2000;163:1565–9.
167. Holmes RP, Assimos DG. Glyoxylate synthesis and its modulation and its influence on oxalate synthesis. J Urol. 1998;160:1617–24.
168. Hesse A, Schneeberger W, Engfeld S, Von Unruh GE, Sauerbruch T. Intestinal hyperabsorption of oxalate in calcium oxalate stone formers: application of a new test with [13C2] oxalate. J Am Soc Nephrol. 1999;10(Suppl 14):329–33.
169. Attalla K, De S, Monga M. Oxalate content of food: a tangled web. Urology. 2014;84:555–60.
170. Ortiz-Alvarado O, Miyaoka R, Kriedberg C, Moeding A, Stessman M, Anderson JK, et al. Impact of dietary counselling on urinary stone risk parameters in recurrent stone formers. J Endourol. 2011;25:535–40.
171. Von Unruh GE, Voss S, Sauerbruch T, Hesse A. Dependence of oxalate absorption on the daily calcium intake. J Am Soc Nephrol. 2004;15:1567–73.
172. Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med. 1997;126:497–504.
173. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. J Am Soc Nephrol. 2004;15:3225–32.
174. Curhan GC, Willett WC, Knight EL, Stampfer MJ. Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. Arch Intern Med. 2004;164:885–91.
175. Taylor EN, Curhan GC. Determinants of 24-hour urinary oxalate excretion. Clin J Am Soc Nephrol. 2008;3:1453–60.
176. Taylor EN, Curhan GC. Oxalate intake and the risk for nephrolithiasis. J Am Soc Nephrol. 2007;18:2198–204.
177. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669–83.
178. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, et al. A comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med. 2002;346:77–84.
179. National Institute for Health and Care Excellence. Renal and ureteric stones: assessment and management. Dietary interventions. 2019. https://www.nice.org.uk/guidance/ng118. Accessed 2 May 2020.
180. Taylor EN, Curhan GC. Dietary calcium from dairy and nondairy sources, and risk of symptomatic kidney stones. J Urol. 2013;190:1255–9.
181. Worcester EM. Stones from bowel disease. Endocrinol Metab Clin North Am. 2002;31:979–99.
182. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med. 1993;328:833–8.
183. Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. J Urol. 1996;155:839–43.
184. Hoppe B, Beck B, Gatter N, von Unruh G, Tischer A, Hesse A, et al. Oxalobacter formigenes: a potential tool for the treatment of primary hyperoxaluria type 1. Kidney Int. 2006;70:1305–11.
185. Hoppe B, Groothof JW, Hulton SA, Cochat P, Niaudet P, Kemper MJ, et al. Efficacy and safety of Oxalobacter formigenes to reduce urinary oxalate in primary hyperoxaluria. Nephrol Dial Transplant. 2011;26:3609–15.
186. Milliner D, Hoppe B, Groothoff J. A randomised phase II/III study to evaluate the efficacy and safety of orally administered Oxalobacter formigenes to treat primary hyperoxaluria. Urolithiasis. 2018;46:313–23.
187. Campieri C, Campieri M, Bertuzzi V, Swennen E, Matteuzzi D, Stefoni S, et al. Reduction of oxaluria after an oral course of lactic acid bacteria at high concentration. Kidney Int. 2001;60:1097–105.
188. Lieske JC, Goldfarb DS, De Simone C, Regnier C. Use of a probiotic to decrease enteric hyperoxaluria. Kidney Int. 2005;68:1244–9.
189. Goldfarb DS, Modersitzki F, Asplin JR. A randomized, controlled trial of lactic acid bacteria for idiopathic hyperoxaluria. Clin J Am Soc Nephrol. 2007;2:745–9.
190. Ferraz RRN, Marques NC, Froeder L, Menon VB, Siliano PR, Baxmann AC, et al. Effects of Lactobacillus casei and Bifidobacterium breve on urinary oxalate excretion in nephrolithiasis patients. Urol Res. 2009;37:95–100.
191. Okombo J, Liebman M. Probiotic-induced reduction of gastrointestinal oxalate absorption in healthy subjects. Urol Res. 2010;38:169–78.
192. Siener R, Bade DJ, Hesse A, Hoppe B. Dietary hyperoxaluria is not reduced by treatment with lactic acid bacteria. J Transl Med. 2013;11:306. https://doi.org/10.1186/1479-5876-11-306.
193. Liebman M, Al-Wahsh IA. Probiotics and other key determinants of dietary oxalate absorption. Adv Nutr. 2011;2:254–60.
194. Baxmann AC, de Mendonça C, Heilberg IP. Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. Kidney Int. 2003;63:1066–71.
195. Ferraro PM, Curhan GC, Gambaro G, Taylor EN. Total, dietary, and supplemental vitamin C intake and risk of incident kidney stones. Am J Kidney Dis. 2016;67:400–7.
196. Borgström B, Dahlqvist A, Lundh G, Sjövall J. Studies of intestinal digestion and absorption in the human. J Clin Invest. 1957;36:1521–36.
197. Hofmann AF, Poley JR. Role of bile acid malabsorption in pathogenesis of diarrhea and steatorrhea in patients with ileal resection. I. Response to cholestyramine or replacement of dietary long chain triglyceride by medium chain triglyceride. Gastroenterology. 1972;62:918–34.
198. Young EA. Editorial: Short bowel syndrome: high-fat versus high-carbohydrate diet. Gastroenterology. 1983;84:872–5.
199. Ovesen L, Chu R, Howard L. The influence of dietary fat on jejunostomy output in patients with severe short bowel syndrome. Am J Clin Nutr. 1983;38:270–7.
200. Simko V, McCarroll AM, Goodman S, Weesner RE, Kelley RE. High-fat diet in a short bowel syndrome. Intestinal absorption and gastroenteropancreatic hormone responses. Dig Dis Sci. 1980;25:333–9.
201. Woolf GM, Miller C, Kurian R, Jeejeebhoy KN. Diet for patients with a short bowel: high fat or high carbohydrate? Gastroenterology. 1983;84:823–8.
202. McIntyre PB, Fitchew M, Lennard Jones JE. Patients with a high jejunostomy do not need a special diet. Gastroenterology. 1986;91:25–33.
203. Fordtran JS, Rector FC Jr, Carter NW. The mechanism of sodium absorption in the human small intestine. J Clin Invest. 1968;47:884–900.
204. Wendland BE, Arbus GS. Oral fluid therapy: sodium and potassium content and osmolality of some commercial "clear" soups, juices and beverages. Can Med Assoc J. 1979;121:564–6, 568, 571.
205. Shi X, Passe DH. Water and solute absorption from carbohydrate-electrolyte solutions in the human proximal small intestine:

a review and statistical analysis. Int J Sport Nutr Exerc Metab. 2010;20:427–42.
206. Spiller RC, Jones BJ, Silk DB. Jejunal water and electrolyte absorption from two proprietary enteral feeds in man: importance of sodium content. Gut. 1987;28:681–7.
207. Newton CR, Drury P, Gonvers JJ, McIntyre P, Preston DM, Lennard-Jones JE. Incidence and treatment of sodium depletion in ileostomists. Scand J Gastroenterol Suppl. 1982;74:159–60.
208. Newton CR, Gonvers JJ, McIntyre PB, Preston DM, Lennard-Jones JE. Effect of different drinks on fluid and electrolyte losses from a jejunostomy. J R Soc Med. 1985;78:27–34.
209. Griffin GE, Fagan EF, Hodgson HJ, Chadwick VS. Enteral therapy in the management of massive gut resection complicated by chronic fluid and electrolyte depletion. Dig Dis Sci. 1982;27:902–8.
210. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJG. What is the ideal sodium concentration of oral rehydration solutions for short bowel patients? Clin Sci (Lond). 1988;74(suppl 18):69. https://doi.org/10.1042/cs074069Pa.
211. Nightingale JM, Lennard-Jones JE, Walker ER, Farthing MJ. Oral salt supplements to compensate for jejunostomy losses: comparison of sodium chloride capsules, glucose electrolyte solution, and glucose polymer electrolyte solution. Gut. 1992;33:759–61.
212. Sladen GE, Dawson AM. Inter-relationships between the absorption of glucose, sodium and water by the normal human jejunum. Clin Sci. 1969;36:119–32.
213. Matarese LE, O'Keefe SJ, Kandil HM, Bond G, Costa G, Abu-Elmagd K. Short bowel syndrome: clinical guidelines for nutritional management. Nutr Clin Pract. 2005;20:493–502.
214. Avery ME, Synder JD. Oral therapy for acute diarrhoea. The underused simple solution. N Engl J Med. 1990;323:891–4.
215. Williams J, Dart J, Van Heel D, Travis SPL. Effect of flavouring on isotonic solutions for short bowel syndrome. Gut. 2003;52(Suppl 1):A10.
216. Culkin A. Variability in the content of oral rehydration solutions used in intestinal failure may render it ineffective. Gut. 2012;61(Suppl 2):A84. https://doi.org/10.1136/gutjnl-2012-302514b.27.
217. Culkin A. Intestinal failure and intestinal resection. In: Gandy J, editor. Manual of dietetic practice. 6th ed. Wiley Blackwell: Chichester; 2019. p. 454–64.
218. Ukleja A, Scolapio JS. Abnormalities in fluid and electrolyte absorption in intestinal failure. In: Matarese LE, Steiger E, Seidner DL, editors. Intestinal failure and rehabilitation: a clinical guide. Boca Raton: CRC; 2005. p. 49–65.
219. Cosnes J, Evard D, Beaugerie L, Gendre JP, Le Quintrec Y. Improvement in protein absorption with a small-peptide-based diet in patients with high jejunostomy. Nutrition. 1992;8:406–11.
220. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJ. The effects of octreotide, soy polysaccharide, codeine and loperamide on nutrient, fluid and electrolyte absorption in the short-bowel syndrome. Aliment Pharmacol Ther. 1989;3:159–69.
221. Rasouli M. Basic concepts and practical equations on osmolality: biochemical approach. Clin Biochem. 2016;49:936–41.
222. Rud C, Pedersen AK, Wilkins TL, Borre M, Andersen JR, Moeller HB, et al. An iso-osmolar oral supplement increases natriuresis and does not increase stomal output in patients with an ileostomy: a randomised, double-blinded, active comparator, crossover intervention study. Clin Nutr. 2019;38:2079–86.
223. Di Baise JK, Matarese LE, Messing B, Steiger E. Strategies for parenteral nutrition weaning in adult patients with short bowel syndrome. J Clin Gastroenterol. 2006;40(Suppl 2):S94–8.
224. Culkin A, Gabe SM, Madden AM. Improving clinical outcome in patients with intestinal failure using individualised nutritional advice. J Hum Nutr Diet. 2009;22:290–8.
225. Matarese LE, Steiger E. Dietary and medical management of short bowel syndrome in adult patients. J Clin Gastroenterol. 2006;40(Suppl 2):S85–93.
226. Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, et al. ASPEN position paper: recommendations for changes in commercially available parenteral multi-vitamin and multi-trace element products. Nutr Clin Pract. 2012;27:440–91.
227. Pearson M, Brundrett D, Gabe S, Culkin A. Micronutrients: are our home parenteral nutrition patients getting enough? Clin Nutr. 2017;36:S51.
228. Shenkin A. Micronutrients in home parenteral nutrition. In: Bozzetti F, Staun M, Van Gossam A, editors. Home parenteral nutrition. 2nd ed. Oxfordshire: CABI; 2015. p. 286–300.
229. Ferreira IM, Braga CB, Dewulf N, Marchini JS, da Cunha SF. Vitamin serum level variations between cycles of intermittent parenteral nutrition in adult patients with short bowel syndrome. J Parenter Enteral Nutr. 2013;37:75–80.
230. Braga CB, Ferreira IM, Marchini JS, da Cunha SF. Copper and magnesium deficiencies in patients with short bowel syndrome receiving parenteral nutrition or oral feeding. Arq Gastroenterol. 2015;52:94–9.
231. Fan S, Ni X, Wang J, Zhang Y, Tao S, Kong W, et al. High prevalence of suboptimal vitamin D status and bone loss in adult short bowel syndrome even after weaning off parenteral nutrition. Nutr Clin Pract. 2017;32:258–65.
232. Engels LG, van den Hamer CJ, van Tongeren JH. Iron, zinc, and copper balance in short bowel patients on oral nutrition. Am J Clin Nutr. 1984;40:1038–41.

Pro-adaptive Hormones in the Rehabilitation of Adult Patients with a Short Bowel

Palle Bekker Jeppesen

Key Points

1. Pro-adaptive hormone treatment includes growth factors which aim is to promote and often exceed the normal structural adaptive process after a bowel resection.
2. Pro-adaptive hormonal treatment aims to reduce the symptoms (less stomal output/diarrhoea) and help reduce or stop the amount of parenteral support required (i.e. to reduce the severity of the intestinal failure). Goals may include a reduction in stomal output of more than 1.5 L/24 h, stopping or having more than 2 night off/week of parenteral support and having an improved quality of life.
3. Growth factors may be considered in patients with a short bowel and dependent upon parenteral support and/or:
   (a) Have had a functioning colon in continuity for at least a year to allow intestinal adaptation to occur. If no functioning colon is in circuit then adaptation will not occur and treatment can be considered sooner (at about 6 months) after the surgery that resulted in the jejunostomy.
   (b) Have no defunctioned small or large bowel that can be brought into continuity. Patients who are candidates for surgical reconstruction should have this surgery before growth factor therapy is considered.
   (c) Patients who have been stable on parenteral support for 1 year, with the volume, nutrient and electrolyte content of the parenteral support and oral intake being optimised prior to starting.
   (d) A patient who, with therapy, may be able to stop parenteral support.
   (e) Patients with an unmanageable high output (e.g. >2 L/24 h) and whose quality of life if poor. These are patients who can be weaned off or have days off PS.
   (f) Patients who with treatment may be able to have nights off parenteral support.
4. Growth factors have the disadvantages of both being expensive (though prices may reduce considerably in the future) and there is the fear that they may promote neoplasia (or increase the growth rate if neoplasia is already present).
5. Before growth factor treatment is given a baseline CT thorax, abdomen and pelvis is performed and in patients with a residual colon, a colonoscopy should be performed to detect and remove colorectal polyps.

Introduction

In normal subjects, a wide range of complex neuro-endocrine regulatory systems modulate the highly coordinated processes of appetite-regulation, food intake, digestion and absorption (i.e. assimilation) that ensure sufficient nutrient in- and uptake to meet the metabolic needs and ensure the metabolic homeostasis of life, thereby preserving body composition, function and the overall health.

Thus, a plethora of hormones, mediators and nerve transmissions are involved in securing the optimal intestinal function at all times. In fact, the intact and healthy gastrointestinal tract has a considerable reserve capacity for nutrient assimilation [1]. However, in patients with inadequate oral intake, intestinal diseases or increased metabolic needs, the nutritional homeostasis may be jeopardized, and malnutrition, dehydration or other deficiencies may develop [2]. Short Bowel Syndrome (SBS) patients with intestinal insufficiency (INS) have preserved oral or enteral autonomy and can compensate for maldigestion or malabsorption (i.e. malassimila-

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tion) by hyperphagia, by reduced physical activity and the body may adapt temporarily to this situation of "semi-starvation", even without suffering from organ impairment, by metabolic adaptation [3]. Patients with SBS and intestinal failure (IF) on the other hand need parenteral support (PS) to ensure the adequate provision of nutrients, fluid and/or electrolytes, to prevent permanent organ damage and ensure proper organ functions, avoid diseases and maintain life [4]. Based on the severity of the degree of malassimilation and the ability to compensate for this, SBS patients can be found within a spectrum ranging from mild, moderate and severe INS across a borderline to mild, moderate and severe IF [5].

Although the malassimilation seen in short bowel syndrome patients following intestinal resection is frequently mainly explained by the reduction in the remnant absorptive mucosal surface-area, it may also relate to detrimental pathophysiological changes in GI secretions (e.g. gastric and pancreatico-biliary), transit, blood-flow, mucosal function and even complex inter-organ communications (e.g. gut-brain and gut-liver axes). Depending on remnant bowel anatomy, the alterations in the meal-stimulated neuro-endocrine feedback mechanisms, caused by the associated under- or over-exposure of endocrine sensor-cells distributed throughout the gastrointestinal (GI) tract, may lead to a dysregulation and either impairment or a compensatory improvement of GI functions.

In general, given a more favourable remnant anatomy with more proximal bowel resection and preservation of the ileum and right-sided colon, positive neuro-endocrine feedback mechanisms may contribute to a "spontaneous intestinal adaptation", which is the process that gradually leads towards a restoration of the intestinal absorption to that pertaining before the intestinal resection. In contrast, distal ileal and right-sided colonic resections tend to favour a condition of GI hypersecretion, rapid transit, and a more severe malabsorption with less spontaneous adaptation [6].

Over the last decades, an increased awareness of the relationship between the heterogeneity and pathophysiological characteristics of SBS patients and the detrimental or beneficial neuro-endocrine changes following intestinal resection has emerged. Based on this knowledge and by the prospect of having potent analogues (agonist or even antagonists) of the relevant endogenously secreted GI hormones for clinical use, a paradigm shift from the empirically based general and symptomatic SBS treatments, consisting of off-label use of anti-diarrheal and anti-secretory agents, to an evidence-based, personalized, targeted and "pathophysiological-phenotype-driven" treatment has been recommended [7]. It is to be anticipated that a further understanding of the processes of importance for best possible assimilation will enhance our ability to intervene, when normal GI physiology is disturbed by intestinal resection. Thus, although the complexity of the normal gastrointestinal digestion and absorption far surpasses the complexity symphony performed by an orchestra, an increased understanding of the roles of the individual musicians and especially of the conductor and the main soloists in the performance will be of significant importance.

This chapter reviews the findings of from clinical trials that have aimed to identify, mimic or even surpass the key hormonal players in the spontaneous intestinal adaptation. Currently, these studies have mainly included the use of somatostatin, growth hormone, glucagon-like peptides or epidermal growth factor either as native hormones or analogues. However, since only the glucagon-like peptide 2 analog, teduglutide, has yet been approved as the first evidence-based drug for the long-term treatment of SBS, the effects of this peptide is the main focus of this chapter. Since the use of these pro-adaptive hormones is relatively new, and since more healthcare professionals outside the established centres of experience are likely to be using these agents in the future, some introductory, general suggestions to their use may be relevant.

In this chapter, the basis for the introduction of pro-adaptive factors in the clinical rehabilitation of SBS patients is summarised and an update of current knowledge and suggestions for future efforts is provided. In addition it recommends when a peptide growth factor may be considered in a patient with short bowel associated intestinal failure (SB-IF). To outline the pre-treatment process and the monitoring required, including when treatment should be stopped.

Theoretical and Practical Consideration Prior to Initiating Treatments

Aim of Treatment

The overall aim of any treatment in patients with SBS is to reduce potential SBS- and IF-symptoms and -complications thereby providing the best possible overall health-related quality of life and longevity in these patients.

Due to the large heterogeneity in the SBS population, and since each SBS patient tend to define their individual disease according to their complaints fears and miseries, a focused interview, objective and paraclinical examinations (e.g. haematology and biochemistry) should seek to determine the cause of the most troublesome inconveniences and potentially, in an individualised approach, address the best means for their successful amelioration or resolution.

In general, treatments should maximize intestinal absorptive capacity, at the same time alleviating the symptoms and inconveniences of malabsorption and prevent, minimize or eliminate the need for compensatory hyperphagia or the need for home PS (HPS). Total weaning from PS, with removal of the tunnelled, central line, is the ultimate goal of treatment of

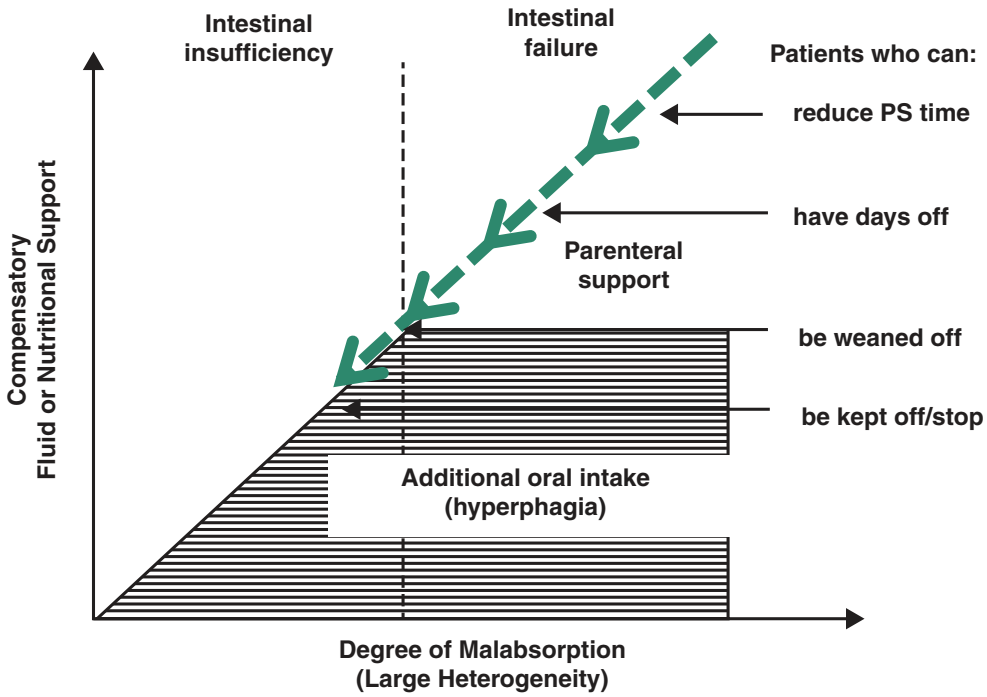

Fig. 1 The benefits/progress of intestinal rehabilitation

SBS-IF patients, but even providing days off and diminishing infusion times may be of significant value to the patients. Evaluation of health-economic benefits should be considered.

Even SBS patients with severe intestinal insufficiency, who struggle on a daily basis to keep nutritional, fluid and electrolyte balances, may benefit by pro-adaptive treatments by gaining a better quality of life and preventing re-admissions due to dehydration and other metabolic disturbances caused by accommodation-induced organ impairments.

The physical symptoms that SBS patients experience may also relate to their gastrointestinal condition leading to SBS or SBS in itself (e.g. diarrhoea, incontinence or stoma problems, abdominal pain), imbalances in body needs leading to organ or system impairments (e.g. malnutrition, dehydration and electrolyte disturbances, insatiable thirst, reduced physical energy level and/or sex drive) or the HPS infusions themselves (e.g. nausea, muscle cramping, headache). The administration of HPS potentially requires daily, timely and skilful adherence, is intrusive and disturbs the sleep pattern of the patients. Infusions are time consuming and restrict the leisure and social activities of the patients. SBS-IF patients are at risk of catheter complications such as catheter related bloodstream infections or even sepsis and thromboembolic events. Catheter dysfunction or accidental tearing out of the catheter may necessitate hospital re-admissions. Chronic organ impairments (e.g. liver and renal failure) may be caused by SBS in itself of by parenteral administrations. The factual or fear of all of the consequences and complications of SBS and PS, as well as the associated signs, symptoms and inconveniences, may eventually lead to significant psychological burden, anxiety and depression [8]. Figure 1 shows the potential benefits and progress of intestinal rehabilitation.

Patient Selection

Successful management of SBS patients is often based on a close dialog informing and teaching the patients about their pathologic conditions, the consequences and the potential options and risks of treatments (benefit-safety). Evaluations and discussions around compliance, adherence and motivation to support therapies may be helpful. It may also be helpful to discuss anticipated outcomes of interventions in order to align expectations to patient needs. Pre-set success criteria may be relevant or justified by high therapy costs.

In order to evaluate effects of new treatments, it is essential that the patients are in a stable condition and already have been optimized according the best available, conventional, individualized care. In all SBS-IF patients, absence in fluctuations in their need for parenteral support, their urine production and body weight will determine their stability, which is required before the initiation of any new treatment interventions.

Although often used in an off-label indication, conventional treatments are likely to be cheaper, and currently their safety profile is often better documented.

In SBS patients with a part of their intestine out of continuity, an attempt for a final restorative surgery should have been performed or rejected by an experienced surgeon in the field.

In SBS patients with a functional colon in continuity, time should be allowed for spontaneous intestinal adaptation to occur, unless an accelerated adaptation is aimed for. Retrospective cohort studies suggest that as much as 75% of SBS-IF patients with a jejuno-ileal anastomosis (Group 3 anatomy) have adapted and are weaned from PS at 5 years following their final surgery [9].

In patients with a jejuno-colonic anastomosis (Group 2 anatomy) the continued, progressive adaptation and PS weaning, at around 50% at 5 years, seems minimal from 2 to 3 years from the final surgery.

Thus, aggressive attempts of weaning from PS seem to be indicated in these two anatomy group of patients. In patients with a jejuno- or ileostomy (Group 1 anatomy) adaptation and total PS weaning is seen in less than 20% of patients at 1 year, and no further adaptation seems to be evident on a group basis from this point onwards. Therefore, an earlier introduction of pro-adaptive agents is reasonable in these patients.

In centres, where metabolic balance studies can be made, a measurement of intestinal energy absorption may be helpful in individual SBS-IF patients, especially in patients with Group 2 and Group 3 anatomy, before and a period of time after the initiation of a pro-adaptive treatment, since it is the provision of the PS of protein-energy and not fluid and electrolytes that may be most critical in these patients.

In SBS patients without a colon in continuity, i.e. patients with a jejuno- or ileostomy (Group 1 anatomy), objective effects of interventions may be demonstrated early following treatment initiation in simple fluid balance studies or by having the patients measuring their urine production and body weight at home.

In general, patients with suspected or active malignancies should not be treated with pro-adaptive agents. This also pertains to patients with a history of malignancies in the GI tract, including the hepatobiliary system and pancreas, within the last 5 years. A colonoscopy with removal of polyps should be performed at the time of starting treatment. Once yearly follow-up colonoscopies (or alternate imaging) are recommended during the first 2 years of treatment. Subsequent colonoscopies are recommended at a minimum of 5 year intervals. An individual assessment, whether increased frequency of surveillance is necessary, should be performed based on the patient characteristics (e.g., age and underlying disease). If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of malignancy, the new therapy must be discontinued. In children and adolescents aged 12 years or less, faecal occult blood testing should be performed prior to initiation of pro-adaptive treatments and annually thereafter. Positive tests should lead to a colonoscopy. Colonoscopy is recommended for all children and adolescents after 1 year of treatment, and at least every 5 years thereafter of continuous treatment (https://www.ema.europa.eu/documents/product-information/revestive-epar-product-information_en.pdf).

Cholecystitis, cholangitis and cholelithiasis as well as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infections and increased blood amylase and lipase levels could occur following treatments with pro-adaptive hormones. In the case of these adverse events, the benefit and need for continued treatment should be reassessed. Additional laboratory and appropriate imaging may be indicated.

Cases of intestinal obstruction have been reported in clinical studies using pro-adaptive hormones. Treatment of patients with a history of chronic abdominal pain and the detection of a narrow stoma should be avoided. In all cases, treatments should be paused until resolution of symptoms and in case of reoccurrence, the indication for treatment and the dose should be reassessed.

It will be important to consider the overall prior medical history of the SBS-IF patient, since the initiation of pro-adaptive treatments in the initial treatment phase may disturb the nutritional and fluid/electrolyte balance. This disturbance may affect any co-morbidity that the patient may suffer from. For instance, patients with a latent cardiac impairment may suffer from overt cardiac decompensation.

Due to increased intestinal absorption, patients receiving oral medication with a narrow therapeutic index may suffer from the consequences of elevated drug levels (e.g. analgesics, anti-coagulants, thyroid or anti-thyroid agents). The prescribing or treating healthcare professionals should be aware of this risk and manage their patients accordingly.

Benefit-Risk Assessment

In the ideal setting, it should always be evaluated, if a drug is so effective that its benefit outweigh its potential risk to patients.

Safety

Short Bowel Syndrome is considered a rare, orphan disease. The care and treatment of SBS patients is often complicated by a large inter-patient and effect-heterogeneity. Thus, in the opinion of the author, the implementation of new pharmacological treatments in SBS patients should ideally, at least initially, be limited to skilled, high volume intestinal failure centres, where sufficient resources are allocated to a dedicated inter- and multi-disciplinary specialist care and surveillance. Thorough effect monitoring and a close post-marketing surveillance are of great importance in order to validate the post-marketing, long-term benefit-risk profile of the specific treatment.

Most of the pro-adaptive agents have multiple physiological effects and are likely to influence both GI mucosal growth and secretions. Therefore, long-term treatments could induce

pathophysiological disturbances in various organ functions and even neoplasia. Since the number of patients included is low and treatment duration is short in the phase 3 programs, multi-national, multi-centre registry studies will be needed to ensure long-term drug safety, when introducing new treatments.

Effect

Although effects or benefit of pro-adaptive treatment may have been demonstrated in groups of SBS patients in randomised, placebo-controlled, phase 3 trials, a large inter-patient and effect-heterogeneity often exist. Therefore, establishment of a clinical meaningful and objectively measurable effect in the individual SBS patient following the initiation of the treatment is the goal.

In the ideal world, the absolute intestinal absorption of fluid, electrolytes and macronutrients in the individual patient may be determined at intervals before and after treatment initiation. This may be done by performing 48–72-h metabolic balance studies, where duplicate portions of oral intakes and faecal and urinary excretions are determined [3, 10]. The use of subjective tools or questionnaires is difficult to implement and objectively evaluate in this orphan condition.

In the real world setting, only few centres have the organisation, logistics and skills to objectivize effects of treatments, but along with conventional standard of care, simple fluid balance measurements with a tracking of changes in urine production, body weight and standard biochemistry should be the minimum for adjusting PS. Subjectively perceived benefits in relation to the treatment with pro-adaptive agents may vary considerably in individual patients, even when patients are allocated according to the various classifications suggested by the ESPEN interest group [4]. Individual effects, that may seem subtle when using conventional measuring tools, may dramatically improve the quality of life in some patients, whereas others, who do not encounter this problem, may find that the treatment has other preferred effects.

Cost Considerations

Since the cost of developing new drugs in orphan conditions is high and the potential patient group is relatively small, the prices of new treatments are much higher than conventional pharmacological treatments. It is also likely, that most patients will require these treatments for the remainder of their life. Therefore, negotiations between health authorities and companies are needed to ensure the right balance, so the barriers to prevent developments that are ethically and scientifically motivated do not become too high, the economic incentives to sponsor this development is fair, and that introduction of these agents do not impair and deprive finances from a well-functioning healthcare system.

The Physiological Basis for Treatment with Pro-adaptive Agents

When discussing the use of pro-adaptive agents in the treatment of SBS patients it is important to emphasize the concept of the intestine as an endocrine organ. Thus, although the enteroendocrine cells only constitutes 1% of the intestinal mucosal cells, a plethora of hormones released in relation to eating ensures the physiological actions required for the optimal digestive process. The gastro-entero-pancreatico-hepatic system is now regarded as the largest endocrine organ in the body [11].

In general, patients with intestinal resection and a jejuno- or ileostomy are characterised by elevated post-prandial, pro-secretory and pro-motility hormones such as gastrin, cholecystokinin, secretin and motilin [12]. This favours rapid propulsion and hypersecretion of gastric acid, bile and pancreatic juice as well as bicarbonate secretion, which in turn may contribute to large stomal losses. A lack of endogenous secretion of more distally secreted pro-adaptive feedback hormones, such as glucagon like peptide (GLP)-1, GLP-2, peptide YY (PYY), oxyntomodulin, and fibroblast growth factor (FGF) 19, may aggravate the accelerated gastric emptying and various hypersecretions, rapid intestinal transit and impaired blood and lymphatic flow as well as mucosal function [13]. Impaired post-prandial secretion of more proximally produced hormones such as glucose-dependent insulinotrophic peptide (GIP) may also contribute to the pathophysiological characteristic of patients with group 1 anatomy.

Patients with group 2 and group 3 anatomies differ by the presence of a part of the terminal ileum and the right-sided colon. Whereas the colon in itself possesses the ability to compensate for small bowel malabsorption by increasing its ability to absorb fluid (up to 5 L/day), sodium (up to 800 mmol/day) as well as energy derived from the fermentation of carbohydrates and protein (up to 4 MJ/day) [14], the terminal ileum and the right-sided colon may also be of significant importance in the hormonal regulation of more proximal GI functions [15]. Thus, the constant hypersecretion of the suggested pro-adaptive distal feedback hormones demonstrated in these patients may also account for the impressive spontaneous adaptation and ability to wean from PS seen in these patients with down to 40 cm of remaining small bowel in the years following intestinal resection. In summary, it is believed that future pro-adaptive treatments in SBS will seek to mimic these effects, potentially by a replacement therapy including a combination of these beneficial feedback hormones.

Overview of Results from Clinical Studies

Somatostatin and Analogues

Somatostatin is widely distributed in the neuroendocrine cells throughout the gastrointestinal tract and in pancreatic D cells. It decreases gastric [16], biliary and pancreatic secretions [17–19] inhibit secretagogue-induced water and electrolyte secretion in the jejunum and the colon [20], stimulate sodium and chloride absorption in the ileum [21], decrease intestinal motility [22] and inhibit the release of hormones that may contribute to the diarrhoea (e.g. VIP, GIP, gastrin) [23]. However, somatostatin could inhibit glucose absorption and pancreatic enzyme secretion, which would impair the macronutrient absorption in patients with SBS. Furthermore, somatostatin reduces splanchnic blood flow [24] and it may reduce the use of amino acids for splanchnic protein synthesis thereby interfering with the physiological process of adaptation to intestinal resection [25, 26].

Dharmsathaphorn et al. were the first to report the acute effects of a 24-h infusion of somatostatin (4 μg/min) in four patients with SBS due to multiple resections for Crohn's disease [27]. Total colectomy was performed in 3 out 4 of the patients and their remnant jejunum was less than 3 m. Having withdrawn all anti-diarrhoeal medications 2 days before admission, patients were placed on a standardised 2000 kcal diet containing 75 g/day of fat. Blood samples, urine and stool collections were obtained for three consecutive 24-h periods before, during and after somatostatin administration. Somatostatin infusion induced a reduction in stool weight in all four patients (from 1892 ± 241 g/day to 1236 ± 254 g/day, on average corresponding to 35%, $p < 0.05$) and a 59% decrease in stool chloride content. Numerical reductions in faecal excretions of fat (9 g/day), nitrogen (1.0 g/day), sodium (30 mmol/day), potassium (7 mmol/day) and magnesium (47 mmol/day) were observed. The urinary volume and electrolytes remained unchanged. Blood glucose levels rose from 25 to 40 mg/dL and fasting and postprandial glucagon, GIP and peptide PP levels were suppressed by the somatostatin infusions. A rebound effect occurred immediately after infusions.

The use of a long acing somatostatin analogue, SMS 201-955 (octreotide), which prolonged the half-life from a few minutes to 3–4 h, was first reported in a woman with Crohn's disease who after colectomy also had a subsequent removal of an ileorectal anastomosis. Four months after the creation of an ileostomy, her output was 4–6 L/day, when on her regular oral intake, and 2–3 L when fasting, and therefore she required PS. In relation to 24-h of infusion of SMS 201-955 (25 μg/h), the ileostomy output decreased from 5300 to 1600 g/day, sodium excretion decreased from 656 to 162 mmol/day and potassium from 48 to 20 mmol/day. In spite of these dramatic effects, the faecal excretion of fat and glucose was not affected. Small bowel transit time was prolonged from 76 to 134 min. Subsequently, the patient was given SMS 201-955, 50 μg subcutaneously twice daily, and her stomal output remained below 2.5 kg/day thereby rendering PS unnecessary [28].

The effect of octreotide was also demonstrated in a 5-year-old boy with an ileostomy placement after an operation due to volvulus. Following unsuccessful treatments with parenteral nutrition for 8 weeks, loperamide, cholestyramine and antibiotics, efficacy of octreotide was demonstrated. Following a phase with continuous analogue infusion followed by twice daily 50 μg subcutaneous octreotide injections, the average ileal output diminished from 1800 g/day to 350 mL/day and was paralleled by reductions in sodium and chloride losses. No side effects were observed.

Rodrigues et al. compared the effects of octreotide to the effects of soy polysaccharide, oral and intramuscular codeine, and loperamide on nutrient fluid and electrolyte absorption in four patients with short bowel syndrome and an end-jejunostomy receiving parenteral nutrition [29]. Following a standardised test meal, the stoma output collected the following 6 h was reduced from 923 ± 213 g to 358 ± 78 g, sodium output from 95 ± 12 to 49 ± 9 mmol, calorie balance increased from 11 ± 6 to 35 ± 8%, and intestinal transit (evaluated as the median time taken to recover 60% of a labelled marker) increased from 64 ± 23 to 205 ± 8 min. However, all four patients found that the subcutaneous octreotide injections were painful, and one patient experienced abdominal pain and distention.

Nightingale et al. studied the effect of octreotide in six SBS patients who all had undergone extensive small bowel resection [30]. Apart from one, who had a jejuno-rectal anastomosis, all patients had end-jejunostomies and a remnant bowel length of less than 70 cm. Two of the patients received codeine and loperamide in relation to participating in the study. The mean daily intestinal output ranged from 3.6 to 6.9 kg, and all patients needed at least 4.5 L of intravenous fluids per day. Following two control days, the patients were given octreotide intravenously through their central catheter in a dose of 50 μg (diluted in 10 mL 0.9% saline given over 10 min) twice daily at 08:00 and 16:00 h for 2 days. This mode of administration was chosen to avoid the painful octreotide injections. When possible, the study was repeated using 100 μg of octreotide three times daily, 30 min before each meal. Treatment with octreotide significantly reduced the mean total intestinal output from 5.13 to 3.30 kg/day (difference 1.83 kg/day, range 0.60–5.01 kg/day, $p = 0.04$). Sodium excretion was reduced from 405 to 248 mmol/day (difference 157 mmol/day, range 56–405 mmol/day, $p = 0.03$) and potassium from 73 to 52 mmol/day (difference 21 mmol/day, range 6–61 mmol/day, $p = 0.05$). A non-significant reduction in faecal energy from 6894 to 5625 kJ/day was observed (difference 1270 kJ/day, range −1092 to

5083 kJ/day, p = 0.20). Increasing the dose to 100 μg TID in three patients did not increase the effect, but the patients preferred this option since it reduced the usual inconvenient postprandial rise in the intestinal output. No side effects were reported. One patient was treated continuously for 1 year without evidence of tolerance occurring and no signs of complications of diabetes, hypothyroidism or gallstones.

Rosenberg et al. investigated the effect of octreotide in doses from 50 μg subcutaneously twice daily to 100 μg three times daily in SBS six patients; two with ileostomies and four with a gastrointestinal tract that was in continuity [31]. Intractable diarrhoea decreased by 73 ± 7% in five of the six patients, but the actual raw-data is not presented in the publication. Although the treatment was very effective in controlling diarrhoea, two patients discontinued treatment within 1 week of commencing treatment due to abdominal cramping and bloating. Two patients were treated successfully as outpatients for 6 weeks. Thereafter the treatment was stopped without the occurrence of diarrhoea. Two other studies were only reported in abstract form. Shaffer et al. performed a randomised placebo controlled crossover trial in six patients with a persistently high stoma effluent (1.3–6 L/day) [32]. After a 2 day control period, the patients received 50, 100 and then 150 μg of octreotide or matching placebo on three successive days. After a 14 days washout, the patients repeated the study with the alternative medication. Octreotide significantly reduced the median stomal volume (2.39 L/day, range 0.62–4.48 vs placebo: 4.03 L/day, range 1.28–5.98, $p < 0.001$), sodium output (153 mmol/day, range 27–271 vs placebo: 311, range 94–594, $p < 0.001$) and potassium output (39 mmol/day, range 8–58 vs placebo: 54, range 23–154, $p < 0.001$). There was a corresponding increase in urine volume (2.09 L/day, range 0.75–6.62 vs placebo: 1.16 L/day, range 0.47–5.13, $p < 0.002$). Body weight was unaffected by the treatment, and no improvements in nitrogen, magnesium, zinc or copper balances were seen. Two patients were followed for more than 2 years on treatment and did not develop any long-term adverse effects or evidence of pharmacological tolerance.

In another abstract, Gilsdorf et al. reported finding in seven SBS patients requiring HPN. Three patients had stomas and in these octreotide, given in doses ranging from 50 to 300 μg subcutaneously in one to three doses, reduced stoma outputs of 5.0, 4.0 and 2.0 L/day to 3.5, 2.5 and 0.6 L/day [33]. Daily bowel movements of up to 20/day decreased in all cases to less than 6/day. Four patients eventually took octreotide in their TPN bags and experienced the same effect as when taken subcutaneously. One patient developed confusion, oedema and a 17 lb weight gain secondary to fluid overload. One had labile blood sugars. All patients complained of dull headaches and nausea which they attributed to octreotide. Thus, three stopped the treatment, whereas three continued the treatment by injecting it into their PS.

These studies were followed by a double blind, placebo controlled balance study by Ladefoged et al. in six SBS patients requiring PS [34]. Five of the six patients had a jejunostomy and less than 225 cm of small intestine, whereas the last patient only had a resection of 30 cm of the terminal ileum. Their stool masses ranged from 2320 to 8125 g/day and their stomal sodium losses ranged from 144 to 601 mmol/day. Four of the six patients were wet weight secretors, and all the patients were sodium secretors. During the study, the patients were maintained on a constant diet composed in accordance with their habitual intake and they received a fixed fluid and sodium intake for all 12 days. After a basal period of 2 days, the patients were randomly allocated to intravenous placebo or octreotide 25 μg/h for 2 days each. After a new basal period of 2 days, the patients were allocated in the same manner to a subcutaneous administration of either placebo or octreotide in a dose of 50 μg every 12 h. In the whole period, double portions of the oral intake was prepared and analysed as was the stools and urine. Infusion of octreotide caused a significant increase in the median wet weight absorption of 1124 g/day (range 347–1854 g/day), $p < 0.005$ and sodium 126 mmol/day (range 52–191 mmol/day), $p < 0.005$, whereas no significant changes in the net absorption of potassium, calcium, magnesium, phosphate, zinc, nitrogen or fat was seen during the infusion of octreotide. Subcutaneous injection of octreotide every 12 h caused similar effects. However, one patient developed symptoms of ileus that resolved after discontinuation of octreotide and conservative treatment. In none of the patients, the improvements in intestinal wet weight or sodium absorption were large enough to make parenteral fluid or sodium supplements superfluous. Four patients opted to continue open label subcutaneous treatment twice daily for 21–28 weeks. In three of these patients, the faecal mass remained below baseline values but in one patient, the faecal mass gradually increased and exceeded baseline values even after doubling the octreotide dose. No side effects were seen.

In an open label study, O'keefe et al. investigated the effect of 100 μg octreotide given subcutaneously TID, 30 min before meals on intestinal absorption after initial 72-h balance studies at days 1–3 that were repeated at days 11–13 [26, 35]. Ten adult SBS patients with end-jejunostomies performed at least a year prior to the investigation were examined. The remaining small bowel was 200 cm or below in all patients, and they all depended on PS (mean PS volume 4.5 L/day, range 1–5.5 L/day and mean sodium provision 387 mmol/day, range 247–982 mmol/day). All patients had received H_2 antagonist therapy until a week before the study and all patients had been given trials of common anti-diarrhoeas. The mean stomal output was 8.1 L/day (range 2.4–20.7 L/day) and sodium losses 510 mmol/day (range 247–982 mmol/day). The study protocol consisted of a 3-day, baseline metabolic balance study, where no

antisecretory or antimotility medications were given. Octreotide therapy was then commenced as 100 μg TID s.c. 30 min before each meal for 8 days before the 3-day balance study was repeated during the same octreotide treatment. After commencement of octreotide, reductions in the stomal fluid were counterbalanced each day by reductions in IV fluid and electrolyte infusions maintaining urine output between 1 and 1.5 L/day. In addition, amino acid metabolism, pancreatic enzyme synthesis and secretion and mucosal protein turnover were measured before and at the end of the 10 days of octreotide therapy. Likewise, mucosal biopsies and hormonal secretions were evaluated before and during stimulation with pentagastrin and cholecystokinin.

The effect of octreotide treatment on stomal output was immediate in all patients, and in spite of a reduction in oral fluid intake, this permitted a significant reduction in the parenteral supplements in all but one of the patients. Thus, on average the stomal losses of fluids and sodium were reduced to 4.8 L/day and 340 mmol/day, respectively (both $p < 0.03$). However, despite increases in net absorption, none of the patients could be weaned from PS. The average parenteral fluid volume and sodium reductions were 1.3 L/day and 118 mmol/day, respectively ($p < 0.03$). In general, the largest effect was seen in patients with the highest stomal losses and highest parenteral needs. No changes in intestinal macronutrient absorption were observed in relation to octreotide treatment.

Octreotide treatment resulted in a significant reduction in the pentagastrin-stimulated acid secretion in all but one of the SBS patients. The exogenous pancreatic excretion of lipase in response to CCK stimulation was significantly reduced before and after 10 days of octreotide treatment, whereas numerical reductions were seen in trypsin and amylase secretion. Although, the time taken to the appearance of carmine dye on average was 12 min longer in comparison with pretreatment values, this was not significant. Mucosal protein turnover and duodenal villus growth rates calculated from isotope incorporation and morphological measurements showed a significant suppression. Plasma concentrations of glucagon, insulin, gastrin and peptide YY all decreased in relation to octreotide treatment. Evidence for improved renal function was obtained from urea clearance with findings of decreases in blood urea concentration and increases in urea nitrogen excretion in the urine. However, although octreotide significantly reduced stomal output and increased fluid balance in the SBS jejunostomy patients, concern was raised that the long-term treatment would interfere with the process of intestinal adaptation. Seven patients continued treatment for over 2 years following the study. Two of these patients died one from septicaemia and the second with intestinal failure associated liver disease. Two patient developed gallstones necessitating a percutaneous cholecystectomy. Mild hair loss was noted by two patients. Two patients complained of occasional abdominal cramps.

In the latest study employing octreotide, Nehra et al. described the use of a long-acting release (LAR) deport, octreotide preparation, sandostatin LAR, in a 15 week, open label trial in eight adult SBS-IF patients [36]. All the patients had been receiving PS for 1–22 years. Three of the patients had a colonic segment in continuity and in all patients the residual bowel was 200 cm or less. Metabolic balance studies and measurements of intestinal transit by radionucleotide scintigraphy employing an egg meal were performed on two separate occasions 15 weeks apart. Following the initial 48-h balance study, the patients received the first 20 mg, intramuscular, Sandostatin LAR injection. This was repeated by self-injection as an outpatient at weeks 3, 7 and 11. The PS was kept constant throughout the study, and patients had fixed habitual like diet during admissions. The average 48-h stool weight was 4.54 g/day (range 2.91–11.16 kg). Sandostatin LAR treatment did not lead to significant differences in body weight, 48-h urine volume, stool weight, faecal sodium or potassium losses or faecal fat excretion. However the depot-treatment significantly prolonged small bowel transit time, whereas the gastic emptying halftime or in the proportion of the meal emptied from the stomach at 2 and 4 h did not change.

According to the ESPEN guideline it is suggested that octreotide is only used in the short term after intestinal resection and in patients with high output jejunostomy in whom fluid and electrolyte management is problematic in spite of conventional treatments. A careful monitoring is recommended to prevent fluid retention in relation to the initiation of treatment as well as potential adverse effects. Although the effects potentially are dramatic in patients with the highest outputs, it is of concern, that sandostatin and analogues have global effects on hormonal secretions and that potential negative interference with the process of intestinal adaptation may be seen following long-term use.

Growth Hormone and Analogs

The concept of “bowel rehabilitation” was introduced by Byrne and Wilmore in relation with treatment with high dose (0.14 mg/kg/day) of growth hormone, glutamine, and a high carbohydrate diet in SBS patients [37, 38]. In eight SBS patients with colon in continuity treated for 5 weeks, wet-weight absorption increased from 1.7 to 2.4 kg/day, and sodium absorption increased from 74 to 113 mmol/day. However, although these patients were receiving PS, it is not clear if they met the criteria for a diagnosis of intestinal failure as defined by Jeppesen et al. [3]. At the same time patients were given a high-carbohydrate diet and oral rehydration solutions as a part of the “rehabilitation-regimen”.

In a subsequent placebo-controlled, double-blind study by Scolapio et al., the effect of growth hormone (0.13 mg/kg/day) and oral glutamine on intestinal sodium and potassium absorption was less than 5 mmol/day [39]. No effects on faecal wet weight excretion were seen.

In a study by Szkudlarek et al., growth hormone (0.11 mg/kg/day) and glutamine, both orally and parenterally administered, tended to decrease wet-weight absorption and increase faecal excretion of sodium and potassium, which reached significance ($p < 0.05$) in comparison with baseline values [40]. However, these findings were accompanied by clinical findings of generalized oedema, increased body weight, a need for diuretics, and a reduction in parenteral saline during treatment. It is believed that the patients were in the process of excreting water and sodium accumulated during the treatment at the time of the post-treatment balance studies 5 days after termination of treatment.

In lower dose studies from Ellegård (growth hormone 0.024 mg/kg/day) [41] and Seguy (0.05 mg/kg/day) [42], no significant positive effects on either wet-weight or sodium absorption were seen.

In the pivotal, randomised, double-blind parallel group study of 41 patients with SBS (mainly with a preserved colon and stool volume less than 3 L/day), who were dependent on parenteral nutrition, the effect of the recombinant human growth hormone, somatotropin (0.1 mg/kg/day for 4 weeks) and glutamine on the need for PS was investigated [43]. The protocol for weaning from PS was based on measurements of body weight, total body water by bioimpedance analysis and measurements of serum sodium, potassium and bicarbonate. A significantly greater reduction from baseline in total parenteral volume occurred in recipients of somatropin plus glutamine or somatropin alone than in recipients of placebo plus glutamine (−7.7 and −5.9 vs −3.8 L/week, respectively). Thus, the effect of somatropin and glutamine averaged 557 mL/day. Balance studies on intestinal absorption were not performed and the results on urinary excretions were not reported [43]. However, it has been reported that growth hormone increases extracellular volume by stimulating sodium reabsorption in the distal nephron and preventing pressure natriuresis [44]. Therefore, when employing bioelectrical impedance analysis during weaning from PS, it should be considered that the effects of growth hormone on fluid balance in SBS patients may also be related to effects on the kidneys and the extracellular space rather than on the intestine.

Results on intestinal energy and macronutrient absorption in studies using growth hormone have been conflicting. In the study by Byrne and Wilmore, the baseline dietary energy intake was 2692 kcal/day, and 1618 kcal/day (~6773 kJ/day, 60%) were absorbed [37]. Thus, according to the parameters that define intestinal failure suggested by Jeppesen et al. [3], the majority of these patients did not need parenteral energy. After 3 weeks of treatment, the intake and absorption were 2367 and 1759 kcal/day (~7363 kJ/day, 74%), respectively, which was a significant improvement in percentage ($p < 0.003$) but an increase of only 141 kcal/day (~590 kJ/day) in absolute amounts. As stated, the "rehabilitation"-regimen included a high-carbohydrate, low-fat diet, which in itself is known to increase energy absorption in SBS patients with a colon in continuity. Supporting the hypothesis that diet alone accounted for the observed benefits, intestinal fat absorption did not improve. In the study by Scolapio et al., where only 2 of 8 patients had colon in continuity, high-carbohydrate diets were provided in both the placebo and treatment arms [39]. Energy absorption was not measured, but no changes were observed regarding nitrogen or fat absorption with growth hormone. In the studies by Ellegård et al. [41] and Szkudlarek et al. [40], no changes were found in intestinal energy or in fat or nitrogen absorption. In the randomized, double-blind placebo-controlled cross-over study by Seguy et al., growth hormone (0.05 mg/kg/day, 9 of 12 patients with colon in continuity) and an unrestricted hyperphagic diet increased intestinal absorption of nitrogen by 14 ± 6% ($p < 0.040$), carbohydrates by 10 ± 4% ($p < 0.040$), and energy by 15 ± 5% ($p < 0.002$), which in absolute terms was 427 kcal/day (~1787 kJ/day) [42]. Fat absorption was unaffected. During growth hormone treatment the mean dietary energy intake was 192 kcal/day (804 kJ/day) higher than during the placebo treatment phase.

In the pivotal study on somatropin, the mean reductions from baseline in total parenteral calories were significantly greater in recipients of somatropin plus glutamine or somatropin alone than in recipients of placebo plus glutamine 5751 and 4338 vs 2633 kcal/week, respectively [43]. Thus, the effect of the combined therapy of somatropin plus glutamine would correspond to an effect of 445 kcal/day (1863 kJ/day). No changes in the dietary energy intake in the three parallel study groups were reported.

In the growth-hormone study by Byrne et al., a weight gain of 5.4 ± 1.2 kg was described in the eight patients after 21 days of treatment [37]. Occurrence of oedema was not reported, but increases in body weight of this magnitude are difficult to explain considering the cumulative effect of approximately 12.4 MJ (590 kJ/day) on the energy balance over the 21 days of treatment. Neither body composition nor urine creatinine excretion was measured. Changes in body weight in the studies by Ellegård et al., [41], Scolapio et al., [39] and Szkudlarek et al., were minor and no changes were seen in urinary creatinine excretion [45]. In the study by Seguy et al., body weight increased 2.0 kg ($p < 0.003$), and the lean body mass, measured by BIA, increased 2.2 kg ($p < 0.006$) [42]. No adverse events to the lower dose growth-hormone treatment were encountered.

In the PS weaning study of somatropin, a dramatic weight loss of 5.2 kg of body weight (from 63.9 to 58.7 kg) was

observed from week 2 (pre-treatment) to week 18 (12 weeks post-treatment) in patients receiving the combined therapy of somatropin plus glutamine. This weight loss closely reflected the anticipated weight loss derived by calculation of the energy deficit obtained by reduction of the parenteral energy support of 1863 kJ/day [43].

In summary, the overall impression is that the effects of high doses of growth hormone were mainly confined to the wet weight absorption and mainly in SBS patients with a preserved colon, whereas the effects on energy absorption were minor. At the lower doses of growth hormone, there may be an effect on energy absorption in SBS patients with a preserved colon, whereas the effect on wet weight absorption was minor regardless of intestinal anatomy.

In 2003, the United States Food and Drug Administration (US FDA) approved Zorbtive® for 4-week treatments in SBS patients. It has not been approved by EMA. The long-term benefits of growth hormone and glutamine on intestinal absorption following discontinuation of treatment remain to be established. The effects of growth hormone are global and not specific for the intestine. The global effects of growth hormone and the presence and severity of adverse events (swelling, fluid retention symptoms, myalgia, arthralgia, gynecomasia, carpal tunnel syndrome, nightmares and insomnia) in relation to high dose growth hormone treatment raises concern especially in relation to a long-term, potentially life-long use of this treatment modality. Trying to reconciliate the conflicting findings in the growth hormone studies a recent Cochrane review concluded: "The results suggest a positive effect of human growth hormone on weight gain and energy absorption. However, in the majority of trials, the effects are short-lived returning to baseline shortly after cessation of therapy. The temporary benefit calls into question the clinical utility of this treatment" [46].

Glucagon Like Peptide-2 and Analogs

Glucagon-like peptide 2 (GLP-2) is a single chain polypeptide of 33 amino acid residues, which is produced by a tissue-specific posttranslational processing of the 160 amino-acid proglucagon molecule in enteroendocrine L-cells. These cells are distributed throughout the gastrointestinal tract with the highest density in the terminal ileum and the colon. GLP-2 is secreted from the intestinal L-cells following meal ingestion. Repeated administration of GLP-2 promotes the expansion of the intestinal mucosa via the stimulation of crypt cell growth and the reduction of enterocyte apoptosis [47]. Exogenous GLP-2 administration inhibits gastric acid secretion and gastric emptying [48, 49] stimulates intestinal blood flow [50–52] increases intestinal barrier function [53] and enhances nutrient and fluid absorption in both preclinical and clinical models [54–56]. GLP-2 has also been suggested to have anti-inflammatory effects [57, 58], and in addition, GLP-2 may decrease bone resorption [59]. The effects are mediated via GLP-2-receptors (GLP-2R), which are G-protein coupled receptors belonging to the class B glucagon-secretin receptor family [60]. GLP-2R expression is primarily found in the gastrointestinal tract and the central nervous system, with limited expression in lung, cervix and vagal afferents [61]. Within the GI-tract the most abundant expression of GLP-2R is found in the jejunum, followed by the ileum, colon and stomach. Different studies have identified expression of GLP-2R in enteroendocrine cells [62], enteric neurons [63] and subepithelial myofibroblast [64]. However, neither crypt epithelial cells nor enterocytes express the GLP-2R and this finding has led to the hypothesis that GLP-2 requires an indirect signal, perhaps functioning through a paracrine mechanism, to induce its effects on intestinal growth. GLP-2R activation results in the release of several growth factors such as IGF-1, EGF and KGF [65].

The biologically active GLP-$2_{1–33}$ is broken down at the alanine residue in position 2 from the N-terminus, catalysed by the proteolytic enzyme dipeptidyl peptidase-4 (DPP-4), and it is thereby transformed into the biologically more inactive metabolite GLP-$2_{3–33}$. Teduglutide is a GLP-2 analog, in which a substitution of alanine with glycine at position two results in a peptide resistant to degradation by DPP-4 and, therefore, has a longer half-life than native GLP-2 [66, 67]. Following subcutaneous (SC) injection, this corresponds to a biological half-life for teduglutide of 2–3 h compared to a half-life of 7 min for GLP-2.

In the first uncontrolled, clinical, "proof of concept" study with native GLP-2 by Jeppesen et al., 8 patients were treated with the empirically derived dose of 400 μg of native GLP-2 twice a day (corresponding to 0.013 ± 0.002 mg/kg/day, a range of 0.011–0.017 mg/kg/day), given subcutaneously for 35 days in an open label study [55]. None of the patients had colon in continuity. Their average wet-weight absorption was 1.2 ± 1.7 kg/day at baseline, and it increased by 420 ± 480 g/day ($p = 0.04$), whereas the effect on sodium absorption did not quite reach statistical significance (33 ± 49 mmol/day, $p = 0.10$). Native GLP-2 treatment improved the relative absorption of energy by 3.5% ($p = 0.04$), and nitrogen by 4.7% ($p = 0.04$). The absolute energy absorption tended to increase by 441 ± 634 kJ/day ([105 ± 151 kcal/day] $p = 0.09$). The effect of GLP-2 on fat absorption was not significant. The improvement in the absolute amount of energy absorbed was obtained in spite of a non-significant decrease in intake of 173 kJ/day, which means that the reduction in the energy malabsorbed (equal to the stomal excretion) was proportionally larger: 617 kJ/day [55].

The first clinical study of the efficacy of teduglutide in SBS was evaluated in an open-label, phase 2, pilot study published in 2005 [68]. In this phase 2, metabolic balance

study, 16 SBS-patients received three different doses of teduglutide for 21 days [68]. The SBS patients were divided into three subgroups based on remnant functional anatomy: end-jejunostomy (n = 10), <50% colon in continuity (n = 1) or >50% colon in continuity (n = 5). The 10 SBS patients with end-jejunostomy received 0.03 mg/kg/day (n = 2), 0.10 mg/kg/day (n = 5) or 0.15 mg/kg/day (n = 3) of teduglutide once daily. The patient with <50% colon in continuity received 0.03 mg/kg/day, and the five patients with >50% colon in continuity received 0.10 mg/kg/day. The doses were chosen to examine dose response in SBS patients over a range of doses expected to provide clinical benefit. It was intended that dietary intake was fixed during the balance studies, and the study did not seek to evaluate the effects of teduglutide on spontaneous dietary intake. Three 72-h balance studies were performed: at baseline; during teduglutide treatment at days 18–21; and after terminating teduglutide treatment at day 39–42. During balance studies, all oral intake, faecal/stomal output and urine was collected, weighed and analysed for energy, nitrogen, fat and sodium and potassium content. Likewise, intestinal mucosa biopsies were done at baseline, day 21 and day 42. The patients took their usual medications such as proton pump inhibitors, codeine or loperamide, and oral and parenteral supplements were kept constant throughout the study.

Compared to baseline, 21 days of treatment with teduglutide increased absolute intestinal wet weight absorption in 15 out of 16 SBS patients. The average increase in wet weight absorption was 743 ± 477 g/day ($p < 0.001$). The overall increase in the relative wet weight absorption was 22 ± 16% ($p < 0.001$), and the magnitude was similar for SBS patients with end jejunostomy (20 ± 18%, $p = 0.007$) and those with >50% colon in continuity (26 ± 16%, $p = 0.023$). In accordance with the increase in wet weight absorption, faecal wet weight decreased significantly compared with baseline in the entire group of SBS patients (711 ± 734 g/day, $p = 0.001$). Since the oral intake and PS were kept constant in this study, the benefits on intestinal wet weight absorption and hydration translated into an increase in urine production in 14 of the 16 SBS patients. The urine weight increased by 555 ± 485 g/day ($p < 0.001$). Furthermore, a significant decrease in faecal energy excretion was observed in the entire group of SBS patients (group 1 = 808 ± 1453 kJ/day, $p = 0.040$), in the subgroup of patients with colon in continuity (group 3 = 1343 ± 916 kJ/day, $p = 0.031$) and in those patients with high dietary compliance (group 4 = 1060 ± 1083 kJ/day, $p = 0.013$). This reduction in energy excretion translated well into both significantly improved absolute energy absorption (group 3 = 1027 ± 798 kJ/day, $p = 0.045$ and group 4 = 963 ± 1290 kJ/day, $p = 0.043$) and relative energy absorption (group 3 = 10 ± 7%, $p = 0.030$ and group 4 = 8 ± 11%, $p = 0.040$). Unfortunately, the results did not translate into a general, significant effect with respect to absolute or relative energy absorption, and it is possible that this is due to variability in dietary intake during the study periods amongst the different groups.

In addition to the metabolic balance studies, the study also examined the possible histological changes in bowel biopsies obtained from the patients. In the jejunum biopsies (obtained from 8 end-jejunostomy patients in group 2) significant histological changes were seen in 7/8 patients. More specifically, an increase in villus height (38 ± 45%, $p = 0.030$), an increase in crypt depth (22 ± 18%, $p = 0.010$) and an increase in mitotic index (115 ± 108%, $p = 0.010$) were demonstrated. Small intestinal biopsies were not obtained from the patients with colon in continuity (group 5), but instead biopsies measuring the colonic crypt depth were obtained in all five group 3-patients, and these showed an increase in crypt depth in 4/5 sets of biopsies. The mean increase in crypt depth (13 ± 22%, $p = 0.330$) was not statistically significant, and neither was the increase in mitotic index (76 ± 112%, $p = 0.170$). Most changes in intestinal absorption and histology related to teduglutide treatment had reversed at follow-up.

Having illustrated that increases in wet weight absorption were paralleled by increases in urine production, the ability to reduce PS according to increases in urine production served as the endpoint in the phase 3 clinical study development of teduglutide.

In each of two 24-week, phase 3, outpatient studies, patients with SBS had their PS and intake of fluids optimized to produce a stable urine output of 1–2 L/day prior to randomization and subsequent efforts to reduce PS requirements while maintaining clinical status and hydration.

The first long-term, multinational, double-blind randomized placebo-controlled teduglutide trail was conducted as a multicenter study in the US, Canada and Europe ("the 004 study"). Eighty-three patients with SBS-IF of various aetiologies were included. Patients with SBS were randomized to teduglutide 0.05 mg/kg/day (n = 35), teduglutide 0.10 mg/kg/day (n = 32) or placebo (n = 16) for up to 24 weeks [69]. The primary efficacy variable in the study was initially the responder rate—that is, the percentage of patients who had a reduction from baseline in parenteral volume of 20–100% at week 20 of treatment and again at week 24. Later on, an expanded graded primary end point was introduced to compare the patients treated with teduglutide versus placebo with respect to a graded response score (GRS) criterion. Secondary efficacy end points included the number and percentage of patients who responded (defined as a parenteral volume reduction of 20–100% from baseline at week 20 and maintained at week 24); the absolute reduction from baseline in parenteral volume and parenteral kilojoules; and the achievement of at least 1 day reduction in the weekly parenteral administration or total weaning from PS. The patients were seen in the outpatient clinic at 2 weeks intervals. The

investigators used a weaning algorithm that allowed PS volume to be reduced by maximum of 10% monthly. The primary efficacy end point of the study, the GRS, was not significantly different from placebo in the teduglutide 0.10 mg/kg/day group. However, it was decided to explore the effect of the 0.05 mg/kg/day dose on the primary end point and these results showed a statistically significant improvement compared with placebo in the GRS ($p = 0.007$). The secondary efficacy end point—the responder rate—was not significantly different between the 0.10 mg/kg/day group and the placebo group, but the responder rate was significantly higher in the 0.05 mg/kg/day dose group compared with placebo (46% (16/35) vs. 6% (1/16)), $p = 0.005$). Three subjects were completely weaned from PS. Two patients in the 0.05 mg/kg/day group became completely independent of PS although they had received this treatment for 25 and 6.5 years, receiving 5.4 L and 3.5 L per week at baseline, respectively. Another patient in the 0.10 mg/kg/day group also became independent off PS at the end of treatment week 24 after having received 4.5 L PS per week for 3.7 years.

None of the active treatment arms resulted in a significant reduction in the number of days on PS, which could be explained by the fact that the algorithm for weaning PS did not specify for conversion of accumulated effects into days off PS and many investigators probably found it easier to just reduce daily parenteral volumes.

In the 0.05 mg/kg/day teduglutide group an observation of significantly more urine production at all time points, in spite of maintaining a constant oral fluid intake and having parenteral volume significantly decreased, was seen. Since urine output increased steadily during the study, this contrasted to the objective of the study protocol, which was to maintain constant urine output by progressively reducing the parenteral volume. Thus, the absolute effect of the teduglutide 0.05 mg/kg/day dose on the reduction in parenteral volume appeared to be underestimated. The concept of "the fluid composite effect" reflects the sum of the reduction in oral fluid intake, the increase in urine volume and reductions in daily parenteral volume. Thus, highlighting the total effect of the 0.05 mg/kg/day teduglutide dose, the fluid composite effect endpoint increased significantly by 816 ± 982 mL/day compared with placebo ($p = 0.03$) at week 20. Highlighting the total absolute effect of the 0.10 mg/kg/day teduglutide dose, the composite effect increased significantly by 489 ± 619, 700 ± 723 and 953 ± 830 mL/day at weeks 12, 16 and 20, respectively (all p-values <0.05) compared to the placebo. Thus, the urine volume increased by ~350 mL/day and the parenteral volume was decreased by ~350 mL/day in the 0.05 mg/kg/day teduglutide dose group, whereas the oral fluid intake decreased by ~350 mL/day and the parenteral volume decreased by ~350 mL/day in the 0.10 mg/kg/day teduglutide dose group. Thereby, it is estimated that the true effect of either teduglutide dose on intestinal wet weight absorption is probably around 700 mL/day (i.e. 4.9 L/week) closely reflecting the effects demonstrated in the phase 2 study.

The reductions in parenteral energy were not significant when comparing the teduglutide groups and the placebo group ($p = 0.11$), but in contrast to the phase 2 study, the oral energy intake and faecal excretions were not measured. It is suggested that the non-significance of the 0.10 mg/kg/day dose vs. placebo could be explained by limitations imposed by the protocol, such as the inability to start reduction of PS until after 4 weeks of initiating teduglutide treatment, the maximally allowed reductions in PS of 10% per month, and a trend towards larger baseline parenteral volume requirements in the 0.10 mg/kg/day group.

The effect on body composition was evaluated by changes in fat mass, lean body mass and total bone mineral content (BMC). Body weight was registered at all appointments and DEXA-scans were performed at baseline and again at week 24. Body weight was significantly increased in both teduglutide groups at various time points compared to placebo and this finding was mainly due to changes in lean body mass. The total bone mineral content (BMC), was significantly higher in both teduglutide groups compared to placebo, but did not result in significant changes in T and Z-scores.

In both teduglutide groups, a significant increase in small bowel villus height in biopsies was demonstrated. A significant increase in colonic crypt depth was demonstrated in the teduglutide 0.10 mg/kg/day group.

Plasma citrulline, an organic compound derived from the amino acid arginine, is used as a biomarker of a reduced enterocyte mass in SBS. Plasma citrulline was increased in both treatment groups compared to baseline and the absolute changes from baseline in plasma citrulline were significantly ($p < 0.0001$) increased after the 24 weeks of treatment in both treatment groups (15.7 ± 12.7 μmol/L in the teduglutide 0.10 mg/kg/day and 10.9 ± 11.3 μmol/L in the teduglutide 0.05 mg/kg/day) compared to placebo (1.9 ± 5.0 μmol/L). Interestingly, while baseline values tended to be lower in the teduglutide 0.10 mg/kg/day compared to placebo group ($p = 0.051$), this group showed the highest increments.

No significant changes in QoL during treatment with teduglutide were demonstrated.

Patients who completed the placebo-controlled study were given the option to enter an open-label, 28-week extension study ("the 005 study") [70]. Fifty two patients were enrolled for continuous treatment of the same dose of teduglutide (25 patients receiving 0.05 mg/kg/day and 27 patients receiving 0.10 mg/kg/day) for a total length of 52 weeks. As in the initial RCT, the primary efficacy end point was a clinical response defined as reduction of 20–100% in weekly PS volume at week 52 compared to baseline.

Throughout the study period a progressive PS volume reduction was reported in the teduglutide-treated groups, greatest in the 0.05 mg/kg/day group. At week 24 (end of Study 004) 46% of the patients in the 0.05-mg/kg/day group and 25% of the patients in the 0.10-mg/kg/day group had achieved reductions of ≥20% of baseline PS volume. These numbers were 68% and 52% in the respective 0.05 and 0.10 mg/kg/day groups. Translated into ≥1 day(s) off PN, this was achieved in 68% of the patients in the 0.05 and 37% in the 0.10-mg/kg/day group. Four patients completely weaned off from PS (3 during study 004 and 1 during the 28-week extension study). Interestingly, 11 of the 19 non-responders at week 24 became responders and achieved reduction of ≥20% of baseline PS volume at week 52. In comparison, 4 of the 24 responders at week 24 became non-responders at week 52 [70].

An increase in fasting plasma citrulline levels from baseline was seen at week 52 of 68% and 86% in the 0.05 and 0.10 mg/kg/day groups respectively. The levels were decreased, but did not return to baseline levels, by 20% and 32% in the respective groups 4 weeks after end of treatment.

A second phase 3 pivotal study (the "020" or "STEPS" study) was subsequently performed using a similar study design but with a modified PS weaning protocol that allowed for earlier (at week 2 vs. week 4) and more aggressive weaning (10–30% vs. 10%) of the optimized PS volume [71]. Forty-three SBS patients were randomized to a 0.05 mg/kg/day dose of teduglutide and 43 patients to placebo for up to 24 weeks. The proportion of teduglutide treated patients achieving a 20–100% reduction of PS at week 20 and 24 was significantly higher compared to placebo (27/43 patients, 63% versus 13/43 patients, 30%, p = 0.002). Teduglutide treatment resulted in a 4.4 L/week reduction in PS volume from a pre-treatment baseline of 12.9 L/week versus 2.3 L/week from a pre-treatment baseline of 13.2 L/week for placebo at week 24. However, placebo-treated patients significantly increased their oral fluid intake by 1.6 ± 3.6 L/week (p < 0.009) in order to maintain stable target urine output of 1.0–2.0 L/day. In patients treated with teduglutide, urine output continued to increase, indicating increased net fluid absorption. Even at the end of the trial, further weaning appeared possible in patients treated with teduglutide. The significant PS volume reduction with teduglutide translated into additional clinical benefits: At the end of the treatment period (at Week 24), the need for PS infusion was reduced by 1 or more days in more than half of the patients in the teduglutide group (53.8%, 21/39) compared with less than one quarter of those in the placebo group (23.1%, 9/39; p = 0.005) [72].

Post-hoc analyses of the 020 study data have revealed that a positive correlation between baseline PS volume and PS volume reduction with teduglutide treatment (y = –0.3870x + 90.0279, r2 = 0.61; *P* < .0001) [73]. Patient were divided in groups based on bowel anatomy (group 1, jejunostomy/ileostomy; group 2, ≥50% colon in continuity without stoma; and group 3, other colon anatomies), and disease features (with inflammatory bowel disease, mesenteric vascular diseases, or other conditions). The absolute effects of teduglutide on absolute PS volume were significantly greater in group 1 patients (reduction of 919 ± 644 mL/day)—not only compared with patients given placebo (reduction of 340 ± 436 mL/day; *P* = .0112) but also compared with teduglutide-treated patients in group 2 (reduction of 355 ± 306 mL/day; *P* = .0066). Teduglutide had an intermediate effect on patients in group 3. A minority of patients with SBS and inflammatory bowel diseases had colon in continuity (10.5% [n = 2/19]), whereas most patients with SBS and vascular or other diseases had colon in continuity (84.4% [n = 27/32] and 67.6% [n = 23/34], respectively). These findings may inform initial parenteral support volume adjustments and management of these severely disabled patients.

Study 021 was an open label long term extension of study 020 in which teduglutide 0.05 mg/kg/day was evaluated for up to 2 years [74]. A clinically meaningful response was defined as a 20–100% reduction from baseline in weekly PS volume. Eighty-eight patients were enrolled; 37 patients had during the 24 week study (study 020) received teduglutide (TED), n = 39 had received placebo (PBO) and =12 had been optimized and stabilized during 020, but not treated with teduglutide (NT). All patients received daily subcutaneous injections of 0.05 mg/kg/day teduglutide (TED). Thus, the study population included three subgroups of TED/TED, PBO/TED and NT/TED. Including the 24 weeks in 020 study, total exposure to teduglutide was up to 30 months for TED/TED and up to 24 months for the NT/TED and PBO/TED subgroups.

A total of 65 subjects (74%) successfully completed the 2 year study period. 28/30 subjects (93%) in the TED/TED group demonstrated a clinical response with a mean reduction in PS volume from baseline of 7.6 (66%) L/week. This number was 3.1 L/week (28 %) in 16/29 subjects (55%) in the PBO/TED group and 4.0 L/week (39%) in 4/6 subjects (67%) in the NT/TED group.

Overall, TED resulted in clinically meaningful reductions in PS requirements, allowing for additional days off PS per week; 25/65 (38%) subjects achieving an additional ≥3 day/week reduction; 13 patients achieved total independence from PS versus 0 patients at the end of study 020.

The effect on parenteral energy supply was reported only in the first of the two phase 3 teduglutide studies. Reductions in parenteral energy at week 24 of 243 ± 450 kJ/day (p = 0.056), 447 ± 1051 kJ/day (p = 0.030) and 912 ± 1333 kJ/day (p = 0.001) were seen in the placebo group, teduglutide 0.10 mg/kg/day group and teduglutide 0.05 mg/kg/day group, respectively, compared with baseline. However, the reductions in parenteral energy were not significant between

active treatment (teduglutide 0.10 mg/kg/day and 0.05 mg/kg/day) and placebo (p = 0.11) [69].

In the 35-day study with native GLP-2 treatment, the overall increase in energy absorption of 15 MJ translated into a significant increase in body weight of 1.2 ± 1.0 kg (p = 0.010) [55]. The study demonstrated positive findings on urine creatinine excretion (0.7 ± 0.7 mmol/day, p = 0.02), which suggests an increase in muscle mass or increase in renal function in relation to GLP-2 treatment.

In both the placebo-controlled clinical teduglutide phase 3 studies, body weights remained stable in spite of PS reductions. Numerical increases in body weight were seen (0.9 ± 2.1 kg, at week 3 [68], 1.4 ± 2.5 kg, teduglutide 0.10 mg/kg/day, and 1.2 ± 2.8 kg teduglutide 0.05 mg/kg/day at week 24 [69], and 1.0 ± 2.8 kg, teduglutide 0.05 mg/kg/day at week 24 [71]. However, none of these reached statistical significance compared to placebo.

Follow-Up Studies

The post-drug consequences of teduglutide treatment were assessed in a descriptive, follow-up study, following the Study 004 [75]. Data were obtained from clinical visits at 0, 3, 6 and 12 months relative to discontinuation. Thirty-seven patients (25 responders, 12 non-responders) were included and classified according to whether their PS volume decreased (DEC), remained unchanged (NEUT) in NEUT/DEC group or increased in INC group.

During the 12 months post discontinuation, in the responders' group, 12 had increased their PS volume (INC) to pre-drug volumes while n = 13 had maintained the same PS volume or had further PS reduction (NEUT/DEC). Of the three patients who weaned off PS while on teduglutide in NEUT, all remained off PS 12 months post-drug. Accordingly, BMI was decreased at 3, 6, and 12 months INC group (P = 001), but not in NEUT/DEC group. NEU/DEC group was characterized by longer median short bowel length (58 cm vs 35 cm), longer median colon length (85 cm vs 58 cm) and more patients with colon in continuity (92% vs 57%) compared to INC group. Also the PS volume reduction while on drug was greater in INC vs NEUT/DEC (−4.7 vs −1.9 L, P = .04). The complication rate was higher in INC (13 total in 3 patients) than in NEUT/DEC (5 total in 3 patients); corresponding to complication incidence rates per person year of 1.5 for INC vs 0.38 for NEUT/DEC (P < 0.01). The complications consisted of multiple hospitalizations in the three INC patients and one bloodstream infection and four hospitalizations in three NEUT/DEC patients.

Other GLP-2 analogues with longer half-lives than teduglutide are currently under development. It is the hope that instead a lyophilized powder that requires daily injections and reconstitution before use, a more ready-to-use product with the potential weekly of monthly injections may be developed. However, in case of adverse events, a short half-life would be desirable.

Other Pro-adaptive Factors and Combinations

As indicated, numerous growth factors may be involved in the postresectional intestinal adaptation, such as such as glucagon-like peptide-1 (GLP-1), oxyntomodulin, peptide YY, neurotensin, insulin-like growth factor-1, hepatocyte growth factor, vascular endothelial growth factor, cholecystokinin, epidermal growth factor, gastrin, insulin, vascular endothelial growth factor, fibroblast growth factors and keratinocyte growth factor. GLP-2 is just one of many endogenously secreted hormones involved in the process of intestinal adaptation following intestinal resection. Therefore, in theory, other hormones, or inhibitors of their degradation enzymes, individually, or in concert with GLP-2, may have positive effects on the intestinal absorption in SBS patients. Results obtained so far have been demonstrated in preclinical studies and in small, open-label, pilot-studies. In mice, inhibiting dipeptidyl peptidase-IV (DPP-IV), which is a serine protease cleaving dipeptides from the N-terminal end with l-proline or l-alanine at the penultimate position (e.g. GIP, GLP-1 and GLP-2), has been suggested as a novel approach to promote adaptation in SBS patients with preserved L-cell secretion [76, 77]. Other peptides such as peptide YY, glicentin, oxyntomodulin and GLP-1 have also been suggested in the treatment of SBS patients. In a small 1-month study, all five consecutive SBS patients with less than 90 cm of small bowel (4 with colon-in-continuity) experienced improvements in stool frequency and form following treatment with the GLP-1 agonist exanatide [78]. PS was stopped successfully in 3 of the 5 patients. Antroduodenal manometry revealed continuous low amplitude gastric contractions during fasting which completely normalized with exanatide. Another pilot study employing the GLP-1 analogue, liraglutide, showed promising results. In an 8-week, open-label, pilot study, liraglutide was given subcutaneously once-daily to eight end-jejunostomy patients, aged 63.4 ± 10.9 years (mean ± SD) and with small bowel lengths of 110 ± 66 cm. Seventy-two-hour metabolic balance studies were performed before and at the end of treatment. Food intake was unrestricted. Oral fluid intake and parenteral support volume was kept constant. Liraglutide reduced ostomy wet weight output by 474 ± 563 g/day from 3249 ± 1352 to 2775 ± 1187 g/day (P = .049). Intestinal wet weight absorption tended to increase by 464 ± 557 g/day (P = .05), as did urine production by 765 ± 759 g/day (P = .02). Intestinal energy absorption improved by 902 ± 882 kJ/day (P = .02) [79].

Likewise, acute effects were observed on intestinal absorption in nine SBS patients (2 with colon-in-continuity) in relation to infusion of native GLP-1, GLP-2 and co-infusion of GLP-1 and GLP-2 [80]. GLP-1 decreased diarrhea and faecal excretions in SBS patients, but it seemed less potent than GLP-2. The combination of GLP-1 and GLP-2 numerically provided additive effects on intestinal absorption compared to either peptide given alone.

Conclusion

The control of function and adaptation following intestinal resection is complex. Thus, the true understanding and development of adequate measurements of the relevant pathophysiological changes in GI function in the individual patients following intestinal resection remains to be resolved. Over the last decades, an increased awareness of some of the key hormones and their functions has emerged. Pharmaceutical companies are now able to provide these pro-adaptive factors and analogues for the clinical use in SBS patients [81]. However, due to the large patient heterogeneity even within recommended SBS classifications, combined with a large effect heterogeneity related to treatments, an individualised approach will be necessary. A wide range of pro-adaptive agents, used singly or in combination, are suggested as potential as future treatments. Since SBS patients are relatively rare, industry interest may be limited. However, physiological findings related to testing these agents in SBS patients may prove relevant for the understanding of human physiology including signalling and regulation of gut-brain and gut-liver axes, appetite regulation and metabolism, which may also benefit other patient groups in the future.

References

1. Kasper H. Faecal fat excretion, diarrhea, and subjective complaints with highly dosed oral fat intake. Digestion. 1970;3(6):321–30.
2. O'Keefe SJ, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J. Short bowel syndrome and intestinal failure: consensus definitions and overview. Clin Gastroenterol Hepatol. 2006;4(1):6–10.
3. Jeppesen PB, Mortensen PB. Intestinal failure defined by measurements of intestinal energy and wet weight absorption. Gut. 2000;46(5):701–6.
4. Pironi L, Arends J, Baxter J, Bozzetti F, Pelaez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34(2):171–80.
5. Jeppesen PB. Spectrum of short bowel syndrome in adults: intestinal insufficiency to intestinal failure. JPEN J Parenter Enteral Nutr. 2014;38(1 Suppl):8S–13S.
6. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology. 1999;117(5):1043–50.
7. Jeppesen PB. Growth factors in short-bowel syndrome patients. Gastroenterol Clin North Am. 2007;36(1):109–21, vii.
8. Baxter JP, Fayers PM, Bozzetti F, Kelly D, Joly F, Wanten G, et al. An international study of the quality of life of adult patients treated with home parenteral nutrition. Clin Nutr. 2019;38(4):1788–96.
9. Amiot A, Messing B, Corcos O, Panis Y, Joly F. Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome. Clin Nutr. 2013;32(3):368–74.
10. Prahm AP, Brandt CF, Askov-Hansen C, Mortensen PB, Jeppesen PB. The use of metabolic balance studies in the objective discrimination between intestinal insufficiency and intestinal failure. Am J Clin Nutr. 2017;106(3):831–8.
11. Chaudhri O, Small C, Bloom S. Gastrointestinal hormones regulating appetite. Philos Trans R Soc Lond B Biol Sci. 2006;361(1471):1187–209.
12. Nightingale JM, Kamm MA, van der Sijp JR, Ghatei MA, Bloom SR, Lennard-Jones JE. Gastrointestinal hormones in short bowel syndrome. Peptide YY may be the 'colonic brake' to gastric emptying. Gut. 1996;39(2):267–72.
13. Jeppesen PB, Hartmann B, Hansen BS, Thulesen J, Holst JJ, Mortensen PB. Impaired meal stimulated glucagon-like peptide 2 response in ileal resected short bowel patients with intestinal failure. Gut. 1999;45(4):559–63.
14. Nordgaard I, Hansen BS, Mortensen PB. Importance of colonic support for energy absorption as small- bowel failure proceeds. Am J Clin Nutr. 1996;64(2):222–31.
15. Jeppesen PB, Hartmann B, Thulesen J, Hansen BS, Holst JJ, Poulsen SS, et al. Elevated plasma glucagon-like peptide 1 and 2 concentrations in ileum resected short bowel patients with a preserved colon. Gut. 2000;47(3):370–6.
16. Gyr KE, Whitehouse I, Beglinger C, Kohler E, Dettwiler S, Fried M. Human pharmacological effects of SMS 201-995 on gastric secretion. Scand J Gastroenterol Suppl. 1986;119:96–102.
17. Creutzfeldt W, Lembcke B, Folsch UR, Schleser S, Koop I. Effect of somatostatin analogue (SMS 201-995, Sandostatin) on pancreatic secretion in humans. Am J Med. 1987;82(5B):49–54.
18. Reichlin S. Somatostatin (second of two parts). N Engl J Med. 1983;309(25):1556–63.
19. Lembcke B, Creutzfeldt W, Schleser S, Ebert R, Shaw C, Koop I. Effect of the somatostatin analogue sandostatin (SMS 201-995) on gastrointestinal, pancreatic and biliary function and hormone release in normal men. Digestion. 1987;36(2):108–24.
20. Dueno MI, Bai JC, Santangelo WC, Krejs GJ. Effect of somatostatin analog on water and electrolyte transport and transit time in human small bowel. Dig Dis Sci. 1987;32(10):1092–6.
21. Krejs GJ, Browne R, Raskin P. Effect of intravenous somatostatin on jejunal absorption of glucose, amino acids, water, and electrolytes. Gastroenterology. 1980;78(1):26–31.
22. Fuessl HS, Carolan G, Williams G, Bloom SR. Effect of a long-acting somatostatin analogue (SMS 201-995) on postprandial gastric emptying of 99mTc-tin colloid and mouth-to-caecum transit time in man. Digestion. 1987;36(2):101–7.
23. Davis GR, Camp RC, Raskin P, Krejs GJ. Effect of somatostatin infusion on jejunal water and electrolyte transport in a patient with secretory diarrhea due to malignant carcinoid syndrome. Gastroenterology. 1980;78(2):346–9.
24. Lucey MR, Yamada T. Biochemistry and physiology of gastrointestinal somatostatin. Dig Dis Sci. 1989;34(3 Suppl):5S–13S.
25. Bass BL, Fischer BA, Richardson C, Harmon JW. Somatostatin analogue treatment inhibits post-resectional adaptation of the small bowel in rats. Am J Surg. 1991;161(1):107–11.
26. O'Keefe SJ, Haymond MW, Bennet WM, Oswald B, Nelson DK, Shorter RG. Long-acting somatostatin analogue therapy and pro-

tein metabolism in patients with jejunostomies. Gastroenterology. 1994;107(2):379–88.
27. Dharmsathaphorn K, Gorelick FS, Sherwin RS, Cataland S, Dobbins JW. Somatostatin decreases diarrhea in patients with the short-bowel syndrome. J Clin Gastroenterol. 1982;4(6):521–4.
28. Williams NS, Cooper JC, Axon AT, King RF, Barker M. Use of a long acting somatostatin analogue in controlling life threatening ileostomy diarrhoea. Br Med J Clin Res Ed. 1984;289(6451):1027–8.
29. Rodrigues CA, Lennard Jones JE, Thompson DG, Farthing MJ. The effects of octreotide, soy polysaccharide, codeine and loperamide on nutrient, fluid and electrolyte absorption in the short-bowel syndrome. Aliment Pharmacol Ther. 1989;3(2):159–69.
30. Nightingale JM, Walker ER, Burnham WR, Farthing MJ, Lennard Jones JE. Octreotide (a somatostatin analogue) improves the quality of life in some patients with a short intestine. Aliment Pharmacol Ther. 1989;3(4):367–73.
31. Rosenberg L, Brown RA. Sandostatin in the management of non-endocrine gastrointestinal and pancreatic disorders: a preliminary study. Can J Surg. 1991;34(3):223–9.
32. Shaffer JL, O'Hanrahan T, Rowntree S, Shipley K, Irving MH. Does somatostatin analogue (SMS 201-995) reduce high output stoma effluent? A controlled trial. Gut. 1988;29:A1432–3.
33. Gilsdorf RB, Gilles P, Gigliotti LM. Somatostatin effect on gastrointestinal losses in patients with short bowel syndrome. A.S.P.E.N.13th Clinical Congress Abstracts 1989, p. 478.
34. Ladefoged K, Christensen KC, Hegnhoj J, Jarnum S. Effect of a long acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome [see comments]. Gut. 1989;30(7):943–9.
35. O'Keefe SJ, Peterson ME, Fleming CR. Octreotide as an adjunct to home parenteral nutrition in the management of permanent end-jejunostomy syndrome. JPEN J Parenter Enteral Nutr. 1994;18(1):26–34.
36. Nehra V, Camilleri M, Burton D, Oenning L, Kelly DG. An open trial of octreotide long-acting release in the management of short bowel syndrome. Am J Gastroenterol. 2001;96(5):1494–8.
37. Byrne TA, Morrissey TB, Nattakom TV, Ziegler TR, Wilmore DW. Growth hormone, glutamine, and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. JPEN J Parenter Enteral Nutr. 1995;19(4):296–302.
38. Byrne TA, Persinger RL, Young LS, Ziegler TR, Wilmore DW. A new treatment for patients with short-bowel syndrome. Growth hormone, glutamine, and a modified diet. Ann Surg. 1995;222(3):243–54.
39. Scolapio JS, Camilleri M, Fleming CR, Oenning LV, Burton DD, Sebo TJ, et al. Effect of growth hormone, glutamine, and diet on adaptation in short-bowel syndrome: a randomized, controlled study. Gastroenterology. 1997;113(4):1074–81.
40. Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomised, double blind, crossover, placebo controlled study. Gut. 2000;47(2):199–205.
41. Ellegard L, Bosaeus I, Nordgren S, Bengtsson BA. Low-dose recombinant human growth hormone increases body weight and lean body mass in patients with short bowel syndrome. Ann Surg. 1997;225(1):88–96.
42. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study. Gastroenterology. 2003;124(2):293–302.
43. Byrne TA, Wilmore DW, Iyer K, Dibaise J, Clancy K, Robinson MK, et al. Growth hormone, glutamine, and an optimal diet reduces parenteral nutrition in patients with short bowel syndrome: a prospective, randomized, placebo-controlled, double-blind clinical trial. Ann Surg. 2005;242(5):655–61.
44. Johannsson G, Sverrisdottir YB, Ellegard L, Lundberg PA, Herlitz H. GH increases extracellular volume by stimulating sodium reabsorption in the distal nephron and preventing pressure natriuresis. J Clin Endocrinol Metab. 2002;87(4):1743–9.
45. Jeppesen PB, Szkudlarek J, Hoy CE, Mortensen PB. Effect of high-dose growth hormone and glutamine on body composition, urine creatinine excretion, fatty acid absorption, and essential fatty acids status in short bowel patients: a randomized, double-blind, crossover, placebo-controlled study. Scand J Gastroenterol. 2001;36(1):48–54.
46. Wales PW, Nasr A, de Silva N, Yamada J. Human growth hormone and glutamine for patients with short bowel syndrome. Cochrane Database Syst Rev. 2010;(6):CD006321.
47. Drucker DJ, Erlich P, Asa SL, Brubaker PL. Induction of intestinal epithelial proliferation by glucagon- like peptide 2. Proc Natl Acad Sci U S A. 1996;93(15):7911–6.
48. Wojdemann M, Wettergren A, Hartmann B, Holst JJ. Glucagon-like peptide-2 inhibits centrally induced antral motility in pigs. Scand J Gastroenterol. 1998;33(8):828–32.
49. Wojdemann M, Wettergren A, Hartmann B, Hilsted L, Holst JJ. Inhibition of sham feeding-stimulated human gastric acid secretion by glucagon-like peptide-2. J Clin Endocrinol Metab. 1999;84(7):2513–7.
50. Guan X, Karpen HE, Stephens J, Bukowski JT, Niu S, Zhang G, et al. GLP-2 receptor localizes to enteric neurons and endocrine cells expressing vasoactive peptides and mediates increased blood flow. Gastroenterology. 2006;130(1):150–64.
51. Bremholm L, Hornum M, Henriksen BM, Larsen S, Holst JJ. Glucagon-like peptide-2 increases mesenteric blood flow in humans. Scand J Gastroenterol. 2009;44(3):314–9.
52. Bremholm L, Hornum M, Andersen UB, Hartmann B, Holst JJ, Jeppesen PB. The effect of glucagon-like peptide-2 on mesenteric blood flow and cardiac parameters in end-jejunostomy short bowel patients. Regul Pept. 2011;168(1–3):32–8.
53. Cani PD, Possemiers S, Van de WT, Guiot Y, Everard A, Rottier O, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut. 2009;58(8):1091–103.
54. Brubaker PL, Izzo A, Hill M, Drucker DJ. Intestinal function in mice with small bowel growth induced by glucagon-like peptide-2. Am J Physiol. 1997;272(6 Pt 1):E1050–8.
55. Jeppesen PB, Hartmann B, Thulesen J, Graff J, Lohmann J, Hansen BS, et al. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. Gastroenterology. 2001;120(4):806–15.
56. Jeppesen PB, Lund P, Gottschalck IB, Nielsen HB, Holst JJ, Mortensen J, et al. Short bowel patients treated for two years with glucagon-like peptide 2: effects on intestinal morphology and absorption, renal function, bone and body composition, and muscle function. Gastroenterol Res Pract. 2009;2009:616054.
57. Ivory CP, Wallace LE, McCafferty DM, Sigalet DL. Interleukin-10-independent anti-inflammatory actions of glucagon-like peptide 2. Am J Physiol Gastrointest Liver Physiol. 2008;295(6):G1202–10.
58. Sigalet DL, Wallace LE, Holst JJ, Martin GR, Kaji T, Tanaka H, et al. Enteric neural pathways mediate the anti-inflammatory actions of glucagon-like peptide 2. Am J Physiol Gastrointest Liver Physiol. 2007;293(1):G211–21.
59. Henriksen DB, Alexandersen P, Hartmann B, Adrian CL, Byrjalsen I, Bone HG, et al. Four-month treatment with GLP-2 significantly increases hip BMD: a randomized, placebo-controlled, dose-ranging study in postmenopausal women with low BMD. Bone. 2009;45(5):833–42.
60. Munroe DG, Gupta AK, Kooshesh F, Vyas TB, Rizkalla G, Wang H, et al. Prototypic G protein-coupled receptor for the intestinotrophic factor glucagon-like peptide 2. Proc Natl Acad Sci U S A. 1999;96(4):1569–73.

61. Dube PE, Brubaker PL. Frontiers in glucagon-like peptide-2: multiple actions, multiple mediators. Am J Physiol Endocrinol Metab. 2007;293(2):E460–5.
62. Yusta B, Huang L, Munroe D, Wolff G, Fantaske R, Sharma S, et al. Enteroendocrine localization of GLP-2 receptor expression in humans and rodents. Gastroenterology. 2000;119(3):744–55.
63. Bjerknes M, Cheng H. Modulation of specific intestinal epithelial progenitors by enteric neurons. Proc Natl Acad Sci U S A. 2001;98(22):12497–502.
64. Orskov C, Hartmann B, Poulsen SS, Thulesen J, Hare KJ, Holst JJ. GLP-2 stimulates colonic growth via KGF, released by subepithelial myofibroblasts with GLP-2 receptors. Regul Pept. 2005;124(1–3):105–12.
65. Bahrami J, Yusta B, Drucker DJ. ErbB activity links the glucagon-like peptide-2 receptor to refeeding-induced adaptation in the murine small bowel. Gastroenterology. 2010;138(7):2447–56.
66. Marier JF, Beliveau M, Mouksassi MS, Shaw P, Cyran J, Kesavan J, et al. Pharmacokinetics, safety, and tolerability of teduglutide, a glucagon-like peptide-2 (GLP-2) analog, following multiple ascending subcutaneous administrations in healthy subjects. J Clin Pharmacol. 2008;48(11):1289–99.
67. Marier JF, Mouksassi MS, Gosselin NH, Beliveau M, Cyran J, Wallens J. Population pharmacokinetics of teduglutide following repeated subcutaneous administrations in healthy participants and in patients with short bowel syndrome and Crohn's disease. J Clin Pharmacol. 2010;50(1):36–49.
68. Jeppesen PB, Sanguinetti EL, Buchman A, Howard L, Scolapio JS, Ziegler TR, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. Gut. 2005;54(9):1224–31.
69. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011;60(7):902–14.
70. O'Keefe SJ, Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B. Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel intestinal failure. Clin Gastroenterol Hepatol. 2013;11(7):815–23.
71. Jeppesen PB, Pertkiewicz M, Messing B, Iyer K, Seidner DL, O'Keefe SJ, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology. 2012;143(6):1473–81.
72. Jeppesen PB. Teduglutide, a novel glucagon-like peptide 2 analog, in the treatment of patients with short bowel syndrome. Therap Adv Gastroenterol. 2012;5(3):159–71.
73. Jeppesen PB, Gabe SM, Seidner DL, Lee HM, Olivier C. Factors associated with response to teduglutide in patients with short-bowel syndrome and intestinal failure. Gastroenterology. 2018;154(4):874–85.
74. Schwartz LK, O'Keefe SJ, Fujioka K, Gabe SM, Lamprecht G, Pape UF, et al. Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. Clin Transl Gastroenterol. 2016;7:e142.
75. Compher C, Gilroy R, Pertkiewicz M, Ziegler TR, Ratcliffe SJ, Joly F, et al. Maintenance of parenteral nutrition volume reduction, without weight loss, after stopping teduglutide in a subset of patients with short bowel syndrome. JPEN J Parenter Enteral Nutr. 2011;35(5):603–9.
76. Sueyoshi R, Woods Ignatoski KM, Okawada M, Hartmann B, Holst J, Teitelbaum DH. Stimulation of intestinal growth and function with DPP4 inhibition in a mouse short bowel syndrome model. Am J Physiol Gastrointest Liver Physiol. 2014;307(4):G410–9.
77. Okawada M, Holst JJ, Teitelbaum DH. Administration of a dipeptidyl peptidase IV inhibitor enhances the intestinal adaptation in a mouse model of short bowel syndrome. Surgery. 2011;150(2):217–23.
78. Kunkel D, Basseri B, Low K, Lezcano S, Soffer EE, Conklin JL, et al. Efficacy of the glucagon-like peptide-1 agonist exenatide in the treatment of short bowel syndrome. Neurogastroenterol Motil. 2011;23(8):739–e328.
79. Hvistendahl M, Brandt CF, Tribler S, Naimi RM, Hartmann B, Holst JJ, et al. Effect of liraglutide treatment on jejunostomy output in patients with short bowel syndrome: an open-label pilot study. JPEN J Parenter Enteral Nutr. 2018;42(1):112–21.
80. Madsen KB, Askov-Hansen C, Naimi RM, Brandt CF, Hartmann B, Holst JJ, et al. Acute effects of continuous infusions of glucagon-like peptide (GLP)-1, GLP-2 and the combination (GLP-1+GLP-2) on intestinal absorption in short bowel syndrome (SBS) patients. A placebo-controlled study. Regul Pept. 2013;184:30–9.
81. Oke S, Nightingale J, Jeppesen P and the BIFA committee. British Intestinal Failure Alliance (BIFA) Position Statement Use of peptide growth factors for adult patients with intestinal failure. August 2018. https://www.bapen.org.uk/pdfs/bifa/position-statements/use-of-peptide-growth-factors-for-adult-patients-with-intestinal-failure.pdf.

Drug Absorption in Patients with a Short Bowel

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Key Points

1. The movement of a drug in the body (pharmacokinetics—absorption, distribution, metabolism and elimination) is altered in patients with a short bowel or small bowel disease due to a reduction in the surface area for drug adsorption, altered gastric or luminal pH (so preventing ionisation), a loss of the specific area where drug absorption takes place and/or reduced drug metabolism within the intestinal wall.
2. Many physicochemical properties influence absorption of an oral drug. These include its: solubility; stability; particle size; dissolution rate; salt form; acid dissociation constant (pKa); lipophilicity; pH of ionisation; polymorphism and molecular weight.
3. A good understanding of the patient's gastrointestinal anatomy and physiology, and the use of basic pharmacokinetic principles should ensure the prescribed medication elicits a pharmacological response.
4. Caution should be used with drugs that are efficacious within a narrow therapeutic range.
5. A knowledge of the biopharmaceutical classification system (BCS) class helps predict absorption of oral drugs. A drug with high solubility and high permeability (Class I) are absorbed quicker and therefore achieve much faster (time to maximum drug concentration (Tmax)) and higher blood concentrations (Cmax) so there is likely to be some absorption even with a very short bowel.
6. Lipid soluble drugs need a long length of bowel to be absorbed so are likely to be poorly absorbed in patients with a short bowel.
7. The formulation of the drug being prescribed must be considered. One that readily forms a solution is optimal but often a medication that by-passes the upper gastrointestinal tract may be the best option (e.g., parenteral (injection/infusion), topical, buccal or rectal).
8. Carefully monitor the patient (sometimes with therapeutic drug monitoring, if available) for both the desired clinical outcome and adverse drug reactions. With appropriate additional qualifications, the core healthcare professions of the nutrition support team should be able to prescribe medication (in most countries).

Introduction

In many countries, with additional qualifications, the core healthcare professions of the nutrition support team (NST) may be legally allowed to prescribe medications. An understanding of how the prescribing of medications for patients with a short bowel (SB) differs from prescribing for patients who have a normal functioning complete gastrointestinal tract (GIT) is critical. The pharmacokinetics of drugs can be altered in SB patients and there need to be strategies that ensure that the desired pharmacological outcome is obtained from the prescribed drug.

This chapter gives a guide on how to better predict the degree of absorption of medications in this heterogeneous group of patients with a SB. Since there is little or no published information on the drug absorption of most individual medicines in patients with a SB (except warfarin, digoxin, cyclosporine, nortriptyline and procainamide [1]), it is necessary to apply basic pharmacokinetic principles to predict the absorption of oral medications (Table 1).

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Table 1 Factors that influence drug absorption in patients with a SB (adapted [1, 2])

Physiological factors
Remaining small bowel length
Condition (integrity) of remaining bowel
Intestinal motility (e.g. fast gastric emptying in jejunostomy patients)
Area where drug is normally absorbed (intact and with good integrity)
Perfusion of the bowel
Presence of bile and mucus
Biotransformation through gut bacteria
Physicochemical properties
Formulation of drug (tablet, capsule, elixir, enteric coated etc.)
Rate/extent of drug absorption
Drug solubility (ability to for a solution) and dissolution time/rate
Stability
Particle size
Salt form
Acid dissociation constant (pKa)
Lipophilicity
pH of ionisation
Polymorphism
Molecular weight
Physiological requirement of drug (acid, alkaline, bile salts, enterohepatic recycling, ileal absorption, specific receptors, drug interactions, food)
Binding and localising in tissues

Introduction to Pharmacokinetics

The word pharmacokinetics is formed from two Greek words; *phamakon* meaning drug and *kinetikos* meaning movement [3]. Pharmacokinetics is often said to be the effect of the body on the drug whilst pharmacodynamics is the effect of the drug on the body. Pharmacokinetics follows the movement of medication through the body from intake or administration to excretion [3]. Pharmacokinetics has four main components:

- **A**bsorption (how the drug enters the systemic circulation)
- **D**istribution (where the drug is dispersed once in the circulation, including binding and storage)
- **M**etabolism (how it is transformed or inactivated)
- **E**xcretion (how it is eliminated from the body)

This forms the acronym ADME.

Pharmacokinetics provides a quantitative and temporal concentration profile of the drug in the patient. Clinical teams may use this to predict how likely a drug is to be adsorbed from the GIT of a patient with a SB.

When considering the pharmacokinetics of a drug, the first step is to identify if the drug is acting locally or systemically. Locally acting drugs are applied only to the areas where they are needed. These include nasal sprays, inhalers, eye drops and topical preparations. Topical medication is often prescribed to manage luminal GIT conditions such as ulcerative colitis (e.g. mesalazine or steroid suppositories or enemas). Systemic drugs are those that enter the blood stream/systemic circulation (from oral or parenteral routes) and are delivered via the circulatory system to the targeted site of action. Sufficient amounts of an active form of the medication must reach the site of action to elicit a pharmacological response. The target cells for some medications are within the lumen of the GIT (e.g. loperamide) [3].

Absorption and Bioavailability

The most common route of medication administration is oral, and the most common formulations are solid such as tablets and capsules. Alternatively, intravenous drug administration ensures that the entire dose enters the systemic circulation, with bolus delivery allowing for high drug concentrations to be rapidly achieved or continuous infusion used to give a more even and constant concentration and response. Only the intravenous route can achieve a desired plasma concentration very rapidly [3, 4] thus it may appear a desirable route for SB patients; however, there are disadvantages with this route:

1. Only a limited number of drugs are formulated for intravenous use.
2. Long-term intravenous access and its maintenance is needed for drugs requiring regular use.
3. The patient will require training on the safe administration of drugs and the disposal of used ancillaries.
4. There is a risk of sepsis and venous thrombosis.
5. In England primary care providers are not able to prescribe many drugs formulated for intravenous use and the additional ancillaries needed for safe administration.

Drug bioavailability is the amount of medication that reaches the systemic circulation, for example oral drug bioavailability is the amount of drug absorbed from the GIT. It ranges from 1, meaning 100% of the drug reaches the systemic circulation, to 0, meaning none of the drug reaches the systemic circulation [4]. Oral bioavailability is usually determined in early phase clinical studies and tends to be based on healthy male individuals. The given value for an individual drug is usually available from the pharmaceutical company that manufactures the drug.

The highest concentration is termed the maximum concentration, Cmax. The time that the maximum concentration is reached is Tmax. (Fig. 1) Both Cmax and Tmax are dependent on the rate at which the drug enters and is removed from the body [1, 4]. Drugs that reach their Tmax quickly tend to

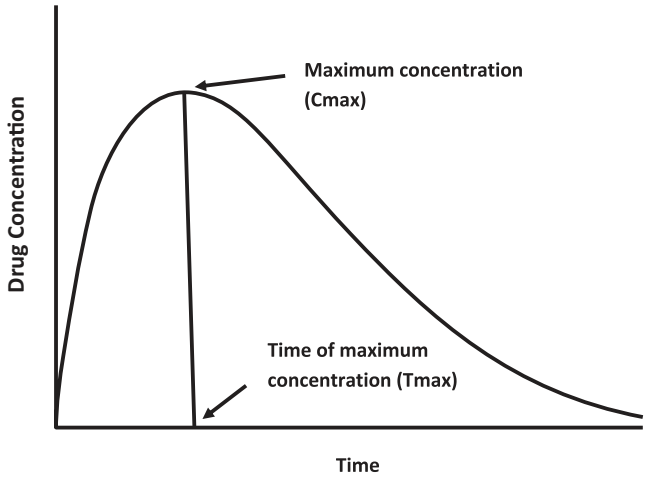

Fig. 1 Drug plasma concentration profile

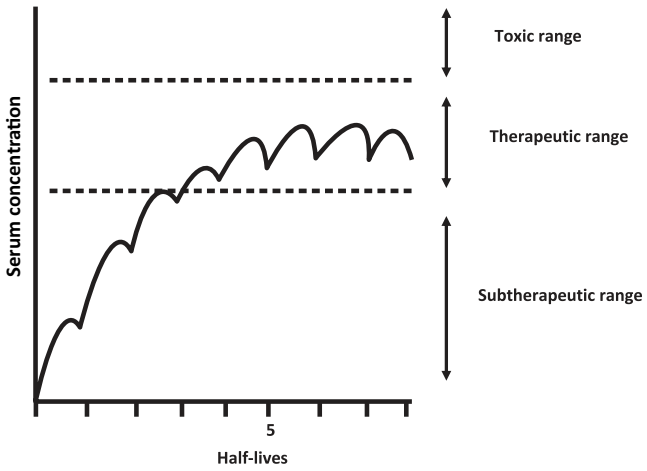

Fig. 2 Therapeutic range of a drug

be absorbed higher in the GIT so are more likely to absorbed in patients with SB (e.g., fluconazole's Tmax ranges from 0.5 to 1.5 h in the fasting state compared to amlodipine's range of 6–12 h post oral administration [5]).

Therapeutic Range of a Drug

The therapeutic range is the concentration range in which the drug is eliciting a therapeutic response [6]. If the amount of drug absorbed is too low then the concentration will fall below the minimum needed to elicit the desired pharmaceutical response and so result in treatment failure, too high and it results in toxic adverse effects (Fig. 2). As patients with SB have numerous additional factors that can alter the drug absorption quite significantly from day to day, drugs with a narrow therapeutic range should be avoided if alternative options are available. Drugs with a narrow therapeutic range are those where small changes in blood concentration can result in serious drug failure very quickly and should be closely monitored for adverse drug effects if prescribed (e.g. warfarin, digoxin, cyclosporine, phenytoin, aminoglycosides and lithium). A higher dose than recommended by the manufacturer, off label/off licensed, (see below) is often needed to compensate for malabsorption of a drug in SB patients. In this case great care must be taken to monitor for adverse drug effects; a list of these are provided by each drug manufacturer. All drugs have a therapeutic range, drugs with a wide therapeutic range are most desirable for SB patients as these have a wider margin of safety.

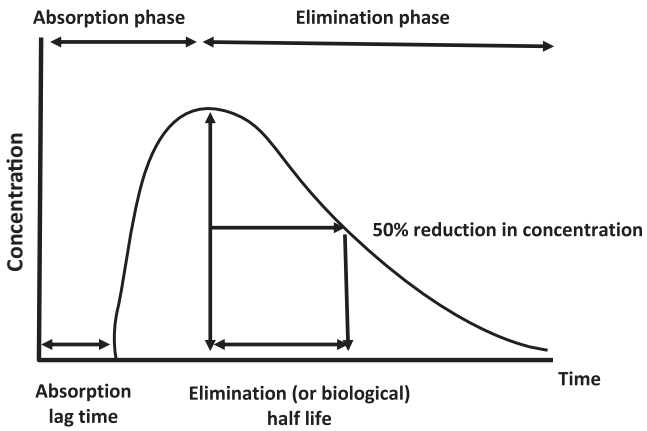

Fig. 3 Area under the concentration-time graph and half-life of a drug

The area under the concentration-time graph (AUC) is a measure of the total systemic exposure the drug measured [7]. The concentration profile before the peak is a measurement of how quickly the drug enters the circulatory system and after the peak would be a measurement of how fast the drug is eliminated from the body. The half-life (T1/2) is the time taken for the plasma concentration of the drug to fall by half [3, 4] (Fig. 3). With regular dosing and any required initial drug loading regimens, in line with the manufacture's recommendations, it takes approximately five half-lives for a drug to reach steady state (Fig. 2). Steady state is when the levels of a drug will stay within the therapeutic range for prolonged periods, if the dosing and the rate of absorption remains unchanged

[8]. Careful consideration needs to be given when prescribing drugs with long half-lives for patients with a SB, as reaching steady state is needed to achieve a pharmaceutical outcome (e.g., the concentrations of antibiotics need to remain within their therapeutic range to ensure optimal treatment).

Drug Absorption from the Gastrointestinal Tract

Formation of a solution is a prerequisite for drug to be absorbed from the GIT. For example, drugs in the solid formulations (tablets and capsules) must first be broken down to allow liberation of the drug from the protective outer casing—called *disintegration*. Once disintegration has occurred the drug can form a solution—called *dissolution*. However, different formulation systems pose challenges. Some capsules and tablets are designed to remain intact for several hours after ingestion and/or only to disintegrate at a specified pH (modified-release/sustained-release preparations) [4]. There are some capsules that have both rapid and prolonged release profiles, and some drugs that once liberated from the main protective capsule or tablet coating, are themselves coated for targeted purposes. For this reason, prolonged release preparations (e.g., enteric coated steroids) are best avoided in SB patients as they are likely to pass through the short length of gut unchanged and without being absorbed.

The rate of gastric emptying is altered in SB patients and so affects the rate of drug absorption. Rapid or increased gastric emptying (e.g., in patients with a high jejunostomy) (chapter "Physiology and Problems of a Short Bowel") may reduce the time available for disintegration and dissolution, and the exposure time to an acidic pH (if the patient is not taking a PPI). For example, when metoclopramide (which promotes gastric emptying) is administered with digoxin, the absorption of digoxin is reduced while the absorption of paracetamol, aspirin and tetracycline is increased. Drugs such as codeine and loperamide are often used in patients with a high output stoma to slow intestinal motility so slowing transit, with the aim of increasing small bowel absorption [9].

Ultimately, the rate of absorption mainly depends upon the time period the medicine is in contact with an appropriate region of cell membrane (Fig. 4). If a medicine does find itself at such an appropriate site that absorption can take place, assuming it has dissolved (is in solution), it can then permeate the cell membrane. In general there are four ways in which medicines can cross the cell membrane. These are via passive diffusion (directly through the lipid membrane); active transport (transporter mediated); facilitated passive diffusion (channel or carrier protein mediated); and pinocytosis (literally meaning cell drinking).

Passive diffusion is where molecules that are small enough can move from a region of higher concentration to a region of lower concentration through a selectively permeable membrane down a concentration gradient. This is the simplest form of transport, not requiring any energy or special transporters. As cell membranes are amphipathic, have both hydrophilic and hydrophobic regions, small lipid soluble molecules diffuse most readily. Most medicines are either weak acids or bases and therefore exist in either an ionised or un-ionised form when in solution. The un-ionized forms are usually lipid soluble and can diffuse readily across the cell membrane. However, the proportion of ionised and un-ionised forms present at any specific region is also influenced by the pH and pKa. Simplistically, medicines that are weak acids are better absorbed in acidic environments and weak bases prefer more alkaline environments, where their un-ionised forms predominate. Strong acids (pKa less than 3) and strong bases (pKa 10 or above) are poorly absorbed as they are fully ionised [4]. pKa is an acid dissociation con-

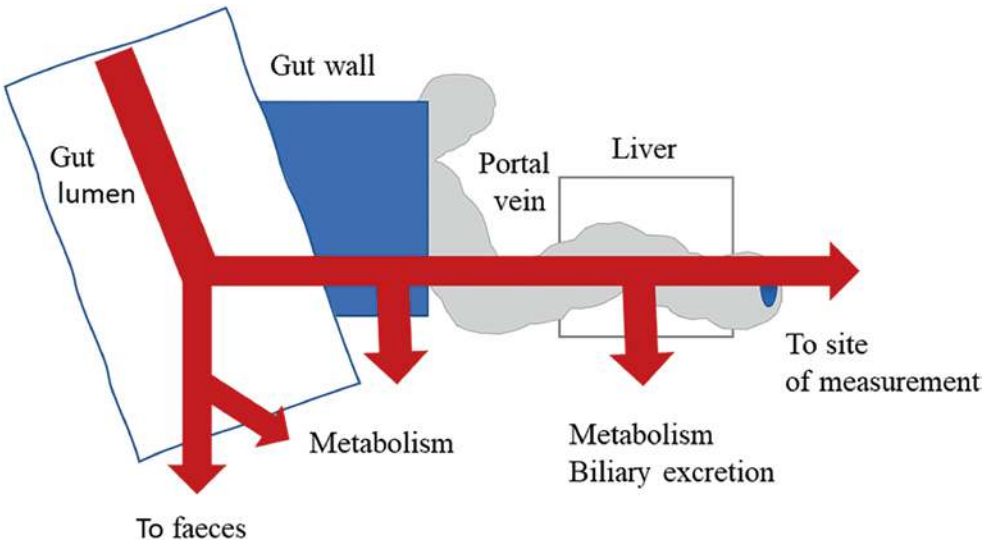

Fig. 4 Factors controlling drug absorption

stant and should not be confused with pH. Absorption will occur at the site in the GIT where the pH is optimal to allow sufficient drug molecules in the non-ionised form to be absorbed into the enterocytes [10]. In reality, the majority of a drug is actually absorbed from the small intestine due to the far greater surface area and epithelia specifically evolved to be more permeable. In relation to gases for inhaled medicines, the same principle applies, but here we refer to the gradient as partial pressures of the gas.

Active transport does require energy and occurs even against a concentration gradient. For molecules to utilise this method, the molecule must attach itself to carrier proteins or transporters found on the membrane surface. The rate of absorption is now dependent on the number of compatible transporters that are expressed on the surface of the membrane and are prone to saturation. Transporters come in many various forms, but the one thing they have in common is that they have evolved to extract those nutrients that we cannot synthesise ourselves. For this reason, most of the medicines that use this method of absorption tend to resemble these nutrients such as vitamins, minerals, amino acids, etc. For the same reason many transporters are only found in certain regions of the GI tract.

Facilitated passive diffusion can apply to those molecules that are not lipid soluble but seem to move through the membranes quite easily, again without the utilisation of energy down a concentration gradient. This is because membranes also contain various channels and carrier proteins that act like small tubes or funnels connecting the outside to the inside. These channels and carrier proteins exist to allow ionised nutrients to be absorbed and so certain medicines can borrow these channels in a similar way to active transporters. The rate of absorption is dependent on the number of compatible channels or carrier proteins that are expressed on the membrane.

Pinocytosis is where external products are engulfed through invagination of the cell membrane to produce a vesicle holding the product inside the cell. This route of absorption is rarely utilised in drug design.

Absorption of drug molecules is also determined by the mucous layer, the expression and regulation of tight junctions, and the presence of trans-porters and enzymes in epithelial cells [10]. The expression of tight junctions differs between the stomach, small intestine and colon thereby affecting the rate of passive paracellular drug absorption within each region. This difference results in a relatively leaky barrier in the small bowel (most leaky in jejunum and less so in ileum), and most efficient epithelial junctions within the gastric and colonic mucosa [10]. The intestinal absorption of a few drugs depends on carrier-mediated transport; levodopa is absorbed via a carrier which usually transports phenylalanine and fluorouracil is absorbed via a carrier which usually transports natural pyrimidines. Calcium is absorbed via a vitamin D-dependent carrier system and iron is absorbed in the jejunum via specific carriers in the mucosa [4].

The most common limiting factor to drug absorption via the GIT is poor aqueous solubility and permeability of a drug molecule. In order for permeation through the GIT membranes to occur, the active ingredient of the drug must first dissolve in gastrointestinal fluids. Hence, drugs which are poorly water soluble will display dissolution rate-limited absorption [11].

The upper small intestine has a relatively high blood flow and contains long villi, which increase the surface area, as well as having an optimal pH for drug absorption. Although drugs can be absorbed in other regions of the gastrointestinal tract, the upper small intestine is the site of most absorption. Minimal drug absorption occurs in the large intestine although some slow-release drugs are absorbed here, as well as drugs such as 5-aminosalicylates where their main target is the large intestine. Patients with a colostomy and an intact small intestine are unlikely to experience significant issues with drug absorption [9].

Studies conducted in rats have demonstrated that drug absorption from the colon is of little significance. The presence of efficient epithelial cell junctions within the colon is one explanation for the negligible paracellular absorption at this site within the gut. Also, due to the colon's active role in water absorption, the colonic contents are highly viscous which leads to decreased dissolution and diffusion through the membrane of the dissolved drug molecules. As a result of this, drugs released in the colon remain exposed to the colonic mucosa for prolonged periods compensating to some extent for the decreased surface area for drug absorption [12]. Consideration should be given when prescribing rectal drug formulations in SB patients if a systemic effect if desired.

Following bowel resection (+/− stoma formation) there is a relationship between remaining small intestine length and drug absorption. Patients with SB experience impaired absorption of macro- and micronutrients as well as fluids and drugs. Another important factor is the quality of the remaining bowel, particularly in patients with underlying disease. Patients with Crohn's disease may experience absorption issues despite having a normal length of remaining small intestine. In Crohn's disease active inflammation reduces villi contact and luminal permeability, and stricturing can prevent tablets and capsules from reaching the necessary absorption sites and in other situations may slow transit allowing more time for absorption [9]. Relieving the stricture in some cases can lead to changes in absorption as the transit times suddenly change, so it is important to always monitor drug efficacy and safety whenever an anatomical change occurs.

Worsening of inflammatory disease can also be a result of reduced bioavailability of oral drugs such as azathioprine and budesonide, therefore leading to increased inflammation, disease progression and further intestine resections. Coeliac disease patients, if untreated have villous atrophy and a reduced functional absorptive area so will have problems in absorbing some medications [9].

Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS) is used by: the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Health Organisation (WHO) to standardise data relating to the aqueous solubility (disintegration and dissolution) and absorption (permeability) of oral drug formulations made by different manufacturers. The drugs are classified in BCS according to solubility, permeability, and dissolution tests (Table 2). All drugs have had to be classified with this system since 2000.

Solubility: A drug substance is considered "highly soluble" when the highest single therapeutic dose strength is soluble in 250 mL or less of aqueous media over a pH range of 1–6.8 at 37 ± 1 °C. At least three pHs within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated, including solubility at the pH of lowest solubility if it is within the specified pH range and should demonstrate that solubility is maintained over relevant timeframes to accommodate the expected duration of absorption [13].

Permeability: A drug substance is considered to be "highly permeable" when the extent of the absorption (parent drug plus metabolites) in humans is determined to be ≥85% of an administered dose, based on absolute bioavailability or mass balance determination i.e., comparison of bioavailability between intravenous and non-intravenous (in this case oral) routes of administration. Alternatively for permeability non-human systems can be used (such as in-vitro culture methods—e.g., Caco-2 cell lines) [13].

A product is considered rapidly dissolving when no less than 85% of the labelled amount of the drug substance dissolves within 15 min in the following media: 0.1 M HCl or simulated gastric fluid or pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid. The BCS Database is open access and can be found on the internet [13]

BCS Class I (high permeability and high solubility) medications are likely to have a lower time to maximum concentration and more likely to be adequately absorbed even in patients with a very short bowel. Examples include metoprolol and paracetamol. See Tables 4, 5 and 6 at the end and the BCS Database (which can be accessed via http://www.ddfint.org) for more examples of commonly prescribed drug's BCS class and Tmax.

Examples of Tmax and biopharmaceutical classification for many commonly used drugs are given in Tables 3, 4, and 5.

Table 2 Biopharmaceutics classification system

Solubility \ Permeability	*High*	*Low*
High	Class I	Class III
Low	Class II	Class IV

Table 3 Common antibiotics and predicted absorption in patients with a SB

Class	ABx	Absorption site	BCS	Tmax (h)
Penicillin[a]	Amoxicillin	Absorbed in the duodenum and jejunum, reduced absorption in ileum, not absorbed in colon [14]	Class IV (high solubility at lowest dose)	1.5
	Flucloxacillin	Unknown	–	–
	Penicillin V	Unknown	Class I	–
Cephalosporin	Cefalexin	Not absorbed in the stomach. Absorbed mainly in upper intestine: mainly in duodenum, reduced absorption in jejunum [15, 16]. (One paediatric study found 10–50% reduction in absorption in children with extensive small bowel resection, but therapeutic range was still achieved) [17]	–	1
Marcolides[a]	Erythromycin	Absorbed mainly in the duodenum [16]. Limited evidence suggesting some absorption in jejunum and ileum	Class II	1[b]
	Azithromycin	Absorbed mainly in the duodenum [18]	Class II	2–3
	Clarithromycin	Absorbed throughout whole GI tract [16]	Class II	–
Quinolones	Ciprofloxacin	Absorbed mainly in upper GI tract/duodenum, limited absorption in jejunum (higher doses maybe needed/consider alternative routes) [16, 19]	Class III	1–2
	Levofloxacin	Absorbed mainly in upper GI tract/duodenum, limited absorption in jejunum (higher doses maybe needed/consider alternative routes) [16]	Class III	1–2

Table 3 (continued)

Class	ABx	Absorption site	BCS	Tmax (h)
Tetracycline	Doxycyline	Mainly absorbed in the duodenum [20]	Class IV	2–4
	Minocylcine	Absorbed in stomach, duodenum and jejunum, but Less suitable for prescribing as per BNF due to higher risk of lupus-erythematosus-like syndrome	–	–
Others	Linezolid	Unknown. (absorption start in stomach and continued in small intestine, maybe limited if administered directly in jejunum) [16]	Class IV	2
	Trimethoprim/ Co-trimoxazole	Unknown. One paediatric study found 10–50% reduction in absorption in children with extensive small bowel resection, but therapeutic range was still achieved [17]	Class IV (high solubility at lowest dose)	1–4
	Metronidazole	Unknown, no studies (well absorbed in the small intestines) [16]	Class IV (high solubility at lowest dose)	1–2
	Rifampicin	Animal studies suggests maximum absorption in the stomach [21]	Class II	2–4 (on empty stomach)
	Isoniazid	Animal studies suggest poor absorption in stomach, mainly absorbed in duodenum, jejunum and ileum [21]	Class III	–

[a] NB: a small study in five children with SBS (>100 cm SB resection) found inadequate absorption of oral penicillin and macrolide to achieve therapeutic concentrations. Author suggested alternative routes of administration [14]
[b] Calculation based on erythromycin ethylsuccinate granules

Table 4 Common antifungal and antivirals drugs and predicted absorption in patients with a SB

Antifungal/antivirals	Absorption site	BCS	Tmax (h)
Fluconazole	Unknown (absorbs well in post-pyloric enteral tubes) [22]. Conflicting recommendations from various guidelines/sources regarding dose adjustments in jejunal administration [16]	Class III	0.5–1.5 (fasting state)
Voriconazole	Unknown (studies show similar absorption in administration via jejunostomy and oral administration) [23]	Class II	1–2
Aciclovir	Upper GI tract—potentially duodenum? (Poor bioavailability even in normal individuals—15–30%) [24–26]	Class IV	–

Table 5 Predicted absorption of drugs commonly prescribed (in the UK) to patients with a SB

Drug class	Drug name	Tmax (h)	BCS class	Comments
Analgesics	Paracetamol [27–29]	0.5–1	I	–
	Codeine Phosphate [27, 30]	1	I	–
	Morphine, liquid [29, 31, 32]	0.25	III	Morphine undergoes significant first pass metabolism in the liver resulting in a systemic bioavailability of approximately 25%
	Oxycodone [27, 33, 34]	1–1.5	IV	This is for immediate release oral formulations
	Fentanyl [27]	–	–	Undergoes significant first pass metabolism in the liver, buccal absorption is used to bypass GIT absorption
	Gabapentin [27]	2–3	III	Absorbed from the proximal small bowel
	Pregabalin [27, 35]	1	I	–
Antiarrhythmics	Bisoprolol [27]	1–3	I	–
	Atenolol [27]	2–4	III	–
	Digoxin [27]	1.5	III	Proximal small bowel
	Amiodarone [29, 36]	4.5	II	The Tmax is recorded when oral tablet administered with food
Anticoagulants	Warfarin [27]	3–6	II	–
	Rivaroxaban [29, 37]	2–3	II	Oral bioavailability increased when taken with food
	Apixaban [29, 38]	3–4	III	–

(continued)

Table 5 (continued)

Drug class	Drug name	Tmax (h)	BCS class	Comments
Anticonvulsants	Sodium valproate [29, 39]	5	I	–
	Phenytoin [27]	2–4	II	–
	Levetiracetam [27]	1–1.5	I	–
	Lorazepam [27]	2	I	–
	Carbamazepine [27]	2–liquid 6–chewable tablets 12–tablets	II	–
Antidepressants	Citalopram [27]	2–4	I	–
	Fluoxetine [27]	6–8	I	–
	Amitriptyline [29, 40]	4	I	–
	Mirtazapine [27]	2	I	–
	Venlafaxine [27]	2	I	–
Antiemetics	Cyclizine [29, 41]	2	I	–
	Ondansetron [27]	1–1.5	I	–
	Metoclopramide [27]	0.5–2	III	–
Antihypertensives	Ramipril [27]	2	I	–
	Doxazosin [27]	2–4	I	–
	Losartan [27]	1	II	–
	Lisinopril [27]	7	III	–
	Amlodipine [27]	6–12	I	–
Antihyperglycemics	Metformin [27]	2.5	III	The effective permeability at the proximal and distal small bowel is similar
	Gliclazide [29, 42]	2–4	II	–
Diuretics	Furosemide [27]	1	IV	Jejunum
	Bumetanide [29]	1–2	II	–
	Bendroflumethiazide [43]	2	–	–
	Spironolactone [27]	1–4	II	–
Sedatives	Zopiclone [29, 44, 45]	1–1.5	I	Time to peak plasma levels has been delayed in cirrhotic patients (from 2 to 4 h)
	Haloperidol [27, 29]	3–6	II	–
	Temazepam [27, 29]	1	II	–
	Midazolam [29, 46]	0.5–1	I	After oromucosal administration midazolam is absorbed rapidly
lipid-lowering medications	Simvastatin [27]	1–2	II	–
	Atorvastatin [27]	1–2	II	–
	Pravastatin [27]	1.5	III	–
Proton Pump Inhibitors	Omeprazole [27, 29]	0.5	II	Proximal to mid–small bowel
	Lansoprazole [27]	2	I	–
	Esomeprazole [27, 29]	1–2	II	Proximal small bowel
	Levothyroxine [27]	2	III	Jejunum
Others	Alendronic Acid [27, 47]	1	III	Better absorbed from jejunum than the duodenum

Table 6 Pharmacokinetics of loperamide formulations [68–72]

Preparation	Onset of action (h)	Half-life (h)	Cost for 2 mg dose (£)
Loperamide syrup 1 mg/5 mL	1	11	0.11
Loperamide capsules	1	11	0.04
Loperamide tablets	1	11	0.05
Loperamide melts	1	11	0.76

Drug Formulations and Routes of Administration for SB Patients

Due to the difficulties of obtaining good oral absorption in SB, alternative routes or methods often need to be considered. When switching from one route of administration or formulation to another, there are potential issues which need to be considered (e.g., with or without food, avoidance of certain foods etc.) and additional monitoring may be needed.

For some medications such as mesalazine, the release profile and therefore the desired effect of the medication differs between brands. For example, Asacol® is released in the terminal ileum and large intestine whereas Pentasa® begins to release from the duodenum, therefore depending on where the desired effect is intended can be affected by the brand of medication prescribed. Brands may also have differences in their licensed indications therefore may not be licensed to be prescribed for the same indications as other brands of the same active drug.

Switching formulations are often made with good reason, for example swapping to liquid preparations can help in administration via an enteral tube and reduce the chances of the tube becoming blocked compared to the administration of crushed tablets. Also, as mentioned above, in SB switching from a modified release to an immediate release formulation allows for better absorption, but switching may lead to dosing changes and potentially more frequent drug administration.

Another difference between various brands of the same active drug or between formulations of the same drug of the same brand are the excipients. Excipients are the constituents of a drug apart from the active substance. These can include fillers, disintegrants, lubricants, colouring, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring, aromatic substances etc., as well as the constituents of the outer covering of the medicinal products, e.g. gelatine capsules [48]. Excipients change when switching from one formulation to another and some of these excipients may not be well tolerated by patients. For example, when switching to liquid preparations, some may contain sweeteners such as sorbitol which can worsen high output stomas, or they may contain alcohol which may not be appropriate for some patients due to their religious beliefs.

Oral bioavailability of medicines can also change when switching from one formulation to another. For example, digoxin tablets and liquid are not bioequivalent therefore dose adjustment may be required. In practice this change is made safer as digoxin levels are closely monitored, however this is not always the case with other drugs. When switching from oral opioids to topical patches adequate pain relief must be maintained. Often a dose reduction is required when switching from oral opioids to patches and this can lead to a subtherapeutic effect [49].

Alternative Routes of Administration in SB Patients

When switching routes of administration (e.g. between oral to oro-mucosal, transdermal, rectal, parenteral, etc.) or formulations of the same drug or to a different drug it is important to ensure the desired clinical effect is still achieved. The switch must be done carefully while understanding the pharmacokinetics of the medication, so the correct dose is prescribed. Once a change is made, monitoring for side effects and efficacy is also important and comes under the prescribing responsibilities.

Oro-mucosal Route

The oro-mucosal route of drug delivery involves two methods, buccal and sublingual.

The buccal mucosa lines the inner cheek and is made of a thin layer of keratinised and non-keratinised epithelia. Drug absorption occurs through the non-keratinised sections of the mucosa. Buccal formulations are placed in the mouth between the upper gums and cheek and absorption into the systemic circulation occurs via the brachiocephalic vein [50].

Some drugs are extracted and metabolised to inactive forms by the liver and sometimes the GIT wall, this is known as first pass or presystemic metabolism. This results in reduced oral bioavailability which can be problematic in patients with SB who already experience reduced absorption after oral administration. Drugs that undergo first pass metabolism include levodopa, propranolol, and verapamil [4].

The advantages of the buccal or sublingual route are that drugs avoid hepatic first pass metabolism as they are absorbed straight into the systemic circulation. The extensive blood supply and permeable membranes make the oro-mucosal route an attractive one for drug delivery. Onset of action is rapid, for example in the case of glyceryl trinitrate in angina. Drug delivery can be better predicted as there is avoidance of numerous pH changes that would be encountered as the drug travel through the gastrointestinal tract. Administration is easy and more appealing to patients in comparison to injections, for example administration of buccal prochlorperazine for nausea and vomiting compared to intravenous cyclizine, which is often used in the UK [51]. If longer term antiemetics are required, buccal prochlorperazine is considered when oral tablets have either not worked or not been well tolerated by patients. In general, using the buccal route can avoid changes in gastrointestinal motility and gastric secretion which can be associated with nausea [52].

Problems can occur however as absorption through this route may be erratic due to the production of saliva which can wash away the drug thereby reducing contact time. Taste

or local irritancy can affect patient adherence. Large, hydrophilic molecules are often not permeable through the membrane and therefore not suitable via this route [51].

The availability of an oro-mucosal formulation option may not automatically mean the drug is absorbed through the buccal or sublingual route (e.g., loperamide and omeprazole). Such preparations result in the disintegration and dissolution only starting in the buccal cavity with the aim of increasing time for absorption and or contact time with the target receptors in the gut, when the drug is in solution [53, 54]. However, drugs such as fentanyl are absorbed directly from the buccal cavity so avoiding first pass metabolism by the liver [55].

Transdermal

The transdermal route of administration is often more desirable to patients as it avoids the oral route altogether, therefore reducing the daily pill burden, reduced GIT absorption issues and potential for GIT side effects of medications is reduced. This route is particularly useful for patients with SB where taking oral medications can cause nausea and vomiting or in whom bowel transit time is too short and therefore the drug is not absorbed. This route of administration is usually in the form of creams, ointments, gels or as patches applied directly to a non-hairy part of the skin which can be hidden under clothing. The pharmacokinetic profiles for medications via the transdermal route provide fewer peaks than with the oral route therefore reducing occurrence of toxicity [56]. Not many drugs can be administered via this route as the drug needs to pass through several layers of skin before it reaches the dermal layer where it can then enter the systemic circulation. The two routes through the skin are intercellularly, usually lipophilic molecules, or intracellularly, usually hydrophilic molecules [56].

For example, in SB, the oral route for opioids is not always effective therefore some patients may be prescribed analgesia via the transdermal route in the form of patches. It is important to note that when switching from an oral formulation to patches, dose modifications may be required. Opioids tend to be the most common class of drug prescribe for SB patients using the transdermal formulation route. Available transdermal preparations, such as fentanyl and buprenorphine, are not suitable for acute pain or in patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. The total daily dose of oral morphine can be switched to an approximate equivalent strength of fentanyl and buprenorphine patches. For example, morphine salt 12 mg daily is approximately equivalent to a buprenorphine 5 μg patch and morphine salt 20 mg daily is approximately equivalent to a fentanyl 12 μg patch. However, when switching due to possible opioid-induced hyperalgesia, the calculated equivalent dose of the new opioid should be reduced by one-quarter to one-half [57, 58].

Another advantage are that formulations of buprenorphine transdermal patches are available as 72-hourly, 96-hourly and 7-day patches. It is important to note the buprenorphine patches come in various brands which all have different pharmacokinetic properties, and this should be taken into account if a patient is to switch from one brand to another [58].

When evaluating the analgesic effect, the patch should be worn for 24 h before making a change to allow for the gradual increase in plasma concentration (e.g. of fentanyl) and previous analgesic therapy should be phased out gradually from the time of first patch application as it can take 20 h or more for the plasma-fentanyl concentration to decrease by 50% [57, 58]. Patients should be warned to remove old patches when placing a new patch as the old patch may continue to provide sub-therapeutic doses of the drug in addition to the new patch and could lead to overdose. In addition changes in temperature have been known to increase drug absorption, with pyrexia, hot bath or sauna or the application of heat to the patch increasing local skin blood flow and hence increase absorption of the drug leading to overdosing [59].

When conventional treatment does not work an alternative analgesia to opioids is a lidocaine patch. However, lidocaine medicated plasters are only licensed for neuropathic pain associated with post-herpetic neuralgia as there is not enough evidence on lidocaine to support neuropathic pain (on its own) or for management of any other pain both acute or chronic but has been used in SB patients. This use is off label/ off license.

Parenteral Administration

Parenteral refers to administering medications without going through the digestive system. The word “parenteral” comes from the roots ‘para-’, or ‘outside of’, and ‘-enteral’ which refers to the alimentary, or digestive, system. The most common parenteral routes of drug administration are intravenous, intramuscular and subcutaneous [60].

The advantages are that it can be used for drugs that are poorly absorbed, degraded, or ineffective if given orally and has predictable pharmacokinetics in SB patients, intravenous administration provides immediate quick onset of action with 100% bioavailability. However, it is invasive, can lead to bruising, bleeding and blood clots at the infusion site. The patient will also need to be trained on how to administer and reconstitute the medication at home, organise repeated visits to a healthcare professional or, if available, a home visit by a healthcare professional may need to be organised to aid

administration and compliance. Intravenous access will need to be installed and maintained. It may also require additional medications and ancillaries to be prescribed such as water for injection, sodium chloride infusion bags, syringes, etc. The patient will also need to adhere to strict aseptic technique, which can be tricky in a home environment. Moreover, considerations need to be made based on the patient's physique as intestinal patients tend to be underweight and malnourished and this can affect the suitability of injecting for example, subcutaneously which is injected into a fatty area of the abdomen or upper thigh and in the muscle if prescribing an intramuscular injection. Other considerations include physical ability and dexterity that may be exacerbated by conditions such as arthritis.

Specific drugs that are often utilised in SB are the somatostatin analogues such as octreotide and lanreotide and are used off label/off license for controlling high output stomas, which are administered as injections. However, care must be taken as the use of octreotide in intestinal failure patients can have disadvantages. The clinical response can be unpredictable, it increases the patients risk of developing cholethiasis, it has been suggested that it may affect intestinal adaptation post-surgery, postprandial hypoglycaemia has been reported and injections can be unpleasant for patients [4]. Furthermore, it has been suggested that macronutrient absorption may be impaired by somatostatin in patients with SB, by inhibiting glucose absorption and pancreatic enzyme secretion hence, somatostatin analogues are only considered for patients when other strategies have not been effective, in reducing a high output [60, 61]. As lanreotide is a more expensive medication and is being used off label/ off-license in this situation and it is often not possible to obtain locally. Therefore prescribing, cost and logistics will rest with the initiating specialised intestinal rehabilitation team, in the UK. These considerations need to be made when trying to manage a high output stoma that is not responding adequately to conventional treatment.

Rectal

While the rectal route is available for some patients, it may not be available for many SB patients due to previous surgical procedures where the rectum has been removed. Rectal drug administration can be erratic and less reliable due to difficulties in drug retention particularly if a patient is suffering with diarrhoea or loose stools. It is also reported that only 50% of drug absorbed via the rectum undergoes first pass metabolism as the upper part of the rectal venous blood supply is connected to the portal system into the liver, whereas the lower part is directly connected with the systemic circulation. This is just an approximation as it may also depend on the formulation of drug used, which tends to be as either a solution or suppository. When considering the rectal route it is important to check if switching is equivalent, for example with carbamazepine, 100 mg tablets are equivalent to 125 mg of suppositories. In general most drugs will not achieve the same plasma levels when equivalent doses are given rectally compared to the oral route, but if oral delivery is proving to be a real concern, then the rectal route can be very useful [62]. Additionally, consider monitoring drug levels when doses have been changed or if there is concern about under or over-dosing [63]. Drugs commonly given rectally for a systemic effect include analgesics (paracetamol), antiemetics (prochlorpromazine) and antibiotics (metronidazole).

Changing the Formulation

Altering a licensed drug formulation can be considered to help improve drug absorption. Often crushing and dispersing tablets in water or opening capsules and dispersing the contents in water before administration are tried. The theory is to start the disintegration and formation of solution sooner.

However, alteration of the dose form can cause risk to healthcare workers. For example, with cytotoxic medications crushing can expose healthcare workers to aerosolization of the powder therefore this should be avoided. Crushing a tablet can cause instability of the medication particularly if it has a coating to protect it from light or the acidic environment of the stomach. This could lead to degradation of the drug or irritation in the body due to release of irritants from the dosage form. Alterations can cause changes in bioavailability and this is important to consider with narrow therapeutic range medications such as digoxin or phenytoin. Also, administration via an enteral tube can increase the chances of the tube becoming blocked [64]. It is always advisable to discuss any consideration to alter a drugs standard delivery method with the local pharmacist.

Classes of Drug Prescribed for SB Patients

Antisecretory Drugs

Acid production may be increased (gastric hypersecretion) in patients with a short bowel SB. High levels of gastric acid can raise the amount of secretions entering the shortened bowel, and interfere with absorption. Drugs that reduce gastric acid secretion reduce jejunostomy output. Omeprazole is readily absorbed in the duodenum and upper small bowel, but if less than 50 cm of jejunum remains, it may need to be given intravenously. Proton pump inhibitors, such as pantoprazole intravenous, are commonly given to patients with a jejunostomy for long term administration; but may increase the risk of osteoporosis, so should maintain an adequate intake of calcium and vitamin D [65, 66].

Antiemetics

Nausea and vomiting is often experienced by patients with SB. All formulations of cyclizine are often prescribed for SB patients, e.g., intravenous, subcutaneous, intramuscular and oral. Cyclizine is licensed for the treatment or prevention of nausea, vomiting and labyrinth disorders including vertigo and motion sickness. It is a class 1 drug in the biopharmaceutical classification which means it has high permeability and high solubility; hence most SB patients will achieve a pharmacological benefit with the oral formulation. However, all formulation of cyclizine can cause euphoric and hallucinatory effects and there have been reports of misuse and abuse of cyclizine. Cyclizine can also damage central and peripheral lines and increase episodes of catheter-related blood stream infections. For this reason, antiemetics such as ondansetron ($5HT_3$ antagonists) are preferred and are as effective as cyclizine (H_1 antihistamine), although more expensive and commonly causes constipation [67].

Antimotility Drugs

When considering other formulations, it is also important to think about whether the new formulation is a better alternative or not. While switching from capsules or tablets to liquids may be easier for enteral administration or in those who find it difficult to swallow, it may not always be suitable. For example, with loperamide for treating high output stomas, an efficacious dose often requires many tablets or capsules, 2 mg are the only strength available in the UK, and patients often complain of seeing capsules being excreted whole into their stoma bags. Switching to liquid loperamide may sound attractive, however the volumes required to achieve the same dose can be significant which could worsen the output. Loperamide liquid may also contain sorbitol that also worsens outputs due to its laxative effect. Often the alternative is to open capsules and dissolve the powder in a small amount of water. This would be an unlicensed form of administration as opening the capsules is not covered in the manufacturers licensing of loperamide capsules. Both options would be unlicensed however by using the capsules, the clinical outcome is more likely to be positive and costs can be reduced. One equivalent dose of liquid loperamide would cost more than double the price of an equivalent capsule dose, see Table 6.

Off Licensed Medicines

An off licence (or "off label") medication is one that is prescribed in a way that is not covered by its product license e.g., indication(s) and dosing regimen(s). A company must have a product license to advertise and sell a medicine, also known as a marketing authorisation. In the UK this is given this by the Medicines and Healthcare Products Regulatory Agency (MHRA), various national regulatory authorities or the European Medicines Agency (EMA) in Europe, and in USA by the Food and Drug Administration (FDA). The licence is often referred to as the label of the drug, hence the term off label. An unlicensed drug has no product license/marketing authorisation.

If the desired pharmacological affect is not being achieved from the prescribed drug, as per its licenced dosing regimen, first it is worthwhile determining if there are alternative drugs that can be used as per their licence before considering off licenced use or using an unlicensed drug to achieve the desired effect. There must be governance in place when prescribing both off licensed and unlicensed medication or routes, to protect the patient and the prescriber. There may be variations in local procedures in prescribing and obtaining off licensed and unlicensed medications. The prescriber holds greater legal responsibilities when prescribing off licensed/unlicensed medications and should monitor the drug's therapeutic efficacy and safety. Cost may be a determining factor in choosing a treatment. There should be clear documentation of off licensed and unlicensed use. This should include a rationale for the choice of drug, governance procedures followed, monitoring, a prescribing plan and documentation of discussions with the patient about risks and benefits [73].

Distal Administration of Medicines

Information on the distal administration of medications is poor and needs further research. Understanding the pharmacokinetics, and the individual properties of a drug help us understand how a drug may be affected by distal administration. As it is unlikely that manufacturers have tested this method during the licensing process, it would be classified as an unlicensed route, and therefore, a clinician recommending this method of drug administration would do so outside of a its license.

There are several factors to be considered if using distal administration; available drug formulations, the manufacturer's intended site of drug absorption, the anatomy of the distal stoma, consequences of potentially bypassing hepatic metabolism, and mechanisms for monitoring the drug's effects (chapter "Distal Feeding and Hydration").

An important element to consider is the distal stoma site location, as this will aid understanding and determine whether the drug will be effectively absorbed/elicit its desired effect. Distal administration of a medicine into an ileostomy or colostomy will differ considerably to a jejunostomy that is in close proximity to the DJ flexure, for exam-

ple. As the latter is further up the GIT, the increased downstream GIT length and surface area will enable a drug to go through dissolution, absorption, and first-pass hepatic metabolism, which may be required for certain pro-drugs i.e. those that require metabolising to be converted to its active form. Distal administration into a colostomy may only be beneficial for drugs that are intended for release into the colon which may be the site of activity.

Knowledge of the available drug formulations is important, so that drug dissolution principles can be considered. A solid tablet or capsule cannot be directly administered via a distal stoma.

Drug efficacy principles are based around improving dissolution in the stomach or faster absorption of the active ingredient throughout the GIT, or both [74]. If the disintegration or dissolution in the stomach is bypassed, for distal administration to be an effective route, the drug needs to be administered in a dissolute form to allow absorption to occur; this may be as a liquid preparation, crushed and dissolved tablets or using the IV form enterally (the latter two options being unlicensed routes).

An awareness of the proportion of remaining small bowel is also important as this will affect the amount of drug being absorbed, and hence undergoing hepatic first-pass metabolism. Where absorption and hepatic first-pass metabolism is expected to be affected, it would be prudent to closely monitor a patient's response to their medication both short and long-term.

It is also important to ensure that patients are monitored for drug effect and/or toxicity. Some drugs have measurable effects, for example, measuring a patient's blood pressure indicates that the antihypertensive prescribed is sufficiently controlling the blood pressure. Other drugs however, do not possess outwardly 'measurable' effects, and so will require another form of monitoring. This is also important in patients who are established on a drug via the enteral route, and then converted to administration via distal route, as this will require re-establishment of clinical effect/benefit, due to a potential shift in absorption site and concentrations.

Drugs that are classified as having a narrow therapeutic index, i.e. narrow window between the effective dose and the dose at which they produce adverse toxic effects, are regularly monitored by blood sampling [75]. This ensures that patients are not put at risk and the dosing is within acceptable limits. However, this requires accurate timing of testing and relying on patients to adhere to monitoring requirements and implementing dose adjustments. This is a useful method to utilise wherever possible if considering administering medication distally. Consulting with local or national hospital laboratories as to what drugs they are able to monitor would be useful especially where the patient is also on high risk drugs, or there are concerns with absorption.

Chyme Reinfusion and Drug Absorption

Chyme is the mixture of the digestive secretions, bile salts, and pre-digested food that is transformed into absorbable nutrients by enzymatic digestion [76]. Medication taken orally would also be present in this mixture, and once in the upper small intestine, drug absorption begins to occur into the portal vein bloodstream to the liver, whereby hepatic first-pass metabolism takes place.

Chyme re-infusion (CR) is a technique used to artificially restore intestinal continuity between a proximal and distal stoma/mucous fistula [76]. The amount of chyme re-infused is an important factor to consider, and this depends on the purpose, or intended outcome, of CR. One purpose is to use CR as the main nutritional source, whereby the majority of the stoma content (chyme) is re-infused. Studies have shown that this is an effective alternative method to parenteral nutrition, with the majority of the patients enrolled in these studies being switched from parenteral nutrition to CR [77, 78].

In some centres or circumstances, only a small proportion of chyme, 50–100 mL for example, is re-infused; the purpose of this is to maintain the distal gut function and reduce atrophic changes; however, the patient will still require nutritional support using an alternative method.

Knowledge of the amount of CR is crucial in understanding how we may predict a drug will perform. Also, we must know what part of the bowel is removed, the bowel length upwards of the proximal and downwards of the distal stomas, and the anatomy of the two stomas.

Patients with a high-output stoma, taking oral medication, will have had careful monitoring and fine dose adjustment to ensure they are receiving a therapeutic drug dose. If they are eligible for a CR device, the drug(s) that were once discarded along with the stoma output will be re-infused, the patient will be re-exposed to the drug, and this extended exposure may impact the plasma drug levels and the dose response curve. A study looking into a novel device mentions how some patients recruited experienced changes to their medication absorption, for example, constipation requiring loperamide withdrawal, drowsiness requiring dose reduction of analgesic/anxiolytic doses, and a flare of trigeminal neuralgia post stoma creation that resolved on initiation of CR, which all indicate that increased drug absorption occurred [78].

Although these are only a handful of patients, they prove the concept that patients should be monitored in the acute phase, and an investment made into observing and adjusting medication doses such that adverse effects are reduced [78].

Box 1: Case Study—Heart Failure/High Output Stoma/Anticoagulation

A 62 year old woman has a high output ileostomy with approximately 2.6 L output over 24 h. She has dry oral mucus membranes, dark rings round her eyes and reduced urine output of 560 mL/24 h.

Events Prior to Reviewing Patient

Recent Medical and Surgical History

- 4th December—Pulmonary oedema secondary to acute coronary syndrome (ACS).
- 7th December—Reduced ejection fraction of 24% and impaired right ventricle (RV) function
- 10th December—underwent percutaneous coronary intervention (PCI) due to ACS, (Troponin 7113 ng/L on 05th December and 3669 ng/L on 07th December).
- 13th December—Developed new right unilateral weakness. CT Head showed a subacute infarct involving middle cerebral artery region.
- 18th December—One week history of pyrexia of unknown origin prompted CT scan of chest/abdomen/pelvis which showed an intestinal ileus in association with a suspected area of bowel ischemia in the distal ileum.
- 19th December—Emergency laparotomy, right hemi-colectomy, small bowel resection and formation of double barrelled ileostomy. Approximately 190 cm of small bowel (SB) remaining from duodenojejunal (DJ) flexure to a small bowel stoma.

Past Medical History

- 11 years ago—Non-ST elevated myocardial infarction (NSTEMI) and PCI
- 8 years ago—Myocardial infarction with a coronary artery bypass graft
- Asthma
- Type 2 diabetes

Current Medication—(No known drug allergies. Simvastatin caused nightmares)

Drug	Dose	Frequency	Route	Alternative for a high output stoma patient
Paracetamol	1 g	Four times daily	Intravenous	Not needed as not using enteral route
Omeprazole	40 mg	Twice daily	Intravenous	Not needed as not using enteral route
Loperamide	16 mg	Four times daily	Oral	Open capsules and sprinkle contents into water. 30–60 min before food
Codeine	60 mg	Four times daily	Oral	Not needed as very small tablets. Could switch to non-sorbitol containing syrup or linctus, 30–60 min before food
Aspirin	75 mg	At night	Oral	Use dispersible tablets, with food
Ticagrelor	90 mg	Twice daily	Oral	Oro-dispersible tablets available which can be dispersed in water or placed on tongue and swallowed without water
Rosuvastatin	10 mg	At night	Oral	Tablets can be crushed and mixed with water for administration
Sertraline	100 mg	At night	Oral	Tablets disperse in water within 1–5 min. They can also be crushed and mixed with food
Bisoprolol	2.5 mg	In the morning	Oral	Tablets can be crushed and mixed with water for administration. Tablets will also disperse in 1–5 min in water
Metformin	1 g	Twice daily	Oral	Consider switching to subcutaneous insulin as Metformin can exacerbate loose stools
Gliclazide	160 mg	Twice daily	Oral	Consider switching to subcutaneous insulin
Losartan	100 mg	Once daily	Oral	Tablets can be crushed and mixed with water for administration
Apixaban	5 mg	Twice daily	Oral	Tablets can be crushed and dispersed in water, glucose 5%, apple juice or puree Switch to Warfarin to allow INR checks and effective monitoring of anticoagulation Therapeutic drug monitoring for apixaban is now available from some specialist centres in the UK
Budesonide/ Formoterol Dry powder inhaler	200 µg/6 µg	Twice daily	Inhaled	Not needed as not using enteral route
Salbutamol 100 µg inhaler	100–200 µg	Four times daily when required	Inhaled	Not needed as not using enteral route

The reason for her high output stoma (HOS) was poor bowel quality despite sufficient small bowel length.

Biochemistry 1st February 2021

Investigation	Result	Normal range
Sodium	160 mmol/L	133–146 mmol/L
Potassium	3.2 mmol/L	3.5–5.3 mmol/L
Urea	15.7 mmol/L	2.5–7.8 mmol/L
Creatinine	63 mmol/L	44–80 mmol/L
Random urine sodium	28 mmol/L	<20 mmol/L indicates dehydration
C-reactive protein	0.8 mg/L	0–5 mg/L
Serum Osmolality	356 mOsmol/kg	275–295 mOsmol/kg. >300 mOsmol/kg can indicate dehydration

Fluid balance chart over last 24 h for 1st February 2021

In	Out
IV = 1000 mL sodium chloride 0.9%	Stoma = 2600 mL
NG = flushes post medication − 60 mL water	Urine = 560 mL
NG = Enteral feed 1000 mL over 24 h	
Total = 2060 mL	**Total = 3160 mL (negative 1100 mL/24 h)**

Physical examination/test	Findings
Abdominal system	Abdomen was flat and non-tender. No abdominal mass noted (if present may indicate tumour or sepsis) and no enlargement of the spleen or liver. Normal bowel sounds. No abnormal findings
Stoma assessment	Stoma pink, warm and healthy, no bleeding or break of skin barrier and no soreness. Stoma protruded approximately 1.5 in. from the skin and had a sealed see-through stoma bag around it. A finger inserted easily into the stoma with no stenosis. Stoma output was dark green/brown in colour and watery
Temperature	Apyrexial. But had been ≥37.8 °C over the last 2 days. (may suggest an underlying infection preventing the stoma output from settling). Regular doses of paracetamol were being taken and this may mask a temperature
Observation chart	Weight 65 kg, height 170 cm. BMI = 22.4 kg/m^2 NEWS = 1. No requirement of oxygen, and was stable with a heart rate of 93 bpm (could be increased due to dehydration or sepsis). Lying blood pressure was normal
Bloods & Urine sodium	Urine sodium was at the low end of the normal range, suggesting a degree of dehydration. Urea was raised and may suggest dehydration but the creatinine is within the normal range suggesting a large amount of protein has been broken down (a bleed or much oral or parenteral feeding)
Peripheral oedema check	Peripheral oedema can prevent optimal hydration. The patient had some pedal oedema which may be due to immobilisation post stroke. Alternatively it can represent excessive parenteral saline or general inflammation
Mucous membrane check	Dry or cracked mucous membranes indicate dehydration The tongue was dry, with no saliva around the teeth or tongue and the patient felt very thirsty
Cramps	No muscle cramps, (Muscles cramps usually reflect sodium depletion but may occur with hypomagnesaemia caused by a HOS)
Fluid balance check	Daily fluid balance checks and daily weight measurement are crucial when managing HOS patients. The fluid balance for the last 24 h showed a negative balance of 1100 mL/24 h
Urine check	Urine output was more than the minimum of 0.5 mL/kg/h. Urine colour was a dark orange

Considerations When Caring for This Patient Cohort

This patient has fluctuating fluid requirements due to both intestinal and heart failure, which depend on the output from her stoma. She may quickly become dehydrated or overhydrated if the incorrect amount of intravenous fluid is given to replace her losses.

According to the British society of gastroenterology (BSG) guidelines for the management of patients with a short bowel, there is further medication optimization which should be done for this patient. This patient is experiencing net loss of fluid and sodium, and so should be prescribed 1 L of an oral electrolyte mix, an unlicensed solution which leads to more sodium being absorbed from the bowel lumen [77]. These guidelines advise that a patient with 150–200 cm normal functioning SB should be able to manage their HOS with optimized medication and electrolyte mix [79, 80].

At this stage she is requiring IV fluids; however, the addition of electrolyte mix could help to reduce and ultimately prevent this requirement.

As the heart starts to fail, renal perfusion reduces. The kidneys respond to this by increasing renin production, leading to aldosterone production, which is consequently followed by sodium and water retention. Arginine vasopressin (AVP) is also released, further enhancing fluid retention, and stimulating thirst [81]. This stimulation of thirst will cause a patient to drink, which in this patient's case is detrimental to her hydration status as it will cause more losses from the stoma if hypotonic fluids are ingested.

It is necessary to consider the absorption of critical cardiac medication in this type of patient. Her anticoagulants and antiplatelet drugs are necessary to prevent another stroke or myocardial infraction. It is advised to look for alternate routes of administration of the medications that can avoid using the bowel, such as transdermal or intravenous or preparations which partly use the bowel such as sublingual or buccal. These drugs may need to be rationalised, such as switching to subcutaneous insulin to manage diabetes rather than metformin, which may cause loose stools. See the last column on the medication table which gives possible alternatives.

Nutrition teams should consider creating a care plan for their patient if they are to be discharged with intravenous fluid. A care plan provides guidance on deciding the volume of fluid required, it utilizes physical assessment skills to follow the plan appropriately.

Daily Monitoring Instructions

- On waking-up please empty your stoma bag and then weigh yourself and record your weight on your daily weight chart.
- Over a 24 h period, measure and record your intakes and outputs on your daily fluid chart.
- Monitor signs of dehydration by noticing whether you feel thirsty, experience any dizziness on standing, pass less urine than usual or whether your urine is darker than usual
- Monitor signs of over hydration by noticing whether you develop any worsening swelling of your ankles or shortness of breath after IV fluid.**Use the information in the following care plan to decide fluid requirements:**

Option A: Adequately hydrated

– Weight is stable – Not thirsty & passing adequate amounts of urine – No worsening ankle swelling	E.g. Give 0.5 L 0.9% saline with 10 mmol $MgSO_4$ three times a week (overnight) over 12 h Monday, Wednesday & Friday

Option B: Dehydration

• Weight loss of more than 2 kg – Feels thirsty, or – Passing less urine which is darker than usual, or – Feels dizzy on standing	E.g. Give additional 1 L sodium chloride 0.9% over 10 h

Option C: Over-hydration

• Weight gain of more than 2 kg – Worsening swelling of ankles, or – Feels short of breath	E.g. Do not give IV fluid until back to dry weight (only use 5% dextrose if any fluid has to be given)

Planned Follow-Up and Monitoring Including Applicable Timeframes

The outcome of additional electrolyte mix measured on any given day reflects the day it is taken. Therefore, 2 days shows two 24 h periods of fluid balance charts, etc., a useful timeframe to make any further changes. The electrolyte mix may need to be stopped if it is simply adding to the fluid loss via stoma output, indicating very poor bowel quality.

It is crucial to re-check the same blood investigations at the next patient review, with a priority to check serum sodium as this was markedly increased due to dehydration.

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References

1. McFadden MA, DeLegge MH, Kirby DF. Medication delivery in the short-bowel syndrome. J Parenter Enter Nutr. 1993;17:180–6.
2. Severijnen R, Bayat N, Bakker H, Tolboom J, Bongaerts G. Enteral drug absorption in patients with short small bowel. Clin Pharmacokinet. 2004;43(14):951–62.
3. Rowland M, Tozer TN. Clinical pharmacokinetics and pharmacodynamics: concepts and applications. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.
4. Rang H, Dale M, Ritter J, Flower R. Rang and dale's pharmacology. 6th ed. Edinburgh: Churchill Livingstone; 2007.
5. Wrexham Maelor Hospital. Pharmacy Department. The NEWT Guidelines. Betsi Cadwaladr University Local Health Board (East); 2021.
6. Baktir G. Therapeutic drug monitoring (TDM). Lectio Sci. 2017;1(1):54–65.
7. Lea-Henry TN, Carland JE, Stocker SL, Sevastos J, Roberts DM. Clinical pharmacokinetics in kidney disease: fundamental principles. Clin J Am Soc Nephrol. 2018;13(7):1085–95.
8. Wadhwa RR, Cascella M. Steady state concentration. In: StatPearls. StatPearls Publishing; 2021.
9. Sood S, Tanner F, Testro A. Prescribing for a patient with reduced intestinal length. Aust Prescr. 2013;36:136–8.
10. Vertzoni M, Augustijns P, Grimm M, Koziolek M, Lemmens G, Parrott N, Pentafragka C, Reppas C, Rubbens J, Van Den Abeele J, Vanuytsel T. Impact of regional differences along the gastrointestinal tract of healthy adults on oral drug absorption: an UNGAP review. Eur J Pharm Sci. 2019;134:153–75.
11. Devadasu VR, Deb PK, Maheshwari R, Sharma P, Tekade RK. Physicochemical, pharmaceutical, and biological considerations in GIT absorption of drugs. In: Dosage form design considerations. Academic Press; 2018. p. 149–78.
12. Kothari V, Joshi C, Patel P, Shahi D, Mehta C, Prajapati B, Patel S, Mandaliya D, Seshadri S. Nanotechnological approaches to colon-specific drug delivery for modulating the quorum sensing of gut-associated pathogens. In: Design of nanostructures for versatile therapeutic applications. William Andrew Publishing; 2018. p. 325–77.
13. International council for harmonisation for technical requirements for pharmaceutical for human use, Biopharmaceutics classification system based biowaivers, M9; 2019.
14. Barr WH, Zola EM, Candler EL, Hwang SM, Tendolkar AV, Shamburek R, Parker B, Hilty MD. Differential absorption of amoxicillin from the human small and large intestine. Clin Pharmacol Ther. 1994;56(3):279–85.
15. Griffith RS. The pharmacology of cephalexin. Postgrad Med J. 1983;59(5):16–27.
16. Wrexham Maelor Hospital. Pharmacy Department. The NEWT guidelines. Betsi Cadwaladr University Local Health Board (East); 2010.
17. Menardi G, Guggenbichler JP. Bioavailability of oral antibiotics in children with short-bowel syndrome. J Pediatr Surg. 1984;19(1):84–6.
18. Padwal RS, Ben-Eltriki M, Wang X, Langkaas LA, Sharma AM, Birch DW, Karmali S, Brocks DR. Effect of gastric bypass surgery on azithromycin oral bioavailability. J Antimicrob Chemother. 2012;67(9):2203–6.
19. Harder S, Fuhr U, Beermann D, Staib AH. Ciprofloxacin absorption in different regions of the human gastrointestinal tract. Investigations with the HF-capsule. Br J Clin Pharmacol. 1990;30(1):35–9.
20. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother. 2006;58(2):256–65.
21. Mariappan TT, Singh S. Regional gastrointestinal permeability of rifampicin and isoniazid (alone and their combination) in the rat. Int J Tuberc Lung Dis. 2003;7(8):797–803.
22. White R, Bradnam V. Handbook of drug administration via enteral feeding tubes. 3rd ed. London: Pharmaceutical Press; 2015.
23. Martinez V, Le Guillou JL, Lamer C, Le Jouan M, Tod M, Dromer F. Serum voriconazole levels following administration via percutaneous jejunostomy tube. Antimicrob Agents Chemother. 2003;47(10):3375.
24. Dhaliwal S, Jain S, Singh HP, Tiwary AK. Mucoadhesive microspheres for gastroretentive delivery of acyclovir: in vitro and in vivo evaluation. AAPS J. 2008;10(2):322.
25. MacDougall C, Guglielmo BJ. Pharmacokinetics of valaciclovir. J Antimicrob Chemother. 2004;53(6):899–901.
26. LaPlante K, Cunha C, Morrill H, Rice L, Mylonakis E. Antimicrobial stewardship: principles and practice. Wallingford: CABI; 2016.
27. Boullata JI, editor. Guidebook on enteral medication administration. American Society for Parenteral and Enteral Nutrition; 2019.
28. Kalantzi L, Reppas C, Dressman JB, Amidon GL, Junginger HE, Midha KK, Shah VP, Stavchansky SA, Barends DM. Biowaiver monographs for immediate release solid oral dosage forms: acetaminophen (paracetamol). J Pharm Sci. 2006;95(1):4–14.
29. Biopharmaceutics classification system database can be found via http://www.ddfint.org/.
30. Dahan A, Wolk O, Zur M, Amidon GL, Abrahamsson B, Cristofoletti R, Groot DW, Kopp S, Langguth P, Polli JE, Shah VP. Biowaiver monographs for immediate-release solid oral dosage forms: codeine phosphate. J Pharm Sci. 2014;103(6):1592–600.
31. IBM Micromedex Morphine Sulfate monograph. Pharmacokinetics. Accessed 9 Apr 2022.
32. Morphine 10mg/5ml oral solution, Summary of Product Characteristics (SmPC). Last updated on emc: 18 Sep 2020. Martindale Pharma, an Ethypharm Group Company.
33. IBM Micromedex Oxycodone monograph. Pharmacokinetics. Accessed 9 Apr 2022.
34. Shortec 10 mg hard capsules, Summary of Product Characteristics (SmPC). Last updated on emc: 19 Nov 2020. Qdem Pharmaceuticals Limited.
35. Cook J, Addicks W, Wu YH. Application of the biopharmaceutical classification system in clinical drug development—an industrial view. AAPS J. 2008;10(2):306–10.
36. Meng X, Mojaverian P, Doedée M, Lin E, Weinryb I, Chiang ST, Kowey PR. Bioavailability of amiodarone tablets administered with and without food in healthy subjects. Am J Cardiol. 2001;87(4):432–5.
37. Xarelto 20mg film-coated tablets, Summary of Product Characteristics (SmPC). Last updated on emc: 17 Jan 2022. Bayer plc.
38. Eliquis 5 mg film-coated tablets, Summary of Product Characteristics (SmPC). Last updated on emc: 28 May 202. Bristol-Myers Squibb-Pfizer.
39. Rha JH, Jang IJ, Lee KH, Chong WS, Shin SG, Lee N, Myung HJ. Pharmacokinetic comparison of two valproic acid formulations: a plain and a controlled release enteric-coated tablets. J Korean Med Sci. 1993;8(4):251–6.
40. Gupta SK, Shah JC, Hwang SS. Pharmacokinetic and pharmacodynamic characterization of OROS(R) and immediate-release amitriptyline. Br J Clin Pharmacol. 1999;48:71–8.

41. Griffin DS, Baselt RC. Blood and urine concentrations of cyclizine by nitrogen-phosphorous gas-liquid chromatography. J Anal Toxicol. 1984;8:97–9.
42. Davis TME, Daly F, Walsh JP, et al. Pharmacokinetics and pharmacodynamics of gliclazide in Caucasians and Australian Aborigines with type 2 diabetes. Br J Clin Pharmacol. 2000;49:223–30.
43. Beermann B, Groschinsky-Grind M, Lindstrom B. Pharmacokinetics of bendroflumethiazide. Clin Pharmacol Ther. 1977;22:385–8.
44. Goa KL, Heel RC. Zopiclone: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy as an hypnotic. Drugs. 1986;32:48–65.
45. Parker G, Roberts C. Plasma concentrations and central nervous system effects of the new hypnotic agent zopiclone in patients with chronic liver disease. Br J Clin Pharmacol. 1983;16:259–65.
46. Buccolam 10 mg oromucosal solution, Summary of Product Characteristics (SmPC). Last updated on emc: 27 Aug 2021. Neuraxpharm UK Ltd.
47. Yun M, Woo J, Kwon K. Bioequivalence and pharmacokinetics of 70 mg alendronate sodium tablets by measuring alendronate in plasma. Arch Pharm Res. 2006;29(4):328–32.
48. European Medicines Agency, Committee for medicinal products for human use, Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product; 2007.
49. Switching between liquid and tablet/capsule formulations—which medicines require extra care? Medicines Q&A; 2020.
50. Hooda R, Tripathi M, Kapoor K. A review on oral mucosal drug delivery system. Pharma Innov. 2012;1(1).
51. Bhati R, Nagrajan RK. A detailed review on oral mucosal drug delivery system. Int J Pharm Sci Res. 2012;3(3):659.
52. Finn A, Collins J, Voyksner R, Lindley C. Bioavailability and metabolism of prochlorperazine administered via the buccal and oral delivery route. J Clin Pharmacol. 2005;45(12):1383–90.
53. Regnard C, Twycross R, Mihalyo M, Wilcock A. Loperamide. J Pain Symptom Manag. 2011;42(2):319–23.
54. Cederberg C, Andersson T, Skånberg I. Omeprazole: pharmacokinetics and metabolism in man. Scand J Gastroenterol. 1989;24(sup166):33–40.
55. Vasisht N, Gever LN, Tagarro I, Finn AL. Formulation selection and pharmacokinetic comparison of fentanyl buccal soluble film with oral transmucosal fentanyl citrate. Clin Drug Invest. 2009;29(10):647–54.
56. Alkilani AZ, McCrudden MT, Donnelly RF. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics. 2015;7(4):438–70.
57. BNF British National Formulary. Buprenorphine [Internet]. London: NICE; 2020 [updated 2021 May; cited May 21].
58. BNF British National Formulary. Fentanyl [Internet]. London: NICE; 2020 [updated 2021 May; cited May 21].
59. England.nhs.uk. Items which should not routinely be prescribed in primary care: Guidance for CCGs. [Internet]. London: NHS; 2019 [cited May 21].
60. Study.com. Parenteral: Definition & Medical Uses. [Internet]. London: study.com; 2020 [cited May 21].
61. Oke SM, Nightingale JM, Gabe SM. Mistakes in short bowel and how to avoid them. UEG Educ. 2018;18:7–11.
62. De Boer AG, Moolenaar F, De Leede LG, Breimer DD. Rectal drug administration. Clin Pharmacokinet. 1982;7(4):285–311.
63. Wrexham Maelor Hospital. Pharmacy Department. The NEWT guidelines. Betsi Cadwaladr University Local Health Board (East); 2021. Carbamazepine monograph.
64. Royal Pharmaceutical Society. Pharmaceutical issues when crushing, opening or splitting oral dosage forms; 2011.
65. Mignot G, Dukes MN, Aronson JK. Proton pump inhibitors. Meyler's side effects of drugs: an encyclopaedia of adverse reactions and interactions. 16th ed. Amsterdam: Elsevier Science Publishers; 2016. p. 1040–5.
66. Nightingale JM, Walker ER, Farthing MJ, Lennard-Jones JE. Effect of omeprazole on intestinal output in the short bowel syndrome. Aliment Pharmacol Ther. 1991;5(4):405–12.
67. Nightingale J, Meade U, Leahy G, BIFA Committee. The use of cyclizine in patients receiving parenteral nutrition; 2018.
68. Imodium 1 mg/5 ml oral solution—Summary of Product Characteristics (SmPC). Last updated on emc: 17 Mar 2020. Janssen-Cilag Ltd.
69. Loperamide 2mg capsules—Summary of Product Characteristics (SmPC). Last updated on emc: 24 Sep 2019. Aurobindo Pharma–Milpharm Ltd.
70. Loperamide 2 mg tablets—Summary of Product Characteristics (SmPC). Last updated on emc: 29 Sep 2020. Cipla EU Ltd.
71. Imodium instant melts—Summary of Product Characteristics (SmPC). Last updated on emc: 28 Aug 2020. McNeil Products Ltd.
72. BNF British National Formulary. Loperamide [Internet]. London: NICE; 2020 [updated 2021 May; cited May 21].
73. MHRA U. Off-label or unlicensed use of medicines: prescribers' responsibilities. Drug Safety Update 2009.
74. Voelker M, Hammer M. Dissolution and pharmacokinetics of a novel micronized aspirin formulation. Inflammopharmacology. 2012;20(4):225–31.
75. Tamargo J, Le Heuzey JY, Mabo P. Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide. Eur J Clin Pharmacol. 2015;71(5):549–67.
76. Picot D, Layec S, Seynhaeve E, Dussaulx L, Trivin F, Carsin-Mahe M. Chyme reinfusion in intestinal failure related to temporary double enterostomies and enteroatmospheric fistulas. Nutrients. 2020;12(5):1376.
77. Picot D, Layec S, Dussaulx L, Trivin F, Thibault R. Chyme reinfusion in patients with intestinal failure due to temporary double enterostomy: a 15-year prospective cohort in a referral centre. Clin Nutr. 2017;36(2):593–600.
78. Sharma P, Davidson R, Davidson J, Keane C, Liu C, Ritchie SR, Chu K, Sutherland G, Bissett IP, O'Grady G. Novel chyme reinfusion device for gastrointestinal fistulas and stomas: feasibility study. J Br Surg. 2020;107(9):1199–210.
79. London North West University Healthcare NHS Trust. Patient information leaflet, High output stoma; 2014.
80. Nightingale J, Woodward JM. Guidelines for management of patients with a short bowel. Gut. 2006;55(Suppl 4):iv1–2.
81. Pellicori P, Kaur K, Clark AL. Fluid management in patients with chronic heart failure. Card Fail Rev. 2015;1(2):90.

Distal Feeding and Hydration

Laurence Lacaze, Denis Picot, and Ronan Thibault

Key Points

1. Infusion of feed and fluids and/or proximal bowel content into distal bowel (ileum or colon) via a temporary loop enterostomy or an entero-atmospheric fistula may be used as the sole source of nutrition/hydration as an alternative to parenteral support. It is called 'distal feeding and/or hydration' (DFH).
2. Enteroclysis and chyme reinfusion with special pumps or devices are two techniques for DFH, and can be continued until surgical reestablishment of bowel continuity.
3. Distal feeding improves nutritional status and liver function, and avoids the complications of parenteral nutrition (especially central venous catheter infections and thrombosis).
4. DFH is safe, low-cost and easy-to-use in hospital and at home, providing contraindications (fistula, perforation or stenosis in the downstream small intestine) are taken into account.
5. DFH needs to be integrated into multidisciplinary care, handled by specialized trained teams, and should be included in patient's education to avoid technique failure.
6. Proximal and distal contrast studies of the bowel prior to starting DFH must be performed to ensure there is no disease, obstruction or leak present in the distal bowel.
7. Feed is delivered through a distal feeding tube using a polymeric or semi-elemental enteral nutrition solution, or chyme, and/or hydration by using fluid containing salt.
8. Besides technical issues, the main side effects of DFH may be abdominal pain and disturbed intestinal transit.
9. DFH acts by reducing upper gastrointestinal secretions and motility, increasing intestinal absorption capacity and thus proximal stomal/fistula output, leading to the reduction of the amount of nutritional/fluid parenteral support. These beneficial effects are driven by neural and humoral mechanisms, including the release of gut hormones by the distal small bowel.
10. DFH is making the surgical reestablishment of bowel continuity more likely to be successful (technically easier, faster post-operative recovery of function, lower risk of anastomotic leak).

Introduction

In the course of an intra-abdominal surgical procedure, several clinical situations lead the surgeon to perform a double (loop or double barrel) temporary enterostomy on the small bowel (e.g. Crohn's disease, mesenteric ischemia, peritonitis, fistulae, and anastomosis protection). Entero-atmospheric fistula (EAF) can also arise spontaneously as a post-operative complication of peritonitis or anastomotic leakage. Initially these conditions leads to type 1 intestinal failure (IF), and then become type 2 IF, especially when the stoma/fistula output is equal or higher than 1500 mL/24 h [1], and this lasts until the surgical re-establishment of digestive continuity. All these situations could lead to serious complications resulting in hospital readmissions (40–50%) [2, 3]: acute or chronic dehydration (18–29% of patients) [4, 5], renal failure [6], electrolyte disturbances, micronutrient and mineral deficiencies, and malnutrition, thus increasing healthcare-related costs [7] and affecting patients' quality of life. According to the clinical classification of the intravenous support (IVS) based on daily fluid [8], electrolyte and nutri-

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tional requirements provided by parenteral route, in case of IF, most of these patients are in categories 3 and 4, defined by very high hydration and nutrient requirements [9, 10].

After such complicated surgeries, it is recommended to wait for at least three months from the last surgery to perform the surgical re-establishment of digestive continuity and stoma closure. During this time, nutritional support should be effective, at low-risk and sufficient to prepare the patient for this surgery. At this time, the current gold standard therapy indicated for IF patients until the surgical re-establishment of digestive continuity, is parenteral nutrition (PN) and/or hydration (IVS) [1]. However, home PN has its own morbidity and, in the absence of expertise, the risks of infectious, hepatic dysfunction, mechanical, and metabolic complications are increased [11]. PN has been associated with infectious and hepatobiliary (e.g cholestasis, steatosis and fibrosis) complications [12–14]. In many developing countries, PN is not available as it is considered too expensive or there are no home PN homecare providers [15].

Distal feeding and/or hydration (DFH) techniques, namely enteroclysis, and chyme reinfusion (CR), are alternative therapies to IVS for type 2 IF patients. Although IVS has long been the standard of care for IF, the use of DFH in patients with EAF or temporary intestinal enterostoma has been described by many authors for a long time [10, 16–18]. DFH by CR was first described by Etienne Levy in 1977 [16].

The scope of this chapter is to describe the technical principles of enteroclysis and CR, to overview their indications, contraindications and clinical benefits, and to give practical details for their use.

This chapter does not discuss the use of small volume bolus fees given once or twice daily into defunctioned bowel to help maintain anatomical structure and motility before a surgical anastomosis is performed (see chapter Insertion, Types and Care of Enteral Feeding Tubes).

What Is Distal Feeding and/or Hydration?: Definitions

Enteroclysis and CR are the two main techniques of DFH. To be eligible for DFH, patients should have a loop or a double-barrelled enterostoma or two stomas apart of the small bowel or an EAF, with access to the downstream small bowel (Fig. 1). DFH will be feasible only if the downstream small bowel can be catheterized.

Enterocutaneous fistula are aberrant connections between the gastrointestinal tract and the skin or atmosphere. They occur in 75–85% of cases after surgery and in 15–25% spontaneously [1]. Most close under medical treatment. EAF is an enterocutaneous fistula developed in a wound in the abdominal wall with a mucocutaneous continuity where the openings are visible as enterostomies. Closure almost always requires surgery.

Enteroclysis consists in infusing water, electrolytes, and/or enteral nutrition solution through an enterostomy or an EAF into the distal (downstream) small bowel. Fistuloclysis is enteroclysis through an EAF. The term enteroclysis seems preferable to fistuloclysis as it refers to the instillation of a fluid (-clysis) into the small intestine (entero-) regardless of the nature of the orifice, enterostomy or EAF, and the nature of the fluid, hydration, nutrition or both.

CR, also called "re-feeding enteroclysis", consists in reinfusing the chyme collected from the proximal stoma (from the upstream small bowel) through the distal stoma, into the downstream small bowel [9, 10, 14, 19, 20]. The chyme is composed of digestive secretions (including growth factors), nutrients from oral food and/or tube feeding and drugs. CR reestablishes the functional continuity of the anatomically present small bowel through an extracorporeal circulation of the chyme [16]. The CR and enteroclysis could be considered as enteral nutrition tech-

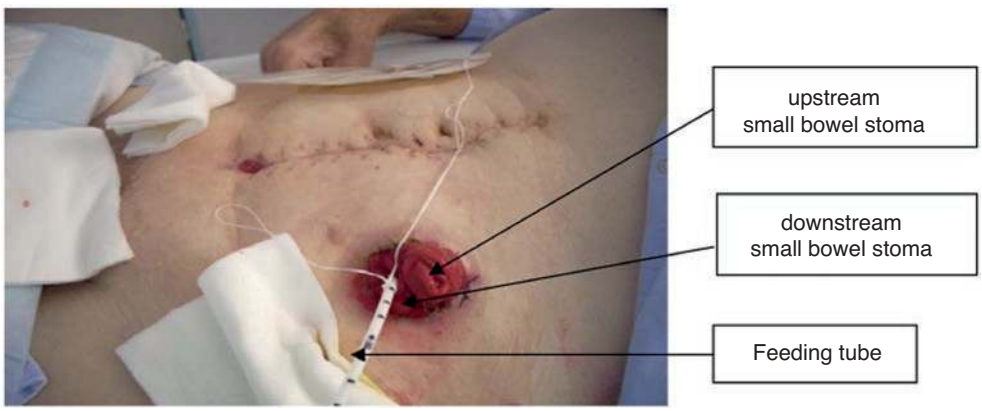

Fig. 1 Example of a temporary double enterostomy [Authorized reproduction from [19]]. The small bowel continuity is disrupted with two small bowel segments exposed to the abdominal wall: the upstream afferent segment, with impaired digestive and absorptive function, and a downstream efferent segment, totally deprived of digestive secretions, bowel flow and succus entericus. The feeding tube is inserted in the downstream small bowel, and is ready for enteroclysis or chyme reinfusion

niques [20]. It means that two options of enteral nutrition could be available in patients with IF. The first, our preferential one, consists in feeding the patient orally with pureed food and reinfusing the chyme into the downstream small bowel. If oral ingestion is insufficient, additional enteral nutrition is infused "en Y" in the CR tube or, rarely, by nasogastric tube or gastrostomy if present. The second is to use enteroclysis to directly infuse the enteral nutrition solution into the downstream small bowel, as is done for enteral nutrition by jejunostomy. The supposed advantages of the first is to keep functional all the digestion functions that prepare food into absorbable nutrients, to increase the intestinal absorption surface area, to restore the enterohepatic cycles of digestive secretions, certain nutrients and drugs and to restore entero-hormone secretions by ileal and colonic L-cells. However, to our knowledge, no study has compared both methods, so that it not possible to recommend one from another. Both methods achieve weaning from IVS by 90% or more. The choice between the two should be made based on the multidisciplinary team expertise and the availability or not of chyme reinfusion devices.

What Are the Indications and Contraindications of DFH?

The European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) (ESPEN) has defined intestinal failure as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth [1]. Enteroclysis or CR are indicated mainly in type II IF. The ESPEN IF specific interest group defines three types of IF. Type I IF is defined by an acute, short-term and usually self-limiting condition. Type II IF is defined by prolonged acute condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and intravenous supplementation over periods of weeks or months. Type III IF is defined by a chronic condition, in metabolically stable patients, requiring intravenous supplementation over months or years. It may be reversible or irreversible [1].

In case of temporary double enterostomy or EAF, the IF is type 2. DFH is particularly indicated in patients with type 1 and type 2 IF, and with EAF or double stoma with high intestinal outputs (≥1200 mL/24 h). ESPEN has endorsed repeatedly recommendations for using CR in this setting [21–23] and American Society for Parenteral and Enteral Nutrition (ASPEN) clinical guidelines published in 2016 [24] suggest the use of enteroclysis for enteral nutrition in patients with IF with double enterostomy or EAF. We propose in Fig. 2 an algorithm of decision for the nutrition support of patients with a double enterostoma or EAF.

Many people who have enterostomies have episodes of dehydration that require readmissions to the hospital for short stays during which they receive intravenous rehydration [2–5]. Because of the absorptive capacities of the colon, enteroclysis in the terminal ileal or colonic downstream segment of a mixture of water, salt, and bicarbonate is an alternative to intravenous fluids for hydration [25].

DFH is safe, low-cost and easy-to-use if some practical aspects and contraindications are well taken into account [15, 19]. Indeed, before starting DFH, there is a need to perform GI imaging, i.e. X-ray intestinal radiography or CT enterography to follow the progression of the contrast product. The aim is to ensure that the downstream small intestine is clearly shown and that there is no contraindication to feeding: fistula, perforation, occlusion or stenosis in the downstream small intestine. This will also allow the measurement of the length of the downstream small intestine: indeed DFH can only be offered to patients with a functional small intestine of at least 15 cm. To achieve GI imaging, a tube is introduced into the first 15 cm of the downstream small bowel; we advise to use a 14F polyurethane nasogastric tube or feeding gastrostomy (balloon of 5 mL max), and not a Foley® catheter because of the risk of ischemia if the balloon is inflated to 20 mL. The contrast product should be infused under real time X-ray imaging to check the luminal progression to the right colon [19] (Fig. 3).

DFH needs to be integrated into multidisciplinary care, handled by specialized trained teams, and should be included in patient's education, to avoid technical failure [19, 26]. Enteroclysis or chyme reinfusion are actually part of intestinal rehabilitation, especially for complex management of opened abdominal wounds or patients with high intestinal outputs [23].

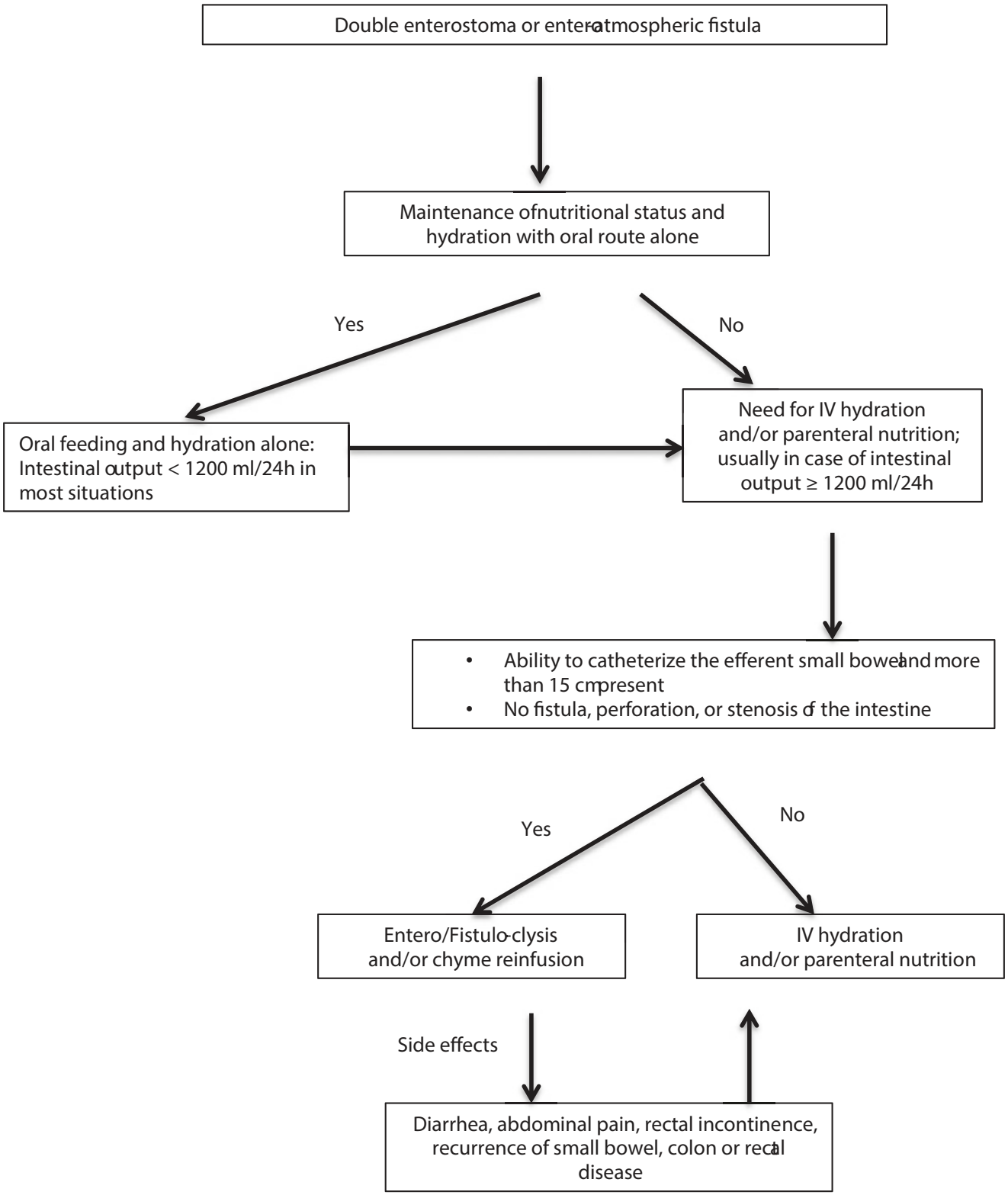

Fig. 2 Proposal for an algorithm of decision for the nutrition support of patients with double enterostoma or entero-atmospheric fistula. Parenteral nutrition would be chosen only if distal small bowel is inaccessible or diseased, or in case of uncontrolled side effects, making the distal feeding contraindicated. In every situation, the patient's agreement must be obtained

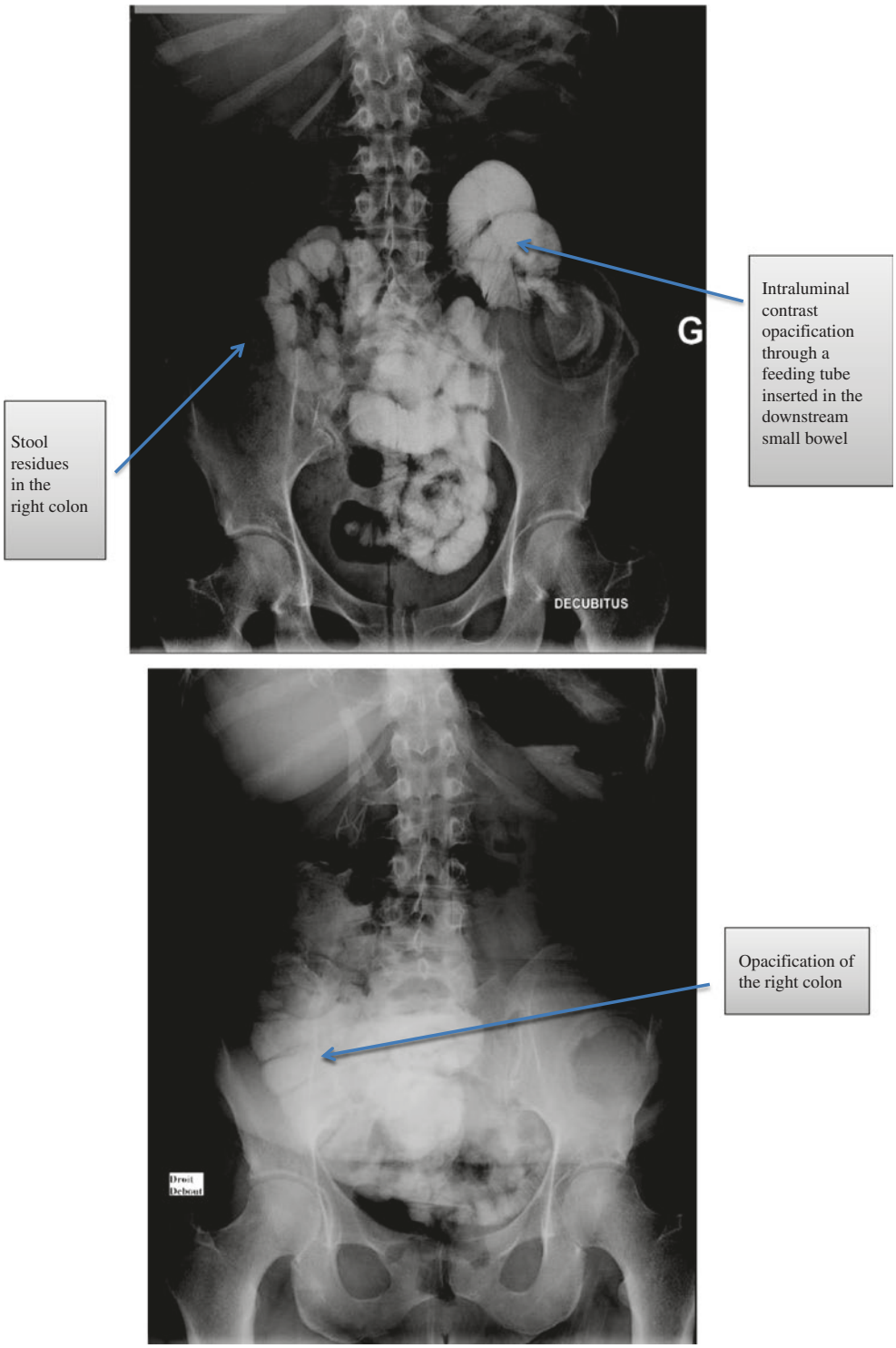

Fig. 3 Opacification of the downstream small bowel through a feeding probe. The presence of fecal residues in the right colon makes the patient at high risk of constipation or subocclusion. The administration of laxatives through the feeding probe is indicated, as well as the stop of anti-motility drugs. In the second image you could observe the progression of the intraluminal contrast into the right colon attesting that there is no proximal intestinal occlusion. The progression should be observed to the rectum (not shown)

Benefits and Side Effects of DFH

Enteroclysis, or chyme reinfusion performed with auto-regulated pumps can be performed until the surgical reestablishment of continuity and stoma closure. One of the first reported benefits of DFH is the reduction of the proximal small bowel output [16]. This is one of the reasons to quickly start DFH in patients with EAF or a high output stoma (≥1200 mL/24 h). DFH contributes to the improvement of nutritional status and liver function, and prevents parenteral nutrition complications, mainly central venous catheter-related infections and thrombosis, and liver complications

Table 1 Summary of the key clinical studies that evaluate the benefits of DFH in patients with intestinal failure

Author	Year	Study design	Patients (*n*)	Type of patients	Type of distal feeding	Main findings
Nagar et al. [15]	2018	Retrospective case series	35	Proximal stoma with a remnant upstream small bowel ≤120 cm	CR	Cost-effective and could effectively substitute PN
Picot et al. [9]	2020	Retrospective case series	306	Double entererostomy or EAF	CR	Improvement of nutritional status, citrulline, plasma liver tests, and feasible at home, weaning from IVS
Wu et al. [29]	2014	Retrospective case series	95	High-output upper EAF, particularly biliary fistula	DFH	Improvement of hepatic and nutritional parameters
Coetzee et al. [14]	2013	Retrospective case series	20	EAF	DFH	Feasible in selected patients with a proximal enteric fistula or stoma. Weaning from parenteral nutrition, reduction of IVS infectious. Adequate nutrition, water and electrolyte balance achieved without the need of PN
Cosnes et al. [27]	1990	Retrospective case series	10	EAF	DFH	Effective nutritional support. Weaning from IVS
Teubner et al. [18]	2004	Retrospective case series	12	EAF	DFH	Effective nutritional support. Weaning from IVS
Levy et al. [17]	1989	Retrospective case series	335	EAF	CR	Viable method of nutritional support in patients with high-output small bowel external fistula(s)

CR chyme reinfusion, *EAF* enterocutaneous fistula, *EN* enteral nutrition, *EF* enteroclysis/fistuloclysis, *IVS* intravenous support

[9, 10, 13, 14, 17, 18]. Besides technical issues, the main side effects of DFH are transient abdominal pain, during the first few hours, and motility disorders (e.g. diarrhoea) [18, 19]. Table 1 reports the main clinical studies having evaluated the benefits of DFH in patients with IF.

Enteroclysis

Enteroclysis has many benefits especially in patients with a high-output fistula.

Cosnes et al. [27] performed an enteroclysis of an elemental diet in the distal small bowel in ten patients with a double enterostomy located between 10 and 95 cm from the duodeno-jejunal flexure. The length of the distal limb was 215 ± 58 cm. Five of these patients had undergone small bowel resections of more than 1 m. All patients were receiving parenteral nutrition. The jejunal losses averaged 3 kg/24 h. The enteral nutrition solution provided 31.9 ± 10.5 kcal/kg/24 h in a volume of 2860 ± 803 mL/24 h. Enteroclysis lasted for 39 ± 9 days until intestinal continuity was restored, 20 h/24 h. Patients had an oral diet. The digestive nitrogen absorption balance ($n = 6$) was positive between 5 and 15 g/24 h in all patients, despite nitrogen losses through the upstream segment. Sodium balance was positive in 9 patients, negative in one patient who required intravenous fluids. Downstream intestinal sodium absorption was measured to be between 176–297 mmol/24 h. Parenteral nutrition was discontinued in 9 patients.

Teubner et al. [18] included 12 patients with EAF, dependent on IVS for hydration balance ($n = 2$) or nutritional needs ($n = 10$), during a median of 7 (range 5–7) nights per week. Median length of proximal small intestine from the duodeno-jejunal was 105 (range 45–200) cm and that of the distal small bowel, 120 (range 75–400) cm. Patients had an oral diet. The median fistula losses were 1360 (range 690–3190) mL/day. Enteroclysis was made with a standard polymeric enteral nutrition solution ($n = 3$) or, if intolerance, a semielemental or elemental solution ($n = 4$ each). One patient did not tolerate the enteroclysis. Eleven patients were weaned from IVS after a median of 28 days.

In summary, enteroclysis is a safe technique and can replace IVS to maintain or improve nutritional status and it reduces the complications and costs of IVS and parenteral nutrition.

Chyme Reinfusion (CR)

CR consists in the chyme collection from the proximal stoma and reinfusion through the distal stoma within the downstream small bowel. In many case reports or short series publications, CR was performed with enteral nutrition pumps or sequentially with a syringe [19]. Nowadays, CR could be performed with specifically designed devices or pump [15, 18]. During three decades, Enteromate® pumps have been specifically marketed for automated CR [9, 10, 18]. The advantages were considerable. In a closed circuit, and therefore without unpleasant odor, they continuously adjust the flow rate of the CR to that of the upstream enterostomy, without needing human manipulation to transfer (and/or sieve) the chyme. Portable pumps with adjustable

continuous flow were also available from 2008, allowing CR to be continued at home [9] until the surgery to close the enterostomy or EAF. CR ensures the use of the entire potentially functional intestine and the correction of the IF. CR restores the function of the entire anatomically present bowel prior to the surgical restoration of continuity, including increasing absorptive capacities, restoring enterohepatic cycles and enterokine secretions, and improving trophicity of the downstream bowel. Patients are fed with what they eat. Some patients with a short or pathological downstream intestine still have intestinal insufficiency but it is less severe. Picot et al. published the largest case series studies of CR [9, 10, 28]. It included 306 patients with intestinal failure patients due to temporary double enterostomy (n = 269) or EAF (n = 37). They demonstrate that CR corrects the IF by restoring intestinal absorption. CR decreased intestinal losses by 85% and allowed strong improvements in nitrogen and fat digestive absorption coefficients. Plasma citrulline levels improved and there was a strong reduction in the proportion of patients with plasma citrulline <20 μmol/L. Nutritional status improved, especially in patients with body mass index <20. According to the ESPEN clinical classification of intestinal failure IVS [8], CR allowed 94% (46/49) of patients receiving only fluids and electrolytes, and 88% (142/162) of those receiving parenteral nutrition to stop IVS. The remainders required lower volumes of PN-IVS ($p < 0.001$).

DFH and Liver Dysfunction

Intestinal failure associated liver disease (IFALD) results in part from the interruption of enterohepatic cycles of bile salts (BSs). Under physiological conditions, BSs reabsorbed in the terminal ileum and right colon, return to the liver where they are re-secreted into the bile. In the L-Cells of the ileo-cacecal area, the transcellular flow of BSs stimulates the secretion of FGF19 into the portal blood. In the liver, FGF19 inhibits cytochrome 7-α-hydroxy-4-cholesten-3-one (C4), which controls the activity of 7-α-hydroxylase responsible for BSs synthesis from cholesterol. In case of a high flow enterostomy or EAF, BSs are lost, this enterohepatic cycle is broken, FGF 19 secretion stops, C4 activity increases and the liver secretes BSs in excess. The prospective study RESCUE shows in 12 patients that CR restored bile salt reabsorption and, within a few days, normalized enterohepatic signaling which corrected the hypersecretion of BSs by the liver [29]. Plasma FGF19 levels increased within a few days, C4 levels fall, and plasma alkaline phosphatase (ALP) and gamma-glutamyl-transpeptidase (GGT) activity decreased. The increase in FGF19 correlated with the decrease in C4, the increase in citrullinemia, and the decrease in plasma ALP and GGT activity.

Previous studies have suggested that CR could improve liver tests and function. Picot et al. showed that the number of patients who had one or several plasma liver tests abnormalities decreased from 83 to 40% ($p < 0.0001$) [9].

The retrospective study by Wu et al. [30] included 95 patients with high output EAF located between 10 and 95 cm from the duodeno-jejunal flexure. They were receiving parenteral nutrition. The distal intact small intestine was longer than 100 cm. The authors compared 60 patients with exclusive enteral nutrition (EN) and 35 patients with exclusive enteral nutrition and chyme reinfusion (EN-CR). Patients with EN-CR had greater liver function test improvements and better one year survival than patients with EN. In addition, in the EN-CR group, bile reinfusion and succus entericus from duodenal fistulas resulted in a greater improvement than jejunal chyme.

In contrast, Cosnes et al. observed no change in liver tests during the duration of enteroclysis, despite weaning from IVS [27].

In summary, CR allows to reestablish the small bowel continuity, to correct the intestinal failure, to restore the intestinal function, to normalize the nutritional status, to wean off IVS and to restore the enterohepatic cycle of bile salts that help with the improvement of IFALD.

Future Perspectives

Research is needed to better understand the positive effects of DFH and determine if CR is more beneficial than enteroclysis with an enteral nutrition solution alone. The mechanisms underlying the improvement of intestinal and liver functions are incompletely understood. One hypothesis could be that CR restores several endocrine functions of ileocaecal L-Cells through the effect of signaling molecules. BSs are signaling molecules. The targets of BSs are dedicated nuclear and plasma membrane bound receptors, in particular the nuclear transcription farnesoid X receptor (FXR) [31, 32]. By targeting these receptors, BSs could influence various metabolic and biological processes including BS and glucose homeostasis, hepatic inflammation, intestinal barrier function, trophicity of the intestinal mucosa, regulation of gastrointestinal motor function, and intestinal barrier function.

The choice to perform CR rather than enteroclysis currently depends on the availability of medical devices or equipment specifically designed to perform CR in a closed circuit, without manipulation or odor, convenient, easy to learn by caregivers and patients, feasible at home, inexpensive, and reimbursed by health insurance. New CR devices are in the advanced stages of development and are awaiting approval for hospital and home use and reimbursement by Medicare [33].

Side Effects of Enteroclysis and CR

As reported above, DFH is a safe technique of enteral nutrition if its contraindications, namely intestinal stenosis, occlusion, fistula and perforation, are well respected. The side effects are mainly represented by abdominal pain, diarrhea, or constipation (see below paragraph 'Practical aspects of DFH'). The most frequently reported technical problem is the accidental expulsion of the feeding tube, because of the peristaltic contractions of the small bowel, requiring its repositioning. Its prevention is based on adequate fixation of the tube to the stoma and stopping drugs that slow down intestinal transit [14, 20]. Patients with downstream occlusion, for example due to peritoneal carcinomatosis, cannot be candidates for DFH because of the major risk of complication and the lack of benefits. The other difficulties of DFH are tube displacement/leakage, and diarrhoea with unpredictable absorption. In the latter, despite DFH, the risk that the patient remains dependent to parenteral support seems high, and surely difficult to predict.

Practical Aspects of DFH

Figure 1 shows a double enterostomy with a feeding tube inside the downstream small bowel. Before initiating DFH, i.e. enteroclysis or CR, it is mandatory to perform GI imaging, i.e. X ray or tomodensitometry with luminal contrast, to ensure that there is no contraindication: fistula, perforation, occlusion or stenosis in the downstream small intestine (see above paragraph "What are the indications of DFH?"). The presence of a stenosis or of a bowel perforation contraindicate the use of DFH. The length of the downstream bowel has to be more or equal to 15 cm. Figure 3 shows an opacification of the downstream small bowel through a feeding tube; the fecal residues in the right colon make the patient at high risk of constipation or subacute occlusion. Their prevention consists in the administration of a laxative drug through the feeding probe.

To be sure of well-functioning downstream small bowel, we suggest, two days before starting the DFH, to instill one liter of oral rehydration solution (e.g. World Health Organization water solution with salt and sugar) through the feeding tube. In case of fecal residues or fecaloma in the colon, laxatives must be added. Anti-motility drugs have to be stopped to avoid intestinal occlusion or constipation just after the start of DFH [19].

Before starting DFH, it is important to obtain the agreement of the patient, and especially for CR, regarding the food constraints of ingesting smooth puree meals. For enteral nutrition through enteroclysis, polymeric formulas can be used. If intolerance occurs, they could be changed into semi-elemental formulas [24]. During DFH, if diarrhea occurs, loperamide can be used. In case of abdominal pain, antispasmodic can be used. In selected patients, CR was feasible at home thanks to portable pumps [20]. Picot et al. showed that this was possible for 30% of patients with an enterostomy, and in this study, no patient had to stop CR [9]. However, in France and other countries, home CR is not yet recognized by health insurances as a nutrition support technique, and unfortunately cannot be recommended.

Conclusions

Enteroclysis and CR, the two techniques of DFH, are recommended by international clinical nutrition societies as nutrition support techniques in patients with type 2 IF and a double enterostomy or EAF. DFH has many benefits: it decreases upstream stoma or fistula output, improves intestinal and liver functions, and nutritional status. Consequently the major benefit of these techniques is that it allows IVS weaning, thus can decrease the IVS and PN-related complications, mainly of central catheter-related infections. DFH is safe if the contraindications and a dedicated protocol are respected. It is important to emphasize the need to integrate DFH into multidisciplinary intestinal rehabilitation, under the supervision of dedicated and trained teams of a physician (with a special interest in nutritional support), a surgeon, dieticians, and nurses. Based on these large benefits for health, DHF may become routine practice in an IF patient before a temporary stoma or fistula is surgically closed.

References

1. Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34(2):171–80.
2. Borucki JP, Schlaeger S, Crane J, Hernon JM, Stearns AT. Risk and consequences of dehydration following colorectal cancer resection with diverting ileostomy. A systematic review and meta-analysis. Colorectal Dis. 2021;23:1721–32. https://doi.org/10.1111/codi.15654.
3. Justiniano CF, Temple L, Swanger A, et al. Readmissions with dehydration after ileostomy creation: rethinking risk factors. Dis Colon Rectum. 2018;61(11):1297–305.
4. Messaris E, Sehgal R, Deiling S, et al. Dehydration is the most common indication for readmission after diverting ileostomy creation. Dis Colon Rectum. 2012;55(2):175–80.
5. Liu C, Bhat S, O'Grady G, Bissett I. Re-admissions after ileostomy formation: a retrospective analysis from a New Zealand Tertiary Centre. ANZ J Surg. 2020;90(9):1621–6.
6. Beck-Kaltenbach N, Voigt K, Rumstadt B. Renal impairment caused by temporary loop ileostomy. Int J Colorectal Dis. 2011;26:623–6.
7. Saunders J, Parsons C, King A, Stroud M, Smith T. The financial cost of managing patients with type 2 intestinal failure; experience from a regional centre. e-SPEN J. 2013;8:e80–5.

8. Pironi L, Konrad D, Brandt C, et al. Clinical classification of adult patients with chronic intestinal failure due to benign disease: an international multicenter cross-sectional survey. Clin Nutr. 2018;37(2):728–38.
9. Picot D, Layec S, Seynhaeve E, Dussaulx L, Trivin F, Carsin-Mahe M. Chyme reinfusion in intestinal failure related to temporary double enterostomies and enteroatmospheric fistulas. Nutrients. 2020;12(5):1376. https://doi.org/10.3390/nu12051376.
10. Picot D, Layec S, Dussaulx L, Trivin F, Thibault R. Chyme reinfusion in patients with intestinal failure due to temporary double enterostomy: a 15-year prospective cohort in a referral centre. Clin Nutr. 2017;36(2):593–600.
11. Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term parenteral nutrition. Aliment Pharmacol Ther. 2013;37(6):587–603.
12. Buchman AL, Moukarzel A, Goodson B, Herzog F, Pollack P, Reyen L, et al. Catheter-related infections associated with home parenteral nutrition and predictive factors for the need for catheter removal in their treatment. JPEN J Parenter Enter Nutr. 1994;18(4):297–302.
13. Zi-Wei X, You-ShengLi. Pathogenesis and treatment of parenteral nutrition-associated liver disease. Review article. Hepatobiliary Pancreat Dis Int. 2012;11(6):586–93. https://doi.org/10.1016/S1499-3872(12)60229-X.
14. Coetzee E, Rahim Z, Boutall A, Goldberg P. Refeeding enteroclysis as an alternative to parenteral nutrition for enteric fistula. Colorectal Dis. 2014;16(10):823–30.
15. Nagar A, Mehrotra S, Yadav A, Mangla V, Lalwani S, Mehta N, et al. Distal bowel re-feeding in patients with proximal jejunostomy. J Gastrointest Surg. 2018;22(7):1251–7.
16. Levy E, Parc R, Loygue L, Loygue J. Stomies terminales, jejunales ou ileales temporaires de sauvetage avec reinstillation autorégulée. Nouv Presse Med. 1977;6:461–2.
17. Levy E, Frileux P, Cugnenc PH, Honiger J, Ollivier JM, Parc R. High-output external fistulae of the small bowel: management with continuous enteral nutrition. Br J Surg. 1989;76(7):676–9.
18. Teubner A, Morrison K, Ravishankar HR, Anderson ID, Scott NA, Carlson GL. Fistuloclysis can successfully replace parenteral feeding in the nutritional support of patients with enterocutaneous fistula. Br J Surg. 2004;91(5):625–31.
19. Thibault R, Picot D. Chyme reinfusion or enteroclysis in nutrition of patients with temporary double enterostomy or enterocutaneous fistula. Curr Opin Clin Nutr Metab Care. 2016;19(5):382–7.
20. Bhat S, Sharma P, Cameron N-R, Bissett IP, O'Grady G. Chyme reinfusion for small bowel double enterostomies and enteroatmospheric fistulas in adult patients: a systematic review. Nutr Clin Pract. 2020;35:254–64.
21. Klek S, Forbes A, Gabe S, Holst M, Wanten G, Irtun Ø, et al. Management of acute intestinal failure: a position paper from the European Society for Clinical Nutrition and Metabolism (ESPEN) Special Interest Group. Clin Nutr. 2016;35(6):1209–18. (paragraphe 3.2.2.5).
22. Pironi L, Corcos O, Forbes A, Holst M, Joly F, Jonkers C, et al. Intestinal failure in adults: recommendations from the ESPEN expert groups. Clin Nutr. 2018;37(6):1798–809. https://doi.org/10.1016/j.clnu.2018.07.036. [Paragraphe 5.3: "…In patients with high output fistulae or stoma and achievable distal access, a chyme reinfusion (enteroclysis) should be considered"].
23. Singer P, Reintam Blaser A, Berger M, Alhazzani W, Calder P, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38:48–79. https://doi.org/10.1016/j.clnu.2018.08.037. [recommandation49: "In case of high output stoma or fistula, the appropriateness of chyme reinfusion or enteroclysis should be evaluated and performed if adequate"].
24. Kumpf VJ, de Aguilar-Nascimento JE, Diaz-Pizarro Graf JI, Hall AM, McKeever L, Steiger E, et al. ASPEN-FELANPE clinical guidelines: nutrition support of adult patients with enterocutaneous fistula. JPEN J Parenter Enter Nutr. 2017;41(1):104–12. (question n°4).
25. Layec S, Seynhaeve E, Dussaulx L, Trivin F, Carsin-Mahe M, Barbottin E, Trivin F, Picot D. Hydration by colonic enteroclysis: an alternative to parenteral hydration in patients with high-output double enterostomy. Nutr Clin Pract. 2021;37:625–33. https://doi.org/10.1002/ncp.10769.
26. Groen H, Neelis EG, Poley MJ, Olieman JF, Scheenstra R, Krabbe PF, et al. Intestinal rehabilitation for children with intestinal failure is cost-effective: a simulation study. Am J Clin Nutr. 2017;105(2):417–25.
27. Cosnes J, Baux F, Gendre JP, et al. Elemental feeding into the distal segment of a temporary small bowel. Gastroenterol Clin Biol. 1990;14:146–52.
28. Layec S, Seynhaeve E, Trivin F, Carsin-Mahé M, Dussaulx L, Picot D. Management of entero-atmospheric fistulas by chyme reinfusion: a retrospective study. Clin Nutr. 2020;39(12):3695–702.
29. Koelfat KVK, Picot D, Chang X, Desille D, van Eijk HM, van KuijkSMJ LM, Layec S, Carsin M, Dussaulx L, Seynhaeve E, Trivin F, Lacaze L, Thibault R, Schaap FG, Olde Damink SWM. Chyme reinfusion restores the regulatory bile salt-FGF19 axis in intestinal failure patients. Hepatology. 2021;74(5):2670–83. https://doi.org/10.1002/hep.32017.
30. Wu Y, Ren J, Wang G, Zhou B, Ding C, Gu G, et al. Fistuloclysis improves liver function and nutritional status in patients with high-output upper enteric fistula. Gastroenterol Res Pract. 2014;2014:1–10.
31. Schaap FG, Trauner M, Jansen PLM. Bile acid receptors as targets for drug development. Nat Rev Gastroenterol Hepatol. 2014;11(1):55–67.
32. Kliewer SA, Mangelsdorf DJ. Bile acids as hormones: the FXR-FGF15/19 pathway. Dig Dis. 2015;33(3):327–31.
33. Sharma P, Davidson R, Davidson J, Keane C, Liu C, Ritchie SR, et al. Novel chyme reinfusion device for gastrointestinal fistulas and stomas: feasibility study. Br J Surg. 2020;107(9):1199–210. https://doi.org/10.1002/bjs.11516.

Chronic Abdominal Pain

Peter Paine and Justin Turner

Key Points

1. Pain is an unpleasant sensory and emotional experience associated with or without tissue damage.
2. Pain related to intestinal failure can be due to a surgical catastrophe, inflammatory bowel disease or dysmotility.
3. Psychological support is needed to help manage chronic pain.
4. Due to absorption problems analgesia may need to be given by topical, buccal (including lozenges), or rectal routes.
5. Narcotic bowel syndrome may occur with chronic opiate use for chronic pain and is characterised by gastrointestinal dysmotility and hyperalgesia.
6. Chronic pain should not be treated with opioids; neuromodulator drugs may be beneficial
7. The approach to chronic pain has changed and there is a shift from that of a *cure* focus to a *care* focus with an understanding that chronic pain cannot be cured medically but can be helped.

Definitions

Pain

The International Association for the Study of Pain (IASP) defines pain as

> *an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage* [1]

This global definition allows for all conditions that have pain. For example acute appendicitis and irritable bowel syndrome, where abdominal symptoms are present for both, but the underlying cause and treatment options may be significantly different.

The definition also highlights that pain is an emotional experience and therefore there is a component of pain which is part of a conscious process. Pain is a reported problem and so the way the patient interprets their symptoms and then the way in which they are able to communicate those symptoms will vary. How a person interprets their experience of pain can be altered by mood, activity or distraction.

Acute Pain

Pain is protective. At the time of initial injury for example when you take a hot drink, the burning pain causes you to stop to prevent significant injury to your mouth or oesophagus.

Pain is then protective by preventing further activity and allowing healing to occur. For example if you fracture a bone this will lead to reduced movement and limiting the weight bearing on the bone, allowing for healing.

Post-operative Pain

Surgery is trauma where the normal responses to pain in the short term have been prevented by anaesthesia. This leads at a later stage to a situation where the subsequent responses to pain are to a degree no longer helpful and in fact may be detrimental to recovery. For example abdominal pain following laparotomy leads the patient to minimise movement, which in turn prevents deep breathing. This in turn increases the risk of chest infection and delayed recovery from surgery. Surgical techniques are aimed at minimising the degree of trauma and anaesthetic techniques aimed at improving pain relief to aid in early return to normal physical function.

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Chronic Pain

Whilst the IASP global definition for pain is generally accepted, the definition of chronic or persistent pain is not as clearly defined. A pain which persists beyond the time of healing can be considered chronic. However the difficulty with this definition is for some patients, for example osteoarthritis, healing may not be possible. For this reason an alternative definition for chronic pain is a pain which has lasted longer than 3 or 6 months. For many forms of chronic pain the protective nature of pain is no longer apparent and the pain itself becomes disabling. Chronic pain within the general population is common [2].

Intestinal failure patients may have chronic non-GI pain which relates to another problem such as osteoarthritis or vertebral compression fracture. The management of these pains is beyond the remit of this chapter. However consideration needs to be given to the effect of intestinal failure on the medications available to the patient. Equally the medicines used would need to be considered with respect to their impact on bowel function.

Acute on Chronic Pain

A patient with chronic pain still has the risk of developing new medical problems relating to their intestinal failure e.g. a parastomal hernia or a new Crohn's disease inflammatory mass. New pains that have different characteristics in terms of the nature of the pain or location may still need to be investigated. Increased intensity in pain that has been established to be a chronic pain however, a "flare up", is unlikely to benefit from further investigation and the costs, both economic for the service, and emotional for the patient would need to be considered.

Mechanisms of Chronic Pain and the Biopsychosocial Model

An understanding of the pathophysiological mechanisms of chronic pain can be helpful in both characterising the pain, tailoring appropriate therapies and in explanatory models to delimit realistic treatment expectations. These mechanisms need to be considered within a biopsychosocial model [3]. From a holistic perspective, the biological, psychological and social components of the pain experience cannot be fully disentangled, and it is likely that there will be disordered processes in play at all these levels concurrently. It is possible however for one or other of these levels to predominate and therefore they will be deconstructed, albeit somewhat artificially.

Biological

At the more biological end of the biopsychosocial spectrum, pain is largely divided into *nociceptive* and *neuropathic*. Nociceptive pain describes the normal and appropriate function of the pain nervous system in response to potentially damaging stimuli and the reversible adaptive pain hypersensitivity ensuing as a protective mechanism for proper healing. Neuropathic pain however reflects damage and prolonged dysfunction to the pain nervous system itself, whereby pain can occur spontaneously, its threshold may fall dramatically such that innocuous stimuli produce pain (allodynia), and the duration and amplitude of its response to noxious stimuli are amplified. This should be considered as an autonomous disease state of the pain nervous system in its own right [4].

A summary diagram of the pain "hardware" involved following nerve injury or inflammation in chronic neuropathic pain states, and possible sites of abnormal function underpinning chronic pain is shown in Fig. 1. It is quite possible that more than one or indeed all of these levels of abnormal pain nervous function could be in operation at once. It is beyond the scope of this chapter to detail these changes further, but they are outlined in a helpful review article [5].

The structural diagram of the pain nervous system changes however does not convey that endogenous pain modulation is also a *dynamic* process and it is likely that there may be a "tug of war" happening between inhibitory and facilitatory processes and between bottom up and top down sensitisers [6]. A practical consequence of this information on neuropathic pain pathophysiology is that it can be helpful to patients to be given *explanatory models* (together with the use of simplified diagrams e.g. Fig. 2) of the "wiring" of their pain alarm system, including sites of malfunction. In particular, the instantiation of chronic pain within the spinal cord, brainstem and central nervous system can help explain why surgical procedures aimed at a peripheral target (such as adhesiolysis or organ removal) are unlikely to remove the pain. Helpful explanatory analogies here can be made with "phantom limb" pain and with a broken fire alarm, whereby the peripheral element or trigger may be resolved, but the central component perpetuates the pain experience. Such "central mediation" of chronic pain helps to explain why this is not readily fixable surgically and why centrally acting drugs ("neuromodulators" such as antidepressants and anti-epileptics) might be helpful to alter central pain neural function. Indeed, the Rome IV classification has recently recast chronic continuous or nearly continuous abdominal pain as "centrally mediated" and highlighted the problematic association with opiates for this kind of chronic pain and the potential role of neuromodulators [7].

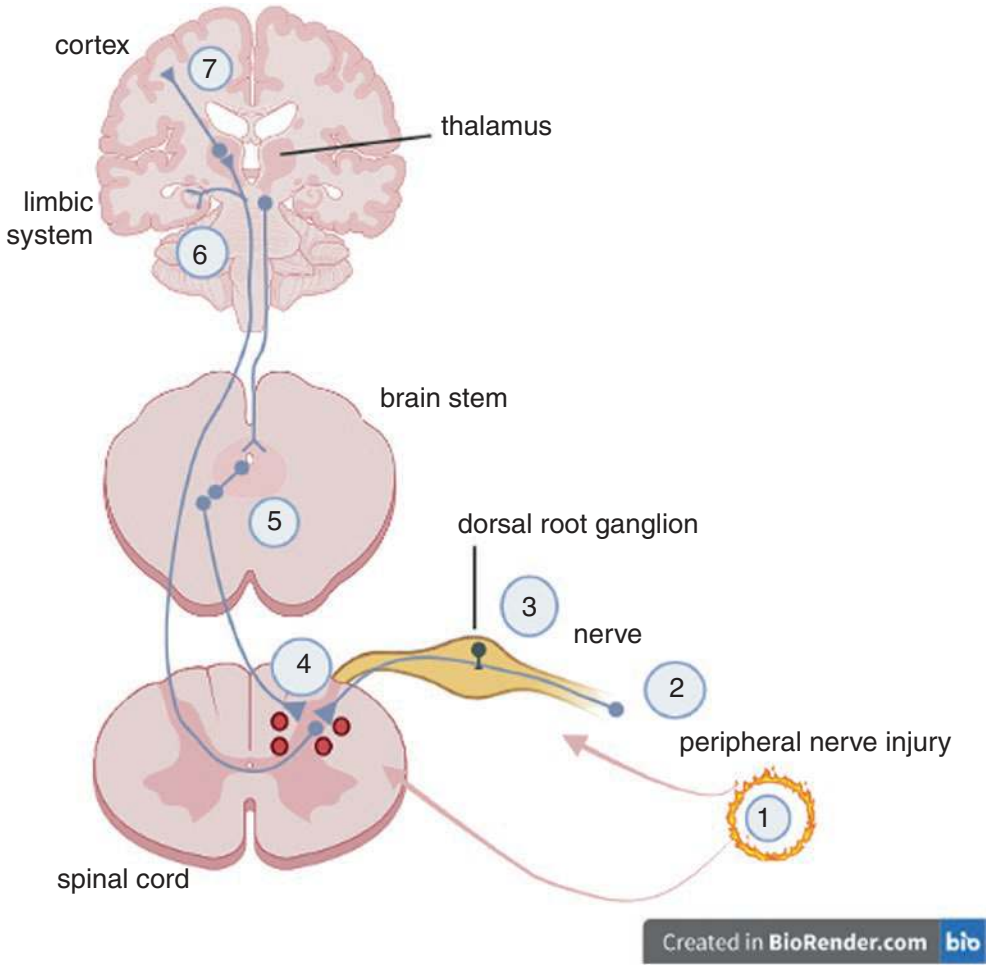

Fig. 1 Sites and mechanisms of chronic post-surgical neuropathic pain. (1) Peripheral sensitisation (distal chemicals), (2) Neuroma at injury site (ectopic excitability), (3) Dorsal root ganglion gene expression (excitability), (4) Central sensitisation (dorsal horn gene expression, inhibitory interneurone loss, microglia activation), (5) reduced Descending Noxious Inhibitory Controls (brainstem), (6) Limbic and hypothalamus (emotion, behaviour, Autonomic Nervous System), (7) Cortex (cognitive-evaluative)

Another important biological concept for understanding and explaining the clinical features of chronic abdominal pain in particular is that of *viscerosomatic convergence* at the level of the dorsal horn of the spinal cord. This can help explain to patients why a previous internal injury is often associated with extreme cutaneous pain sensitivity (allodynia). An example of this is seen in patients with chronic pancreatitis [8]. Furthermore, chronic pain that has been triggered or initiated from the viscera may also be quite diffuse and poorly localised because of the multi-level spinal inputs. Moreover the close association of the viscera with limbic and autonomic areas may predispose chronic visceral pain to greater levels of autonomic upset and fear/anxiety components. Lastly, the role of the microbiome in the bioactive luminal chemical soup in chronic pain is an area of increasing but poorly characterised interest.

Finally, opiate induced hyperalgesia is a specifically important mechanism to consider here. Whilst the clinical aspects of recognising and managing this will be dealt with later, in brief chronic opiate usage likely produces molecular biological changes in pain neural pathways such that the net result is further exacerbation of the underlying chronic pain state [9]. This is a highly counterintuitive concept for both the patients and the team looking after them but is important to recognise and understand that this has a molecular biological basis which appears to be largely reversible by careful controlled opiate reduction and withdrawal [10].

Psychological

Psychological risk factors for patients developing disabling chronic pain include pre-existing anxiety, depression and pain catastrophizing. Pain catastrophizing combines rumination (preoccupation with fear of worsening pain), magnification (amplify the significance of pain) and helplessness (inability to control the pain experience). A dissociative coping style may be a risk factor for opiate abuse [9].

Psychological factors that make patients more resilient and protect from disability with chronic pain include Pain Acceptance which involves activity engagement (engage in activities even if pain is experienced) and Pain Willingness (not attempting to control or avoid pain). Pain self-efficacy which is the confidence to cope with pain and engage with activities despite pain [5].

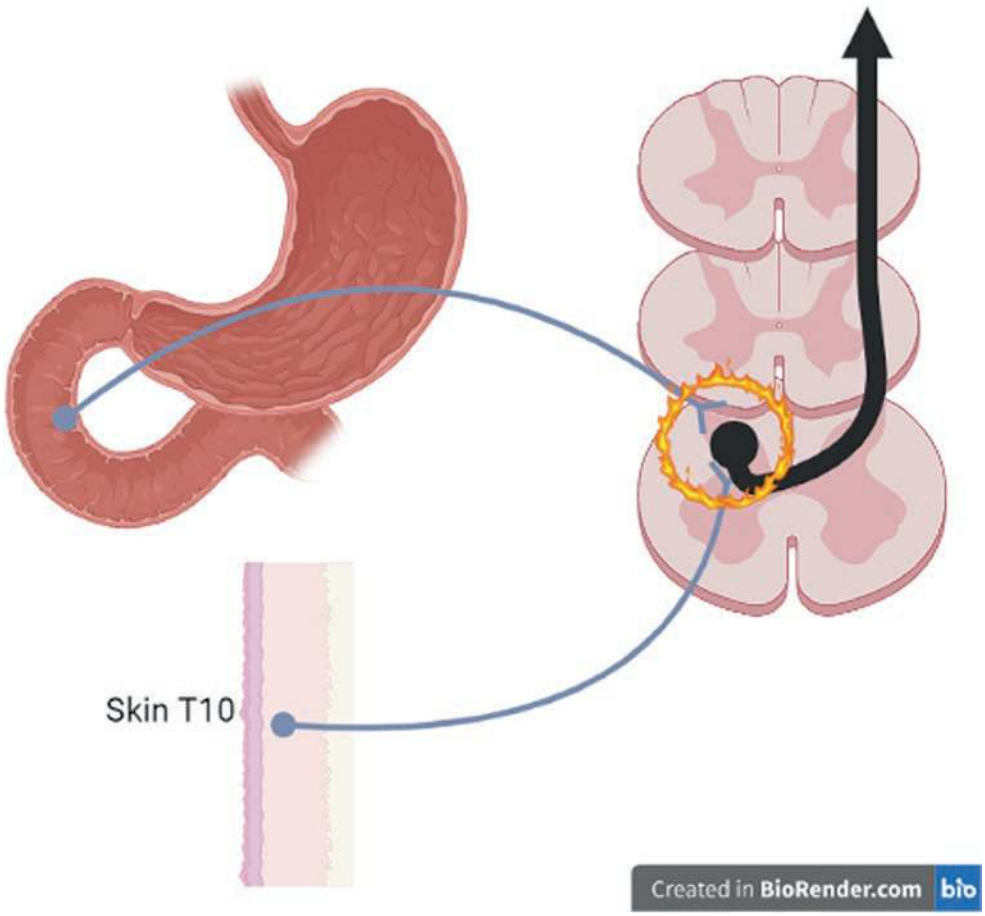

Fig. 2 An example of a simple diagram that can be used with patients to explain concepts such as viscerosomatic spinal convergence giving rise to cutaneous allodynia, central sensitisation in the spinal cord dorsal horn, and increased afferent barrage

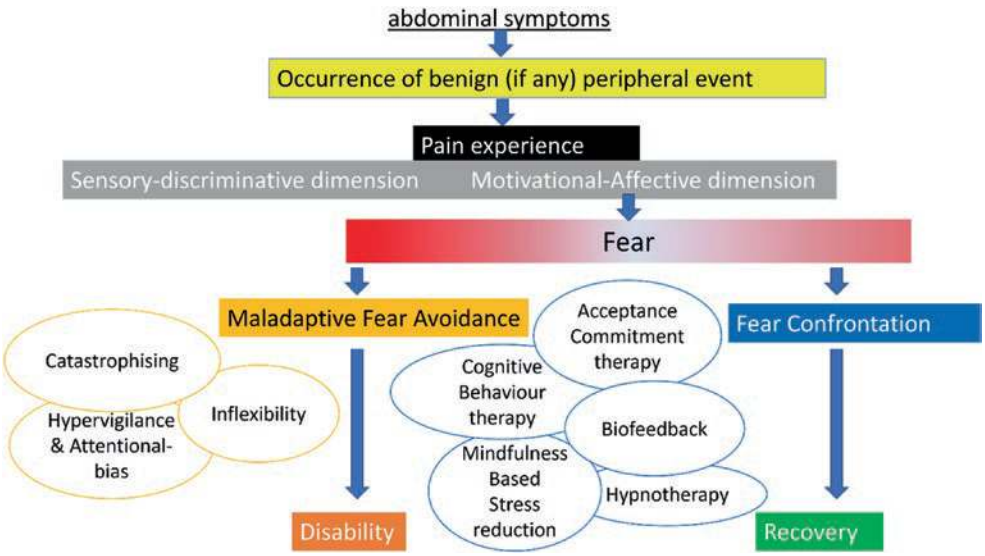

Fig. 3 Psychological factors involved in chronic pain outcomes

Some of the psychological vulnerability and resilience factors associated with outcomes are summarised in Fig. 3, which includes the key concept of maladaptive fear avoidance and both other maladaptive psychological processes and rehabilitative therapeutic approaches [11]. Trauma memory and pain meaning can also be important psychological aspects of the pain experience for a patient and therefore it is essential that clinical pain psychology forms part of any approach to chronic pain assessment and management.

Social

Finally, it should also be recognised that pain behaviours take place in a social context as displays of distress to elicit support. In a similar way to psychological responses, some of these pain behaviours and ways of attempting to elicit support can become maladaptive. At an extreme end of this spectrum are manipulative and deceitful behaviours such as in Munchausen's syndrome or in malingering for secondary financial or emotional gain. More commonly however, maladaptive social dimensions of pain can reflect the values and meaning given to certain expressions of pain within the learnt behaviour environment of the family or culture [12]. Pain behaviours can also sometimes therefore serve as proxies for other kinds of emotional, psychological or social distress when direct expression of these have been suppressed, for example when patients experience bereavement or relationship breakdown. Patterns of maladaptive social interactions with health care providers can also form a sociological vicious cycle exacerbating the pharmacological vicious cycle in the narcotic bowel syndrome [13]. Clear agreed and consistently practiced boundaries and sometimes written contracts can be necessary in some cases where maladaptive social interactions, for example frequent emergency department attendance for injectable opiates, is occurring.

Patients in Pain

Each patient in an intestinal failure unit presents with their own story, their own pain and how they present and manage their pain will be different for each individual Fig. 4. These will include components of nociception, the pain experience with or without nociceptive activation, suffering and pain behaviours [14].

If treatment of pain as a "signal" removes the signal completely then there is no progression to suffering and consequently no need to consider a model of pain as the wider experience described above.

Whilst teams treating patients are often guided to treatments by pain, in chronic pain, it is an unrealistic goal that medical interventions will provide a resolution of the pain [15].

Unfortunately, in chronic pain associated with intestinal failure, treatment of pain as a "signal" very rarely produces absolute relief, and so the aim should be to manage pain as the larger experience and resultant problems.

Treatment of pain in the intestinal failure unit for most patients should be multimodal with medical, psychological and physical therapies considered.

When assessing any patient it is important to firstly exclude new symptoms which may represent new pathology and consequently should be investigated as felt to be clinically appropriate.

The assessment of Chronic Pain should consider the various components of pain, the impact of pain on levels of physical function, psychological well-being, and resultant levels of disability.

Assessment of Pain

The assessment of the components of pain [16, 17] should include:

- ***Pain intensity***—A 11 point numerical rating system (0–10 with 10 being the worst pain) is a repeatable system that is easy to administer.

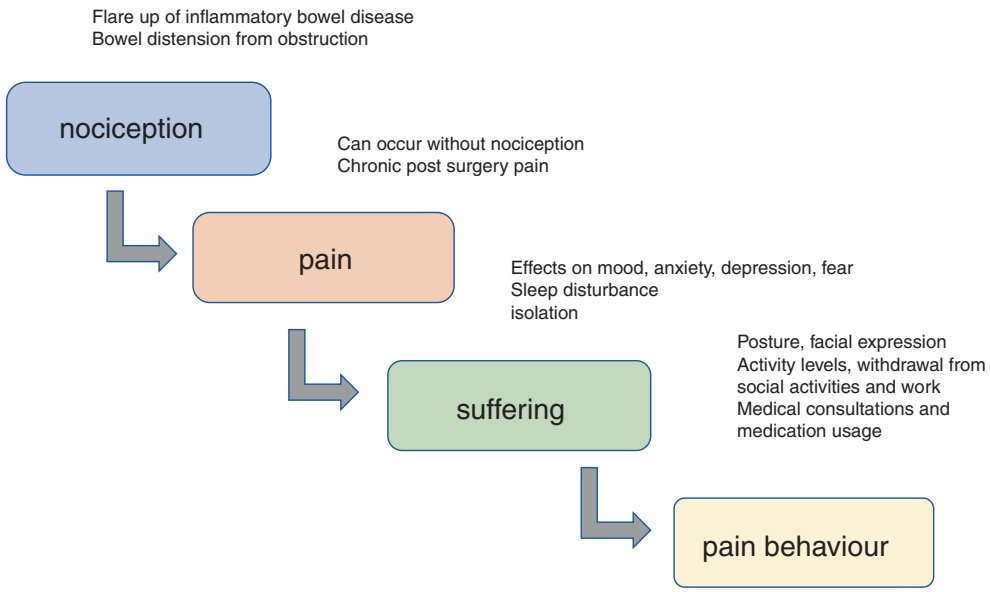

Fig. 4 Components of individual pain presentations

- ***Distribution of Pain***—Both origin of the pain and radiation are useful in assessing possible causes of pain. Pain Diagrams may provide useful information that can be repeated.
- ***Sensory quality of the Pain***—Pain described as colicky in nature and following feed would suggest a mechanism for pain different to a neuropathic pain with burning or stabbing pain, or pain on light touch (allodynia). It is possible to use various scales to assess the descriptive components of pain with standardised questionnaires such as the Short Form McGill Pain Questionnaire.
- ***Temporal Nature of Pain***—Duration of Pain is an important factor since chronic pain in intestinal failure does not exclude the patient from the risk of developing new pathology, for example a flare up of Crohn's disease or development of parastomal hernial. Equally chronic pain which has increased in intensity or flared up is unlikely to need further investigation. Triggers for worsening and improving pain are important to explore, they help suggest a cause for the pain such as ischaemia or obstruction or alternatively they may be linked to changes in psychological or social state. For some patients a Pain Diary is a useful tool to look at intensity overtime.

These aspects of assessment may guide which therapies may be helpful in the management of their ongoing pain.

For the majority of patients on the intestinal failure unit, medical management of their condition has been an ongoing process for a significant length of time.

Aetiology of the individuals' intestinal failure needs to be elicited as well as the amount of functioning bowel. Choices in terms of medications may well vary depended upon the length of small bowel available and transit times through the bowel.

Assessment needs to include a review of previous pain therapies and the reasons particular therapies were found not to have any value. A significant degree of distress occurs if therapies that have previously been found to be unsuccessful are revisited without addressing patients concerns and expectations linked to each therapy. For example patients who have trialled gabapentin and found it to cause recognised side effects such as drowsiness or forgetfulness are unlikely to find it helpful to retry the same medication again.

Current medication usage and the reasons for usage needs to be elicited. Medication route of administration and frequency of dosing need to be clarified. The reasons why particular routes of administration have been adopted also needs to be explored. This is of particular importance when looking at opiates. In our experience many patients will continue to be on opiates. The majority will have started these opiates during an acute exacerbation of pain, but at some stage their pain will have changed from acute to chronic but the opiates remain in place. Reasons for particular routes of administration of opiates needs to be elicited and also why other routes are no longer used. For example it is important, if a patient is using a subcutaneous opiate regime management, to clarify why subcutaneous morphine was prescribed and what prevents use of other routes of administration.

Patient concerns about therapy are also important to review. For a significant group of patients concerns may be about medical desire to reduce opiates, and if this occurs without patient understanding and agreement, our experience is this leads to increasing levels of iatrogenic distress and a poor experience for both the patient and the staff caring for that patient. It is important therefore to understand the patient's perspective on the role of medication. For other patients the awareness that opiates are not helpful in the long term and concerns about addiction are significant and management of those patients will have different priorities.

An assessment of ongoing pain and the potential challenges to management of pain or any change in therapy is not possible without an assessment of the psychological risk factors the patient may have. Patients understanding of what their pain means in terms of further damage (hurt/harm), and pain catastrophizing needs to be explored.

Disability for patients on the intestinal failure unit is multifactorial. Understanding the patient's level of disability and their perception as to how pain plays a part in ongoing disability needs to be explored, to aid in the setting of realistic goals for treatment.

Examination

For some patients on the intestinal Failure unit, examination is complicated by the stoma dressing and wound dressings that are required.

For some of those patients, any pain related to inflammatory irritation to the abdominal wall is best treated by management of the cause of that problem which is covered in other parts of this book.

Examination is important however to look for signs associated with ***neuropathic pain***. These include:

- *Numbness*
- *Dysesthesia* (e.g. tingling, burning)
- *Allodynia*—Pain on light touch

Table 1 Summary of assessment and examination for chronic pain

Pain	Onset, intensity, distribution, quality, duration, triggers
Cause of gastrointestinal failure	Bowel function, previous surgery
Current therapies	Medication dosages, frequency, route of administration other therapy e.g. physiotherapy
Previous therapies	As for current therapies and reason stopped
Past history	Medical, pain, psychological
Psychological factors	Hurt/harm, anxiety, depression
Function	Levels of disability and cause, family and friends, financial pressures
Examination	Inflammation, infection, stoma output, neuropathic signs, nerve entrapment

Table 2 Common themes/phenotypes

Initial cause of intestinal failure	Triggers for pain
Surgical catastrophe	Chronic post-surgical [5, 19]
	Adhesions or Stricture formation leading to obstruction
Inflammatory bowel disease	Ulceration of bowel
	Stricture formation.
	Fistula formation.
	Surgery to remove stricture, which may need to be repeated [20]
Dysmotility	Abdominal distension
	Opiate bowel dysfunction
	Narcotic Bowel syndrome [21]

- *Hyperalgesia*—Increased pain on pinprick
- *Summation*—Increasing pain on repeated stimuli rather than the normal reduction in stimulus
- *Altered Temperature sensation*—Reduced or increased sensation to cold or heat.

It may be possible to elicit pain associated with scars from previous surgery.

If anterior abdominal wall nerve entrapment is considered a possible diagnosis, a specific tender area is located, it is then possible to ask the patient lift their legs and contract the abdominal wall. If this is associated with increased pain this may suggest a nerve entrapment—Carnett's sign [18].

The approach to assessment and examination is summarised in Table 1:

Chronic Pain "Phenotypes" on the Intestinal Failure Unit

Whilst the assessment and examination approach outlined above emphasises an individualised approach, nonetheless we do see common clusters or themes of three main groups of patients presenting with chronic pain on the intestinal failure unit which may be taken into consideration (Table 2).

There tends to be a reasonable degree of overlap in the approaches for the surgical catastrophe and IBD group of patients, but there is a perception that the dysmotility group may present with some particular assessment and management challenges. This may in part reflect more general difficulties in characterising and determining aetiology for the dysmotility patients [22]. This is an emerging and not well evidenced based area currently, and would merit more multi-centre comparative group outcome data as the prevalence of this group of patients in IFU practice would appear to be increasing.

Treatment of Pain in Intestinal Failure Patients

The treatment of chronic pain in all patients on the intestinal failure unit needs to be considered within a biopsychosocial model. No single therapy is likely to provide the solution to a patient's ongoing symptoms.

Therapy for patients with chronic pain associated with intestinal failure therefore needs to be multimodal and interdisciplinary with coordinated care often from multiple medical specialties, nursing care and allied healthcare professionals. The staff on the intestinal unit are key to coordinating the care.

Assessment not only provides the information to guide further therapy but also provides an opportunity to allow the patient to know they have been listened to about their ongoing problems and for some patients this in itself is therapeutic.

For a significant group of patients' psychological factors will play a significant role in their presentation and a full psychological assessment by a clinical psychologist will be necessary and psychological therapies to aid in the ongoing management of pain will be needed.

There are a group of patients in the intestinal failure unit who due to multiple factors including the length of stay in hospital, previous surgeries and recovery, underlying medical conditions who become increasingly de-conditioned and physiotherapy aimed at increasing strength, range of movement and endurance is essential. Occupational therapy assistance with managing ongoing disability may also be required.

Medical Management

It is important to recognise that there are no currently available drugs which can abolish chronic pain completely in all or even most patients. A rule of thumb is that in patients who have some response to analgesics, will find a 30–50% reduction in the intensity of the pain experience useful and are likely to continue that medication. Furthermore, it is clear that in a majority of patients with chronic pain, opiates are ineffective and indeed can be counterproductive and harmful. Non-opiate drugs for chronic pain are often termed adjuvant or neuromodulator drugs. We will deal first with opiate management however, as this appears to be particularly problematic in intestinal failure patients.

The Management of Opiates

For the majority of patients with gastrointestinal failure, due to the chronic nature of the condition it is usually possible to take a considered approach to management of pain and medication changes.

Alterations to therapeutic regimes are more successful with patient agreement and there is less risk of reversion to treatment that the patient believes to be more successful in symptom alleviation whilst the treating team believes it to have a greater risk of harm. For example, ongoing use of subcutaneous opiate injections despite oral intake.

There has been increasing awareness of the harmful and indeed counterproductive effects of opiates on gastrointestinal function and chronic pain management. At the extreme end of the spectrum of negative effects, the "***narcotic bowel syndrome***" has been described. This is a combination of severe opiate induced gastrointestinal dysmotility (including sometimes pseudo-obstruction), combined with opiate induced hyperalgesia. This is described as occurring in a context of a vicious cycle of inadvertent iatrogenic healthcare re-enforcement of dependence on short acting and escalating opiate use, often via the emergency department route [7]. On the other hand, evidence has accrued that "detox" from opiates, especially if sustained, can be associated with a significant improvement (although not abolition) of pain levels and improvement in GI motor function [10]. In the intestinal failure setting, there is some evidence that opiate use is associated with some greater risk of harms, in particular catheter related blood stream infections [23]. Opiates at high doses suppress aspects of immune function including inhibitory effects on humoral and cellular immune responses including antibody production, natural killer cell activity, cytokine expression, and phagocytic activity [24] leading to greater susceptibility to infections. Finally, the risks of opiates in regard to addiction and abuse is well known.

The ideal situation therefore is not to commence opiates for chronic pain in the first place, even if no alternative pain medication is available [25]. However, many patients in the IFU setting will have already been started during acute exacerbations of pain. Unfortunately, often as the pain settles they are not removed due to on-going low level symptoms. Overtime with further exacerbations of pain the opiates are increased. The result is a significant group of patients arriving at a gastrointestinal unit do so with large doses of opiates already on board. The immediate priority in this situation is ***stabilisation*** of the opiate dose and ***optimisation*** of the route.

As the medical profession increasingly recognises the potential for harm of opiate usage in all patients with chronic pain it is understood that opiates play only a small role in the management of ongoing pain and high-dose opiates (equivalent to more than a 120 mg/day) should be discouraged.

In assessing opiate usage in intestinal failure areas of management that need to be explored are:

- ***Route of administration****:* due to various factors including nausea, vomiting, short small-bowel, gastrostomy, patients are prescribed opiates via multiple routes of administration.
  - Intravenous route is preferred by some patients.
  - Intramuscular injection.
  - Subcutaneous injection.
  - Sublingual or intranasal.
  - Oral
  - Transdermal

  The reason why a patient continues to use their opiates via one or other of these routes needs to be explored as does their understanding of potential risks and benefits of that route compared to other routes of opiates.
- ***Frequency of dosing:*** When opiate use becomes prolonged the half-life of all the drugs is at least 3 h and so it seems reasonable to expect opiate usage to be less frequent than this, however some patients are using opiates more frequently and it is important to assess what factors lead to more frequent dosing with opiates.
- ***Dose:*** A significant group of patients in the intestinal failure unit will be on a greater dose of opiates than the upper limit of currently recommended doses.

  This is likely to be multifactorial. For example, during "flareups" of pain or acute admission opiates may have been increased to aid in analgesia at that time, however if the patient has an ongoing chronic pain it is unlikely the opiates alleviate the symptoms completely, once the acute episode settles however due to the ongoing pain the opiate dose often remains unaltered and therefore escalated. The risk is that this happens with multiple admissions.

Pain and perceived improvement in symptoms transiently from dose increases also leads to a reduction in distress for the patient and consequently the treating team. Unfortunately, once the initial improvement abates and pain returns, as does ongoing distress for the patient and then as a result the treating medical team. As the dose increase was effective in alleviating the problems previously, the same behaviour can be repeated, and the result is further dose increases. In the literature on the narcotic bowel syndrome, a "***soar and crash***" phenomenon of escalating doses of opiates is described where the opiate side effects on GI function, opiate induced hyperalgesia and withdrawal side effects on de-escalation are actually driving the dosage prescribing higher and higher [9]. This seems to be a particular problem with the shorter acting opiates.

- ***Aims of therapy:*** Opiates for a significant group of intestinal failure patients, particularly those with slow transit times such as enteric dysmotility, are unlikely to be helpful and so reduction of opiates and if possible removal of opiates can be considered the long-term goal.

  For other patients where slowing transit time is not an issue, opiates nonetheless remain of limited benefit and therefore again dose reduction to recommended limits is necessary and removal of opiates should still be considered.

  Rapid changes are likely to produce withdrawal symptoms which in an intestinal failure unit may be very similar to the symptoms of a flareup of pain. The result being further changes are met with opposition from patients.

  If patients are willing to make multiple changes then this may be an option, however in a reluctant patient in our experience it is better to make gradual changes with the patients' agreement. However, dose escalation or reversion to previous route of administration is discouraged.

Alteration of Opiates Regime and Route

Intravenous opiates The use of intravenous opiates is encouraged in the management of *acute* pain and patient-controlled analgesia systems allow the self-administration of opiates within set parameters. These systems are very useful in the acute pain setting, however in a *chronic* pain setting intravenous opiates are no longer appropriate. The use of lines for opiates which are aimed primarily at on-going nutrition increases the risks of line infection and in our opinion is an unnecessary risk. Bioequivalent doses of opiates can be achieved using subcutaneous injections in the short-term and this can be considered as an alternative route in the shorter term for patients unable or unwilling to manage other routes of administration.

Intramuscular injection Historically this was used for patients with ongoing pain, however as subcutaneous injection is equally effective in the majority of patients this is no longer part of the practice within our intestinal failure unit. Patients who use repeated intramuscular injections to manage their pain are at risk of myofibrosis and muscle contractures and so long-term usage is discouraged [26].

Subcutaneous opiates have the advantage of not requiring an oral route and for some patients allow the use of a syringe driver to allow continuous dosage. The placement of a butterfly allows repeat injections without the need for multiple needle stabs. Whilst this route is used particularly during episodes of vomiting if opiates are required, there is still the potential for developing infections at the site of the needle and so there is still a potential for harm which can be avoided if the opiates are either stopped or the route of administration changed.

For all the routes of administration detailed above it is our practice to inform patients of the potential risks not only of the opiate but also of the route of administration and the potential therefore of harm to the individual from on-going injection therapy and that this risk will increase with prolonged reliance upon each route. One option would be to reduce opiates and then stop the opiates without changing the route of administration, however for many patients the removal of opiates is not at this point an achievable goal and so alteration of mode of delivery is more achievable.

Sublingual and Intranasal Opiates offer a route of administration of opiates that avoids absorption via the intestinal system. For patients with intestinal failure this potentially may be seen as advantageous in allowing opiate administration. These medications are licensed only for palliative care and are designed for pain episodes which are relatively short lived. The speed of onset is relatively rapid, but they are not designed for multiple uses per day. The cost of these medications is relatively high and therefore this needs to be considered when considering their usage. It is our practice to use these only as a potential option for the management of painful dressing change.

Transdermal opiates in intestinal failure represent an ideal route of administration as the absorption of the opiate (fentanyl or buprenorphine) is through the skin and not the gastrointestinal system. They provide continuous opiate release, absorption can however be altered by fever and caution with hot baths is also advisable. It is important to consider the

relative potency of these medications to morphine when considering dosage.

Oral Opiates usage is dependent upon both tolerability by the patient and also bowel transit time. Modified release medications often have a limited role as bowel transit times may be short and so absorption of the opiates is limited. Immediate release opiates however which can be given as a liquid or tablets do appear to be effectively absorbed for many patients on the intestinal failure unit. They allow for medications to be given during flareups of pain, however as the half-life is over 3 h for all these medications our policy is to provide opiates no more frequently than three hourly.

For the majority of patients, the initial goals in management of opiates are ensuring the route of administration is either transdermal or oral or a combination of both.

Table 3 Dose equivalences of commonly used opiates

Oral opiate	**Dose**	**Oral morphine dose**
Codeine Phosphate	60 mg	6 mg
Dihydrocodeine	60 mg	6 mg
Tramadol	50 mg	7.5 mg
Hydromorphone	1.3 mg	10 mg
Oxycodone	5 mg	10 mg
Tapentadol	50 mg	20 mg
Transdermal opiate	**Dose**	**Oral morphine equivalent per 24 h**
Fentanyl	25 μg/h	90 mg
Buprenophine	20 μg/h	50 mg
Approximate dose equivalents for opiates compared to morphine		

Based on faculty of pain medicine dose equivalent and changing doses webpage, Royal College of Anaesthetists 2018

Opiate Reduction

Due to the absence of supporting data for any benefit from opiates in chronic pain and increasing evidence of harm from high-dose opiates, it is important to engage the patient in discussion about the risks of harm from opiates as well as any benefits.

An explanation of the effects of opiates on the bowel and also the increasing evidence of effects of opiates on hormone production, potential effects on white blood cell function and immunity, as well as paradoxical worsening of pain are among risks that should be discussed with patients. There is evidence from the narcotic bowel syndrome literature that a sustained detoxification from opiates is associated with a reduction (but not abolition) in pain intensity, thought to be due to improved gut function and removal of opiate induced hyperalgesia [9].

Explanation of *gradual* reduction in opiates to prevent withdrawal symptoms, and that it is unlikely that there will be worsening of pain symptoms despite dose reduction need to be clarified.

Also, the potential benefits of improved pain relief during any *acute* episode of pain needs to be explained.

Opiate reduction needs to be considered in two parts—(1) The frequency of dosing and (2) total daily dose of opiates. The frequency of immediate release opiates should not need to be more frequent than every 3 h and for patients with chronic pain and a background of sustained-release opiates, breakthrough doses should be needed less frequently than this. As opiates have only a limited role in chronic pain, dose escalation of sustained opiates based upon breakthrough dosing is of minimal value. Prior to commencing dose reduction, it may be necessary to limit frequency of administration of immediate release opiates and then consider how to achieve dose reduction.

Overall opiate doses should be considered for all, with a reduction of opiates encouraged with patients on higher doses. It is important to start a process of dose reduction but at a rate of reduction that is acceptable to the patient. Table 3 below summarises dose equivalences for commonly used opiates.

There are no evidence-based guides on reduction but in broad terms a reasonable aim is a 10% reduction at agreed intervals, not more frequently than weekly but potentially longer, and no dose increases.

The method of administration will be an important factor in deciding which opiate is used during dose reduction.

It is possible to reduce any opiate gradually and so the preference of patient and the familiarity of staff with a drug on the unit are important factors in deciding which drug to use.

In addiction clinics, methadone is used due to the once daily dosing and some patients in pain clinics find it an effective opiate for analgesia. Unfortunately, due to the stigma attached to the drug from the association with addiction many patients are unwilling to see this as a therapeutic option. Buprenorphine is a partial opiate agonist which has a ceiling effect to the opiate action. This has been used increasingly in opiate reduction and therefore is an option available if a change of opiate is desired.

If opiate rotation or switch is used at the time of change a lower dose (than equipotent) should be used to prevent toxicity at the time of change.

Adjuncts to opiate dose reduction to minimise withdrawal side effects might be considered such as clonidine [9]. Where opiate abuse is suspected, there may be a role for engaging liaison psychiatry drug and alcohol input.

Peripherally acting mu opiate receptor antagonists, including naloxegol and methylnaltrexone may also be useful adjuncts to mitigate against some of the bowel dysmotility side effects of opiates, however they do not appear to help pain symptoms [9].

Neuromodulator (Adjuvant) Drugs

The Rome foundation have reviewed evidence for the use of drugs which have activity in the brain-gut axis for pain and associated symptoms, which have been termed gut-brain "neuromodulators" [27]. In the chronic pain setting these drugs are also called adjuvant analgesics.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are recommended for use in the range of 25–75 mg at night for chronic abdominal pain, with amitriptyline and imipramine more likely to produce anticholinergic and anti-histaminic dose limiting side effects than desipramine and nortriptyline. Their analgesic efficacy is thought to be due to combined 5-HT and NA reuptake inhibition. Muscarinic1 receptor antagonism accounts for side effects of dry mouth, constipation, drowsiness and blurred vision. The constipating side effect can be useful therapeutically in the setting of diarrhoea. Alpha 1 adrenergic receptor antagonism may lead to dizziness, drowsiness and orthostatic hypotension. Histamine 1 antagonism may lead to weight gain which can be helpful in functional dyspepsia. Sodium channel blocking properties can risk arrhythmias and seizures in overdose.

Serotonin Noradrenalin Reuptake Inhibitors

Serotonin Noradrenaline Reuptake Inhibitors (SNRI) may have at least equal benefit as TCAs for chronic GI pain. They have a more favourable side effect profile than TCAs as they are largely devoid of other receptor affinities. Venlafaxine may be more prone to side effects than duloxetine. Duloxetine has equal affinity for 5HT and NA transporters and at lower doses than venlafaxine and so should be the preferred SNRI to use.

Delta Ligand Agents (Gabapentinoids)

Delta ligands (Pregabalin and Gabapentin) have less direct data in chronic abdominal pain but nonetheless are considered of potential benefit, and there is also some data that gabapentin may be helpful in reducing opioid-induced hyperalgesia [9]. They block the alpha2delta subunit of voltage-sensitive calcium channels to reduce excitatory glutamate production. This likely underpins their anticonvulsant, anxiolytic and analgesic actions.

Augmenting Agents

The Rome Foundation working party on neuromodulators also supports a concept of "augmentation treatment" where combinations of different classes of the neuromodulators may give rise to synergistic positive effects. They also provide some data for adding in the atypical antipsychotic quetiapine to a TCA or SNRI at low doses of 25–200 mg. If this approach is considered then awareness of the hazards of serotonin syndrome should be considered and also monitoring for metabolic syndrome and involuntary movements [27].

Other Drugs

Cannabis and cannabinoids act via cannabinoid receptors, the endogenous cannabinoid system is found throughout the body's neural system including the viscera [28]. Cannabis is not currently available in the United Kingdom and there are no cannabinoid treatments licensed in the U.K. for use in chronic pain. Cannabis may be a potential treatment for chronic pain in neuropathic and visceral pain although there is limited evidence of benefit and the value of this reduction in pain compared to risk of longer term side-effects is unclear [29].

Gastrointestinal side-effects that have been associated with cannabis usage include visceral pain with acute heavy cannabis use and in prolonged usage cannabinoid hyperemesis syndrome [30].

Ketamine acts at the *N*-methyl-D-aspartate receptor and it may also act on descending inhibition of pain pathways. It is an anaesthetic drug that has been used at sub-anaesthetic doses to treat resistant chronic pain syndromes. It has been given as short-term infusions and also orally over prolonged periods. There has been limited research into its use in chronic pain and no evidence of improved functionality despite its use. Potential side-effects include memory effects and urological problems although most of this evidence is gathered from recreational ketamine users [31].

Nerve Blocks and Ablation

For some patients' injections may produce an improvement in symptoms which enables reduction in medications and potentially increased levels of function. The aim of a nerve block is to alter the conduction or transmission of pain signals by blocking the nerves involved in carrying the pain signal.

Injections can be diagnostic, using only short-acting local anaesthetic. If injections produce a short-term improvement in symptoms and then symptoms recur this is suggestive that a further block may be therapeutic.

Longer term pain relief can be achieved in some patients using a combination of local anaesthetic and steroid which can produce a longer-term effect. For those with chronic abdominal wall pain this may be possible to consider as an injection to the abdominal cutaneous nerve [18].

It is possible to consider neurolysis for some nerve blocks. This involves the injection of a neurotoxic drug e.g. phenol which may produce longer term effects, however due to the risk of recurrence of symptoms and also more serious and long-term side-effects with neurolysis, this is often reserved for palliative care.

Radiofrequency ablation is increasingly used as a modality of treatment to provide prolonged pain relief. It works by using a high-frequency alternating current to heat tissues to temperatures (above 45 °C) which will cause denaturing of the tissues at the tip of an electrode which is placed near the nerve. This has been used to provide pain relief for patients with abdominal pain although not within an intestinal failure setting.

Splanchnic nerves and coeliac plexus blocks have been used as treatments for managing visceral pain [32].

Spinal Cord Stimulation

Melzack and Wall described the gate theory of pain in 1965. The principal being that transmission of pain signals could be altered by stimulation of other pathways that would stop onward transmission of noxious information and as a result reduce pain.

Spinal-cord stimulation was introduced as a way to alter the experience of pain.

Spinal cord stimulation involves the implantation of an electrode either percutaneously or surgically into the epidural space. A pulse generator is then implanted in the subcutaneous tissue and this then produces the stimulation to the spinal-cord.

Initially it was thought spinal-cord stimulation acted in the dorsal horn of the spinal-cord, however it is thought spinal-cord stimulation also acts via posterior columns of the spinal-cord to recruit endogenous inhibitory pathways. There is also an autonomic effect. However, mechanisms of pain relief are still not fully understood.

Spinal-cord stimulation has been found to be effective in the treatment of neuropathic pain following back surgery, complex regional pain syndrome, neuropathic pain secondary to peripheral nerve damage and pain associated with refractory angina [33].

Medical contraindications to spinal cord stimulation include local or systemic sepsis and ongoing anticoagulant therapy.

However visceral abdominal pain has been treated with spinal cord stimulation, reducing opiate requirements. Potentially this may be a treatment option for some patients with chronic abdominal pain and gastrointestinal failure [34, 35].

Psychological Approaches to Pain

There is considerable evidence that various psychological interventions such as cognitive behavioural therapy and mindfulness training for chronic pain can be effective. There is also data to support hypnotherapy for chronic abdominal pain [9]. The treatment of co-morbid anxiety and depression may indirectly also improve patients coping with chronic pain. Psychological aspects and treatments in general on the IFU are dealt with in greater detail in chapter "Psychological Aspects of Intestinal Failure".

Chronic Pain: A Paradigm Shift

Finally, an optimal approach to chronic pain requires a series of "paradigm shifts" for both the patient and the doctors looking after them. The first element of this paradigm shift is from that of a *cure* focus to a *care* focus. At the most basic and simple level this is an understanding that chronic pain is "chronic" and currently cannot be cured medically.

A second shift is from the *biomedical* model of "test and treat" to a *biopsychosocial* model. On-going fruitless and frustrating cycles of investigations and searches for the "cause" of the pain can be costly, harmful, and counterproductive in preventing patients from moving on with engagement with a chronic pain rehabilitative focus. There is no objective reliable test that can show the abnormal nerve function underpinning chronic pain and so after initial structural evaluations, unnecessary rounds of repeated tests should be avoided. Explanatory models of the pain system and the role of the central nervous system, and eliciting specific clinical features of neuropathic pain, can be helpful as a positive alternative to negative tests.

Since most of these patients are not in the terminal phase of their lives, rather than a *palliative* approach of increasing narcosis, a third shift therefore is to minimise approaches which reinforce dependence and helplessness (avoidant coping) and to improve self-efficacy in patients (active coping), with an aim to promote improved function and coping in the face of on-going chronic pain—a *rehabilitative* approach.

References

1. Bogduk M. Classification of chronic pain. Seattle, WA: IASP Task Force on Taxonomy. IASP Press; 1994.

2. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open. 2016;6:e010364. http://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2015-010364. Accessed 17 Jun 2018.
3. Van Oudenhove L, Levy RL, Crowell MD, Drossman DA, Halpert AD, Keefer L, et al. Biopsychosocial aspects of functional gastrointestinal disorders: how central and environmental processes contribute to the development and expression of functional gastrointestinal disorders. Gastroenterology. 2016;150:1355–1367.e2. http://www.ncbi.nlm.nih.gov/pubmed/27144624. Accessed 17 Jun 2018.
4. von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron. 2012;73:638–52. http://linkinghub.elsevier.com/retrieve/pii/S089662731200133X. Accessed 17 Jun 2018.
5. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367:1618–25. http://linkinghub.elsevier.com/retrieve/pii/S014067360668700X. Accessed 17 Jun 2018.
6. Wilder-Smith CH. The balancing act: endogenous modulation of pain in functional gastrointestinal disorders. Gut. 2011;60:1589–99. http://gut.bmj.com/cgi/doi/10.1136/gutjnl-2011-300253. Accessed 17 Jun 2018.
7. Keefer L, Drossman DA, Guthrie E, Simrén M, Tillisch K, Olden K, et al. Centrally mediated disorders of gastrointestinal pain. Gastroenterology. 2016;150:1408–19. http://linkinghub.elsevier.com/retrieve/pii/S0016508516002250. Accessed 17 Jun 2018.
8. Olesen SS, Graversen C, Bouwense SAW, van Goor H, Wilder-Smith OHG, Drewes AM. Quantitative sensory testing predicts pregabalin efficacy in painful chronic pancreatitis. PLoS One. 2013;8:e57963. http://www.ncbi.nlm.nih.gov/pubmed/23469256. Accessed 17 Jun 2018.
9. Szigethy E, Knisely M, Drossman D. Opioid misuse in gastroenterology and non-opioid management of abdominal pain. Nat Rev Gastroenterol Hepatol. 2018;15:168–80. http://www.nature.com/doifinder/10.1038/nrgastro.2017.141. Accessed 17 Jun 2018.
10. Drossman DA, Morris CB, Edwards H, Wrennall CE, Weinland SR, Aderoju AO, et al. Diagnosis, characterization, and 3-month outcome after detoxification of 39 patients with narcotic bowel syndrome. Am J Gastroenterol. 2012;107:1426–40. http://www.nature.com/articles/ajg2012142. Accessed 17 Jun 2018.
11. Keefer L, Mandal S. The potential role of behavioral therapies in the management of centrally mediated abdominal pain. Neurogastroenterol Motil. 2015;27:313–23. http://doi.wiley.com/10.1111/nmo.12474. Accessed 17 Jun 2018.
12. van Tilburg MAL, Levy RL, Walker LS, Von Korff M, Feld LD, Garner M, et al. Psychosocial mechanisms for the transmission of somatic symptoms from parents to children. World J Gastroenterol. 2015;21:5532–41. http://www.wjgnet.com/1007-9327/full/v21/i18/5532.htm. Accessed 17 Jun 2018.
13. Grunkemeier DMS, Cassara JE, Dalton CB, Drossman DA. The narcotic bowel syndrome: clinical features, pathophysiology, and management. Clin Gastroenterol Hepatol. 2007;5:1126–39; quiz 1121–2. http://linkinghub.elsevier.com/retrieve/pii/S1542356507006295. Accessed 17 Jun 2018.
14. Loeser JD. Perspectives on pain. In: Turner P, Padgham C, Hedges A, editors. Clinical pharmacology & therapeutics. London: Palgrave Macmillan UK; 1980. p. 313–6. http://link.springer.com/10.1007/978-1-349-05952-2_34. Accessed 17 Jun 2018.
15. Waddell G. The back pain revolution. London: Churchill Livingstone; 2004.
16. Zaccagnino MP, Nedeljkovic SS. Pain assessment tools. In: Yong R, Nguyen M, Nelson E, Urman R, editors. Pain medicine. Cham: Springer International Publishing; 2017. p. 77–81. http://link.springer.com/10.1007/978-3-319-43133-8_21. Accessed 17 Jun 2018.
17. Fillingim RB, Loeser JD, Baron R, Edwards RR. Assessment of chronic pain: domains, methods, and mechanisms. J Pain. 2016;17:T10–20. http://linkinghub.elsevier.com/retrieve/pii/S1526590015008652. Accessed 17 Jun 2018.
18. Koop H, Koprdova S, Schürmann C. Chronic abdominal wall pain: a poorly recognized clinical problem. Dtsch Aerzteblatt Online. 2016;113:51–7. http://www.ncbi.nlm.nih.gov/pubmed/26883414. Accessed 17 Jun 2018.
19. Lavand'homme P. "Why me?" The problem of chronic pain after surgery. Br J Pain. 2017;11:162–5. http://journals.sagepub.com/doi/10.1177/2049463717722119. Accessed 17 Jun 2018.
20. Pauly NJ, Michailidis L, Kindred MG, Flomenhoft D, Lofwall MR, Walsh SL, et al. Predictors of chronic opioid use in newly diagnosed Crohn's disease. Inflamm Bowel Dis. 2017;23:1004–10. https://academic.oup.com/ibdjournal/article/23/6/1004-1010/4561125. Accessed 17 Jun 2018.
21. Bharucha AE, Chakraborty S, Sletten CD. Common functional gastroenterological disorders associated with abdominal pain. Mayo Clin Proc. 2016;91:1118–32. http://linkinghub.elsevier.com/retrieve/pii/S0025619616302749. Accessed 17 Jun 2018.
22. Paine P, McLaughlin J, Lal S. Review article: the assessment and management of chronic severe gastrointestinal dysmotility in adults. Aliment Pharmacol Ther. 2013;38:1209–29. http://doi.wiley.com/10.1111/apt.12496. Accessed 17 Jun 2018.
23. Richards DM, Scott NA, Shaffer JL, Irving M. Opiate and sedative dependence predicts a poor outcome for patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr. 1997;21:336–8. http://doi.wiley.com/10.1177/0148607197021006336. Accessed 17 Jun 2018.
24. Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. Am J Ther. 2004;11:354–65. http://www.ncbi.nlm.nih.gov/pubmed/15356431. Accessed 17 Jun 2018.
25. RCOA. 2018. https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware.
26. Alvarez EV, Munters M, Lavine LS, Manes H, Waxman J. Quadriceps myofibrosis. A complication of intramuscular injections. J Bone Joint Surg Am. 1980;62:58–60. http://www.ncbi.nlm.nih.gov/pubmed/7351417. Accessed 17 Jun 2018.
27. Drossman DA, Tack J, Ford AC, Szigethy E, Törnblom H, Van Oudenhove L. Neuromodulators for functional gastrointestinal disorders (disorders of gut–brain interaction): a rome foundation working team report. Gastroenterology. 2018;154:1140–1171.e1. http://www.ncbi.nlm.nih.gov/pubmed/29274869. Accessed 15 Jun 2018.
28. Preedy VR. Handbook of cannabis and related pathologies: biology, pharmacology, diagnosis, and treatment. London: Academic Press; 2017.
29. Nugent SM, Morasco BJ, O'Neil ME, Freeman M, Low A, Kondo K, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. Ann Intern Med. 2017;167:319–31. http://annals.org/article.aspx?doi=10.7326/M17-0155. Accessed 17 Jun 2018.
30. Woods JA, Wright NJD, Gee J, Scobey MW. Cannabinoid hyperemesis syndrome: an emerging drug-induced disease. Am J Ther. 2016;23:e601–5. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00045391-201603000-00039. Accessed 17 Jun 2018.
31. Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. Br J Clin Pharmacol. 2014;77:357–67. http://doi.wiley.com/10.1111/bcp.12094. Accessed 17 Jun 2018.
32. Kapural L, Cheng J. Abdominal pain. In: Cheng J, Rosenquist R, editors. Fundamentals of pain medicine. Cham: Springer International Publishing; 2018. p. 261–9. http://link.springer.com/10.1007/978-3-319-64922-1_29. Accessed 17 Jun 2018.
33. The British Pain Society. Spinal cord stimulation for the management of pain: recommendations for best clinical practice. London:

The British Pain Society; 2009. www.britishpainsociety.org. Accessed 17 Jun 2018.
34. Kapural L, Nagem H, Tlucek H, Sessler DI. Spinal cord stimulation for chronic visceral abdominal pain. Pain Med. 2010;11:347–55. https://academic.oup.com/painmedicine/article-lookup/doi/10.1111/j.1526-4637.2009.00785.x. Accessed 17 Jun 2018.
35. Deer TR, Mekhail N, Provenzano D, Pope J, Krames E, Leong M, et al. The Appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. Neuromod Technol Neural Interf. 2014;17:515–50. http://www.ncbi.nlm.nih.gov/pubmed/25112889. Accessed 17 Jun 2018.

Psychological Aspects of Intestinal Failure

Yoram Inspector

Key Points

1. Attend to the person who has the disease as much as to the disease a person has.
2. Psychological support is normal and essential for most patients with intestinal failure (IF) and especially if needing PN at home.
3. The needs are different if the IF is acute (e.g. mesenteric infarction) or chronic (e.g. Crohn's disease).
4. All patients will go through the 5 stages of mourning (denial, bargaining, anger, depression and finally acceptance) at different rates.
5. Ask the patient how they experience their condition and what do they think about it.
6. Psychopharmacology, Cognitive Behavioral Therapy, Acceptance and Commitment Therapy, Psychodynamic Interpersonal Therapy, Eye Movement Desensitization and Reprocessing, and Gut Directed Hypnotherapy are all useful and helpful for our patients.

Introduction

Reflecting on the title I gave to my chapter, I immediately felt the urge to amend it to:

> ***The Psychological support offered to the person who experiences Nutritional Failure***

This title allows us to acknowledge the reality that IF occurs within the body of a unique human being who needs to recruit all possible psychological resources in order to cope with this extreme condition. As William Osler said: "You have to be interested in the person who has the disease as much as you are interested in the disease the person has" [1]. Each patient faces different challenges and needs and therefore an individually tailored therapeutic approach must be formulated to suit her/his different medical history, life story, personality and their various adaptation capacities. This is one of the most important lessons I have learnt from the last 10 years of providing weekly psychiatric and psychological treatment to the patients of the Intestinal Failure Unit (IFU). The name of the unit was changed around 3 year ago to The Intestinal *Rehabilitation* Unit (IRU). The word *Failure* has been purposefully replaced by *Rehabilitation* in order to provide a rather more hopeful and constructive message to the patients and the medical staff alike. IF, which nearly always involves the need for PN, will affect all domains of one's existence: physical, emotional, social and even spiritual. All these aspects need to be addressed by the multidisciplinary team in order for the treatment to succeed to significantly improve the patient's wellbeing and quality of life.

The Psychiatric and the Psychological Assessment

St Mark's Hospital has a dedicated in-house Psychological Medicine Unit (PMU) that provides psychiatric and psychological treatment and support for patients who suffer from various gastrointestinal diseases and disorders, among which

"Funny little thing about this tummy o'mine,
doesn't wanna work like once upon a time,
I can eat the food but it just sits,
making my tummy hurt and throw a lot of fits!
The food doesn't wanna stay,
I feel like a cow chewing cud all day.
Then there is the pain with no end in sight,
I hurt all through the day and through the night.
Off comes the weight down another size,
God how I miss those burger and fries!
But gone are those foods, this is hard to endure.
What can I have?
Oh, Goody Ensure!!!"
The poet was a patient at the Intestinal Rehabilitation Unit of St Marks' Hospital.
She called herself "a Gastroparesis Fighter".
I want to dedicate my chapter to all the fighters of the Intestinal Rehabilitation Unit of St Mark's Hospital- to all the patients and to all the members of the multidisciplinary team who fight for having a good, happy and fulfilling life alongside intestinal failure.

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are a large group of patients who cope with IF. The PMU's team meets weekly with the IRU's team to discuss patients with IF who need and/or possibly would benefit from a psychiatric and psychological assessment. Getting to know the background of the patient usually begins in this this joint meeting, when the nurse, dietitian and or the gastroenterologist presents the patient's information to the PMU. This is then naturally followed by the PMU clinician's first meeting with the patient at the IRU after the patient has given consent to the meeting.

The Physical Condition: It Is Not Just in Your Head!

Although I already know something about the patient from the initial team meeting, I do not know him or her yet. To know is to experience. I try to put aside the information and start afresh. After I introduce myself I always tend to add: "Don't worry, the fact that you've been asked to see a psychiatrist and a psychotherapist doesn't mean that you are mad; It means that your gastrointestinal system became a bit mad and if this happens it can madden anyone and as I am allegedly an expert on madness you are seeing me". I have found that this sentence immediately puts a smile of relief on patients' faces as it validates the fact that whatever they experience mentally and emotionally, as extreme as it may be, is a normal reaction to the abnormal situation of the IF.

To consolidate this message, in which I strongly believe, I tend to start my assessment with taking a detailed account of the history of their gastrointestinal disease. When and how did they start suffering from it? How it behaved over the years? I always also endeavor to create the space to speak about the physical pain the disease causes and inquire how the patient manages to live with it. Many gastrointestinal diseases and conditions can involve an acute or severe and enduring IF and each patient has her/his unique journey, an account of which one must listen to carefully. It is important for the mental health clinician who works in the psychosomatic field to fully embrace the physical bodily experience of the patient—"The Body Keeps the Score" [2].

It is not just psychosomatic (the psyche affecting the body) it is also, first and foremost in the case of IF, the impairment of this vital, crucial physical function to which the psyche acutely reacts.

How Does IF Affect The Psyche?

> ***"Losing my colon felt like losing a part of my mind" a patient on the IRU***

As the causes of IF vary considerably, so do its psychological consequences. It is rather different to find oneself needing home PN after gradually losing, over the course of some years, most of one's intestine due to aggressive inflammatory bowel disease, for example, than to be needing the same after an acute mesenteric artery occlusion that was incurred spontaneously. In the first instance one might actually experience relief due to the improved quality of life PN can provide, yet in the latter situation one would perhaps enter a state of shock and grief in reaction to the sudden and brutal loss of one's capacity to digest food. In any case the experience is traumatizing.

The word trauma in Greek means "wound". It is also etymologically related to the word *Trema* which means a mark or a "hole" (used for the dots on dice, for example) as well as the words "tremor" and "tremendous"—indeed, trauma designates an event as beyond the realm of the ordinary. The wound has created a hole that marked you and that has brought about a physical and emotional trembling. Every person who faces IF has experienced trauma along his journey to recovery through PN.

This may seem like stating the obvious, but it is nevertheless crucial to state it: PN is a life-saving therapy in patients with severe IF. Importantly, these patients do not chose PN out of their free will, but it is usually the ultimate remaining option to maintain or improve their nutritional status [3]. This lack of choice means that every patient undergoing treatment necessarily experiences the five stages of the mourning process that was described by the Swiss-American Psychiatrist Elisabeth Kubler Ross [4].

Denial: "I feel fine, this cannot be happening to me"
Bargaining: "I can still do something to change the situation"
Anger: "Why me? It's not fair; how can this happen to me? Who is to blame?"
Depression: "I am so sad, why bother with anything?"
Acceptance: "I can't fight it, I may as well prepare for it; It's going to be okay"

Granted, this should not be understood as some linear ideal chronology by which a patient's attitude always and unvaryingly develops and progresses. It may start and end with any stage - but all the above five stages will at some point in time be encountered. We hope to end with acceptance, yet many researchers have found that depression is the most common emotional response to home parenteral nutrition (HPN) (the most common end result of IF) and can be found in up to 80% of the patients who are commonly overwhelmed with feelings of worthlessness, helplessness and hopelessness [3].

Most of us take for granted our ability to eat spontaneously and be nurtured through our mouth. Imagine that this capacity is suddenly taken away from you; you will obviously feel deprived and deeply frustrated. So much of one's communal

activity revolves around food that not being able to eat in a natural way might give anyone a feeling of being a "second class citizen" in normal society. It is easy to comprehend how having a permanent catheter inserted in a central vein in your neck for feeding can make you feel like an alien.

Many HPN patients suffer as a result of their condition from poor self-esteem and body image.

A constant source of concern for almost all patients was the cosmetic effect of multiple surgical procedures and the actual location of the catheter. Some patients perceived themselves as unattractive or even repulsive, experiencing feelings of embarrassment and shame concerning disfigurement due to scars and weight loss. Such embarrassment and shame often lead to impairment in sexual relationships. Other psychological problems include: changes in dependency (mostly loss of independence), changes in one's ability to travel (which was the activity most disturbed by HPN), the feeling of being a nuisance or burden to others, feeling that one lacks understanding of others as well as perceiving a lack of understanding from others [3].

All the above states are accompanied and even maintained by anxiety. IF and HPN naturally provoke various fears; of the unknown, of catheter infection, of pump malfunction, liver damage or fear of death. Anxiety is composed of two major elements: (1) uncertainty and (2) dread that something irreversible will happen. Any psychological support provided will need to address this anxiety in order to transform overwhelming fear into a constructive life affirming and celebrating attitude. In the treatment section I will reflect on how this might happen. In the assessment—I ask how does it affect you?

How Does the Psyche Affect IF?

The brain-gut axis is a "dual carriage way": What happens in the gut affects the brain through the gut microbiome and the enteric nervous system and at the same time what is happening in the brain is perceived by the gut through the autonomic nervous system. It is not rare to hear from patients who suffer from IF that their gastrointestinal disease erupted following an emotional trauma: An attachment trauma, being bullied at school or other various forms of abuse. Our ancestors thousands of years ago already knew about such a possible linkage: Chapter 22 of the Book of Psalms in the Old Testament opens with the poignant Hebrew words which Jesus quoted on the cross: [5].

> *Eli Eli Lama Azavtani"—"My God My God why have you forsaken me.*

In line 14 of this poem we can find an accurately moving description of what the lonely, abandoned, trapped, traumatized person experiences in his body:

> *I am poured out like water and my bones are out of joint;*
> *My heart melted like wax;*
> *It melted* ***into the midst of my bowels.***

This has been confirmed in modern scientific literature: 62% of women with idiopathic gastroparesis (which often ends with HPN) reported a history of physical or sexual abuse, and physical abuse was significantly associated with abdominal pain, somatization, depression and life time surgeries [6]. Approaching such issues should be undertaken with great sensitivity and at the right timing as childhood and/or adult trauma often is not merely remembered—it is relived. Opening up these wounds can be retraumatizing.

The Treatment-How to be the Second Mouse?

When I need to define what the PMU does, I always write (as mentioned above): "The PMU provides psychiatric and psychological treatment and *support* for patients who suffer from various gastrointestinal diseases and disorders". A mental health clinician suggested to me to omit the word *support* from this description, as according to them it is not suitable to the highly specialized service we provide. The word *support* might be perceived as too broad or unspecified—your aunt or friend can *support* you as well. After reflecting on this issue for a while I told them that while I see their point, I believe that the word *support* is the most important one for me in this definition and would be the last one I would be omit. I went on to talk about the *Supporos* in Greek antiquity—those who *supported* you when you came to heal yourself in the "The Asklepion" the temple of Asclepios - The God of Medicine [7]. After being given a bath with all sorts of aromatic oils and healing plants the patient was sent to "incubate", have a dream at night which will hopefully contain a healing symbolic message from the Gods and in the morning the *Supporos* would come and *support* you physically from both sides (by the way the world *support* is related etymologically to the word *Sub*-from underneath, to *support* bottom up, which is very connected to gastroenterology). Then they would accompany you to stand in front of the image, the sculpture of Asclepios and say: "We Support and God Heals". I said to my colleges that in my view this humility regarding our role in healing and at the same time the crucial role of the humane *support* in this process that is embodied in the *Support* of the *Supporos*, should guide us even more now in our technological age of the 21st and added that Hippocrates the father of scientific medicine was initially a follower of Asclepios and that maybe from this period he came with his important sentence: "You completely cure rarely, you give therapy (makes things better) frequently and you must comfort always. Comfort and support are naturally interwoven.

The question is how to support the patient who is suffering from IF? The first thing I would recommend is: Be the second mouse! This suggestion needs obviously a bit of explanation. It is based on the experiment done with mice presented by the French surgeon Professor Henri Laborit in the French Director Alain Renais's film: Mon Oncle d'Amerique which translates into English as "My American Uncle" in which mice are used as an illustration to the humane condition. What happens in the experiment? It has three stages:

1. A mouse is put in a cage but the door of the cage remains open. The mouse received a disturbing but not a dangerous electrical shock and it immediately escaped through the open door of the cage to avoid further pain. Its health was not affected.
2. A mouse receives the same disturbing but not dangerous electrical shock, but this time the door of the cage is locked. It cannot escape and is **alone!** This **lonely, trapped** mouse starts to become ill-it develops alopecia and a peptic ulcer and vomits blood.
3. Two mice are put in a locked cage and are electrocuted (given same non dangerous electric shock). They cannot escape like in the first stage of the experiment but they are **together- not alone**! They interact with each other, discharge their pain on each other and share it. These mice remain physically healthy!

There is scientific evidence that "stressed mice look like depressed humans. This is actually the subtitle in a fairly recent textbook on *The New Mind-Body Science of Depression* [8]. Which explores fascinating and surprising interlinks between inflammatory processes and depression. Not being alone and interacting with others has a healing potential for depression and according to the above textbook even for inflammation. How then to interact with the patient who is trapped in the "Electrocuted cage of IF"? In order to really help, healthcare professionals need to step into the cage of the IF patient and be ready to be "Electrocuted": Be ready to compassionately take the patient's experience in.

The Word Compassion in Latin Means to Suffer With!

Compassion does not require one to achieve complete understanding of the other's perspective and circumstances, engendering exactly the same feeling; it merely calls on one to imagine what it might be like to suffer in a way that the other is suffering. If achieved, this will engender the corresponding emotion, which can then be conveyed [9]. If you are really ready to "suffer **with**, and have a true genuine rapport with the patient don't worry about being "electrocuted", because you will not be alone, the patient can become your protecting second mouse in the "electrocuted cage of IF".

The remedy to "My God My God why have you forsaken me", in Psalms 22, mentioned above, can be with found in the next poems Psalms 23:"Even though I walk through the valley of the shadow of death, I will fear no evil, for you are **with** me." Again it is about being **with!**

In addition to the core essential healing modality of compassion or "being the second mouse" we have two more additional "specialized", "professional" tools aimed at improving the patient's quality of life and wellbeing: psychopharmacology and psychotherapy.

Psychotropics drugs can help to improve various mental disorders:

The different types of anxieties, depression, post-traumatic stress disorder and mood swings. I encountered all of them at the RIU and if indicated I would prescribe psychotropic drugs to reduce the psychic pain of the patients. Being also a psychotherapist, inspired by the Swiss Psychiatrist Carl Gustav Jung saying: "Man cannot stand meaningless suffering", I know that medications are not enough to address the suffering of a person who suffers from IF. Finding the unique meaning she or he attributes to this radical condition is crucial to their healing and recovery.

Psychotherapy—"The Talking Cure" aims at widening the repertoire of how the person relates to himself and to others, which is helping in getting redeemed from the feeling of being trapped. Psychotherapy aims at creating a sense of self-agency (you can reflect about and influence your life) and at providing tools for affect regulation. Many times it is not only focusing on fixing psychopathology 'it is also a mean to support individual development and growth in every aspect of one's life including the spiritual domain.

There are numerous psychotherapies based on different psychological theories and I will mention just a few of them, the ones we commonly use at the IRU:

Cognitive Behavioral Therapy

A basic assumption of cognitive behavioral therapy (CBT) is the recognition that there is a reciprocal relationship between our cognitive processes (what we think) and our affect (emotional experience), physiology and behavior. Although Cognitive Behavioral treatments for individual disorders differ in both their form and application, they all emphasize the importance of changing cognitions and behaviors as a way of reducing symptoms and improving the functioning of the person.

In CBT we commonly challenge automatic thoughts -The self-critical or exaggerated negative self-statements that go through a person's mind and are accepted as true by the person without testing their accuracy [10]. We put question marks after the exclamation marks-!? For example, if a

patient who is diagnosed with IF thinks that he is a worthless human being because of it, that he is helpless and there is nothing he can do to improve his life and that he is hopeless - the situation will never get better, he will feel deeply depressed and will withdraw from many life affirming activities (thought changes feeling which alter the behavior). The CBT therapist will explore together with the patient the validity of his assumptions which lead to his depressing conclusions and with the technique of "Cognitive restructuring" will help the patient to realize that they can be modified.

The CBT therapist will assess the patient's beliefs about the causes for the IF, the consequences, symptoms experienced, personal and treatment control, chronicity and recurrence and the feeling of anger, upset, anxiety, low mood and fear that accompany their beliefs.

The principal predictors of the above negative feelings in IF patients were:

1. Poorer appraisals of patients' ability to exert personal control over aspects of their condition and treatment
2. The perception that the condition and treatment makes little sense to the patient [11].

Therefore the CBT therapist at the IRU has also a psychoeducational role-they need to be knowledgeable and fully understand what it entails to live with IF in order to help the patient to have a sense of coherence of their illness and discover the meaning they give to their suffering.

Acceptance and Commitment Therapy

This is a "third wave" CBT therapy that has some similarities to the way the Buddhist philosophy approaches pain-with compassion and acceptance. The acceptance and commitment therapy (ACT) model holds that culturally supported attempts to control and eliminate unpleasant experiences result in personal suffering, behavior disorders and lack of vital and purposeful living. ACT attempts to teach clients to accept, rather than control or eliminate painful experiences that are not amenable to first order change. Acceptance is accomplished through teaching the client to see these experiences as conditioned verbal responses, rather than literal truth. ACT emphasizes that the patient approach rather than avoid, valued life goals, even though pursuing such goals may stimulates uncomfortable experience [12].

ACT uses Mindfulness, an approach, a technique which aims at "Consciously bringing awareness to you're here and now experience with openness, interest and receptiveness." It makes no attempt to reduce symptoms, its goal is to create a rich and meaningful life, while accepting the pain that inevitably goes with it. ACT has proven effective with a diverse range of clinical psychiatric conditions [13].

The use of ACT at the IRU focuses on consolidating the commitment to life alongside the IF. We hope that future work may show that ACT is helpful in the treatment of chronic abdominal pain and so provide an alternative to the abuse of analgesics (especially opiates).

Psychodynamic Psychiatry/Psychotherapy

As the name indicates, this type of therapy is engaged with exploring and facilitating the dynamics between all levels and aspects of the psyche—the conscious as well as the unconscious ones. This is how the psychiatrist Glen O Gabbard describes the psychodynamic attitude: "Psychodynamic psychiatrists approach their patients by trying to determine what is unique about each one-how a particular patient differs from other patients as result of a life story like no other. Symptoms and behaviors are viewed only as final common pathways of highly personalized subjective experiences that filter the biological and environmental determinants of illness. Furthermore, dynamic psychiatrists place paramount value on the patient's internal world -fantasies, dreams, fears, hopes, impulses, wishes, self-images, perceptions of others and psychological reactions to symptoms" [14].

In the context of IF the psychodynamic oriented psychiatrist might then be interested in exploring childhood early feeding experiences, relationships with parents siblings, the relationship with the therapist the possible symbolic meaning the patient might attribute to the central venous catheter: An intrusion or maybe a feeding umbilical cord?

Will this encourage regression, separation or individuation? The meaning the patient will give to the HPN might be influenced by his attachment patterns that can be for example reenacted with the medical team caring for him/her or with the psychotherapist.

Psychodynamic Interpersonal Therapy

Psychodynamic interpersonal therapy (PIT) is a form of Psychotherapy [15] that was developed by the Jungian Psychiatrist Robert Hobson. His Unique Conversational Model to Psychotherapy is presented in his Book—Forms of Feelings—The Heart of Psychotherapy [16]. It has been Further adapted by Professor Else Guttery to treat unexplained and or Functional Bowel Disorders [17]. It is now a relatively short term therapy up to 8–10 sessions but what is special about it is that the first session is not restricted to an hour. The therapist allows the patient all the time needed to describe in his own language the physical experience of his gut disorder and waits patiently for the unique metaphors of the patient to organically emerge from the description in

order to create a bridge to the patient's feelings. For example, if the patient is using a metaphor of a volcano to describe bouts of pain it may lead to exploring feelings of rage and anger; speaking about trapped air in the bowel may lead the patient to speak about how he feels trapped in life. This approach frees us from needing to decide is it physical or psychical, as it holistically embraces the gut disorder experience.

Eye Movement Desensitization and Reprocessing

Eye Movement Desensitization and Reprocessing (EMDR) is an eight -phase treatment approach that facilitates resolution of distressing historical events, desensitization of present triggering stimuli, and acquisition of desired behaviors [18]. It is a structured therapy that encourages the patient to briefly focus on the trauma memory while simultaneously experiencing bilateral stimulation of the brain (typically by eye movements), which is associated with a reduction in the vividness of the intrusion of post traumatic flashbacks and the overwhelming emotions associated with the trauma memories. It can be very useful in treating severe avoidance behaviors and phobias.

Gut Directed Hypnotherapy

Hypnotherapy is a NICE recommended treatment for Irritable Bowel Syndrome that can be also a very efficient tool to reduce the intensity of various forms of anxiety that many patients at the IRU are coping with them, to enhance deep relaxation as well as improving self-confidence and esteem [19].

Disordered Eating or an Eating Disorder? And Why Does It Matter?

All the patients who suffer from IF experienced disordered eating. Until PN had been introduced they could not eat normally: vomiting if they have gastroparesis, gut dysmotility or obstruction, or diarrhea due to poor absorption of food as result of a short bowel or intestinal inflammation. However few of them suffered from an Eating Disorder.

An Eating Disorder is a psychiatric disorder in which eating becomes disordered due to psychological and social reasons not due to physiological reasons.

The Eating Disorders are classified into four main categories (see also chapter "Eating Disorders in Adults). Anorexia Nervosa (restricting and binge-purging type), Bulimia Nervosa (purging and non- purging type), Binge Eating Disorder and the Atypical Eating disorder (which has some elements from each of the other groups but does not fulfil the full criteria to any of them).

A "transdiagnostic model" has been suggested by Fairburn [20] who argues that this division should be abandoned as 50% of the patients who suffer from anorexia nervosa will turn into bulimic patterns and because the largest group is actually the atypical one. Moreover, they all share according to Fairburn the same psychological problems:

1. Core Low Self-Esteem
2. Clinical Perfectionism
3. Mood Intolerance
4. Interpersonal difficulties.

One of main issues that maintains the Eating Disorder is that self-esteem becomes totally dependent on body shape and weight. This is definitely not the case with the patients who suffer from disordered eating due to IF. Rarely an Eating Disorder might be unveiled or triggered by IF due to the fact that in addition to PN some patients are encouraged to have a hyperphagic diet to compensate for the malabsorption they experience aiming for 3000 Kcal/day [21].

More often I found myself needing to redeem patients at the IRU from an Eating Disorder diagnostic label that was put on them unjustly in the past. This became commonly the case with young women that developed IF due to gastroparesis and or severe gut motility disorders that was part of a previously undiagnosed Ehrler Danlos Syndrome (EDS). The gastrointestinal manifestations of EDS which appear all along the gastrointestinal track have received little attention despite the observation that they represent a considerable symptom burden on sufferers [22]. In addition to abdominal pain they include: Oral: periodontitis, loss of teeth and bone; Oesophagus: hiatus hernia (33.3%) rarely rupture; Stomach: nausea and vomiting (29–34%), gastric emptying abnormalities (75%) with most frequently a delay in gastric emptying; Small bowel: perforation; Colon: spontaneous colonic perforation, chronic constipation; Rectum and Anus: fecal incontinence, obstructed defecation.

The EDS patients I have seen are mostly young women and nearly all of them had a long and painful "Via Dolorosa" until their symptoms were taken seriously and properly diagnosed. Often as they were young women who struggled to eat they were misdiagnosed as suffering from an Eating Disorder or Somatization-meaning that a psychological conflict or distress is expressed through their bodily symptoms. The risk of ignoring the reality of a physical disorder when the mind of the psychiatrist is already set on a psychological cause for the physical symptoms is unfortunately not an uncommon mistake and can be fatal.

It happened even to "the father of Psychoanalysis "Sigmund Freud:

> "A little girl was sent to him (to Freud) suffering abdominal pains. He diagnosed her as an 'unmistakable" case of Hysteria and "cured" her with psychoanalysis. Two months after he discharged her she died, the cause being abdominal lymphoma. Apparently unabashed, Freud denied all culpability, insisting that he had cured the hysteria which he declared: "had used the tumor as a provoking cause". Dr. Anthony Stevens the Jungian Psychiatrist who discusses this case in his book: An intelligent guide to Psychotherapy [23] says that "clinical arrogance of this degree and magnitude was ill-designed to protect Freud against the kind of missed physical diagnosis of which all psychotherapists live in dread".

The Story of S

The treatment of S. at the IRU and the PMU illustrates the complexities that are at the core of the confusing gray area between Disordered Eating and an Eating Disorder and highlights the importance of taking the time and the patience to make the right diagnosis as it crucial for finding the right therapeutic approach that will improve the wellbeing and the quality of life of the patient. When I first met S. she was 19 years old. Her BMI was extremely low −12 kg/m^2! She presented with recurrent episodes of low potassium due numerous episodes of vomiting especially after eating any amounts of food and at times even after drinking. In her vomit there were lumps of undigested food even from the previous day. She also suffered from continuous feeling of nausea and constant acid reflux and regurgitation. To complicate matters, she had a period of 18 months during which she was a patient in an inpatient Eating Disorders' unit where she was at times under extremely strict 2:1 observation for 24 h 7 days a week. S. passionately insisted that she does not have an Eating Disorder! that she doesn't have a body image problem! and that wants to restore a healthy wait but simply cannot do it physically!

As a specialist for nearly 30 years now in the field of Eating Disorders, I made a conscious choice to firstly fully believe my patients although I know that at times they tend to disguise or hide their disturbed eating patterns. They do not lie about it because they are immoral, they are simply afraid these maladaptive eating habits will be taken away, leaving them with no other coping mechanism to regulate their emotional traumas.

When S. told me that she tried to eat fish and chips numerous times but couldn't hold it in, I knew she did not suffer from Anorexia Nervosa. She did not have a conscious drive toward thinness and did not induce vomiting. On the other hand her initial refusal to receive PN raised again the suspicion that she is "hiding something". So I asked her why are you refusing to receive PN? She answered me straightforwardly:

"I am afraid that if a fire will burst in the ward and I will be connected to the PN pump, I will not be able to escape". Her unexpected surprising answer made sense later when we were able to link it to her feeling of being trapped in the Eating Disorders unit being misdiagnosed with Anorexia Nervosa and to the ongoing feeling of being trapped in her body that is not capable to absorb and food. Her answer reassured what all my best mentors in psychiatry and medicine taught me: Don't assume! First ask the patient what do they think about their condition, they know! they are the one who has the experience! This is true in any specialty of medicine but should especially not be forgotten in mental health where the danger is that the opinion of the person will be disregarded as already he has a label that challenges his capacity to make a sensible judgment.

So What Happened to S? How Did Her Problems Evolve?

Her mother confirmed that when she was one year old she contracted a campylobacter infection in a swimming pool that might have been followed by a post infectious irritable bowel syndrome as since she was a little girl she has complained a lot about "tummy pains" which were diagnosed as "tummy migraine". She also had unexplained bouts of vomiting from a young age. At the age of 3 she had two episodes of a prolapsed rectum. S. who was hyper mobile and very flexible became an outstanding athlete. She won a national competition for under 10 years old in her field. During that time her coach made a thoughtless, unsensitive remark: He told her that she needs to be careful how she eats as she might become too heavy to compete in the team. As her success in her sport was so important to her at that time and part of her identity she took his comment extremely seriously and nearly stopped eating completely. She started obviously to lose weight and when it started to become too much she was diagnosed with Anorexia Nervosa. However; when she was threatened with admission to a hospital and cessation of her sporting activity, she immediately started to eat and restored a healthy weight. This is something that a "true Anorexic" will never do. She recovered very quickly from this period but then at the age of 14 she started to suffer from projectile vomiting up to 3–4 times a day and started to lose weight again.

Although she did not have any Anorexic Ideations at that time she was "accused" of making herself vomit on purpose. When she reported that she vomits "white lumps looking like hard dumplings" she was told that this is imaginary.

When the symptoms continued at some point feeding with a percutaneous endoscopic gastrostomy (PEG) was tried followed by a percutaneous endoscopic jejunostomy (PEJ). During its insertion a bowel peroration occurred

which was followed by peritonitis. Then she was as mentioned above treated in an Eating disorder unit and as this had not succeeded to improve her state she was referred to the IRU for further assessment and PN.

Believing her narrative, taking it seriously as her own experiential truth was the most important initial step to enable her to engage in therapy and regain trust in the medical team that tried to help her. After I explained to her and warmly reassured her that even if a fire would burst in the ward she will not be trapped even if she is connected to the PN pump; thus she agreed to receive the PN.

The traumatized person does not remember the trauma they re-live it!

They immediately enter a Fight-Fight-Freeze mode. They become stupefied with fear (this is the origin of the word stupid) and cannot reflect or think rationally because they are fighting for their life. Creating a secure, safe base within the therapeutic relationship is the most essential component in enabling engagement in the treatment process.

Unfortunately, during the PN S. developed sepsis and it had to stop but as she was already motivated to try and restore a better nutritional state she was willing to see me on a weekly basis as an out-patient at the PMU. Once the right name to her condition was given -a gut motility disorder with delayed gastric emptying/gastroparesis most probably as part of the gastrointestinal manifestations of EDS and she was "redeemed" of being misdiagnosed as an "Eating Disorder patient" she became significantly less anxious, and very motivated to work together .

The psychiatric differential diagnosis of Gastroparesis is complex and in addition to Eating Disorders includes Somatization Disorders, Post-Taumatic Stress Disorder and other Anxiety disorders, Opioid Withdrawal and even Schizophrenia. In addition the Gastroparesis itself in a vicious cycle triggers a Phobia to eat, Panic Attacks and personality changes [24]. The key thing that helps to navigate in this "labyrinth" is to address the uniqueness of each patient-to find his/her "Pin Number". This can be found only through mutual work.

An old Chinese proverb says:

Tell me something and I will forget,
Show me and I will learn,
Involve me and I will understand.

The psychotherapist working with patients on the IRU needs at times to actively involve the patient with psychoeducational material about the brain-gut axis, the links between stress and fatigue and inflammation etc. With S. I had to speak with her a lot about the importance of maintaining a stable safe potassium level, about its influence on the regular heart rhythm; we had to think creatively about what she can absorb and when and how to be more "jazzy" and improvise with what she can eat. As she was no longer afraid to be disbelieved she came regularly to the meetings and was able for the first time to have a life outside hospital whilst maintaining a safer bodily state and a stable potassium level.

At the end of each session she gave me a little animal made of paper. I realized that she is a master of Origami work. Then she showed me her drawings which were absolutely amazing in their originality and delicacy. I then discovered that she dreams to be an illustrator for children's books. She did not believe that she will be able to be accepted to an art or an illustration school or class. I actively encouraged her to do that. It was not hard for me to do as I was deeply moved by her images. I told her: "Just show them your work and you will be accepted". Exactly this happened! She started to study illustration in a professional highly regarded art school and kept herself nurtured and physically safe as much as possible.

When she was discharged she gave me this picture (Fig. 1) that she drew:

For me this moving symbolic image of hope and fragility is her self-portrait. It is also what life with IF is about: The

Fig. 1 Picture drawn by patient

paper boat can represent her fragile body that carries her motivation represented by the fisherman in the yellow coat and hat who patiently waits to find, to bring something from the depth of the lake. In German the word lake is SEE and the word Soul is SEELE. The lake and the soul are connected. She doesn't give up on the connection with her soul. The yellow color symbolizes the sun, consciousness, joy and humor.

S. was only one of the many patients at the IRU who humbled, inspired and thought me each day about courage, resilience and about how with the right motivation and support IF stops being an obstacle for living life to the full.

References

1. Bliss M. William Osler: a life in medicine. New York: Oxford University Press; 1999.
2. Van Der Kolk BAMD. The body keeps the score; brain, mind, and body in the healing of trauma. London: Penguin; 2014.
3. Huisman-de Waal G, Schoonhoven L, Jansen J, Wanten G, van Achterberg T. The impact of home parenteral nutrition on daily life—a review. Clin Nutr. 2007;26(3):275–88.
4. Kübler-Ross E, Wessler S, Avioli LV. On death and dying. JAMA. 1972;221(2):174–9.
5. PSALM 22. To the chief musician upon Aijeleth Hashahar, a Psalm of David, 14 the bible, the new Cambridge paragraph bible with the apocrypha: King James version, vol. MMVIII. London: The Folio Society; 2005. p. 693.
6. Soykan I, Sivri B, Sarosiek I, Kiernan B, McCallum RW. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. Dig Dis Sci. 1998;43(11):2398–404.
7. Wickkiser BL. Asklepios, medicine, and politics of healing in fifth-century Greece, between craft and cult. Baltimore: The Johns Hopkins University Press; 2008.
8. Maletic V, Raison C. The new mind-body science of depression. London: Norton; 2017.
9. Heath I. How medicine has exploited rationality at the expense of humanity: an essay by Iona Heath. BMJ. 2016;355:i5705.
10. Roth DA, Eng W, Heimberg RG. Cognitive behavior therapy, encyclopedia of psychotherapy, vol. 1. Amsterdam: Elsevier; 2002. p. 451–8.
11. Donal GF, Varden J, Parker S, et al. Illness beliefs of patients on home parenteral nutrision (HPN) and their reaction to emotional distress. Clin Nutr. 2005;24(6):896–903.
12. Strosahl K. Acceptance and commitment therapy, encyclopedia of psychotherapy, vol. 1. Amsterdam: Elsevier; 2002. p. 1–8.
13. Harris R. Embracing your demons: an overview of acceptance and commitment therapy. Psychother Aust. 2006;12:2–8.
14. Gabbard GO. Chapter 1. In: Psychodynamic psychiatry in clinical practice. 4th ed. Philadelphia, PA: American Psychiatric Publishing; 2005. p. 6–7.
15. Barkham M, Guthrie E, Hardy GE, Margison F. Chapter 11. In: Psychodynamic-interpersonal therapy, a conversational model. London: Sage; 2017.
16. Hobson RF. Forms of feeling, the heart of psychotherapy. London: Tavistock Publications; 1985.
17. Guthrie E, Creed F, Dawson D, Tomenson B. A controlled trial of psychological treatment for the irritable bowel syndrome. Gastroenterology. 1991;100(2):450–7.
18. Shapiro F, Maxfiled L. Eye movement desensitization and reprocessing, encyclopedia of psychotherapy, vol. 1. Amsterdam: Elsevier; 2002. p. 777–85.
19. Peters SL, Muir JG, Gibson PR. Review article: gut-directed hypnotherapy in the management of irritable bowel syndrome and inflammatory bowel disease. Aliment Pharmacol Ther. 2015;41(11):1104–15.
20. Fairburn CG, Cooper Z, Shafran R. Cognitive behaviour therapy for eating disorders: a "transdiagnostic" theory and treatment. Behav Res Ther. 2003;41(5):509–28.
21. Culkin A, Gabe SM, Peake ST, Stern JM. A dangerous combination of binge and purge. Int J Eat Disord. 2012;45(2):302–4.
22. Beckers AB, Keszthelyi D, Fikree A, Vork L, Masclee A, Farmer AD, Aziz Q. Gastrointestinal disorders in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type: a review for the gastroenterologist. Neurogastroenterol Motil. 2017;29(8).
23. Stevens A. Chapter 2. In: An intelligent person's guide to psychotherapy. London: Duckworth; 1998. p. 22.
24. Ortiz-Torrent N. Chapter 25. In: Parkman HP, McCallum RW, editors. Psychiatric aspects of gastroparesis, gastroparesis, pathophysiology, presentation and treatment. Totowa, NJ: Humana Press; 2012. p. 303–13.

Part VI

Outcome of Intestinal Failure

Home Enteral Nutrition in Adults: Indications and Outcomes

André Van Gossum, Asuncion Ballarin, Marianna Arvanitakis, Xavier Hébuterne, and Jeremy M.D. Nightingale

Key Points

1. The use of Home Enteral Nutrition (HEN) is increasing throughout the world.
2. The prevalence of HEN is variable at about 100–1400/millions inhabitants in Western countries.
3. HEN is indicated in patients who are at high nutritional risk or malnourished, who are unable to meet nutritional requirements by the oral route and who have a functional gastrointestinal tract.
4. Dysphagia due to neurological disorders or head-and-neck cancer are the main indications for HEN.
5. Most (80%) of HEN is through a gastrostomy tube. Some are by a naso-gastric tube or rarely a jejunostomy.
6. Survival on HEN depends upon the prognosis of the underlying disease.
7. The objectives of HEN must include nutritional targets (e.g. achieving/maintaining a pre-determined body weight), quality of life, ethical issues and the criteria for stopping.
8. The initiation and monitoring of HEN should be performed by a multidisciplinary nutrition support team in collaboration with the community/family/caregivers.

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Introduction

The use of HEN started in the early seventies in response to the interest and need for ambulatory care. For the majority of the patients, enteral nutrition is initiated during their hospital stay and then continued at home. Procedures and funding for home parenteral nutrition (HPN) preceded that of HEN in many European countries [1]. Globally, HEN is used for patients with oral failure (OF) but having a functional gut. On the contrary, home parenteral nutrition (HPN) is indicated in patients with severe chronic intestinal failure requiring intravenous supplementation to meet nutritional or fluid requirements [2].

The use of HEN progressively increased around the world after the introduction of the percutaneous endoscopic gastrostomy (PEG) technique [3], the availability of commercially-designed enteral formula and the development of home care services.

HEN must be considered as a medical treatment. Before starting HEN, not only nutritional needs but also prognosis, quality of life and ethical issued have to be discussed and regularly evaluated [4]. Although HEN can be initiated by any medical team, it is highly recommended that the route of administration, timing and composition of feeding, organization or services are best made by a multidisciplinary nutritional support team (NST).

OF is often unrecognized, partly because it is not thought of and partly because these patients are looked after by a myriad of medical specialties. This contrasts to IF which usually recognized because these patients tend to be under the care of appropriate specialists and have more immediate problems. It is paradoxically more difficult to recognize and treat the problems of OF than IF.

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Epidemiological Data

The incidence and prevalence of HEN is not known in many countries but when reported is increasing [5–7]. There are few national registries that try to record all patients receiving HEN (BANS in UK or NADYA-SENPE group in Spain), [7, 8] but still are likely to give an under-estimate as registration is not compulsory (perhaps only a third were registered in UK) [7]. In the USA, information comes primarily from Medicare and Medicaid Services [6]. Many other hospital/university centres in different countries report their own case-series.

There is no standardization in the way in which incidence (new cases/registrations), prevalence (one-day point and annual occurrance) and outcome data are presented. Most prevalence data are per 10^6 inhabitants (or population). Comparison between these data sets can be difficult to interpret.

During the nineties, it was estimated that the number of patients receiving HEN was ten times higher than those on HPN [9–11]. For example, in the UK, the one-day prevalence of HEN in 1998 was 200–267 patients/10^6 inhabitants and for the region of Nice in France, the annual incidence of HEN was 99 patients/10^6 million inhabitants [12, 13]. In 2017, the Spanish Home Enteral Nutrition Registry reported a prevalence of 102/10^6 million inhabitants [14]. It is estimated that 18,232 people (284/million population) received home HEN in the UK in 2013 [15]. In Italy the incidence was 406 ± 58 patients/million inhabitants/year for patients living at home and 319 ± 44 for patients living in a nursing home in 2012 [5]. In USA. 437,882 patients (1385 per million U.S. inhabitants) were receiving HEN in 2013, which was a large increase from 1992 (415 per million) [6, 9].

In some countries, HEN reports combine oral supplements and enteral feeding (via a tube) [16]. For example in New South Wales (Australia), the HEN population of participating hospitals was approximatively 7600, with 81% oral nutritional support and 19% tube-fed patients [17].

It is estimated that 10% of nursing home residents in the USA are receiving HEN [8].

Indications for HEN

HEN is indicated in patients who are at high nutritional risk or malnourished, who are unable to meet nutritional requirements by the oral route and who exhibit a functional gastrointestinal tract [18]. They should have a life expectancy of more than a month [18]. Short term or predicted short term enteral nutrition for 4–6 weeks is usually via a naso-gastric tube [18]. According to the ESPEN Guidelines, an inadequate nutritional state is confirmed if patients cannot eat for a week or if the energy intake is less than 60% of estimated requirements for 1–2 weeks [19].

There are three major underlying physiological reasons for HEN to be needed: dysphagia, anorexia (OF) and intestinal failure. Dysphagia and anorexia cause a reduced intake, and intestinal failure results in reduced absorption. Some patients may have several reasons for needing HEN (e.g. anorexia and moderate intestinal failure) (Table 1).

Globally, neurodegenerative, and neurovascular diseases account for 50–60% of the indications. Dysphagia due to head-and-neck or upper GI cancer is the second most common indication. In the recently published experience in Poland, the primary diseases for a total of 4586 patients were 54.5% neurological, 33.9% cancer (20.2%—head and neck, 11.7% gastrointestinal, 2.5% gastroenterology and 1.5% inherited diseases [14]. In the UK in 2015 (3216 patients) 42.9% had cancer (mostly head and neck), 39.6% central nervous system and mental health problems, 9.0% non-malignant gastrointestinal disease and 8.4% others [7] (Table 2).

Table 1 Clinical features that lead to the need of HEN

• Swallowing disorders because of neurological diseases
• Dysphagia because of malignancies (mostly head and neck cancer or upper GI tract)
• Cancer-related cachexia
• Chronic malnutrition related to chronic obstructive pulmonary disease/chronic heart disease or chronic infections (i.e. cystic fibrosis)
• Malabsorption/maldigestion because of liver, pancreas or intestinal disorders

Table 2 Common underlying disease for which HEN is given to new adults in the UK in 2009 [19] and Poland 2007–13 [20]

UK classification		UK *n = 3282*	Poland *n = 456*
CNS and mental health (*n* = 1226)	Cerebrovascular disease	649	137
	Motor neurone disease	197	17
	Multiple sclerosis	122	17
	Parkinson's disease	109	7
	Cerebral trauma	75	22[a]
	Dementia	48	18
	Cerebral palsy	36	74
	Anorexia nervosa	26	1
Cancer (*n* = 1226)	Head and neck	673	23
	Oesophageal	239	
	Oropharyngeal	183	
	Gastric	45	19[b]
Non-malignant gastrointestinal (*n* = 291)	Dysphagia (unknown cause)	58	
	Crohn's disease	20	4
	Dysmotility	15	
Other (*n* = 205)	Cystic fibrosis	24	6

[a]Includes spinal injury
[b]Labelled as abdominal cancer

Most adults are over 60 years though those with cerebrovascular disease tended to be older; 66% were aged 71–90 [7]. Head and neck cancer patients tend to be younger and have HEN due to dysphagia (69%), disease-related malnutrition (19%) or gastrointestinal obstruction (3%) [7].

Physiological Reasons for HEN

Dysphagia

Dysphagia is the major reason for a patient to receive HEN. It may be secondary to a neurological problem (usually cerebrovascular disease), a vegetative state, a head and neck cancer, or a rare benign cause. In most cases dysphagia will remain a permanent problem; in some cases it is temporary, for example, during radiation therapy or chemotherapy or prior to removal of an upper gastrointestinal cancer.

Anorexia

Anorexia represents a growing indication for HEN and defines a patient without dysphagia who cannot take adequate nutrition by mouth to meet his or her nutritional requirements. Some patients may have associated increased energy requirements (cancer or rarely AIDS patients). Anorexia is generally found in very old patients, is secondary to an acute or chronic illness (surgery, infection, dementia or psychological disorder) and is associated with the problems of undernutrition. Active dietetic support is needed for these patients; if sip-feeds are unsuccessful, enteral feeding in the hospital may be given for 3–4 weeks. If voluntary intake improves significantly during this time, enteral nutrition can be stopped; if not, there is a high chance that long-term HEN will be needed.

Intestinal Failure

In the case of intestinal failure, oral intake is insufficient regardless of the gastrointestinal problems that have led or will lead to undernutrition. A patient with chronic diarrhoea may be a candidate for enteral rather than parenteral nutrition if the daily stool weight is less than 500 g and the daily faecal fat less than 20 g (72 mmol). There are many diagnoses responsible for maldigestion (e.g. chronic pancreatitis or previous gastrectomy) or malabsorption (e.g. short bowel, small bowel dysfunction or HIV/AIDS). Patients with more than 200 cm of small intestine remaining and a functioning colon may need a period of enteral support. Long-term enteral support may be needed in patients with a jejunostomy and 100–200 cm of remaining small intestine [21].

Persistent Vegetative State

Persistent vegetative state (PVS) is a clinical condition of complete unawareness of self and the environment, accompanied by sleep–wake cycles, with either complete or partial preservation of hypothalamic and brain stem autonomic functions [22]; there is no interaction between the patient and others, and the patient is doubly incontinent [23]. Some authors argue that physicians are not obliged to provide nutritional support in this condition because there is no clinical benefit although physiological functions can be maintained [24]. Others strongly disagree with this attitude on the basis that every human being has the right to food and water, even in situations in which medical interventions can be ethically withheld [25]. The physician needs to explain all outcomes to the family and then, in some countries, let them decide. In the UK, an application to stop the feeding has to be made to the High Court. If the family wishes to care for their family member at home, it can be argued that the medical profession must provide both the means by which food and water can be given, and the feed itself (Chap. 53).

Reasons Not to Give HEN

Before starting HEN, the absence of contraindications must be checked (Table 3) and the criteria for starting confirmed (Table 4) (Fig. 1).

The success of HEN depends on patient selection, safe placement of a feeding tube/device, suitable nutrients and administration system, adequate education about enteral feeding, and regular monitoring. The European and international guidelines advice against initiating tube-feeding in patients with severe dementia. Orlandi et al. challenged this issue reporting a series of 585 consecutive patients of the mean age of 85 ± 7 years [26].

Table 3 Contraindications to HEN [18]

1. A life expectancy estimated to be less than 1 month
2. The existence of severe functional disturbances of the bowel, gastrointestinal obstruction, gastrointestinal bleeding, severe malabsorption or severe metabolic imbalances
3. Patients and/or their legal careers who do not agree to a HEN program or are unlikely to comply with and/or if there are organizational/logistic problems which cannot be overcome

Table 4 Criteria for proposing that a patient be started on HEN

Oral failure and a functional/usable gastrointestinal tract
Ability to tolerate enteral nutritional therapy in the hospital (for at least 7 days)
No other medical or surgical problems—ready to be discharged
A clean and safe home
Patient or carer able to perform all enteral procedures safely

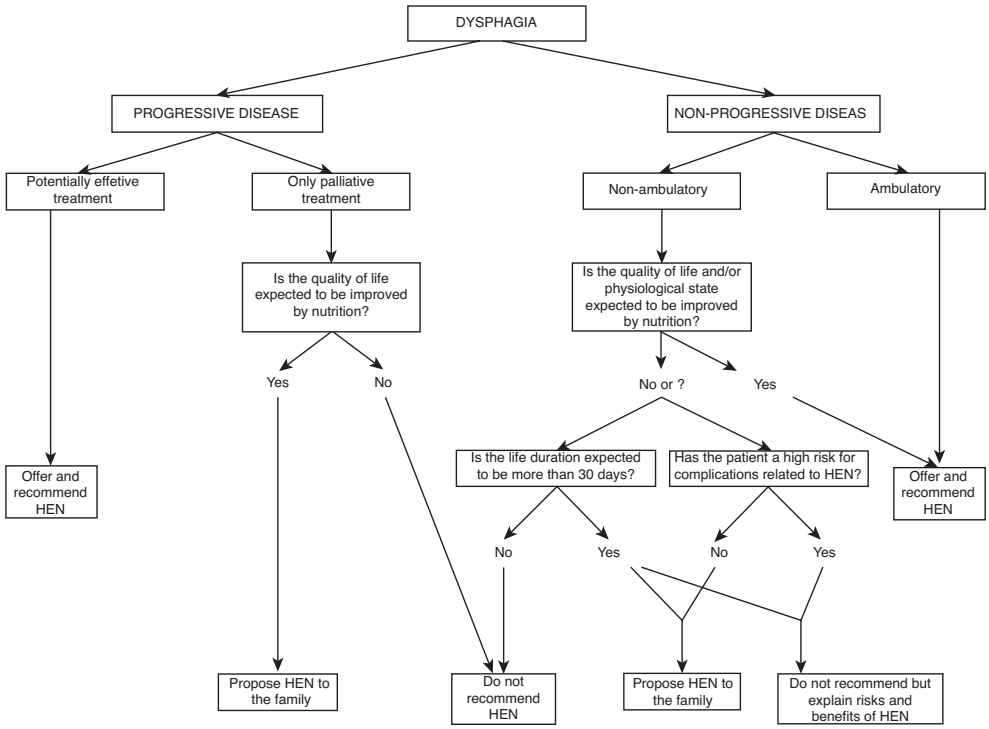

Fig. 1 Algorithm for starting HEN

Table 5 Items to address before the patient can discharged (adapted from [18])

• The quantity of EN, and which brand should be administered
• Total amount of fluid administrated
• Duration of administration, during day or night
• The use of the enteral feeding pump and what to do in case of dysfunction of the pump (if a pump is used at all)
• Whether the patient is allowed to have oral intake next to HEN (any restrictions?)
• Personal care, impact of HEN on daily life (shower, swimming, party, holiday)
• Who will take care of the administration of the EN (patient, family, [home care company] nurse)
• How to secure the tube adequately
• How to administrate medications through the tube
• Who will change or reinsert the tube in case of dislocation
• What to do in case of blocked tube:
– Who to contact in case of material or physiologic complications (material: dislocation, blocked tube and/or breaking material) and physiologic complications (diarrhea, constipation, aspiration, change of weight, dehydration)
• How often the patient should be evaluated, by whom and where

Interestingly, Velapati G et al. described a series of 72 patients who presented with malnutrition due to bariatric surgery [27]. They reported that HEN was safe and effective leading to avoidance of parenteral nutrition in most cases.

Before discharging the patient at home, a checklist must be completed for assuring a good quality of care at home (Table 5) [18]. A Canadian survey underlined that 74% out of 390 adults on HEN did not have any record of visiting a community registered dietitian up to 6 years after tube placement [28].

Mode and Method of Delivery

The most common tube inserted is a gastrostomy, usually done endoscopically (percutaneous endoscopic gastrostomy (PEG)). In the UK in 2015, 80% of HEN patients were fed via a gastrostomy, 10% via a nasogastric tube, 6% via a jejunostomy and 3% by a nasoduodenal or nasojejunal tube [7]. In Spain in 2012, 45.3% were fed by a nasogastric tube and 29.4% by a gastrostomy [8]. In Poland in 2018 a gastrostomy tube was used most commonly (PEG 65.3%, other gastrostomy 11.6%), 14.3% had a naso-gastric tube, 7.0% a jejunostomy, 0.6% a naso-jejunal tube and 0.2% a gastro-jejunostomy (PEGJ).

Feeding through a tube may be by a continuous infusion (with pump assistance), intermittent drip, or a bolus technique. Bolus feeding involves 4–6 feeds a day of 200–400 ml given by a 50 ml syringe over 15–60 min [18]. Overnight feeding tends to be over 10–12 h using a static or mobile pump. In Poland 74.4% had feed given as a bolus, 17.6% by gravity flow and only 8.0% through a pump [29]. In most countries feed is currently given with the aid of a pump. However in the USA Medicare will provide reimbursement for a pump if: The administration rate is less than 100 ml/h,

if circulatory overload, if increased aspiration risk/pneumonia or if diarrhoea, dumping syndrome, gastrointestinal reflux, vomiting or blood glucose fluctuations [30].

The feed may be polymeric (with or without fibre) or increasingly consist of homemade blenderized food.

Outcome of HEN

Data about the complications of nutritional support are often given as the proportion of patients developing a specified complication though it is better (as for PN) to be per EN feeding days.

Fourteen percent of those who had a stroke returned to oral feeding, thus it is important to assess continually a patient's ability to swallow as it may improve and allow tube feeding to be stopped [31].

Survival

Folwaski [29] et al., in Poland, described a series of 4586 HEN patients in 2018. The median overall survival on HEN was 354 days but 615 days for neurological diseases and 209 days for cancer patients (Table 6) [29]. Ruggeri et al. reported a mean survival of 22.1 weeks in cancer patients with dysphagia who received HEN [32]. A retrospective Italian study found a median duration of HEN of about 196 days [17]. Regarding the underlying disease, duration was 261 days for neurovascular diseases, 251 days for neurovegetative disease, 118 days for head and neck cancer, 82 days for abdominal cancer, 788 days for head injuries. In this series, only 7.9% of the patients resumed oral nutrition; the median survival was 9.1 months. The median survival and the rate of complications were similar between those with or without dementia [26].

Cawsey et al. reported a series of 727 adult patients [33]. Median duration of HEN for cancer patients was 122 (range, 1–1259) days, duration for neurological disorders was 187 (range, 1–1752) days, and duration for GI disorders was 161 (range, 1–1849) days.

Table 6 Outcomes of adult HETF during 2015 [7] in UK and 2018 in Poland [29]

		UK	Poland
	n	%	%
Continuing	6270	70	48.5
Died	1436	16	40.2
Return to oral diet	1039	12	5.3
Lost to follow up	131	2	4.7
In hospital	14	<1	
Withdrawn/refused	14	<1	1.2

Table 7 Outcome of patients on HEN (follow-up 18–65 months) [34]

	Full oral nutrition *n* = 51 (%)	Continued HEN *n* = 19 (%)	Died *n* = 93 (%)	Stopped for other reasons *n* = 20 (%)
Neurological disease	16	13	65	6
Head and neck cancer	33	5	54	8
Digestive disease	49	3	26	22
Post-traumatic dysphagia	14	43	0	43
Anorexia (elderly)	30	6	58	6
AIDS	0	0	100	0
Other	50	25	17	8

Table 8 Survival at 1 month, 1 year and 5 years [35]

	n	1 month (%)	1 year (%)	5 years (%)
Neurological disease	148	83	41	21
Digestive disease	76	90	59	49
Head and neck cancer	64	88	37	24
Dementia	54	54	20	3
Anorexia	32	81	56	21

The overall probability of survival was 44% at 1 year and 29% at 5 years in one study (Table 7) [34], and similar results of 80, 42 and 25% at 1 month, 1 year and 5 years respectively in another (Table 8) [35].

There is a low mortality for cerebral palsy, cystic fibrosis and multiple sclerosis. However it is higher for patients with motor neurone disease, dementia and malignancy (30–60% in the first year. Patients who had a cerebrovascular accident and were over 75 years were 3–4 times more likely to die while on HEN than those patients aged less than 65 [31]. Patients with small bowel malabsorption needing HEN are uncommon, but at 1 year 82% were alive, 43% had 'complete rehabilitation', and 45% had stopped HEN and resumed an oral intake [36].

In a retrospective cohort study of 253 older patients with dysphagia in Japan 180 patients were randomised to PEG and EN feeding and 73 to TPN. The PEG group had a significantly longer survival time (median, 317 vs 195 days); but a significantly higher incidence of severe pneumonia (50.9% vs 25.5%); however the incidence of sepsis was significantly lower (10.9% vs 30.9%) [37].

Quality of Life

While the health-related quality of life for patients with gastrostomy tubes is poor (usually due to severe physical disability) compared to that of the general population, the

majority of patients and carers rated the gastrostomy 'positively' [38]. The recorded quality of life for most patients in the UK receiving HEN is poor. 72% in UK were living alone at home. 42% were able to manage independently but most needed total 37% or some help 22%. Only 10% were housebound and 15% bedbound. 25% were in residential care. Those with cerebrovascular disease had a greater need for total help (82%). Only 4% managed independently, 70% required nursing home care. Those with head and neck cancer are relatively independent and active, 96% were in their own home, 75% were independent and only 4% needed total help and 20% some help. 73% achieved full normal activity, 25% a limited activity and <2% were housebound or bed bound. 24% of these patients returned to oral feeding alone, 61% continued and 14% died [7].

Complications

The overall HEN-related complication rate such that hospital admission was required was 0.3–0.4 per patient per year (with little difference between the diagnoses); this was half that of patients receiving HPN [9]. Readmission to hospital in the USA for non-HEN problems was less common for patients with neuromuscular disorders of swallowing (0.9/year), than with cancer or small bowel disease (both 2.7/year) [36].

Nine percent of patients receiving gastrostomy tube feeding developed aspiration pneumonia and in this event most needed hospital admission [39]. Aspiration is less likely to occur with a PEG than with a nasogastric feeding tube [40]. To reduce the risk of aspiration pneumonia a nasogastric tube's position is checked before each use and it is replaced with similar checks if it becomes displaced ("falls out"). Although in a healthy person with no dysphagia it is very difficult to inadvertently pass a tube into the lungs, this can easily be done in patient with neurological disease or reduced consciousness as they do not cough/become hypoxic as soon as the tube is misplaced.

Tube malfunction, breakage, site infection and a blocked tube all occur (Chaps. 33 and 54).

The poor clinical outcomes of HEN suggests that better selection of candidates for HEN will be needed and this will be helped by studies focusing on the quality of life and prognostic factors. Each case needs to be carefully discussed with the patient and family, and there needs to be an awareness of the aims and potential benefits before a decision is made to start HEN.

References

1. Moreno JM, Shaffer J, Staun M, et al. Survey on legislation and funding of home artificial nutrition in different European countries. Clin Nutr. 2001;20:117–23.
2. Pironi L, Arends J, Baxter J, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34:171–80.
3. Gauderer MW, Ponsky JL, Izant RJ Jr. Gastrostomy without laparotomy: a percutaneous endoscopic technique. J Pediatr Surg. 1980;15:872–5.
4. Druml C, Ballmer PE, Druml W, et al. ESPEN guideline on ethical aspects of artificial nutrition and hydration. Clin Nutr. 2016;35:545–56.
5. Paccagnella A, Marcon ML, Baruffi C, et al. Enteral nutrition at home and in nursing homes: an 11-year (2002–2012) epidemiological analysis. Minerva Gastroenterol Dietal. 2016;62:1–10.
6. Mundi MS, Pattinson A, McMahon MT, Davidson J, Hurt RT. Prevalence of home parenteral and enteral nutrition in the United States. Nutr Clin Pract. 2017;32(6):799–805.
7. Stratton R, Evill R, Smith T. On behalf of the BANS Committee. BANS report 2018. Home enteral tube feeding (HETF) in adults (2010-2015). A report by the British Artificial Nutrition Survey (BANS) - a committee of BAPEN. 2018. www.bapen.org.uk/pdfs/reports/bans/bans-report-2018.pdf.
8. Wanden-Berghe C, Matía Martín P, Luengo Pérez LM, Cuerda Compes C, Burgos Peláez R, Alvarez Hernández J, Calleja Fernández A, Pérez de la Cruz A, Gómez Candela C, Leyes García P, Laborda González L, Martínez Olmos MA, Campos Martín C, Suárez Llanos JP, Penacho Lázaro MA, Gonzalo Marín M, Salas Salvadó J, Irles Rocamora JA, Cánovas Gaillemin B, Carrero Caballero MC, Moreno Villares JM, Garde Orbaiz C, Miserachs Aranda N, Del Olmo García MD, Apezetxea Celaya A, Mauri S. Home enteral nutrition in Spain; NADYA registry 2011-2012. Nutr Hosp. 2014;29(6):1339–44.
9. Howard L, Ament M, Fleming C, et al. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. Gastroenterology. 1995;109:355–65.
10. de Francesco A, Fadda M, Malfi G, et al. Home parenteral nutrition in Italy: data from the Italian national register. Clin Nutr. 1995;14(suppl 1):6–9.
11. Van Gossum A, Bakher H, Bozzetti F, et al. Home parenteral nutrition in adults: an European multicenter survey in 1997. Clin Nutr. 1999;18:135–40.
12. Elia M, Russel C, Shaffer J, et al. Report of the British Artificial Nutrition Survey – August 1999. British Association of Parenteral and Enteral Nutrition.
13. Werklen-Martini S, Hebuterne X, Pugliese P, et al. 47 months activity of a center for home-enteral nutrition and long-term follow-up of the patients treated. Nutr Clin Metabol. 1997;11:7–17.
14. Wanden-Berghe C, Campos C, Pelaez R, et al. Spanish home enteral nutrition registry of the year 2016 and 2017 from the NADYA-SENPE Group. Nutr Hosp. 2019;36:233–7.
15. Serjeant S, Tighe B. A meta-synthesis exploring caregiver experiences of home enteral tube feeding. J Hum Nutr Diet. 2022;35(1):23–32.
16. You Q, Li X, Ma Y, et al. A retrospective analysis on epidemiological characteristics of home enteral nutrition: results from a Chinese tertiary hospital in 2018. Eur J Clin Nutr. 2021;75:473–9.
17. Tang D, Parker E, Faruquie S, et al. Evaluation of home enteral nutrition services at public hospitals in New South Wales, Australia. Nutr Diet. 2019;76:6–13.
18. Bischoff S, Austin P, Boeykens K, et al. ESPEN Guidelines on home enteral nutrition. Clin Nutr. 2020;39:5–22.
19. Smith T. Annual BANS report, 2010 artificial nutrition support in the UK 2000–2009 a report by the British Artificial Nutrition Survey (BANS), a committee of BAPEN (The British Association for Parenteral and Enteral Nutrition). www.bapen.org.uk/pdfs/bans_reports/bans_report_10.pdf.
20. Klek S, Hermanowicz A, Dziwiszek G, Matysiak K, Szczepanek K, Szybinski P, Galas A. Home enteral nutrition reduces complications, length of stay, and health care costs: results from a multicenter study. Am J Clin Nutr. 2014;100(2):609–15.

21. Nightingale JMD, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces the need for parenteral therapy, increases the incidence of renal stones but does not change the high prevalence of gallstones in patients with a short bowel. Gut. 1992;33:1493–7.
22. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state. N Engl J Med. 1994;330:1499–508, 1572–1579.
23. Lennard-Jones JE. Ethical and legal aspects of clinical hydration and nutritional support. London: British Association for Parenteral and Nutrition; 1998.
24. Rabeneck L, McCullough LB, Wray NP. Ethically justified, clinically comprehensive guidelines for percutaneous endoscopic gastrostomy tube placement. Lancet. 1997;349:496–8.
25. Rosner F. Guidelines for placement of percutaneous endoscopic gastrostomy tube. Lancet. 1997;349:958.
26. Orlandoni P, Peladic N, di Rosa M, et al. The outcomes of long-term home enteral nutrition (HEN) in older patients with severe dementia. Clin Nutr. 2019;38:1871–6.
27. Velapati SR, Schroeder SE, Schroeder DR, Buttar NS, Mohamed Elfadil O, Hurt RT, Mundi MS. Use of home enteral nutrition in malnourished post-bariatric surgery patients. JPEN J Parenter Enteral Nutr. 2021;45(5):1023–31.
28. Sandhu R, Saran D, Ho G, et al. High costs and limited dietitian services for home enteral nutrition users: a Canadian study. Nutr Clin Pract. 2022;37(1):167–75.
29. Folwarshi M, Klek S, Zoubek-Wojcik A, et al. Home enteral nutrition in adults – Nationwide multicenter survey. Nutrients. 2020;14:2087.
30. Martin K, Gardner G. Home enteral nutrition: updates, trends, and challenges. Nutr Clin Pract. 2017;32(6):712–21.
31. Elia M, Russell C, Shaffer J, et al. Report of the British Artificial Nutrition Survey – August 1999. British Association of Parenteral and Enteral Nutrition.
32. Ruggeni E, Giannantonio M, Agostini F, et al. Home artificial nutrition in palliative cancer patients: impact of survival and performance status. Clin Nutr. 2020;39:3346–53.
33. Cawsey S, Soo J, Gramlich L. Home enteral nutrition: outcomes relative to indication. Nutr Clin Pract. 2010;25:296–300.
34. Wehrlen-Martini S, Hébuterne X, Pugliese P, Pouget I, Volpei F, Mousnier A, Rampal P. 47 months activity of a center for home-enteral nutrition and long-term follow-up of the patients treated. Nutr Clin Metab. 1997;11:7–17.
35. Schneider SM, Raina C, Pugliese P, Pouget I, Rampal P, Hébuterne X. Outcome of patients treated with home enteral nutrition. JPEN J Parenter Enteral Nutr. 2001;25(4):203–9.
36. Howard L, Patton L, Dahl RS. Outcome of long-term enteral feeding. Gastrointest Endosc Clin N Am. 1998;8:705–22.
37. Masaki S, Kawamoto T. Comparison of long-term outcomes between enteral nutrition via gastrostomy and total parenteral nutrition in older persons with dysphagia: a propensity-matched cohort study. PLoS One. 2019;14(10):e0217120.
38. Bannerman E, Pendlebury J, Phillips F, Ghosh S. A cross-sectional and longitudinal study of health-related quality of life after percutaneous gastrostomy. Eur J Gastroenterol Hepatol. 2000;12:1101–9.
39. Parker T, Neale G, Elia M. Home enteral tube feeding in East Anglia. Eur J Clin Nutr. 1996;50:47–53.
40. Norton B, Homer-Ward M, Donnelly MT, Long RG, Holmes GKT. A randomised prospective comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding after acute dysphagic stroke. Br Med J. 1996;312:13–6.

Home Parenteral Support for Adults

Laura Cohen, Francisca Joly, Simon Gabe, and Jeremy Woodward

Key Points

1. Improved availability and safety of home parenteral support (HPS) has led to a significant (two- to fourfold) increase in its usage and indications over the last two decades.
2. The most common reasons for HPS are surgical complications, Crohn's disease and mesenteric infarction.
3. Complications include those due to the venous access, the non-physiological route of delivery, and the pharmacological composition of the PN and are often difficult to separate from the effects of the underlying intestinal failure.
4. Long-term survival is possible on HPS, and most deaths on treatment are due to the underlying disease. Less than 25% of deaths are due to HPS-related causes, most frequently IF-associated liver disease (IFALD) and catheter-related blood stream infection (CRBSI).
5. Some patients maintain a good quality of life on HPS whereas others carry a significant burden of symptoms and interference with daily activities.
6. Failure of HPS (for reasons of impending loss of vascular access, IFALD or unmanageable/intolerable complications of intestinal failure) can be managed by intestinal transplantation. Early detection of IFALD or those at high risk and treatment with pre-emptive isolated intestinal transplantation is preferable to allowing end stage liver disease to develop, that then requires combined liver and intestinal transplantation.

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Introduction

It is currently just over 50 years since the first demonstration of successful life support using sole intravenous nutrition in beagles by Stanley Dudrick [1]. Given that intestinal failure (IF) was a rapidly terminal condition at this time, the first use of parenteral nutrition in humans followed shortly afterwards, with patients learning how to manage their own parenteral nutrition at home from the early 1970s [2, 3]. Over the intervening half century, it is surprising how little has changed in the basic principles of intravenous nutrition and its delivery. However, with greater understanding of the complications and risks involved in home parenteral nutrition (HPN), and subsequent developments in nutrient composition, monitoring and support of patients, HPN therapy has become safer and more efficient. As a consequence the indications for HPN have broadened, it has become more widely available, and new challenges in its use have inevitably arisen.

In this chapter we address the need for HPS, the economics of its use, the requirements for establishing HPS, the practical avoidance of its complications and developing changes in HPS provision. The term home parenteral support

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(HPS) is used except where the data or information relates only to parenteral nutrition (PN) when the term home parenteral nutrition (HPN) (which excludes those who receive parenteral fluid alone) is used.

The Need for HPS

Long-term PN and fluid support as an inpatient in hospital is not a valid option for most patients with intestinal failure. In order to retain any meaningful quality of life, this treatment needs to be available in the home environment. HPN may be required for only a limited period of time where there are surgical options available for the restoration of sufficient intestine in continuity ('type 2 intestinal failure'), or it may be required indefinitely ('type 3 intestinal failure') [4, 5]. Whilst a useful classification in clinical use, the distinctions between type 2 and type 3 IF are not always clear given the heterogeneity of conditions requiring PN support and the increasing medical and surgical options for treatment, including intestinal transplantation.

HPN is expensive [6, 7] with costs that escalate when nursing care is required for the connection and disconnection of infusions. Nevertheless, in most westernised health economies it is still more cost effective to provide PN at home rather than in hospital where capacity for inpatient treatment is in high demand. It is this cost differential (rather than concern for improving quality of life) that has largely driven the use of HPN for increasingly short periods of time whilst awaiting restorative surgery.

Organisational improvements that have led to increased efficiency, support and safety in HPS provision, have enabled a significant increase of HPS use in many countries over the first two decades of the twenty-first Century. In the UK for instance, the number of patients receiving HPN has increased from around 10 per million population in 2000 [8] to 40 per million in 2015 [9]. However there remain significant differences in HPN prevalence between countries—for instance in 2013, Spain reported 4.2 cases per million [10] whereas there were approximately 79 per million in the USA [11]. Interestingly, in the USA, HPN prevalence has actually dropped from 157 cases per million in 1992 [11], possibly due to an increase in availability of home enteral nutrition support or due to issues related to charging and benefits associated with the healthcare system.

Indications for HPS

HPS is indicated for the long-term support of any condition where enteral feeding is either impossible or inadequate. A pathophysiological definition (rather than the above 'func-

Table 1 Indications for home parenteral nutrition (HPN) (adapted from [5])

Pathophysiological group	Mechanism of intestinal failure	Examples
Short bowel	• Reduced absorptive surface area	• Intestinal resection due to:
	• Increased fluid losses	• Mesenteric infarction arterial or venous, volvulus, Crohn's disease, radiation enteritis, trauma
	• Secondary reduced oral intake to control losses	• Congenital intestinal malformation, gastroschisis, atresia
	• Rapid gastrointestinal transit	
Intestinal fistula	• Bypass of gastrointestinal absorptive mucosa	• Iatrogenic due to surgical bowel injury
	• Increased fluid losses	• Trauma
	• Secondary reduced oral intake to control losses	• Crohn's disease
	• Metabolic demands due to associated sepsis or inflammation	• Tumour
		• Infection (TB, actinomycosis)
Intestinal dysmotility	• Intolerance of oral/enteral feeding due to symptoms	• Chronic intestinal pseudo-obstruction either primary (visceral myopathy or neuropathy) or secondary to a wide variety of underlying medical conditions or medication use
	• Small bowel bacterial overgrowth	
	• Increased fluid secretion in obstructed segments	
	• Increased GI losses due to vomiting, diarrhoea or gastric drainage	
Mechanical obstruction	• Reduced oral intake due to symptoms and lack of absorption	• Obstructing tumour of the GI tract
	• Increased fluid secretion in obstructed segments	• Obstruction due to peritoneal disease including tumours or adhesions
	• Increased GI losses due to vomiting, diarrhoea or gastric drainage	

(Continued)

Table 1 (continued)

Pathophysiological group	Mechanism of intestinal failure	Examples
Extensive intestinal mucosal disease	• Inefficient nutrient absorption or nutrient and fluid loss from mucosal surface	• Refractory coeliac disease, Crohn's disease, common variable immunodeficiency with chronic noroviral infection, tufting enteropathy, microvillous inclusion disease

tional' classification of IF types) identifies five main types of indication [5] (see Table 1). In the UK, the British Artificial Nutrition Survey (BANS) [9] has kept comprehensive data on the usage of home enteral and parenteral nutrition since 1996. Short bowel remains the commonest indication, but has dropped from 44% of patients receiving HPN in 2005 to 34% in 2015, largely accounted for by a proportionate reduction in patients with Crohn's disease. In the UK, malignant bowel obstruction and dysmotility disorders contribute approximately equal proportions of existing HPN patients, however the UK-BANS registry collects separate data for 'point' prevalence (on a specified census date) and 'period' prevalence (between two time points). Patients with malignancy generally have a shorter life expectancy than those patients with dysmotility and therefore contribute approximately a quarter of new HPN registrations compared to around 7% for chronic intestinal pseudo-obstruction. Ovarian cancer is the commonest malignant indication for HPN in the UK.

The proportion of new HPN registrations for malignancy in the UK has doubled over the last 10 years and a similar trend is apparent in other national registries such as Canada [12] and Spain [10] where malignancy now comprises the commonest indication in adults.

Establishing a Patient on HPN

A hospital providing an HPN service requires a comprehensive and integrated nutrition support team that comprises nutrition nurse specialists, medical staff with appropriate expertise and training, pharmacists, and dietitians. The team will require close links with vascular access and community homecare teams [13].

To be suitable for receiving parenteral nutrition at home, a patient requires a stable PN prescription with regard to nutrient and electrolyte composition and volume [14]. This may take several days or weeks to establish as volume and electrolyte losses can vary from day to day in patients with high output fistulae or proximal stomas. Much will depend on their ability to limit hypotonic fluid intake. It is crucial to ensure that the patient fully understands the importance of this as it is not uncommon for patients to comply with such fluid restrictions in hospital only to take hypotonic fluids *ad libitum* when at home, resulting in rapid readmission with acute kidney injury. The clinician is often best advised to allow the patient to set a fluid regimen in hospital that they will be able to comply with in order to maintain the same at home, even if this is at the expense of a larger PN fluid volume.

Whereas hospital PN is often run over 24 h for patients with type I IF, patients generally prefer shorter infusion times at home so that they can feed overnight, allowing them to be active during the day. There is some evidence to suggest that this cyclic PN is also preferable from a metabolic viewpoint [15]. In some countries such as the UK it is traditional not to add lipid to all of the PN bags but to provide the patient's full lipid requirements in just 1–3 bags each week. Initial reasons for this were that daily lipid containing feeds were found to clog central venous catheters (and required ethanol flushes to clear). Subsequent evidence suggested that parenteral lipid is associated with hepatotoxicity, although this evidence is largely limited to the former use of soy-based 'intralipid' as the main parenteral nutrition lipid source [16]. Indeed, many patients describe symptoms of nausea and headache after receiving lipid-containing infusions, but not after aqueous bags. The mechanism of such symptoms requires further study. As a result, clinicians have attempted to reduce the lipid component of the PN. Whilst this can be achieved by providing a smaller amount of lipid on a daily basis in every PN bag, it risks physical instability and shorter shelf life of the PN mixture.

The downside of reducing the lipid content of the PN is that a higher proportion of calorie requirements are then provided by simple carbohydrate, and (especially given the pressure by patients to reduce infusion times) it is possible to exceed the body's glucose oxidation capacity. This can result in de novo lipogenesis in the liver which is associated with steatosis, inflammation and fibrosis through increased local generation of reactive oxygen species [17]. Clearly a balance needs to be achieved for each patient regarding lipid frequency and the overall PN infusion times. At the moment, the underlying cause of IFALD is not established and it is likely to be multifactorial.

Reducing the infusion time of PN needs to take place whilst still in hospital in order to confirm tolerance—particularly in the elderly or those with myocardial compromise where high fluid infusion rates may not be tolerated.

Prior to discharge on HPN, the prescription needs to be stable on a day-to-day basis but also to have proven physicochemical stability to ensure suitable shelf life for weekly or fortnightly deliveries to take place. Pharmaceutical tables of stable additive ranges now allow for this to be calculated without recourse to 'trial and error', but may limit the quanti-

ties of electrolytes or trace elements that can be provided. In practice this requires a hospital pharmacy to have the capability for 'scratch' or 'bespoke' bag compounding.

Patients need a suitable central access device for infusion of HPN. Increasingly patients are being discharged initially with 'PICC' lines (Peripherally Inserted Central venous Catheters), although these are associated with an increased risk of thrombosis and require extension sets to allow patients the ability to access them [18]. Therefore, such devices would be used only as a temporary access until a tunnelled central line can be placed. A tunnelled, cuffed CVC should be considered to be the central venous access device of choice. However, other options that can be considered are implantable ports (portacaths) and even using an arterio-venous fistulae. Some patients prefer implanted subcutaneous 'portacath' devices that require needle access. These have the advantage of permitting activities such as swimming and exercising and may be more cosmetically satisfactory—they may therefore be more popular with younger and fitter patients. However there is no evidence that infection rates are lower with such devices, they have a limited lifespan depending on how often the membrane is punctured for access and associated infections may be more severe and difficult to treat than for tunnelled central lines [19, 20]. In addition, a small number of centres preferentially use surgically created arterio-venous fistulae for PN access for their patients [21].

Before discharge on HPN patients will have to find space for a large enough refrigerator to hold the bags for weekly or fortnightly deliveries. Standard domestic specification refrigerators are inadequate as they rarely have uniform temperature distribution (bags might freeze at the back, yet be too warm at the front) or have adequate responsiveness for temperature fluctuations outside the necessary limits. They will also require dedicated space for ancillaries and for sterile connection and disconnection of their feed. Patients will need to be educated to handle the settings of their infusion pump (which may be different at home from that in hospital) and be able to know what to do in case of unexpected events such as inadvertent disconnection, refrigerator failure or pump faults. There is good evidence to suggest that patient education is able to reduce central venous catheter infection and hospital readmission rates.

In many countries, dedicated homecare nursing for feed connection and disconnection is not available and patients or their family members need to be trained in sterile procedures in order to do so themselves. This can substantially delay discharge (by an average of around 3 weeks), and economics currently dictate that where suitable community nursing support is available, patients return home with twice daily visits for connection and disconnection and are trained to manage their PN themselves whilst at home.

HPN provision is often undertaken by specialised homecare companies with dedicated compounding facilities, cold-chain delivery capability and 24 h telephone support availability for problem solving.

While this model of delivery and providing PN for use at home may be ideal, it is costly for healthcare services and requires considerable infrastructure. In some countries (e.g. Poland) the PN components are delivered to patients who are trained to mix the components together into an infusion bag and then subsequently infuse this directly. It may be viewed that the risk is higher regarding bacterial contamination but if infused immediately and a 0.2 μm filter is used on infusion (this is standard anyway) then infections may not necessarily occur. In addition, the issues relating to stability of the PN over time are much less of an issue. As less infrastructure is required, this is a cheaper way of delivering HPN.

Supporting HPS

The support of patients on HPS requires close communication between the hospital nutrition team and the homecare support team [22]. Liaison prior to discharge will co-ordinate the first delivery of feed and homecare nursing visit. One of the clear advantages of patients learning to manage their own PS at home after discharge is that there is ongoing regular (usually twice daily) contact with nursing staff who can instantly report any problems back to the hospital nutrition team or the homecare delivery team. Despite having achieved electrolyte stability prior to discharge it is often necessary to recheck blood tests shortly after the patient returns home. It is important to ensure that wherever possible patients do not become dependent on nursing support at home—for economic and logistical reasons as well as the benefits for patients in having a greater degree of freedom and confidence to manage their own PN.

When patients are able to manage their own connection and disconnection and are therefore liberated from twice daily nursing visits, they need to be confident of 24 h back up arrangements and to be aware of whom to call in case of problems arising. At this stage, the homecare delivery driver often plays a role in reporting back quantities of unused feed or ancillaries which can give the hospital team an idea of compliance with therapy and early warning of problems. Home healthcare providers have identified significant benefits in providing continuity in delivery drivers in order to foster trust with patients which provides an additional safety net of support.

As well as having an overall umbrella of care and support, the hospital nutrition team should arrange a clinic follow up appointment within the first month after discharge and thereafter at regular intervals dependent on clinical stability (Table 2).

For patients on long term HPN, in addition to regular anthropometric assessment and adjustment of feed nutrients,

Table 2 Outpatient check list with multidisciplinary team (doctor, nurse, dietitian and pharmacist)

Review and treat underlying diagnosis
Assess symptoms (e.g. diarrhoea, vomiting, abdominal pain etc.)
Assess hydration/nutrition status
Assess the vascular/enteral access and catheters/enteral tubes
Review catheter care regimen
Review wounds/stomas
Check for complications (e.g. CRBSI, thrombosis, liver, bone or kidney disease)
Assess surgical plans (if any) and bowel mapping status
Review deliveries and storage of equipment, ancillaries and feed
Review medications and PN prescription, consider stopping/changing HPS (e.g. nights off feed)
Assess the goals of the nutritional support
Consideration of transplantation/links to other units or services
Review the psychological state, coping mechanisms, ways of improving the quality of life
Put information onto local or national register (eBANS in UK)

monitoring from the hospital clinic should include a baseline bone density scan and liver ultrasound (to determine the presence or absence of gallbladder and stones, liver texture and degree of steatosis), and intermittent measurement of micronutrients and trace elements.

Renal and liver function tests should be performed regularly as well as checking magnesium, zinc, haematinics (B_{12}, folate, ferritin/iron studies) and vitamins (vitamins A, D, E are the most easily measured). A lipid profile is valuable occasionally to ensure that triglycerides are adequately cleared from the circulation. A CRP should also be checked at the same time and measuring a spot urinary sodium concentration can be helpful to assess hydration status. Generally patients are followed up every 3–4 months, depending on their stability ("Monitoring of Parenteral Nutrition at Home" chapter). However a survey from the ESPEN-HAN working group in 2008 showed that there was considerable variability in the follow-up frequency and the type of blood tests performed for these patients [23].

Manganese accumulation and subsequent neurotoxicity is a rare complication in this patient group. It is excreted in bile (and a degree of cholestasis is not uncommon with HPN), and the quantity present in proprietary trace element admixtures was previously excess to requirements. It is also sensible to optimise selenium and iron quantities in the PN according to blood measurements.

Voluntary patient advocacy groups such as PINNT (Patients on Intravenous and Nasogastric Nutrition Therapy) [24] in the UK and the Oley Foundation in the USA [25] are a key element to supporting patients on HPN. They can provide shared experiences and open up routes of communications for new patients on HPN to talk to others with experience of living with the condition, as well as useful practical advice and tips on aspects such as travelling and insurance.

Living with HPS

The impairment of quality of life on HPN should not be underestimated by clinicians. Although many patients adapt their lifestyles extremely well to manage the burdens of their chronic condition and treatment, many experience ongoing and long term difficulties. The ability to adjust will depend on the prior illness experiences of the patient, their stage in life and expectations, and the degree of family and community support available. Tragically, many patients with short bowel syndrome are young, previously fit and well and experience a sudden catastrophic mesenteric vascular insult that results in a high output proximal stoma and the need for life long HPN. Many will have ongoing symptoms such as thirst, hunger, pain, nausea and vomiting as well as a high stoma output risking dehydration and acute kidney injury and socially embarrassing noise and leakage from the stoma itself. Some patients will have additional gastric venting tubes or enteral feeding tubes to cope with as well. These will have profound psychological consequences and affect physical intimacy with partners and their relationships.

On top of these issues are the need for central venous access which may be visible to others and can limit physical activities, and poses a worry of infection. Overnight parenteral nutrition can lead to disturbed sleep, waking with pump alarms (occlusion or air in the line), and nocturnal polyuria due to the altered diurnal fluid delivery.

Social consequences also include mealtime embarrassment and exclusion, especially if patients are unable to eat, the need to take large amounts of paraphernalia with them when away or visiting friends restricting travel and holidays. Medical insurance cover can be problematic, and security arrangements at airports and borders need to be addressed given the excess baggage and fluid requirements. Often the patient advocacy groups are best placed to advise patients of these issues and also they often have information relating to holiday insurance as well that is helpful to patients.

Tools have recently been developed to attempt to quantify the quality of life impact on patients needing HPN—the HPNQOL [26] and the PNIQ (Parenteral Nutrition Impact Questionnaire) [27]. Surveys generally show a significant detriment to quality of life [28] that tends to improve over time, but is affected markedly by the age of onset and nature of the underlying disease and the number of nights over which HPN is required. Patient-related outcome measures (PROM) may be the best approach and the PNIQ was developed on that basis. However, more studies are required using this tool to see if it is effective.

Complications of HPS

Many complications of long-term parenteral nutrition are consequent to its non-physiological route of delivery that bypasses enteroendocrine regulation of metabolism and gut function (Table 3). These can aggravate or be difficult to separate from the effects of intestinal resection in those with a short bowel [29]. Such metabolic complications include the lack of co-ordinated incretin stimulation of insulin secretion to match intravenous carbohydrate delivery, and altered levels of other gut hormones such as oxyntomodulin and ghrelin which influence glucose and lipid metabolism and regulation of energy intake. Gastrointestinal effects of reduced oral intake include cholestasis and high risks of gallstone formation due to lack of cholecystokinin secretion. This is exacerbated by interruption of the enterohepatic cycle and altered bile acid pool. Impaired epithelial barrier integrity and reduced villus height result from a lack of luminal nutrients and consequent reduced secretion of GLP-1 which has trophic effects on the mucosa. Malabsorption may be increased by rapid intestinal transit due to reduced secretion of PYY, GIP and GLP1 from distal intestine or colon that act to slow motility. Patients with short lengths of residual intestine are prone to overabsorption of oxalic acid from the colon—thought to be due to preferential complexing of divalent cations with malabsorbed free fatty acids—and lead to renal calculus formation.

The composition of PN compromises the physiological form of the nutrients in order to provide physico-chemical stability in a complete mixture. The lipid component in particular has been problematic in view of its delivery as lipid micelles rather than chylomicrons. Initial formulations required a high phospholipid:triglyceride ratio for emulsification and led to phospholipid accumulation in the reticulo-endothelial system. Abnormal lipid accumulation in the reticulo-endothelial system can also rarely result in 'sea blue histiocytosis' syndrome causing hepatosplenomegaly, thrombocytopaenia and bleeding [30]. Original soy-based lipid formulations contained significant amounts of phytosterol and contributed to intrahepatic cholestasis and steatosis by direct inhibition of the liver Farnesoid X receptor [31]. Delivery of >1 g/kg/day of soy-based lipid emulsion has been identified as a risk factor for advanced IFALD [16]. Newer lipid preparations with a higher omega 3:6 fatty acid appear to be better tolerated and metabolised and can reverse cholestasis associated with soy-based lipid [32]. Hepatotoxicity is still probable although the effects of the PN and the underlying cause of intestinal failure are difficult to dissociate—the increased risk of IFALD associated with 'ultrashort' intestine (<20 cm to stoma) may be due to the anatomy or the associated need for more calories to be delivered intravenously [33].

Metabolic complications of HPN also relate to the inflexibility of a fixed composition of the feed unregulated by enteroendocrine signals that affect not only overall energy intake through satiety and hunger regulation but can also alter the volitional intake of specific nutrients under normal physiological circumstances. There is therefore little opportunity with HPN for 'fine-tuning' nutrient intake, absorption and disposition on a day-to-day basis. As a result, nutrient deficiencies and/or excesses may occur. Impaired salt and fluid balance can lead to fluid overload, fatigue, or acute or chronic kidney

Table 3 Complications of HPN

Complication	Related to	Mechanism	Frequency
Sepsis	Catheter care, gut disease	Catheter related blood stream infection (CRBSI)	CRBSI 0.35–2.27/1000 catheter days
Thrombosis/stenosis	Catheter tip position, PN composition, coagulation abnormalities	Vein damage, high osmolality solution	0.027–0.082/1000 catheter days
Gallstones	Pigment gallstones	Gallbladder stasis, biliary sludge	38% at 20 years of HPN, 76% of these have complications
IFALD	Sepsis, drug therapy, pre-existing liver disease or PN composition	Excess macronutrients, copper or manganese; deficiency of choline, taurine, carnitine, essential fatty acids	Variable frequency 15–40% May be more common if ultrashort bowel 3–26% of deaths on PN
Renal impairment	High gut fluid losses, sepsis, medication	Dehydration, repeated kidney injury, excess oxalate absorption, CRBSI related glomerulonephritis	eGFR <60 mL/min—15% at 5 years
Osteoporosis	Young when starting PN, low BMI, underlying disease	Chronic high acid load, vit D and K deficiency, reduced physical activity, low sunlight exposure, smoking/alcohol, chronic inflammation and medication	Osteopenia occurs in 13–57%, osteoporosis in 18–44% of long-term HPN patients
Anaemia	PN composition, disease, remaining gut anatomy	Inadequate iron, folate, B12 or copper	Common
Reticulo-endothelial dysfunction	Gut absorption and PN composition	Phospholipidosis "Sea-blue histiocytosis"	Rare
Neurological dysfunction	Gut absorption and PN composition	Manganese toxicity; thiamine or B12 deficiency	Rare

injury. The aetiology of muscle 'cramps' is poorly understood but this is the commonest symptomatic complaint of patients receiving HPN and is thought to relate to membrane electrolyte imbalance. Magnesium and calcium deficiency can lead to painful muscle spasm and tetany. Trace elements are often required as the catalytic centres of enzymes or to form tertiary protein structures—zinc for instance is required in over 10% of human proteins and deficiency can profoundly affect protein synthesis. Copper deficiency can result in microcytic anaemia resembling that of iron deficiency, and copper has previously been shown to precipitate with some amino acid mixtures used in PN [34]. Excess manganese can result in neurotoxicity through basal ganglia deposition [35]. Selenium is required in glutathione oxidase and is fundamental for redox balance—deficiency is not uncommon in HPN patients.

Vitamins are also provided in PN, with the usual exception of Vitamin K which might interfere with attempts to therapeutically anticoagulate. In some patients with a short bowel who require warfarin anticoagulation, vitamin K deficiency can be a difficult problem to overcome. As fat soluble vitamins can now be provided in a form that is miscible with aqueous solution, the removal of lipid from HPN formulations is less likely to result in their deficiency. However, vitamin D deficiency is common in HPN patients, particularly those with significant fat malabsorption, likely due to interruption of the enterohepatic cycle. Bone density can be adversely affected, leading to osteoporotic vertebral and long bone fractures and skeletal deformity. However, metabolic bone disease in patients receiving HPN is undoubtedly multifactorial and not solely related to vitamin D deficiency [18]. Aluminium toxicity was previously implicated due to high levels found in casein hydrolysates and has been prevented by using alternative amino acid sources. The optimal PN solution pH of 5–5.5 (that maintains calcium phosphate in solution, prevents lipid micellar aggregation and prevents toxic Maillard reactions between glucose and amino acids) may also contribute a significant renal acid load. Whilst not demonstrating overt metabolic acidosis this could lead in the chronic state to buffering through bone loss [36].

Remaining complications of HPS relate to the need for central venous access that provides a potential portal for bacterial and fungal bloodstream infection ("Prevention, Diagnosis and Management of Catheter-Related Blood Stream Infections" chapter), and can be compromised by thrombosis or stenosis of large veins up to and including the vena cava ("Central Vein Thrombosis" chapter). As well as threatening future access for PN, the latter can lead to venous hypertension in the draining territories with resulting facial swelling and headaches (from intrathoracic vein occlusions) or resistant peripheral oedema of the legs. Large collateral vein formation can present a surgical hazard, and reduced rates of venous return can affect cardiac and renal physiological responses.

Changes in HPS Provision over Time

Since the introduction of HPN as a possibility for selected patients in the 1980s, there have been considerable advances in the equipment and homecare service that have occurred over time, to the benefit of patients. Regarding equipment, previously the pumps were large, noisy and had to be connected to the mains electricity supply, now they are much smaller, portable and able to run on batteries. In addition, the PN infusion needed to be attached to a drip stand at home, which was cumbersome but now the whole system (PN infusion and pump) will usually fit into a backpack that can be carried or pulled on wheels, making this much more convenient at home or when travelling. Regarding the tunnelled CVCs, these were initially placed surgically by cut-down into the subclavian vein and the method used (with a purse string to secure) usually resulted in loss of the vein once the CVC was removed. Now a minimal access approach means that the CVCs can be placed under local anaesthetic with or without sedation. The jugular veins are preferably used as well as there are fewer complications that occur when using this approach (e.g. pneumothorax). These minimally invasive techniques mean that central venous access is maintained for longer. Also, the homecare service has developed over time in many countries, allowing more patients with comorbidities to receive HPN safely, with a specialist nursing service allowing patients to receive HPN who are not able to do the connections and disconnections themselves. Finally, with the digital revolution it is becoming possible for data relating to the infusions (volume, time, pump infusion pressures) to be collected securely on a platform that may enable the early detection of complications [37].

A large single centre survey over a period of 36 years has demonstrated that since the 1980s, the mean age of patients receiving home parenteral support increased from an average of 31 to 52 years [38]. In addition, the percentage of patients receiving home parenteral support due to surgical complications increased (3.4–28.8%). This clearly demonstrates that older patients with more comorbidities are being offered home parental support. While this has affected long-term survival when analysed by era, overall life expectancy remains good (55% 10 year survival for non-malignant aetiologies). In addition, the frequency of complications for patients on home parenteral support has been reducing over the last 30 years (catheter-related bloodstream infections [71% to 42%], CVC thrombosis [36% to 5%] and IFALD [10% to 2%]) [38, 39].

Life Expectancy on HPN

Sustenance by parenteral nutrition can provide long term survival in patients who would otherwise succumb rapidly to the nutritional and hydrational depletion of intestinal failure. The wide heterogeneity of underlying causes of intestinal failure, patient ages and comorbidities make unselected mortality figures difficult to interpret. However, it is clear that the majority of deaths of patients on HPN result from the underlying disease rather than complications of the HPN itself.

Unselected survival data demonstrate a 1 year survival of 86–95%, a 5 year survival of 66–82% and a 10 year survival of 55–71% [39–43]. Outcomes depend on age (better when young) and underlying disease (better with Crohn's disease or pseudo-obstruction than other causes of intestinal failure) (Table 4). HPN related complications are responsible for 13–22% of deaths with approximately equal proportions due to liver disease and catheter related bloodstream infection. Nearly two thirds of deaths occur within 2.5 years of commencing HPN [40]. Some studies have demonstrated an inverse association of survival with length of residual intestine for patients with short bowel [43–45], whereas others have not [42] although in the latter case survival was shorter in those with a stoma compared to those without.

Evolving Considerations in HPS

With increasing ease of establishing patients on HPS in the community, and the possibility of educating and training patients in their own homes rather than in the hospital, the use of HPS has increased significantly over recent years. This is reflected in the number of patients receiving HPS and also the nature of the indications. As a result new challenges are emerging:

Use of HPN in advanced malignancy It was previously impractical to consider using HPN for patients with advanced malignancy (even if there was no other route of nutrition available) as patients required prolonged admissions for HPN establishment. With limited life expectancy this would mean spending a large proportion of their remaining time in hospital. Homecare nursing and HPN training at home have now facilitated early discharges, and this allows the possibility of feeding such patients parenterally at home. The downsides of HPN remain, as described above, and may further impair quality of life which is already adversely affected by the underlying disease. There is also very limited evidence to suggest that life is prolonged by HPN at all even in the presence of complete bowel obstruction [46]. However palliative benefits include maintenance of performance status and the energy and wellbeing to allow patients even in the last weeks of life to put their affairs in order and adjust to their situation. Nutrition support may also empower patients to make decisions regarding their end of life, including choosing the time of stopping PN. The balance of benefits and burdens of HPN is therefore highly individual and needs careful consideration by an experienced multi-professional team and a well informed and supported patient [47].

As the key aim of HPN in this setting is to preserve quality rather than length of life, it follows that patients with good performance status at initiation are most likely to benefit. This is unusual in patients with advanced malignancy and therefore by using this as a selection criterion, the number of potential candidates for HPN is small. It is most often used in the setting of malignant bowel obstruction. Ovarian cancer and appendiceal or colonic tumours causing 'pseudomyxoma peritonei' [48] can be associated with a survival of many months or even some years despite widespread peritoneal metastasis. Such patients may outlive many who are commenced on HPN for 'benign' indications demonstrating that decisions made on this distinction are artificial and potentially discriminatory. Prognosis nomograms have been

Table 4 Percentage survival on HPN based upon IF aetiology from St Mark's Hospital [39]

		Percentage survival (%)						
Aetiology	Number of patients	1 year	5 years	10 years	15 years	20 years	30 years	35 years
Surgical complications	244	83	65	50	50	18	–	–
Crohn's/IBD	242	95	77	68	52	30	15	15
Malignancy	62	33	0	–	–	–	–	–
Mesenteric infarction	183	88	61	46	43	35	29	–
Intestinal dysmotility	93	92	79	70	60	45	45	–
Radiation enteropathy	53	80	28	18	9	9	–	–
Volvulus	15	71	71	71	71	71	71	–
Scleroderma	21	80	52	33	17	–	–	–
Congenital	10	100	88	88	88	88	88	–

developed in order to aid appropriate patient selection [49], but unfortunately these have not been adequately validated. Needless to say, more data is required on the outcomes of patients with advanced malignancy started on HPN.

HPS in the elderly and with additional organ dysfunction With the possibility of long-term survival, some patients started on HPS may reach old age and have to cope with its associated burden of accrued co-morbidity. The ability to provide HPS in care home settings also allows the possibility of offering it to more elderly patients. This brings additional challenges as older patients may lose the ability to manage their own infusions, to comply with fluid restriction and medications (which may be poorly absorbed due to the underlying intestinal failure) and require more nursing assistance. However, it is the advent of additional organ dysfunction that most complicates the use of HPS in the elderly.

Loss of cardiac reserve makes fluid and salt balance more precarious with an increasingly narrow therapeutic window between fluid overload and inadequate renal perfusion. The duration of PS infusion may need to be increased as well as reducing the volume or sodium content in order to compensate. It is unclear whether there are additional benefits of central veno-dilatation by using loop diuretics in this circumstance.

Renal failure may also compound fluid and electrolyte balance in patients with HPS and increase the risk of complications such as osteoporosis due to acidosis. Maintenance of renal perfusion may be challenging and the long term effects of significant central volume depletion during the day with restoration by overnight PS infusion are unclear. However, in patients with high stoma or fistula losses the omission of even one infusion due to mechanical line or pump issues may result in acute kidney injury. Repeated such insults can lead to permanent renal failure. Additional risks to the kidney in HPS patients arise from CRBSI sepsis causing hypoperfusion or infection related glomerulonephritis.

Venous access may be severely limited for haemodialysis, and the lifestyle detriment of requiring two separate intravenous organ support modalities may be unacceptable. Volume management may be challenging and even require daily dialysis to remove excess fluid in those who do not have high volume stoma losses (which can be unexpectedly advantageous). The outcomes of renal transplantation in patients requiring HPN are not reported but this scenario usually leads to consideration of a combined intestine and kidney graft when feasible.

Similarly, the effect of long term HPS after liver transplantation is still unclear, and is again usually avoided by the use of a combined graft. Where isolated liver transplantation has been used in this setting it is usually in children who are likely to wean from HPS in the near future, but sequential liver and intestinal grafts have been undertaken.

HPN and diabetes The carbohydrate load of HPN may result in hyperglycaemia in patients with impaired glucose tolerance or overt diabetes, and can be difficult to manage. Oral hypoglycaemics may be contra-indicated or poorly absorbed in patients with intestinal failure. Rebound hypoglycaemia after stopping the PN infusion may require a slow 'ramp down' rather than sudden cessation. With overnight infusion there is a risk of uncontrolled hyperglycaemia and the use of insulin as a bolus regimen with corrective doses may risk hypoglycaemia or further nocturnal disturbances for blood sugar monitoring. Currently, glycaemic control is either achieved through subcutaneous basal-bolus insulin regimens or the addition of insulin to the PN solution. By combining insulin with the PN, the risk of unopposed insulin (for instance with unexpected PN pump failure) is mitigated. Although used in this way routinely in some countries such as the USA, there is still reluctance to do so in others due to the potential for incomplete mixing or insulin adsorption to the container and giving set [50]. In the future, the use of continuous glucose monitoring devices and closed loop algorithms for subcutaneous insulin infusion devices will significantly improve the safety of HPN in diabetics.

HPS in performance athletes With the growth of paralympic sports there are now athletes who are dependent on HPS who wish to compete in endurance sports [51]. This highlights the problems associated with the inflexibility of day-to-day variation in requirements, particularly with regard to fluid and sodium intake due to excessive loss in sweat and breath rather than the gastrointestinal tract. There is also the desire to alter body composition and provide suitable amino acid sources for muscle building. Experience in this area is currently limited. In our practice we meet the requirements through a complex additional PN bag regimen that can be provided for the athlete's use on training days and infused over a short time course after the exercise.

Failure of HPS

HPS can be considered to have failed when central venous access is no longer achievable, when it is associated with life threatening CRBSI or organ dysfunction (such as IFALD or renal failure), or when it becomes unmanageable due to gastrointestinal fluid losses or unacceptable quality of life. In these situations intestinal transplantation with or without

other organs (liver, stomach, pancreas, colon) can be considered.

The indications and optimal timing of intestinal transplantation have changed considerably due to significantly improved outcomes and greater experience of the management of such patients with and without transplantation. Complete loss of vascular access is rare and new techniques for recanalization and stenting have improved access for central venous catheters—however it is currently unclear how sustainable these are for the long term and at present such measures may be seen as merely providing the temporary central access required for the transplant operation to go ahead.

Recent evidence of improvement in IFALD related hepatic fibrosis after isolated intestinal transplantation has driven a move towards 'pre-emptive' intestinal transplantation. Around 90% of patients in our unit currently survive 5 years or more after isolated intestinal transplant in this setting compared to less than 40% in whom a liver containing graft is required due to advanced IFALD [52]. Early detection of IFALD therefore leads to better post-transplant outcomes and more appropriate allocation of donor livers that are in short supply. Unfortunately, ultrasound elastography ('fibroscan') and liver blood tests have proven to be unreliable tools for the detection and assessment of IFALD and liver biopsy is currently still required. Given the rapidity with which advanced liver disease can develop in patients with 'ultra-short' intestine (less than 20 cm to a stoma), many now consider that sub-total enterectomy should be followed by intestinal transplantation as soon as feasible and before the development of complications. This is supported by a European study of patients on long-term HPN which demonstrated that IFALD and desmoid tumours threatening the mesenteric vasculature (requiring major intestinal resection) were at that time the only two 'standard' indications that could potentially achieve better outcomes after transplantation than without [53]. Transplantation purely for quality-of-life indications remains a disputed indication as the issues that affect quality-of-life change once a transplant has been performed. The benefit of stopping PN support may be adversely affected by the presence of a stoma, fear of rejection or other factors.

The Future of HPS

HPS use will undoubtedly continue to evolve with improved safety and quality as national services become more organised, along with advances in the establishment and maintenance of central venous access and improvements in composition (particularly the lipid component). Financial and logistical (for instance nursing support) constraints are likely to limit the expansion of HPN provisions even in wealthy countries. However, the outcomes of isolated intestinal transplantation are already excellent and with continued improvement it is likely that it will begin to supplant long-term HPS in suitable candidates as it more cost effective and has the ability to improve quality of life. Further and ongoing systematic study of the symptoms of intestinal failure and the burdens of HPS in comparison with intestinal transplantation will be required.

References

1. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery. 1968;64(1):134–42.
2. Scribner BH, Cole JJ, Christopher TG. Long-term parenteral nutrition; the concept of an artificial gut. JAMA. 1970;212:457–63.
3. Shils ME, Wright WL, Turnbull A, Brescia F. Long term parenteral nutrition through external arteriovenous shunt. N Engl J Med. 1970;283:341–3.
4. Shaffer J. Intestinal failure: definition and service development. Clin Nutr. 2002;21(Suppl 1):144–5.
5. Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34(2):171–80.
6. Canovai E, Ceulemans LJ, Peers G, et al. Cost analysis of chronic intestinal failure. Clin Nutr. 2019;38(4):1729–36.
7. Arhip L, García-Peris P, Romero RM, et al. Direct costs of a home parenteral nutrition programme. Clin Nutr. 2019;38(4):1945–51.
8. Glencorse C, Meadows N, Holden C. Trends in artificial nutrition support in the UK from 1996–2002. A BAPEN BANS report. 2003. https://www.bapen.org.uk/pdfs/exec_summ9602.pdf.
9. Smith T, Naghibi M. Artificial nutrition support in the UK 2005–2015. Adult home parenteral nutrition and intravenous fluids. 2016. https://www.bapen.org.uk/images/pdfs/reports/bans-report-2016.pdf.
10. Wanden-Berghe C, Luengo LM, Álvarez J, et al. Spanish home enteral nutrition registry of the year 2014 and 2015 from the NADYA-SENPE Group. Nutr Hosp. 2017;34(1):15–8.
11. Mundi MS, Pattinson A, McMahon MT, Davidson J, Hurt RT. Prevalence of home parenteral and enteral nutrition in the United States. Nutr Clin Pract. 2017;32:799–805.
12. Hortencio TDR, Arendt BM, Teterina A, et al. Changes in home parenteral nutrition practice based on the Canadian Home Parenteral Nutrition Patient Registry. JPEN J Parenter Enteral Nutr. 2017;41(5):830–6.
13. Davila J, Konrad D. Metabolic complications of home parenteral nutrition. Nutr Clin Pract. 2017;32(6):753–68.
14. Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term parenteral nutrition. Aliment Pharmacol Ther. 2013;37(6):587–603.
15. Stout SM, Cober MP. Metabolic effects of cyclic parenteral nutrition infusion in adults and children. Nutr Clin Pract. 2010;25(3):277–81.

16. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med. 2000;132(7):525–32.
17. Ito K, Hao L, Wray AE, Ross AC. Lipid emulsion administered intravenously or orally attenuates triglyceride accumulation and expression of inflammatory markers in the liver of nonobese mice fed parenteral nutrition formula. J Nutr. 2013;143(3):253–9.
18. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35(2):247–307.
19. Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN guidelines on parenteral nutrition: central venous catheters (access, care, diagnosis and therapy of complications). Clin Nutr. 2009;28:365–77.
20. Kovacevich DS, Corrigan M, Ross VM, McKeever L, Hall AM, Braunschweig C. American Society for Parenteral and Enteral Nutrition Guidelines for the selection and care of central venous access devices for adult home parenteral nutrition administration. JPEN J Parenter Enteral Nutr. 2019;43(1):15–31.
21. Versleijen MW, Huisman-de Waal GJ, Kock MC, Elferink AJ, van Rossum LG, Feuth T, Willems MC, Jansen JB, Wanten GJ. Arteriovenous fistulae as an alternative to central venous catheters for delivery of long-term home parenteral nutrition. Gastroenterology. 2009;136(5):1577–84.
22. Kumpf VJ. Challenges and obstacles of long-term home parenteral nutrition. Nutr Clin Pract. 2019;34(2):196–203.
23. Wengler A, et al. Monitoring of patients on home parenteral nutrition (HPN) in Europe: a questionnaire based study on monitoring practice in 42 centres. Clin Nutr. 2006;25(4):693–700.
24. PINNT. https://pinnt.com/Home.aspx.
25. OLEY Foundation. https://oley.org/default.aspx.
26. Baxter JP, Fayers PM, McKinlay AW. The clinical and psychometric validation of a questionnaire to assess the quality of life of adult patients treated with long-term parenteral nutrition. JPEN J Parenter Enteral Nutr. 2010;34(2):131–42.
27. Burden ST, Jones DJ, Gittins M, et al. Needs-based quality of life in adults dependent on home parenteral nutrition. Clin Nutr. 2019;38(3):1433–8.
28. Jeppesen PB, Langholz E, Mortensen PB. Quality of life in patients receiving home parenteral nutrition. Gut. 1999;44(6):844–52.
29. Bielawska B, Allard JP. Parenteral nutrition and intestinal failure. Nutrients. 2017;9(5):466–80.
30. Bigorgne C, Le Tourneau A, Messing B, et al. Sea-blue histiocyte syndrome in bone marrow secondary to total parenteral nutrition including fat-emulsion sources: a clinicopathologic study of seven cases. Br J Haematol. 1996;95(2):258–62.
31. Carter BA, Taylor OA, Prendergast DR, et al. Stigmasterol, a soy lipid-derived phytosterol, is an antagonist of the bile acid nuclear receptor FXR. Pediatr Res. 2007;62(3):301–6.
32. Nandivada P, Fell GL, Gura KM, Puder M. Lipid emulsions in the treatment and prevention of parenteral nutrition-associated liver disease in infants and children. Am J Clin Nutr. 2016;103(2):629S–34S.
33. Cazals-Hatem D, Billiauws L, Rautou PE, et al. Ultra-short bowel is an independent risk factor for liver fibrosis in adults with home parenteral nutrition. Liver Int. 2018;38:174–82.
34. Cochran EB, Boehm KA. Prefilter and postfilter cysteine/cystine and copper concentrations in pediatric parenteral nutrition solutions. JPEN J Parenter Enteral Nutr. 1992;16(5):460–3.
35. Jin J, Saqui O, Allard JP. Effect of discontinuation of manganese supplementation from home parenteral nutrition solutions on whole-blood levels and magnetic resonance imaging of the brain: a 5-year cohort study. JPEN J Parenter Enteral Nutr. 2018;42(1):164–70.
36. Iacone R, Scanzano C, D'Isanto A, Vitalone A, Frangipane I, D'Angeli M, Santarpia L, Contaldo F. Prediction of renal acid load in adult patients on parenteral nutrition. Pharmaceutics. 2018;10(2):E43.
37. Gabe SM, Small M, Kallis M, Tsoukalis A, Cascailh JC. Pump infusion pressures in patients on long term parenteral nutrition: a novel approach and monitoring technique to anticipate catheter occlusion. Clin Nutr. 2015;10(5):E182–3.
38. Oke S, Gabe SM. Changes in aetiology of type 3 intestinal failure over 36 years a single center experience. Transplantation. 2017;101:S16.
39. Oke SM, Nightingale JM, Donnelly SC, Naghibi M, Willsmore J, Lloyd DAJ, Gabe SM. Outcome of adult patients receiving parenteral support at home: 36 years' experience at a tertiary referral Centre. Clin Nutr. 2021;40(11):5639–47.
40. Joly F, Baxter J, Staun M, et al. ESPEN HAN CIF group. Five-year survival and causes of death in patients on home parenteral nutrition for severe chronic and benign intestinal failure. Clin Nutr. 2018;37(4):1415–22.
41. Lloyd DA, Vega R, Bassett P, Forbes A, Gabe SM. Survival and dependence on home parenteral nutrition: experience over a 25-year period in a UK referral Centre. Aliment Pharmacol Ther. 2006;24(8):1231–40.
42. Dibb M, Soop M, Teubner A, Shaffer J, Abraham A, Carlson G, Lal S. Survival and nutritional dependence on home parenteral nutrition: three decades of experience from a single referral centre. Clin Nutr. 2017;36(2):570–6.
43. Vantini I, Benini L, Bonfante F, et al. Survival rate and prognostic factors in patients with intestinal failure. Dig Liver Dis. 2004;36:46–55.
44. Wu G, Jiang Y, Zhu X, et al. Prevalence and risk factors for complications in adult patients with short bowel syndrome receiving long-term parenteral nutrition. Asia Pac J Clin Nutr. 2017;26(4):591–7.
45. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long term survival and parenteral nutrition dependence in adult patients with the short-bowel syndrome. Gastroenterology. 1999;117:1043–50.
46. Cotogni P, De Carli L, Passera R, et al. Longitudinal study of quality of life in advanced cancer patients on home parenteral nutrition. Cancer Med. 2017;6(7):1799–806.
47. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11–48.
48. Disney BR, Karthikeyakurup A, Ratcliffe J, et al. Palliative parenteral nutrition use in patients with intestinal failure as a consequence of advanced pseudomyxoma peritonei: a case series. Eur J Clin Nutr. 2015;69(8):966–8.
49. Bozzetti F, et al. Development and validation of a nomogram to predict survival in incurable cachectic cancer patients on home parenteral nutrition. Ann Oncol. 2015;26(11):2335–40.
50. McCulloch A, Bansiya V, Woodward JM. Long term addition of insulin to home parenteral nutrition for the control of hyperglycaemia. Clin Nutr ESPEN. 2019;30:204–7. https://doi.org/10.1016/j.clnesp.2018.11.014.
51. Tillman EM, Opilla M. Considerations for fueling an endurance athlete with home parenteral nutrition. Nutr Clin Pract. 2017;32(6):782–8.
52. Woodward JM, Massey D, Sharkey L. The long and short of IT. Intestinal failure associated liver disease (IFALD) in adults. Recommendations for early diagnosis and intestinal transplantation. Frontline Gastroenterol. 2019;11:34–9.
53. Pironi L, Joly F, Forbes A, et al. Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. Gut. 2011;60(1):17–25.

Home Enteral and Parenteral Support for Children

Theodoric Wong and Gabriela Jiménez-Arguedas

Key Points

1. Dietary foods for special medical purposes are classified into three categories: nutritionally complete foods with standard nutrient formulation, nutritionally complete foods with a nutrient-adapted formulation specific for a disease, and nutritionally incomplete foods.
2. EN is indicated when energy and nutrient requirements cannot be met by regular food intake in a patient with at least a partially functional gut.
3. Fifty percent of patients receiving home enteral nutrition (HEN) have neurological or genetic reasons and about 25% have digestive diseases.
4. There are three types of patient with IF needing PN. Type 1 have a loss of intestinal function for less than 2 weeks (e.g. acute gastroenteritis or post operative ileus); type 2 for less than 28 days (e.g. intestinal atresia or uncomplicated gastroschisis), and type 3 long term.
5. Reasons for HPN include necrotising enterocolitis (NEC), atresia, intestinal resection/short bowel syndrome as well as enteropathies (e.g. tufting enteropathy and microvillous inclusion disease).
6. Survival of patients receiving HPN has steadily improved from around 50% in the early 1990s to 90% in 2008–2013.

Home Enteral Nutrition

Definition of Enteral Nutrition

The term EN in paediatrics is often recognized as referring to liquid feeds (e.g. formulas). Currently, dietary foods for special medical purposes as defined by the European legal regulation directive 1999/21/EC of March 1999 [1] is classified into three categories: (a) nutritionally complete foods with standard nutrient formulation, (b) nutritionally complete foods with a nutrient-adapted formulation specific for a disease and (c) nutritionally incomplete foods. EN can be encompassed by all three of these categories.

Prevalence of HEN

The use of home enteral nutrition varies across the world. This is due to availability of enteral equipment (e.g. feeds, tubes, pumps and syringes), trained community support and access to regular reviews by clinicians. The lack of consensus in HEN eligibility criteria has meant that reported data are not comparable. However, the general trend has been an increase in the use of HEN in developed countries (Table 1). The prevalence varies between 1.4 per 100,000 to 69.5 per 100,000 [2, 3]. These studies have large time gaps between them, geographic as well as patient demographic differences making them difficult to compare.

Indications and Considerations for HEN

EN is indicated when energy and nutrient requirements cannot be met by regular food intake in a patient with at least a partially functional gut. Every possible effort should be made to ensure that those patients who have no mechanical

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Table 1 Showing the comparison of the prevalence of HEN in different countries

Country	Total/prevalence of HEN	Reference	Date completed	Age group
New Zealand	Total: 630 69.5 per 100,000	Jelleyman 2013	2013	<15 years
Spain	Total: 529	Gomez-Lopez 2010	2007	Paediatric
Poland	Total 525 1.375 per 100,000	Szlagatys-Sudorkiewicz 2012	2010	Paediatric
United Kingdom	Total: 1336	BANS 2011	2010	<16 years
	7.9 per 100,000	Pironi 2007	2003	<16 years
Italy	3.47 per 100,000	Diamanti 2013	2009	0–18 years
	0.84 per 100,000	Pironi 2007	2005	<18 years

Table 2 Examples of aetiology of HEN patients

Insufficient oral intake
Oral motor immaturity or dysfunction
Neurologic impairment
Maldigestion and malabsorption
Type II/III intestinal failure including short bowel syndrome
Cystic fibrosis
Inflammatory bowel disease
Chronic liver disease
Increased nutritional requirements
Cyanotic heart disease
Burns
Metabolic diseases

issues be fed orally where possible and have any psychological barriers are looked at and managed accordingly.

There is no strict consensus as to when HEN would be indicated. Generally speaking, this is determined by (a) anticipated length on EN, (b) financial considerations of provision of EN and (c) ability of family/community support for EN. This decision should ideally be made at the start of starting enteral nutrition and not in an unanticipated fashion.

Setting goals such as target weight, target volume, target calories or resolution of symptoms (e.g. lack of diarrhoea or vomiting) will allow healthcare professionals and patient/families to know what to expect over a particular timeframe.

Clinicians have mainly used clinical judgement when deciding whether a patient requires HEN. That is usually patients with insufficient oral intake and those who present with wasting and stunting [4, 5]. There are also patient groups who, due to their medical diagnoses, are more likely to require HEN than others (e.g. patients with neurological disorders, feeding disorders and intestinal failure) (Table 2). In one study, about 50% of patients on HEN have neurological or genetic reasons and about 25% were due to digestive diseases [3].

Enteral Access Devices

Enteral access devices such as nasogastric tubes (NGT) has had a long history and were first described by Hunter in 1790 [6]. The selection of an enteral access device is an important step and requires evaluation of the following [7]:

- patient's disease.
- past surgeries and current anatomy.
- gastric and intestinal motility and function.
- intended length of therapy.

Normal gastric emptying with no obstruction or fistula is required for a gastric placed enteral access device. Direct small bowel feeding maybe appropriate for patients with gastric outlet obstruction, gastroparesis and in those with known gastro-oesophageal reflux disease (GORD) and aspiration of gastric contents.

Nasoenteral Tubes/Devices

Although the tubes/devices are often described according to access point and/or entry point in the gastrointestinal tract, their only difference is the material, the length (cm) and the diameter (Fr sizes) of the tube/device. The materials can be polyvinyl chloride (PVC), silicone or polyurethane. PVC tubes use are generally short term (3–5 days) whilst the silicone/ polyurethane tubes/devices can be used for up to 8–12 weeks. The length of the tube/device should be selected according to the age of the patient and anatomy so that the access point (stomach or jejunum) can be reached. The diameter of the tube should be selected also according to the age and size of the nasal passage (if this is the route of entry).

Methods for tube insertion are detailed elsewhere [8] but all tubes/devices should be inserted only by trained staff or caregivers because of the risk of misplacement and oesophageal or pulmonary perforation [4]. Confirming the position of the NG tube is essential not only on insertion but also on subsequent use. Radiology is the recommended method but has the drawback of radiation exposure. Other methods of confirmation of placement such as pH of aspirates or auscultation for "bubbling," when air is flushed down the tube are unreliable [4, 9].

There are a number of methods that can be employed for the placement of nasojejunal tubes. They include a "blind" bedside insertion with the use of a prokinetic agent such as metoclopramide or erythromycin, use of weighted/magnetic tubes [10], string tie on the end of the tube, fluoroscopic and endoscopic placement. Despite the use of these techniques, the success rates have not surpassed 75–80% [11]. Radiological confirmation of position would still be required in most of these methods.

Complications of Nasoenteral Tubes

Complications associated with nasoenteral tubes are less frequent since the introduction of fine-bore tubes. Passage maybe facilitated with guidewire. Currently available tubes are more flexible and less likely to cause erosions, oesophagitis or strictures.

Tube related complications include blockage, dislodgement, nasopharyngeal discomfort and trachea-oesophageal fistula. Blockage can occur when the tube is not properly managed, for example: leaving drug remnants, having a viscous formula, using gravity and not a pump, a small lumen or yeast colonization. Up to 24% of neonates have a NGT for feeding with oesophageal and gastric perforation in low birth weight babies seen in 4% of cases [9].

Tube misplacement may occur in patients who have lack of gag, swallow and cough reflexes, for example in children on mechanical ventilation or altered consciousness but may also occur in an otherwise well child. Reinsertion of guidewire, with the feeding tube in situ, is not recommended.

Gastrostomy Tube/Jejunostomy Tube

As a general rule, when EN is expected to be long term, feeding via a gastrostomy, or in certain situations enterostomy, should be the preferred route [4]. Gastrostomy allows access directly into the stomach and enterostomy directly into the small intestine. This allows the patient the option of being free from having tapes on the face, which can cause skin breakdown and pain on removal. The presence of a tube in the oesophagus is also thought to be a hindrance to oromotor skills development.

There is much debate is as to the minimal time on EN to justify gastrostomy insertion but generally should not be for less than 12 weeks, and in many cases should be longer. Percutaneous endoscopic gastrostomy (PEG) technique, initially described by Gauderer et al. [12] has largely replaced open gastrostomy placement via laparotomy. Absolute contraindication for PEG insertions include: (1) inability to perform UGI endoscopy (laryngeal or oesophageal stricture) and (2) uncorrectable coagulopathy. Relative contraindications could be: failure to transilluminate abdominal wall, patient's comorbidity (portal hypertension, severe gastritis or gastric ulcer, massive ascites, peritonitis, peritoneal dialysis, peritoneal metastases, left ventriculoperitoneal shunts) and terminal illness with limited life expectancy [4].

Many centers also now use laparoscopic assisted placement of gastrostomies to allow direct visualization. This is thought to be a safer method avoiding inadvertent colonic injury.

Gastrostomy feeding appears to have better outcomes compared to NGT feeding with better comfort and less irritations, ulcerations, bleeding, displacement or clogging. Improved nutritional adequacy and reduced rate of GOR and aspiration pneumonia are also seen [13, 14].

In patients with high risk of aspiration or a dysfunctional stomach, a long term jejunal access should be considered i.e. gastrojejunal tube, jejusnostomy tube or surgical jejunostomy. A surgical jejunostomy is a part of the intestinal tract brought out to the surface of the skin and requires intubation by a tube for delivery of enteral nutrition. They are fashioned to bypass any upper GI anatomical or mechanical issues.

Complications of Gastrostomy Tubes

Initial one piece system PEGs can be exchanged to low profile devices (with removable attachments to the device). This should only be done once the gastrostomy tract is matured and this may take from 6 to 12 weeks. As with nasoenteral tubes, gastrostomies can present with blockage or dislodgement. Dislodgement might cause catastrophic complication of peritonitis if dislodged into the peritoneal space.

Local complications like pain around site and skin irritation can be seen in patients who have a tight fixation, infection or leakage. In these cases, fixation needs to be checked; infection treated and consideration of the use of PPI for leakage. Granulation tissue, also known as hypergranulation tissue, has been reported in up to 44–68% of patients with gastrostomy tubes [15]. It presents as a red, spongy, proliferation of tissue that produces exudate and bleeds easily [16]. It can be removed using silver nitrate or cauterisation. Application of a steroid ointment (hydrocortisone/dexamethasone/betamethasone) with antibacterial agent might help to reduce granulation tissue.

Leakage of nutrients or gastric juice can occur with a large stoma. This can be improve by replacement with a smaller tube size. In severe cases, feeding needs to be stopped and parenteral nutrition considered in order to reduce the stoma size and heal the surrounding skin.

Enteral Feeds

Formulations

EN can be offered as liquid ready-to-feed formulations or powdered preparations that are mixed with cooled boiled water before feeding. Products available for children can be categorized as either "enteral feeds" or "supplemental feeds" [4].

Current medical enteral feeds are designed to be nutritionally complete when taken as the only source of nutrition to meet caloric requirements. The nutrient composition of enteral feeds should be age adapted [17]. Most of the newborn formulas have energy density start at 0.67 cal/ml. The energy density can be increased to beyond 1 kcal/mL depending on tolerance and age. Feeds with a high energy density (1.5 kcal/mL) are used in children with increased energy requirements, however, it may not always provide sufficient fluids to meet requirement.

Supplement feeds ("sip feeds") may be provided in addition to normal food to increase energy and nutrient supply when required. Supplements contain a concentrated source of energy, protein, and other selected nutrients, but do not need to provide all of the nutrients in a balanced composition.

Most formulas are cow's milk (protein) based and is usually referred to as polymeric feeds. Protein molecules (usually casein) can be broken down into smaller less antigenic units by heat treatment, enzymatic hydrolysis and also final ultrafiltration to separate larger molecules. When the degree of hydrolysis is >50% then the formula can be referred to as extensively hydrolysed. The size of the protein is usually less than 1000 Daltons. Partially hydrolysed or extensively hydrolysed formulas are usually the first line specialized feeds in those patients with cow's milk protein intolerance/allergies. It can also be used in those children with short bowel syndrome when expressed breast milk is no longer available.

Note that some formulas might use porcine enzymes to break down proteins and so might not be halal. A lot of commercially available hydrolysed formulas not only manipulate the protein component of the formulas but also the percentage of long chain fatty acids (e.g. higher medium chain triglyceride) and carbohydrate source (i.e. lactose free) and so the effects from the formula might not be purely from the protein component.

Elemental feeds are those feeds that have amino acid as their source of nitrogen. Elemental feeds are usually prescribed when infants cannot tolerate hydrolysed formulas for due severe cow's milk protein reactions. Prescribers should also be cautioned that some elemental formulas might use soya as their protein source. This might continue to cause reactions in those infants who are susceptible.

High osmolality feed (such as elemental feeds) can induce diarrhoea, so iso-osmolality (300–350 mOsm/kg) is preferable. This is particularly important in patients with transpyloric continues feeds. Fibre and its fermentation products (short-chain fatty acids) have potential beneficial effects on intestinal physiology and the prevention of both diarrhoea and constipation [18].

For those patients (e.g. with short bowel syndrome) where there is no commercially available feeds to complement the absorptive capacity of the gut, a modular feeds might be required. This involves providing the individual macronutrient and micronutrient components in a special combination that the gut can tolerate and absorb. This should only be done in specialized units where there is technical dietetic experience in managing these patients.

Blenderised Diet

Blenderised diet refers to using everyday foods and atomising them into a puree consistency. There has been an increased interest and shift towards blenderised diets as this is seen by parents and caregivers as more natural than commercially available formulas in providing nutrition. Studies have also shown improved stooling, weight and height gain in patients with intestinal failure who transition to Blenderised tube feeding (BTF) [19]. Other benefits such as improve gagging and retching in children post fundoplication [20] has also been reported.

In another study, blenderised tube feeding analysis found that the samples provided 50% less energy and macronutrient values than prescribed and had higher water content [21].

Good candidates for blenderised diet are:

- children who are on bolus feeding via their gastrostomy.
- stable growth and otherwise healthy.
- with a motivated family.

Patients who are contraindicated for BTF [22] are:

- those with acute illness or immunosuppression.
- gastrostomy tube size of less tan 10 Fr.
- fluid restricted.
- continuous feeding.
- jejunstomy tubes.
- multiple food allergies.
- lack of resources.

Blenderised tube feeding is labor intensive and requires additional food storage space and equipments which might not be covered by medical insurance. Blenderised diets should be discussed with a qualified dietitian to ensure that caloric and nutrient requirements are met. Often blenderised diets are used in conjunction with formulas, at least initially.

Organization of HEN

Discharge Planning

In order for discharge to take place, there are a number of requirements must be satisfied prior. They consist of:

Table 3 Example of some HEN equipment required

Pump, Stand, Frame, hooks	Feed bags/bottles/containers, sets, syringes, connectors
pH indicator strips	Tape and dressings
Disinfectant wipes	Gloves

- Training; this includes practice of basic hygiene, setting up of pump and giving sets, making up of feeds (if required), NGT testing and/or reinsertion (if applicable).
- Suitable home environment (to clean water, secured electricity)with available storage space
- Community support (usually nursing as well as medical) for troubleshooting.
- Home care company who is able to supply feeds and consumables (Table 3).

If possible, a multi-disciplinary meeting should take place with parents/caregivers, community services and hospital staff prior to discharge to discuss what has been achieved during the admission, what is to be expected after discharge and clear guidance as to who to contact in what circumstances.

Ongoing Review

Patients on long term HEN should be reviewed on a regular basis. Issues that should be looked at during these reviews include issues with managing EN at home, tolerance of EN, nutritional and growth status of the child on HEN, whether HEN could be weaned and adequacy of community support. Goals should be set with the caregivers at each review and this could be used as a measure of progress or lack of it.

Weaning patients off HEN might require a multi-disciplinary approach with the skills of nurses, dietitians as well as speech and language specialists. The central goal is to be weaned off tube feeding in the quickest possible time whilst maintaining nutritional and growth status. For those children who are at school, a comprehensive plan that offers input from the school is also vital for success.

Home Parenteral Nutrition for Children

The survival of children on HPN has increased significantly over the last 20 years to the point that death is the exception rather than the norm. Even so, the provision of HPN is not entirely risk free. A lot of the improvements in HPN survival come from a team approach in training children and families in recognising early signs of complications and line infection and getting prompt treatment.

The prevalence of type III intestinal failure in the paediatric population varies between countries. The UK experience has been that it had risen from 4.4 per million in 1993 to 16.6 per million in 2012 [23]. Other centres have had similar experience [24]. Although the prevalence has increased but the long term survival and rates of significant complications have decreased.

The criteria for offering Home parenteral nutrition (HPN) are the following:

- Requiring inpatient PN for at least 3–6 months
- Not requiring any imminent further surgery
- Clinically stable (e.g. without fluctuating electrolyte requirements)
- Suitable PN formulation
- Suitable long term venous access
- Suitable home setting (both physical and social)
- Contract of engagement for ongoing reviews

Aetiology and Classifications

Currently, a combination of aetiology and intestinal function help to predict and describe those patients who might require HPN. In children, aetiologies that are commonly seen requiring HPN include: necrotising enterocolitis (NEC), gastroschisis associated with other aetiologies, atresia, intestinal resection/short bowel syndrome as well as enteropathies such as tufting enteropathy and microvillous inclusion disease just to name a few.

In the last 10 years, intestinal function/failure has been classified into three main groups [25]. Type 1 pertains to loss of intestinal function for less than 2 weeks. Patients in this category might require iv fluids and/or short term parenteral nutrition during their illness. Aetiologies which might be in this category could include acute gastroenteritis or post-operative ileus. Type 2 pertains to the requirement of PN for less than 28 days. Typically patients in this category might have intestinal atresia(s) or uncomplicated gastroschisis with prolong dysmotility. Type 3 intestinal failure are those who are might benefit from HPN due to the need for prolong PN. The concept of permanent intestinal failure refers to those patients with aetiologies which are unlikely to ever become independent of PN. This will include patients with ultrashort intestinal length and enteropathies such as microvillous inclusion disease. The definition of ultrashort has changed through the last decade with patients now surviving with little or no small intestinal length, where previously a length of 30 cm has been proposed.

Clinical Stability

Patients who have ongoing intensive nursing needs are unlikely to benefit from being sent home with PN. These

patients might include those with large variable daily stomal output and require close fluid and electrolyte monitoring. Stability of bespoke PN might be influenced by the electrolytes added to the PN. Traditionally, calcium and phosphate are the minerals that are looked at closely as precipitation can occur.

Those patients with ongoing repeat line infections and requiring definitive line care management are also not eligible to be discharged home on HPN. See below with respect to line care.

PN Formulation

Paediatric HPN are usually tailored made (bespoke). This is due to HPN patients often have electrolyte and macronutrient requirements that are not standard from the recommended guidelines to account for stomal/stool, renal losses or altered metabolic demands.

Although this must be common knowledge, consideration for PN composition should include the following macronutrients: amino acid, carbohydrate and lipid source. Whether all macronutrients are to be provided with each infusion will depend on clinical need of the patient and local practices (e.g. some units might have lipid free nights). In addition to macronutrients, electrolytes, trace elements and vitamins supplementation would need to be considered. Although guidelines (e.g. ESPGHAN 2018) exist for providing the maintenance requirement, they do not take into account the pathology of the individual patient and each patient will need careful review as to whether guideline recommendations for electrolytes or micronutrients suit that of the patient to ensure toxicities and deficiencies are avoided. Biochemical monitoring is often used to assist in this determination.

Having mentioned the above, there is guidance when formulating HPN.

From an energy point of view, lipid should represent about 25–40% of non-protein energy, and linoleic acid should be 1–2% of total energy. The maximum lipid utilization rate is about 3.3–3.6 g/kg/day [26]. The maximum infusion rate of glucose through a central vein should be 1.0–1.5 g/kg/h; if it is greater than this glycosuria may occur [26].

Ingredients that generally require special attention are: calcium and phosphate (as they might precipitate out of solution and greater amount will be required for premature infants), cation and anion imbalances, trace elements and vitamins contributing to longevity of formulated bag. Before supplying PN as formulated, manufacturers need to certify the stability of and shelf life of the composition.

Infusion

Currently, there are a number of presentations of PN bags for administration into the patient. (1) Separate lipid and aqueous bags, (2) separate chambers (roll in one) and (3) all in one bag. The infusion requires a portable pump. These pumps are usually light weight, allow programming of different settings (e.g. maximum infusion rates or maximum pressure to deliver infusion) and allow delivery of PN without constant need to be plugged into a power source after charging.

The infusion is prescribed as ml/h over a set number of hours (e.g. 50 ml/h over 12 h). When the hours of PN infusion is condensed, this is termed cycling of PN. Most units aim to cycle PN over 12 h. There are several rationale behind this is for (1) for practical reasons, 12 h free from PN would allow relatively normal activities to be performed during the day such as schooling and work. (2) reduce the total time that the liver is exposed to glucose from the PN. This has been suggested to provide a beneficial role in minimizing IFLAD [28].

There needs to be caution not to become too fixated on achieving a12 h infusion time as some patients who cannot tolerate any oral/enteral intake may develop dehydration and electrolyte disturbances. In some patients, sudden cessation/increase of a glucose infusion precipitates hypoglycaemia/hyperglycaemia. In these patients, it may be beneficial to include a stepping up and down regime depending on glucose tolerance. The stepping up or down rate of infusion is generally half the full rate for 30–60 min at the start or prior to the cessation of PN infusion.

Early morning vomiting is not an uncommon symptom voiced by patients and family who have overnight PN. The exact reason for this is unknown but maybe related to large fluid shifts in the body over a short period of time. Other causes for vomiting should be sought before diagnosing it to be PN related vomiting.

PN Administration

Aseptic non touch technique (ANTT) has largely replaced the use of sterile gloves to prepare the person for connection and disconnection of PN at home. The main principles of the ANTT is that sterile products are used and the sterile part of the product does not come into contact with anything that is not sterile, thus preventing contamination from occurring [27]. The identification of key parts e.g. the tip of a syringe, and these should be kept sterile so that the use of sterile gloves and/or a sterile field is not required [27] (chapter "Nursing Care of Patients Receiving Home Parenteral Support").

Table 4 Equipment required for HPN

Pump (with clamps, leads, backpack, wheels, admin set)	Towel dispenser	filters	Sharps container
Drip stand	Soap dispenser	IV caps/ bungs	Waste bags
Fridge (thermometer)	Extension cords	Towel	Hand wash/soap
Collapsible trolley	Dressing (for line site, line end)	Needles	
Blue procedure tray	Elasticated tubular bandage	Dressing pack	
Blue clamps	Gloves and aprons	Syringes	
Patient thermometer	Wipes (chlorhexidine)	Tape	

The delivery of PN will require certain basic equipment to be available in the home (Table 4). These can be procured from the hospital or from the home care companies.

Storage of PN

Stability of PN is a major consideration and factors such as temperature variability will affect the chances of precipitations or of the browning effect of carbohydrate within PN. To increase the longevity of PN, refrigeration is often required (especially for bespoke bags) while off the shelf multi-chamber bags (standard bags) can often be stored at room temperature for a long period of time. Refrigerators will need to be able to accommodate the number of bags for each delivery from the manufacturing company and this might be in access of 2 week's supply of PN bags. The PN fridge should not have any other food or beverages in it as the opening and closing of the fridge will contribute to temperature fluctuations.

Home Care Company

Every country will have different national/regional procurement laws and policies. In essence, the responsibility for the PN prescription lies in the nutrition support team looking after the patient and the home care company's responsibility will be to deliver the PN and other associated consumables. Some home care companies also offer nursing services to compliment the PN delivery service. In the UK, the current setup with HPN is that each patient needs a unique high cost drug number and the services need to be commissioned locally. There is a list of approved providers from which the hospitals can choose or be assigned with. Hospitals will need to take into account different factors such as previous service performances, responsiveness to issues arising and geographical constrains when choosing a particular provider. Some hospitals have elected to choose from a selected number of providers and rotating the providers for each new patient. The advantages of doing so is to distribute risks of relying on only one provider but this might not match suitable companies with suitable patients.

Venous Access

Home parenteral nutrition cannot be delivered without central venous access and the maintaining of their integrity (i.e. Free from breakage or infection) has been the cornerstone of the delivery of parenteral nutrition.

Line care begins even before the line is inserted. Considerations include:

- Position of venous access (e.g. stoma site & vascular anatomy).
- Type of access (e.g. peripherally inserted central catheter, port or skin tunnelled lines).
- Number of lumens.
- Thrombotic risk (patients with coagulopathy).
- Previous line infection and preventive measures (skin washes prior to insertion).
- After line care (regular skin washes, line locks and frequency of use).

There are some general principles/recommendations that are to be adhered to [29]:

- Avoid using the femoral vein for central venous access.
- Where possible, ultrasound guidance is used for placement of central venous access to avoid multiple attempts of cannulation.
- Use the minimum number of ports or lumens essential for the management of patient.
- Promptly remove the central venous catheter when no longer required.

Integral to reducing catheter related blood stream infection (CRBSI) is also the selection of appropriate hubs for central venous access [30]. Catheter hubs which allow turbulent flow and easy wear and tear at the access points are to be avoided.

In addition to good line care, good skin care should also be incorporated into any HPN protocol to reduce the risk of skin contamination. These can be in the form of skin washes such as octenidine and the use of chlorhexidine gluconate impregnated sponges/patches applied to the skin exit site [31].

With adherence to these principles, the rate of CRBSI has decreased over the years with reported rates of 2–3 per 1000 catheter days [32]. Local data from Birmingham Children's

Hospital suggests that this could be further decreased to 0.2 CRBSI in 1000 catheter days with the aim to achieve 0 CRSBI infections in the HPN cohort.

Home Setting

A home assessment will need to take place prior to discharge. This is to assess a number of different factors:

- Cleanliness and hygiene of house and rooms.
- Enough space to house the child and equipment.
- Access for deliveries and emergency escapes.
- Number and relationship of family members who will reside at the same address.

In general, the house should not be overcrowded both with people and belongings. This is so that PN could be place on and taken off without chances of contamination.

The space available for storage should be large enough to hold at least 2 weeks' worth of ancillaries and equipment as well as a PN fridge. Proximity of handwashing facilities to the place of PN being put up/taken down.

Nutrition Support Teams and Intestinal Rehabilitation Programs

Nutritional support teams (NST)/intestinal rehabilitation programs (IRP) have been the cornerstone of nutritional care for patients with intestinal failure. Although the composition of team members vary in their title, in essence the skill mix that is required are:

1. Parenteral nutrition: detailed knowledge of PN composition, stability (and aseptic manufacturing knowledge and managerial skills if making PN on site), medication interactions with PN, procurement of PN (if it is not made in house).
2. Caloric requirement, nutrient selection, body composition determination.
3. Nursing, Line care, organisation and continuing support of home PN provision.
4. Medical overview of progress, medication review.
5. Social and psychological support of families.

It is difficult to pinpoint the exact reasons as to why a NST/IRP would produce benefits to patients with intestinal failure and on HPN. What is clear though from a number of studies is that the benefits can be seen in a number of different outcomes. They include decrease mortality whilst on HPN, earlier achievement of enteral autonomy, improvement in intestinal transplant success rates, decrease in CRBSI, improved mortality and morbidity related to IFALD [33].

Long Term Management

Growth and Nutrition

All children receiving long-term parenteral nutrition at home need to be regularly reviewed by the multidisciplinary team in the specialist centre.

A number of studies have documented the growth of patients on HPN. These in general have been much poorer than the general population [34] especially during the first 2 years of life [35, 36]. It has also been shown that perhaps these growth and developmental abnormalities persist even when parenteral nutrition has been weaned off [37]. It is uncertain as to the reasons for this but it has been postulated that this might be related to e.g. nutrient insufficiency, constitutional short stature.

The current methods of measuring growth and nutrient sufficiency have many flaws. The use of weight and height measures might be inaccurate due to variation in equipments, body fluid fluctuations and technical problems with children not being still when they are measured. Anthropometric measures can supplement weight and height measurements to give a better picture in terms of progress and these include mid arm circumference and tricep skin folds.

Biochemical measurements do not often reflect actual macro/micronutrient status until late in the piece. Even so, clinicians often measures full blood count, electrolytes, liver functions, trace elements and vitamins to guide them in PN prescriptions. As a guide, children receiving long-term PN as inpatients should have weekly measurements of blood count, urea, sodium, potassium, calcium, magnesium, phosphate and liver function tests and monthly copper, zinc and selenium measurement until they are stable. In those patients who are stable, 2–3 monthly biochemical estimations should be sufficient. 6 monthly measurements of fat-soluble (ADEK) vitamins is advised. Yearly liver/gallbladder ultrasound as well as B group and C vitamins and thyroid function need to be checked [26].

Outcome

Survival

The Survival of children on HPN has steadily improved from around 50% in the early 1990s to 90% in 2008–2013 (Table 5). Much of the improvement in survival has been attributed to the understanding of the benefits of early use of enteral nutrition, more aggressive PN weaning practices, multi-discipline nutrition support teams getting involved early on [38, 39].

Weaning and Stopping Parenteral Nutrition

The ability to wean patients off parenteral nutrition is dependent on a number of factors. Patients with congenital mucosal

Table 5 Survival of HPN patients through different era at Birmingham Children's Hospital (*Table courtesy of Ms T Johnson*)

	1987–1997	1998–2007	2008–2013
Number of patients	15	45	46
Outcome:			
Full EN	6 (40%)	23 (51%)	24 (52%)
Full EN after liver transplant		(2)	(1)
Full EN after bowel transplant		(1)	(1)
Continues HPN	2 (13%)	7 (16%)	18 (39%)
Overall Survival	*53%*	*67%*	*91%*
Died	7 (47%)	15 (33%)	4 (9%)
IFALD (on transplant list)	5 (4)	5 (1)	2(1)
Post transplant	0	3	2
Sepsis	0	3	0
Underlying diagnosis	2	4	0

diseases such as tufting and microvillous inclusion disease will take years to come off PN completely, if at all. Those patients with short bowel syndrome secondary to bowel resection are more likely to come off PN but this is dependent on a number of factors e.g. total small bowel length, associated intestinal dysmotility and bowel dilatation [40].

As there is no marker for intestinal failure (unlike in liver or renal failure), the only way is to challenge the gastrointestinal tract's function until symptoms appear or the appearance of unabsorbed substances in the stool (faecal reducing substances, pH, faecal fat globules and alpha 1-antitrypsin). When there is malabsorption of particular components, changing the relative composition of them in the enteral feed to achieve the same caloric provision might be necessary e.g. via a modular feed.

Quality of Life on HPN

There are a number of disease specific quality of life (QoL) instruments in paediatrics such as that for biliary atresia and liver transplant but there is currently no such instrument for paediatric intestinal failure or HPN. Despite this, a number of centres have produced some qualitative measure of paediatric patients on HPN. These studies have found that the QoL is reduced and in domains such as physical and cognitive functioning in 13–24 months old and physical health and social functioning in the 2–6 years old [41]. Abdominal pain and stool frequency >3 times per day was associated with higher parental stress. Longer time interval since the last bowel operation and hospitalisation was associated with lower parental stress level [42].

Children with IF and their parents also might have common themes of concerns such as thoughts about living with illness, restricted life, social support and interactions, identity and the future [43]. This affirms what has been found earlier that this group of patients have psychological distress with high parental social integration but attachment is negatively affected [44].

Clearly there is much need to have a universally agreed QoL instrument to allow better description of paediatric intestinal failure patients on HPN and their parents/caregivers' QoL.

Transition of Paediatric HPN Patients

With the increase in the number of paediatric HPN patients as well as the better survival of these patients, it is inevitable that more patients will graduate into adult services.

It is imperative that both paediatric and adult services are equipped in making sure that not only the medical needs are met for these young persons but their educational and psychosocial needs are being met. It is in this light that NICE has produced guidance [45] to assist healthcare professionals in delivering a unified approach to transitioning for young persons. The important points are:

- The transition process is to set young persons to develop independence to meet their healthcare, educational and psychosocial needs.
- Transition should begin no later than 13/14 years of age.
- Young person's needs and views are to be taken into account in individualised plans.
- Joint statement (paediatric/adult/young person) for vision of transition in writing.
- Transition should be developmentally appropriate.
- A key worker should be identified to lead this process with the young person.
- Process should encompass before, during and after move to adult services.

With respect to young persons with intestinal failure, the following are examples of some goals that are to be agreed as a marker for readiness for transition into adult services:

- Young person understands their underlying medical condition.
- Physically allowing, be able to manage home PN independently.
- Know and administer any medications/feeds independently.
- Discuss aspirations, issues or concerns independently.
- Knowledge of access to help (medical, psychological or social) when required.

References

1. Commission directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes. [cited February 10, 2006]. http://www.idace.org/legislation/fsmps/Dir%2099-21%20FSMPs.pdf.

2. Gomez-López, et al. Current status of pediatric home enteral nutrition in Spain: the importance of the NEPAD register. Nutr Hosp. 2010;25(5):810–3.
3. Diamante, et al. Home enteral nutrition in children: a 14-year multicenter survey. Eur J Clin Nutr. 2013;67:53–7.
4. Bragger C, et al. Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010;51:110–22.
5. Axelrod D, Kazmerski K, Iyer K. Pediatric enteral nutrition. J Parenter Enter Nutr. 2006;30:S21–6.
6. Duncan HD, Silk DB. Insertion and care of enteral feeding tubes. In: Nightingale JM, editor. Intestinal failure. London: Greenwich Medical Press; 2001. p. 281–30.
7. Bankhead R, et al. Enteral nutrition practice recommendations. J Parenter Enter Nutr. 2009;33(2):1–45.
8. Lyman B, et al. Use of nasogastric feeding tubes for children at home: a template for caregiver education. Nutr Clin Pract. 2017;32:831–3.
9. Makama JG. Uses and hazards of nasogastric tube in gastrointestinal diseases: an update for clinicians. Ann Nigerian Med. 2010;4:3.
10. Gabriel SA, Ackermann RJ. Placement of nasoenteral feeding tubes using external magnetic guidance. JPEN J Parenter Enteral Nutr. 2004;28:119–22.
11. Phipps LM, Weber MD, Ginder BR, et al. A randomized controlled trial comparing three different techniques of nasojejunal feeding tube placement in critically ill children. JPEN J Parenter Enteral Nutr. 2005;29:420–4.
12. Gauderer MW, Ponsky JL, Izant RJ Jr. Gastrostomy without laparotomy: a percutaneous endoscopic technique. J Pediatr Surg. 1980;15:872–5.
13. Mekhail TM, Adelstein DJ, Rybicki LA, et al. Enteral nutrition during the treatment of head and neck carcinoma: is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube? Cancer. 2001;91(1785–90):71.
14. Norton B, Homer-Ward M, Donnelly MT, et al. A randomised prospective comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding after acute dysphagic stroke. BMJ. 1996;312:13–6.
15. León AH. Prevention of hypergranulation tissue after gastrostomy tube placement: a randomised controlled trial of hydrocolloid dressings. Int Wound J. 2019;16:41.
16. Borkowski S. Clinical challenge case #1 irritation, redness, and drainage at the site of a pediatric gastrostomy. Clin Advisor. 2005;8:90–1.
17. Koletzko B, Hermoso M. Reference nutrient intakes for infants, children and adolescents. In: Koletzko B, Cooper P, Garza C, editors. Children's nutrition—a practical reference guide. Basel: Karger; 2008. p. 285–92.
18. Aggett P, Agostoni C, Axelsson I, et al. Non-digestible carbohydrates in the diets of infants and young children. A commentary by the ESPGHAN Committee on nutrition. J Pediatr Gastroenterol Nutr. 2003;36:329–37.
19. Samela K, et al. Transition to a tube feeding formula with real food ingredients in pediatric patients with intestinal failure. Nutr Clinl Pract. 2016;32:277–81.
20. Pentiuk, et al. Pureed by gastrostomy tube diet improves gagging and retching in children with fundoplication. JPEN. 2011;35(3):375–9.
21. Vieira M, et al. Nutritional and microbiological quality of commercial and homemade blenderized whole food enteral diets for home-based enteral nutritional therapy in adults. Clin Nutr. 2018;37(1):177–81.
22. Epp L, et al. Use of Blenderized tube feeding in adult and Pediatric home enteral nutrition patients. Nutr Clin Pract. 2017;2:201–5.
23. Barclay, et al. The continued rise of paediatric home parenteral nutrition use: implications for service and the improvement of longitudinal data collection. Clin Nutr. 2015;34:1128–32.
24. Gandullia, et al. Long-term home parenteral nutrition in children with chronic intestinal failure: a 15-year experience at a single Italian Centre. Dig liv dis. 2011;43:28–33.
25. Pironi, et al. Clinical classification of adult patients with chronic intestinal failure due to benign disease: an international multicenter cross-sectional survey. Clin Nutr. 2018;37(2):728–38.
26. Milla PJ. editor. Current perspectives on paediatric parenteral nutrition. British Association for Parenteral and Enteral Nutrition; 2000.
27. Ingram P, Murdoch MF. Aseptic non-touch technique in intravenous therapy. Nurs Stand. 2009;24(8):49–57.
28. Risks and benefits of prophylactic cyclic parenteral nutrition in surgical neonates nutrition in clinical practice. 2013;28(6):745–52. https://doi.org/10.1177/0884533613502813.
29. O'Grady, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52(9):e162–93.
30. Mahieu, et al. Risk factors for central vascular catheter-associated bloodstream infections among patients in a neonatal intensive care unit. J Hosp Infect. 2001;48:108–11.
31. Biopatch for venous or arterial catheter sites. https://www.nice.org.uk/advice/mib117.
32. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc. 2006;81(9):1159–71.
33. Belza C, Wales PW. Impact of multidisciplinary teams for management of intestinal failure in children. Curr Opin Pediatr. 2017;29(3):334–9.
34. Cole CR, Hansen NI, Higgins RD, Ziegler TR, Stoll BJ. Very low birth weight preterm infants with surgical short bowel syndrome: incidence, morbidity and mortality, and growth outcomes at 18 to 22 months. Pediatrics. 2008;122(3):e573–82.
35. Ralston CW, O'Connor MJ, Ament M, Berquist W, Parmelee AH Jr. Somatic growth and developmental functioning in children receiving prolonged home total parenteral nutrition. J Pediatr. 1984;105(5):842–6.
36. Pichler J, Chomtho S, Fewtrell M, Macdonald S, Hill SM. Growth and bone health in pediatric intestinal failure patients receiving long-term parenteral nutrition. Am J Clin Nutr. 2013;97(6):1260–9.
37. Leonberg BL, Chuang E, Eicher P, Tershakovec AM, Leonard L, Stallings VA. Long-term growth and development in children after home parental nutrition. J Pediatr. 1998;132(3 Pt 1):461–6.
38. Merras-Salmio L, Mutanen A, Ylinen E, Rintala R, Koivusalo A, Pakarinen MP. Pediatric intestinal failure: the key outcomes for the first 100 patients treated in a National Tertiary Referral Center during 1984-2017. JPEN J Parenter Enteral Nutr. 2018;42(8):1304–13.
39. Petit LM, Girard D, Ganousse-Mazeron S, Talbotec C, Pigneur B, Elie C, Corriol O, Poisson C, Goulet O, Colomb V. Weaning off prognosis factors of home parenteral nutrition for children with primary digestive disease. J Pediatr Gastroenterol Nutr. 2016;62(3):462–8.
40. Fullerton BS, Hong CR, Jaksic T. Long-term outcomes of pediatric intestinal failure. Semin Pediatr Surg. 2017;26(5):328–35.
41. Sanchez SE, McAteer JP, Goldin AB, Horslen S, Huebner CE, Javid PJ. Health-related quality of life in children with intestinal failure. J Pediatr Gastroenterol Nutr. 2013;57(3):330–4.
42. Mutanen A, Kosola S, Merras-Salmio L, Kolho KL, Pakarinen MP. Long-term health-related quality of life of patients with pediatric onset intestinal failure. J Pediatr Surg. 2015;50(11):1854–8.
43. Emedo MJ, Godfrey EI, Hill SM. A qualitative study of the quality of life of children receiving intravenous nutrition at home. J Pediatr Gastroenterol Nutr. 2010;50(4):431–40.
44. Engström I, Björnestam B, Finkel Y. Psychological distress associated with home parenteral nutrition in Swedish children, adolescents, and their parents: preliminary results. J Pediatr Gastroenterol Nutr. 2003;37(3):246–50.
45. Transition from children's to adults' services for young people using health or social care services. https://www.nice.org.uk/guidance/ng43.

Home Parenteral Support for Patients with Incurable Advance Cancer

Mani Naghibi and Federico Bozzetti

Key Points

1. Patients with incurable advanced cancer may be considered for home parenteral support (HPS) if they have intestinal failure (IF) or significant nutrition deficiencies from bowel obstruction (partial, intermittent or complete), enterocutaneous fistula(s), a short bowel, dysmotility or severe mucosal disease (often following chemotherapy or radiotherapy).
2. The patients with the best survival and quality of life on HPS are those with higher performance status and low serum markers of inflammation (C-reactive protein <10 mg/L and albumin >32 dg/L).
3. Some guidelines (e.g. ESPEN) suggest selecting patients with an expected prognosis of 2–3 months or greater but this is challenging in practice.
4. All patients who may be considered for HPS should have an early multidisciplinary team (MDT) review by the nutrition support team (NST), oncologists and palliative care teams. The desired aim(s) of starting PN and the plans for withdrawal (either at the end of life, or any time after commencing) should be discussed.
5. Patients who require HPS support for bowel obstruction should be considered for a venting gastrostomy placement (20F or larger) in order to palliate vomiting and, if wanted, to allow eating and drinking of a limited diet. Abdominal interventions do risk the tumour growing along any medically or surgically created tract, although this is less clinically relevant in the palliative phase and symptom control should take priority.

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Introduction

When a malignant disease reaches a stage where curative treatments are no longer available, or amenable, this is termed 'incurable' or 'palliative' cancer. The term palliative is not clearly defined in the medical literature, although 'palliative care' is defined by the World Health Organisation (WHO) as "the approach that improves the quality of life of patients and their families, facing the problems associated with life-threatening illness, through the prevention and treatment of pain and other problems, physical, psychosocial and spiritual" [1]. For this reason the use of parenteral support (PS) for patients with incurable cancers does not fully meet the definition for palliation, as one of its main aims is to also increase survival length.

In this chapter we will explore the effect on survival and quality of life for patients with incurable cancer when treated with PS and consider tools available to optimise patient selection. We will also consider the health economics of this treatment.

Cancer, Nutritional Status and Outcomes

Involuntary weight loss is often present as a symptom of cancer. Depending on the site of the cancer, between 31% and 87% of patients have involuntary weight loss [2–5]. In pancreatic cancer, it has been shown that 85% of patients have weight loss at diagnosis, with 30% displaying severe weight loss of greater than 10% in the preceding 6 months [2].

Weight loss correlates with stage of cancer, as well as the clinical outcome [6]. Malnourished cancer patients have a poorer response to medical oncology treatments [7–9]. There is also evidence that malnutrition negatively influences length of hospital stay, readmission rates, symptom burden and quality of life in cancer patients [10].

The causes of weight loss in patients with cancer vary by the primary site and metabolic activity of the tumour, but common themes are reduced intake through inflammatory

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and cytokine driven loss of appetite [11–13] or obstructed gastrointestinal tract, increased resting energy expenditure in some cancers [14–16], insulin resistance leading to increased gluconeogenesis [17] and lipolysis [18, 19].

Cancer cachexia differs from simple starvation, as it encompasses weight loss despite sufficient or excess supply of nutrients, which can be via natural or artificial routes. Cachexia is a complex multifactorial syndrome that leads to progressive functional impairment [20].

The pathophysiology of cancer cachexia is characterised by reduced food intake and abnormal metabolism. The hallmarks are anorexia, early satiety, weight loss, muscle wasting, anaemia and in the late stages, oedema. The definition of cachexia overlaps with other diagnosis such as sarcopenia and malnutrition, and can be distinguished from them by the presence of a disease process, which may be benign or malignant.

The current understanding of cancer cachexia has led to its classification into pre-cachexia, cachexia and refractory cachexia [20]. To combat the progression of cachexia early supplementation of nutrition need to be combined with therapies that can slow or stop the metabolic process contributing to its development. The term refractory cachexia is being challenged, as multimodal treatments in cancer, including nutritional supplementation, are showing reversal of cancer cachexia previously termed refractory.

Many cancers induce inflammation, causing peripheral and centrally mediated catabolism and appetite suppression, with inverse correlation of survival length in those with higher markers of inflammation [21]. A systematic review of the use of non-steroidal anti-inflammatory drugs (NSAIDs) in cancer cachexia, identified 13 trials, of which 11 demonstrating stabilisation in weight or lean body mass where NSAIDs were used, though the studies were small with risk of false positives [22].

These findings suggest that we may be able to manipulate the processes leading to weight loss associated with cancer, with potential for effective utilisation of nutrient intake to positively influence clinical outcomes including response to anti-cancer medical and surgical treatments.

The ability to alter the type of nutrients supplied to cancer patients may also play a role in improving utilisation of energy. Waterhouse and Kemperman in 1969 [23] demonstrated that fat is metabolised more efficiently than carbohydrates in cancer patients. The mechanism for this may be the increased inherent reliance on mobilisation of fatty acids, from fat deposits, as the major source of energy in any semi-starved state. Further studies have also observed improved fat metabolism in cancer patients [14, 24, 25]. For example, lipid clearance, after intravenous administration of short chain and medium chain triglycerides, has been found to be more effective in malignancy patients, compared to healthy controls [26].

Cancer and Intestinal Failure

The cause of intestinal failure (IF) in patients with cancer is most commonly bowel obstruction (BO), followed by fistulation, short bowel resulting from surgery, infarction or dysmotility. BO is estimated to occur in 10–28% of colorectal cancers and 5–50% of ovarian cancers [27].

When IF occurs in the context of palliative cancer, life expectancy is dramatically reduced. Without parenteral support the immediate cause of death would be dehydration rather than tumour progression or, if hydration is maintained, malnutrition. Commencement of burdensome PN would be neither ethical nor acceptable in most patients with incurable cancer. The challenge is, therefore, to optimally select patients with end stage cancer in whom the benefits outweigh the drawbacks of treatment. However, the proportion of patients suitable for HPS treatment in end stage cancer is still unknown.

Prevalence of HPS for Incurable Cancer

Table 1 summarises the published data for prevalence rates across the world for PN use in cancer patients. These data can be challenging to evaluate and compare directly with each other as the prevalence rates are expressed differently (i.e. period prevalence vs. point prevalence) and from varying time periods. Nevertheless, despite these limitations, it is clear that the practice of HPS therapy for incurable malignancy is common in economically developed countries, but varies considerably, even between countries with comparable health systems.

In those countries with published data, the lowest appear to be in the UK [28, 29] and highest in Italy and North America [30, 31], with evidence of increasing prevalence in all reporting countries [31–33].

HPS in Incurable Cancer Patients

HPS is defined as ‘total’ when the intravenous administration of nutrients represents the exclusive (or the near-exclusive) way of feeding the patient. In cancer patients this happens most frequently due to gastrointestinal obstruction from the tumour or due to metastatic peritoneal invasion. In such cases the obstruction may be incomplete, where it worsens when patient attempts to eat and is associated with early satiation, nausea, vomiting, abdominal distension and pain.

In this context a randomised control trial (RCT) is considered to be unethical. If the incurable cancer patient is suitable for HPS therapy, randomising to non-HPS, when

Table 1 Prevalence of malignant conditions as indication for home parenteral nutrition

Study	Country	Total HPS patients	Number of HPS patients with cancer	Proportion of HPS with cancer (%)	Period or point prevalence (years)	Data source
Vafa et al., 2010 [34]	Belgium	125	60	48	*Period* prevalence (1987–2007)	Single academic centre database
Soo and Gramlich, 2008 [31]	Canada	158	38	48	*Period* prevalence (Jan–Dec 2006)	North Alberta Home Total Parenteral Nutrition program database
Cozzaglio et al., 1997 [35]	Italy	125	75	43	*Period* prevalence (1983–1990)	Italian Home Parenteral Nutrition registry
Wanden Berghe et al., 2011 [33]	Spain	148	29	20	*Period* prevalence (Dec 2009–Dec 2010)	Nutricion Artificial Domiciliaria y Ambulatoria (NADYA) database
Gillanders et al., 2011 [36]	Australia and New Zealand	124	19	15	*Period* prevalence (July 2010–July 2011)	Australian Society of Parenteral and Enteral Nutrition (AuSPEN) database
Jirka et al., 2011 [37]	Czech republic	138	51	37	*Period* prevalence (2010)	National Home Parenteral Nutrition registry *(Poster abstract)*
Takagi et al., 1995 [38]	Japan	231	93	40	*Period* prevalence up to 1990 (start not reported)	National survey
Baxter et al., 2003 [29]	Scotland	72	7	10	*Period* prevalence (Aug 2010–Aug 2011)	Managed Clinical Network Database
Smith et al., 2011 [28]	UK	523	42	8	*Point* prevalence 31/12/2010 (Percentage of new registrations during 2010—14%)	British Artificial Nutrition Survey (BANS) database
Howard et al., 1995 [39]	USA	4520	2122	47	Period prevalence (1985–1992)	North American Home Parenteral Nutrition database

the deleterious effects of a prolonged starvation in malnourished subjects are well known and as the benefits of HPS have been demonstrated, would not be ethical. The control group for such a study may be those who are hypo/aphagic due to incurable cancer, qualify for HPS, have been offered HPS, but have chosen, for personal reasons, to decline. This would allow for observational studies, but precludes randomisation. To date this group has not been studied.

HPS is 'supplemental' when the patient is able to maintain a limited oral intake of nutrients, and the PN is given in parallel to meet requirements. In cancer patients this occurs secondary to low grade gastrointestinal obstruction, severe uncontrolled anorexia, or due to high stoma or fistula output.

In 5–23% of cancer patients the main cause of death has been reported as cachexia [40–43] and weight loss of cancer patients is proportional to the severity of anorexia or to the reduction of nutrients' intake or to the persistence of a negative energy balance. There is now a growing bulk of evidence showing that a PN support for incurable cancer patients can improve survival and is able to improve not only the body weight but also the lean tissues.

Outcomes: Survival Length

The survival of 'healthy', non-cancer individuals undergoing extreme starvation, but not dehydration, is approximately 2 months, as observed in the tragic events of the Leningrad siege [44], Warsaw ghetto [45] and Irish hunger strike [46], where the longest length of survival was 2.4 months (73 days). The longest length of survival of cancer patients undergoing a total or almost total nutrients deprivation is similarly reported to be approximately 2 months in hospitalized patients [47] and only 17–29 days in patients followed at home [48, 49], though the survival is often shorter due to predisposing weight loss even before the onset of bowel obstruction. Since the 1990s International Consensus [50] has existed to support the use of HPS in advanced hypo/aphagic cancer patients if the expected survival due to the cancer is approximately greater than 2 months, in combination with other favourable factors outlined in Table 2.

Most of the studies on HPS in advanced cancer patients are retrospective, with small case series leading to inherent limitations that come from small patient numbers, with wide confidence intervals that lead to data which is not clinically reliable. Naghibi et al. (2014) systematically reviewed these

Table 2 American and European guidelines regarding parenteral nutrition therapy in palliative malignancy

American Society of Enteral and Parenteral Nutrition (2009) [51]
1. Must be physically and emotionally capable of participating in their own care
2. Should have estimated life expectancy of >40–60 days
3. Require strong social and financial support, including a dedicated in home lay carer
4. Must have failed trials of less invasive medical therapies such as appetite stimulants and enteral feeding
European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) (2009)[a] [10]
In intestinal failure and incurable malignancy, long-term PN should be offered, if:
1. enteral nutrition is insufficient
2. expected survival due to tumour progression is longer than 2–3 months
3. it is expected that PN can stabilise/improve performance status and quality of life
4. the patient desires this mode of nutritional support
There is probable benefit in supporting incurable cancer patients with weight loss and reduced nutrient intake with "supplemental" PN

[a]Updated in 2016 with further narrative guidance

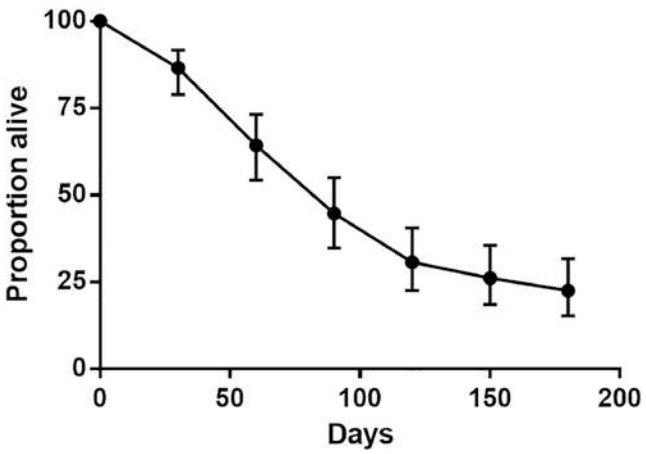

Fig. 1 Proportion of patients alive at monthly intervals during the first 6 months, with corresponding 95% confidence intervals (n = 244)

studies and applied random effects modelling to meta-analyse the data, incorporating 12 studies and 244 patients in the final meta-analysis of survival length (Fig. 1) [52]. This demonstrated 3.9 months and 2.8 months mean and median survival, respectively. In this systematic review it was also demonstrated that higher performance status at baseline of HPS therapy for advanced cancer patients is predictive of longer survival (Fig. 2).

Only a few studies in this patient group have been carried out prospectively [45, 53, 54]. The largest prospective study is by Bozzetti et al. (2014) on 414 incurable cancer patients treated with HPS, reporting a comparable survival length of

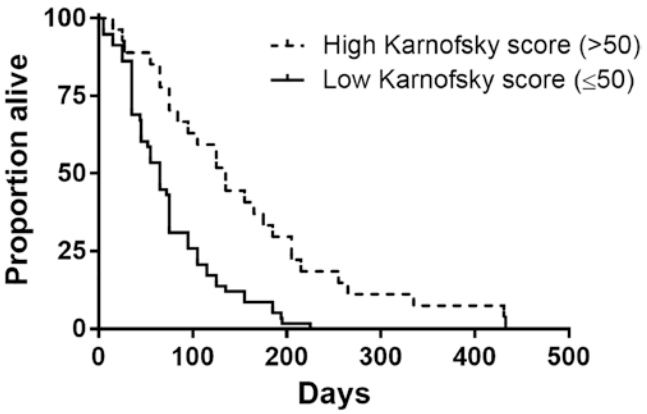

Fig. 2 Kaplan Meier survival curves, based performance status (measured by Karnofsky performance score) (p = 0.01)

4.7 months and 3.0 months mean and median survival, respectively [54].

These studies have lead to two main considerations: first, if we accept a threshold of 3 months as the longest potential survival in patients undergoing total starvation, HPS will prolong survival in over half of patients (though likely to be a higher proportion); second, while this patient population is heterogeneous and several factors can finally affect the length of survival, large multi-centred and international retrospective and prospective studies have resulted in similar survival lengths.

Quality of Life and Body Composition

Data on quality of life (QOL) for incurable cancer patients treated with HPS are scanty and difficult to interpret. QOL can only be assessed by the person who is experiencing the factors studied, hence, retrospective studies of QOL scores completed by clinicians or family members are not validated methods, which currently make up the majority of the data in this field.

A prospective QOL study by August et al. (1991) reported that in 14 patients (82%) both patients and their families perceived their therapy as beneficial or highly beneficial [55]. Their Nutritional Support Team agreed with this assessment in 11 patients, but did not share this perception in three patients. These three patients had a short duration of HPS (less than 25 days) or minimal rehabilitation.

In another prospective study [45] investigating the QOL in 69 incurable cancer patients using the validated cancer QOL tool, Rotterdam Symptom Checklist questionnaire, variables were collected at the start of HPS and then at monthly intervals. Results showed a median survival of 4 months (range 1–14) and QOL parameters remained approximately stable till 2 months before death.

Table 3 Prospective studies on the effects of HPS on QoL measured through validated scores in malnourished advanced cancer patients on chemotherapy

Author	#PTS	Mode of sHPS	Methods	Results	Comments
Finocchiaro 2002 [58]	70	27 Kcal + 1.1 gAA/kg/d	TIQ at >2 months	QoL: =48%, ↑31.5%, ↓20.5%	Evaluated 27 patients
Culine 2014 [61]	437	Usually overnight 26 Kcal + 1.1 gAA/kg/d	FACT-G day 1–28	↑ Physical, functional, emotional, familial/social status	Responsiveness to therapy may affect QoL
Seys 2014 [57]	221	Overnight	FACT-G day 1–28	↑BW and global QoL in 68% and 59% of pts. (and sub-score physical, functional and emotional)	Regimen of NPS ill-defined; No statistical analysis; Responsiveness to therapy may affect QoL
Vashi 2014 [60]	52	Cyclic, total oral + PN Kcal and AA: 25–30 and 2 g/kg/d	EORTIC QLQ-C30	↑Global QoL index at 1–3 mos	Small sample, loss of patients; Responsiveness to therapy may affect QoL; Assessment of requirements unpractical
Girke 2016 [59]	23	–	EORTIC-QOL-C30 day 1–28	↑Emotional/social domains = muscle strength, physical activity, BMI ↓ phase angle	Nutritional regimen not assessed; Large drop out of patients
Cotogni 2017 [63]	111	21 Kcal + 0.8 g AA/Kg/d	EORTIC QLQ-C30 monthly for 1–4 months	↑Global QoL, physical functioning, role functioning, emotional functioning, appetite loss and fatigue scores	High attrition rate due to death 49/111 completed at 4 months
Obling 2017 [62]	47 random HPS VS	Overnight, 2–4 times/week, 10 Kcal + 0.5gAA/Kg/d × 3 months	Bioelectrical impedance analysis and EORTIC QLQ-C30	↑ at 3 months of FFM and overall QoL	Loss of patients during the study

These studies are also in keeping with QOL assessed by Orrevall et al. [56], where structured interviews were carried out with incurable cancer patients and their family members. This study reports both positive and negative aspects. The positive aspects were centred around the sense of relief and security in both patients and relatives because the nutritional needs were being met through HPS. The burden of treatment did have reported negative effects on the patient and family social life, but the salient summary was of positive effects out weighing the negative.

Given HPS in context of incurable cancer is often for a short period of time, this leads to few patients and/or family members fully training in the care of HPS. Hence, HPS treatment is accompanied by up to twice daily visits by trained nurses, who often give emotional support and security to patients in addition to the technical procedures that they carry out. The security felt by patients and family members on HPS may be, in part, be related to this close relationship with a health professional.

As regards the QOL of patients receiving supplemental parenteral nutrition, multiple studies [57–61], using validated methods (Therapy Impact Questionnaire, Fact-G, EORTC-QOL-C30) have also reported an improvement in quality of life (summarised in Table 3). These findings were also observed in the RCT by Obling et al. which found that PN also increased fat-free mass [62].

Table 4 Karnofsky performance status

Score, %	State of health
100	Healthy, no symptoms or signs of disease
90	Capable of normal activity, few symptoms or signs of disease
SO	Normal activity with some difficulty, some symptoms or signs
70	Caring for self, not capable of normal activity or work
60	Requiring some help, can take care of most personal requirements
50	Requires help often, requires frequent medical care
40	Disabled, requires special care and help
30	Severely disabled, hospital admission indicated but no risk of death
20	Very ill, urgently requiring admission, requires supportive measures or treatment

Patient Selection

In the above mentioned international prospective study by Bozzetti et al. (2014) three prognostic factors for survival at the multivariable analysis were identified [54]; performance status, as measured by Karnofsky performance Status (Table 4), Glasgow Prognostic Score and presence of tumour metastasis. The prognostic value of these variables coupled with type of primary tumour, was subsequently validated on

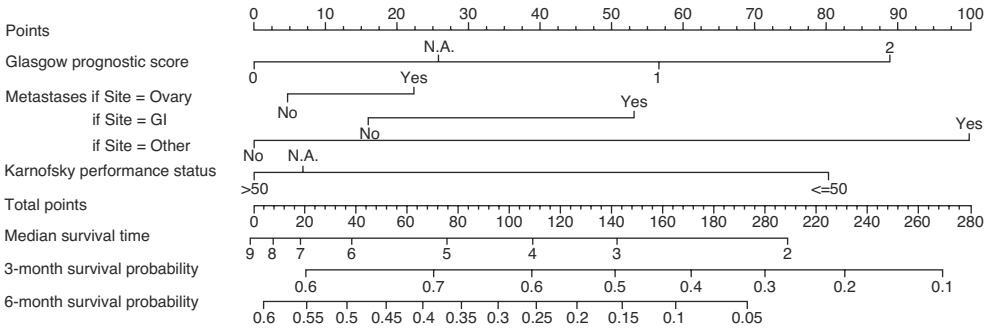

Fig. 3 Cox model based nomogram for predicting 3-, 6-month and median length of survival. Score are added up for each patient factor and the total points correspond to survival estimates at the bottom of the figure

a separate series of patients [64] and led to the construction of a prognostic nomogram (Fig. 3).

It is worth noting that a sub-analysis of patients with so-called 'refractory' cachexia according to an International Consensus [20], showed a 3- and 6-month survival of 29.4% and 8.4%. These figures were 31.7% and 12.2% for patients without vital organ involvement, 27.1% and 5.9% for those with vital organ involvement. These figures would suggest such patients can still benefit from HPS therapy, and we would advise multidisciplinary team assessment of performance status as the most predictive of favourable outcome for these patients.

In these incurable patients HPS was generally withdrawn a few days before death. In one third the main reasons for stopping HPS treatment was tumour progression (73%), patient choice (20%) and HPS central venous catheter complications (CVC) was the least common cause (6%). The cause of death was vital organs failure (46%), progressive wasting (34%) and HPS CVC complications (1%) and unknown in the remaining patients.

Ethical Considerations

Both the decision to commence HPS, as well as to withdraw it, should directly involve the patient, which requires the patients be aware of their diagnosis and their prognosis to express informed consent. However, the conveyance of the information can be challenging and there are considerable variations between countries, within countries, cultures and health systems. There has been a trend for increased direct involvement of the patient over the last few decades, with evidence that a greater proportion of patient would welcome this information. Clinical experience suggests the presence of a multidisciplinary team, involving palliative care practitioners to fully explore the alternatives of not accepting this high burden treatment to be highly valuable.

In the 1990s, in Southern Europe, only 25–38% of patients were aware of their cancer diagnosis at an advanced stage and studies suggested less than half of these wanted to be given more information [65–68]. A survey of over 2000 patients with metastatic cancer, carried out in Italy in 1999, found that 39% believed it to be 'difficult to cure' and 47% considered their disease 'severe' [69]. In Spain only 12% of patients with a terminal diagnosis knew about their short-term prognosis [70]. More recent studies suggest there is evidence that these practices and attitude have changed significantly. In a multicentred Italian study, Costantini et al. [71], reported that 87% of patients were aware of their cancer diagnosis, although 49% of those with metastatic cancer were of the opinion that they have curable disease.

Family members may sometimes be responsible for the patient's ignorance regarding their diagnosis and prognosis. In some cultures, those surveyed (73%–84%), reported a wish not inform the patients in a straightforward manner about the state of disease advancement [65, 70].

The Council of Europe (European Treaty Series, Chapter III, Article 10, Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine) came into force on 1st December 1999, states that 'everyone is entitled to know any information collected about his or her health. However, the wish of an individual not to be so informed shall be observed.' One third of physicians in Europe, questionnaire at the turn of the millennium, believed that patients never want to know the truth [65], while an equal percentage believe that informed consent is necessary to respect patient autonomy [72].

While adequate information should always be given to patients when actively or implicitly requested, there is much uncertainty about the true comprehension of the communication. Indeed, the ability of the patient to actively negotiate in a decision with the caregiver requires four intact cognitive functions: (1) the ability to clearly understand the information relevant to the decision; (2) the ability to fully appreciate the situation and the consequences of alternatives approaches; (3) the ability to elaborate and weigh the information rationally in the context of a coherent set of values and goals, and (4) finally, the ability to communicate or transfer choices to the physician regarding care.

A self-report survey measuring 'desire for death' distributed to 92 incurable cancer patients with a life-expectancy of less than six months demonstrated substantial fluctuations in this score over time, within various intervals of time (hours to 1 month) [73]. Therefore, the assessment of a patient's will to live (and consequently to accept a HPS program which primarily aims to prevent an early death from starvation) may be repeated several times during the assessment and only if the answers are consistent should this information be utilised to determine whether to initiate or withdraw a life-sustaining treatment.

It is noteworthy that a study carried out in a Canadian palliative care centre in the mid-1990s reported the presence of cognitive deficit in 44% of patients at the moment of hospitalization and in 55% at time of death or upon hospital discharge [74]. Asking for informed consent by anticipating some situations before they occur is also fraught with difficulties. Coppola et al. (1999) have shown in 2536 patients that there was no constancy in the choices of preferences regarding life-saving treatments expressed in advance, both verbally and in writing [75]. Specifically, the desire to undergo artificial nutrition as a life-sustaining procedure ranged from a very low percentage of subjects by Coppola et al. (1999) to about 70% of patients by Pearlman et al. (2000) [75, 76]. Many factors would contribute to this variability; the context, manor of communication, symptom burden, chance of treatment success conveyed and cultural/religious background of the patient, clinicians attitude and background society will have varying effects.

A survey of the UK based intestinal failure clinicians in 2013 [77], showed that clinicians would support HPS for incurable cancer more often for improvement of QOL rather than increased survival time alone. While the attitude of intestinal failure clinicians influences the treatment advanced cancer patients receive, the attitude of oncologists, gastrointestinal surgeons, gynaecologists, palliative care teams and other clinicians who meet incurable cancer patients is also paramount to referring patients to intestinal failure services, and this is, as yet, unstudied.

Withdrawing of HPS can be a difficult task and should be discussed with the patient and relatives prior to the start of HPS. Should the patient's condition change causing a deterioration of general status the composition and frequency of PN may change or treatment withdrawn. Reassurance should be given that this joint decision will be taken with the direct involvement of the patient and family with the multidisciplinary team. HPS complications such as medically resistant ascites or pleural effusions, central line blood stream infections and thrombosis related to the HPS therapy should also trigger treatment cessation discussions.

Health Economics

The costs of medical therapies are relevant when considered in the context of a health economy with limited financial resources. When comparing the cost of treatments, the absolute costs may be misleading because of the variable impact of treatments on survival length and QOL. Incremental cost effectiveness ratio (ICER) is currently the most prevalent measure of the cost of a treatment per quality adjusted life year, allowing for direct comparison of a wide variety of treatment with variable impacts.

In addition to allowing comparison of different treatments, ICERs also allow for thresholds to be set when treatments are assessed for economically viability. While there is debate about the existence of a fixed ICER thresholds used by the National Institute of Clinical Excellence (NICE) in England and Wales, there is evidence that £30,000/QALY is often used as a cut off threshold [78, 79]. It has been demonstrated that treatments associated with ICER over £30,000/QALY only have an 8% probability of approval [80]. Comparable thresholds are used in several other countries, but controversy exists about the threshold that should be used, for example, in the Netherlands a threshold of up to Euros 80,000/QALY has been proposed according to severity of disease [81].

In health systems where thresholds are used, when the ICER for a desired treatment is above the threshold, the justification for that treatment needs to be strong, with increasing justification needed with higher ICERs. In an example only directly relevant to England and Wales, criteria have been set by NICE for appraisal of 'end of life' treatments that exceed £30,000/QALY. These are: a limited number of patients expected to require the treatment, the treatment should be expected to extend life by greater than three months, the extended survival length is experienced at a QoL anticipated for a healthy individual at a similar age and health economic assessment models would need to be carried out.

The only detailed analysis of the health economics of *benign* indication HPS was carried out in the UK in the study of Richards and Irving in 1996 [82] and did not include any patients with incurable cancer. In their model they calculated the absolute cost of HPS over the first year to be £44,288 with a corresponding ICER of £85,825/QALY. The ICER value reduced to £68,975/QALY after 4 years due to the health economic concept of 'discounting' with longer survival (initial set up cost only needed once, QOL slowly improves in conditions such as inflammatory bowel disease and short bowel on commencing HPS, thereby the ICER is reduced over time).

The health economic assessment of HPS treatment for *incurable cancer* in the UK was carried out in 2013 [52]

showing the ICER for this circumstance is higher at £176,587/QALY. The shorter survival lengths for such patients means that 'discounting' does not apply. To allow for comparison with the benign cost estimates, inflation would need to be taken into account. With uplifting to 2013 prices, due to inflation, the ICER for the first year of benign treatment corresponds to £135,610/QALY, (inflated to 2013 prices, applying 2.9% inflation per year – UK Office of National Statistics). Hence the ICER for incurable cancer patients remains higher, but comparable in the first year at £176,587/QALY.

The multi-variant analysis of incurable cancer HPS therapy costs also suggests that selection of patients with favourable factors for longer survival, better quality life, in combination with reduced PN costs (frequency, complexity, independent of nursing at home) would bring the ICER costs significantly lower [52].

This ICER health economic model is the dominant method used currently in health economy, but this model may not be the most appropriate to appraise all treatments. Several experts have stated a preference for Willingness to Pay (WTP) in setting the thresholds [83]. Research recently commissioned by the UK Department of Health [84] estimated the threshold of WTP to range as high as £70,000/QALY.

Despite the high health economic costs of this treatment, there are special circumstances for supporting the use of this expensive treatment to extend life, such as giving individuals valuable time to reach a short term goal (e.g. impending birth of child or other life events of equal magnitude), which could have long-lasting positive effects on the family and on the image of a health system that has a compassionate attitude towards the care of the terminally ill patients.

References

1. Sepúlveda C, Marlin A, Yoshida T, Ullrich A. Palliative care: the world health organization's global perspective. J Pain Symptom Manag. 2002;24:91–6.
2. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior tochemotherapy in cancer patients. Am J Med. 1980;69(4):491–7.
3. Chute CG, Greenberg ER, Baron J, Korson R, Baker J, Yates J. Presenting conditions of 1539 population-based lung cancer patients by cell type and stage in new hampshire and vermont. Cancer. 1985;56(8):2107–11.
4. Wigmore SJ, Plester CE, Richardson R, a, Fearon KC. Changes in nutritional status associated with unresectable pancreatic cancer. Br J Cancer [Internet]. 1997;75(1):106–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2222706&tool=pmcentrez&rendertype=abstract.
5. Andreyev HJN, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? Eur J Cancer. 1998;34(4):503–9.
6. Bozzetti F, Migliavacca S, Scotti A, Bonalumi MG, Scarpa D, Baticci F, et al. Impact of cancer, type, site, stage and treatment on the nutritional status of patients. Ann Surg. 1982;196(2):170–9.
7. Van Eys J. Effect of nutritional status on response to therapy. Cancer Res. 1982;42:747–54.
8. Tubiana M, Attié E, Flamant R, Gérard-Marchant R, Hayat M. Prognostic factors in 454 cases of Hodgkin's disease. Cancer Res. 1971;31(11):1801–10.
9. Swenerton KD, Legha SS, Smith T, Hortobagyi GN, Gehan EA, Gutterman JU, et al. Prognostic factors in metastatic breast cancer treated with combination chemotherapy. Cancer Res. 1979;39(5):1552–62.
10. Bozzetti F, Arends J, Lundholm K, Micklewright A, Zurcher G, Muscaritoli M. ESPEN guidelines on parenteral nutrition: non-surgical oncology. Clin Nutr. 2009;28(4):445–54.
11. Moldawer LL, Copeland EM. Proinflammatory cytokines, nutritional support, and the cachexia syndrome: interactions and therapeutic options. Cancer. 1997;79(9):1828–39.
12. De Blaauw I, Deutz NEP, Von Meyenfeldt MF. Metabolic changes in cancer cachexia -first of two parts. Clin Nutr. 1997;16(4):169–76.
13. Inui A. Cancer anorexia-cachexia syndrome: are neuropeptides the key? vol. 59. Cancer Res; 1999. p. 4493–501.
14. Fredrix EWHM, Soeters PB, Wouters EFM, Deerenberg IM, Von Meyenfeldt MF, Saris WHM. Effect of different tumor types on resting energy expenditure. Cancer Res. 1991;51(14):6138–41.
15. Moses AWG, Slater C, Preston T, Barber MD, Fearon KCH. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer. 2004;90(5):996–1002.
16. Gibney E, Elia M, Jebb SA, Murgatroyd P, Jennings G. Total energy expenditure in patients with small-cell lung cancer: results of a validated study using the bicarbonate-urea method. Metabolism. 1997;46(12):1412–7.
17. Lundholm K, Holm G, Schersten T. Insulin resistance in patients with cancer. Cancer Res [Internet]. 1978;38(12):4665–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/719645.
18. Shaw JHF, Wolfe RR. Fatty acid and glycerol kinetics in septic patients and in patients with gastrointestinal cancer. Ann Surg [Internet]. 1987;205(4):368–76. Available from: https://insights.ovid.com/crossref?an=00000658-198704000-00005.
19. Zuijdgeest-Van Leeuwen SD, Van Den Berg JWO, Wattimena JLD, Van Der Gaast A, Swart GR, Wilson JHP, et al. Lipolysis and lipid oxidation in weight-losing cancer patients and healthy subjects. Metabolism. 2000;49(7):931–6.
20. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12:489–95.
21. McMillan DC, Elahi MM, Sattar N, Angerson WJ, Johnstone J, McArdle CS. Measurement of the systemic inflammatory response predicts cancer-specific and non-cancer survival in patients with cancer. Nutr Cancer [Internet]. 2001;41(1–2):64–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12094630.
22. Solheim TS, Fearon KCH, Blum D, Kaasa S. Non-steroidal anti-inflammatory treatment in cancer cachexia: a systematic literature review. Acta Oncol. 2013;52(1):6–17.
23. Waterhouse C, Kemperman JH. Carbohydrate metabolism in subjects with cancer. Cancer Res. 1971;31(9):1273–8.
24. Hansell DT, Davies JWL, Burns HJG, Shenkin A. The oxidation of body fuel stores in cancer patients. Ann Surg. 1986;204(6):637–42.
25. Arbeit JM, Lees DE, Corsey R, Brennan MF. Resting energy expenditure in controls and cancer patients with localized and diffuse disease. Ann Surg. 1984;199(3):292–8.
26. Lindmark L, Bennegard K, Eden E, Svaninger G, Ternell M, Lundholm K. Thermic effect and substrate oxidation in response to intravenous nutrition in cancer patients who lose weight. Ann Surg

[Internet]. 1986;204(6):628–36. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med2&NEWS=N&AN=3098197.
27. Ripamonti C, De Conno F, Ventafridda V, Rossi B, Baines MJ. Management of bowel obstruction in advanced and terminal cancer patients. Ann Oncol. 1993;4:15–21.
28. http://www.bapen.org.uk/resources-and-education/publications-and-reports/bans/bans-reports.
29. Baxter JP, McKee RF. The Scottish home parenteral nutrition managed clinical network: one year on. Clin Nutr. 2003;22(5):501–4.
30. Pironi L. Development of home artificial nutrition in Italy over a seven year period: 2005–2012. BMC Nutr [Internet]. 2017;3(1):6. Available from: http://bmcnutr.biomedcentral.com/articles/10.1186/s40795-016-0118-y.
31. Soo I, Gramlich L. Use of parenteral nutrition in patients with advanced cancer. Appl Physiol Nutr Metab [Internet]. 2008;33(1):102–6. Available from: http://www.nrcresearchpress.com/doi/abs/10.1139/H07-152.
32. King LA, Carson LF, Konstantinides N, House MS, Adcock LL, Prem KA, et al. Outcome assessment of home parenteral nutrition in patients with gynecologic malignancies: what have we learned in a decade of experience? Gynecol Oncol. 1993;51(3):377–82.
33. Wanden Berghe C, Candela Gómez C, Chicharro L, Cuerda C, Martínez Faedo C, Virgili N, et al. Registro del año 2010 de nutrición parenteral domiciliaria en España: Grupo NADYA-SENPE. Nutricion Hospitalaria. 2011;26:1277–82.
34. Vafa H, Ballarin A, Arvanitakis M, Vereecken S, Dutat F, Lagasse C, et al. Lessons from a 20 year experience of Home Parenteral Nutrition in adult patients. Acta Gastroenterol Belg [Internet]. 2010;73(4):451–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=362742994.
35. Cozzaglio L, Balzola F, Cosentino F, Decicco M, Fellagara P, Gaggiotti G, et al. Outcome of cancer patients receiving home parenteral nutrition. J Parenter Enter Nutr [Internet]. 1997;21(6):339–42. Available from: http://doi.wiley.com/10.1177/014860719702106339.
36. Gillanders L. Annual report to AuSPEN council. 2011.
37. Jirka A, Svanda J, Tesinsky P, Smejkalova V. National registry of home parenteral and enteral nutrition in Czech Republic: the 2010 data. Clin Nutr Suppl [Internet]. 2011;6(1):87. Available from: http://mcgill.on.worldcat.org/atoztitles/link?sid=OVID:embase&id=pmid:&id=doi:&issn=1744-1161&isbn=&volume=6&issue=1&spage=87&pages=87&date=2011&title=Clinical+Nutrition%2C+Supplement&atitle=National+registry+of+home+parenteral+and+enteral+nutrition+in+C.
38. Takagi Y, Okada A, Sato T, Fukushima T, Shirotani S, Osawa Y, et al. Report on the first annual survey of home parenteral nutrition in Japan. Surg Today [Internet]. 1995;25(3):193–201. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed3&NEWS=N&AN=1995158845.
39. Howard L, Ament M, Fleming C, Shike M. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. Gastroenterology [Internet]. 1995;109(2):355–65. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed6&NEWS=N&AN=25239364.
40. Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and a statistical study. Am J Cancer. 1932;16:1358–414.
41. Drugova TA. Causes of death in patients with cancer of the pancreas who have undergone palliative surgery. Klin Khir. 1972;6(2):28–32.
42. Ambrus JL, Ambrus CM, Mink IBPJ. Causes of death in cancer patients. J Med. 1975;6(1):61–4.
43. Sesterhenn A, Szalay A, Zimmermann A, Werner J, Barth P, Wiegand S. Significance of autopsy in patients with head and neck cancer. Laryngorhinootologie. 2012;91(6):375–80.
44. Brozek J, Wells S, Keys A. Medical aspects of semistravation in Leningrad (siege 1941-1942). Am Rev Sov Med. 1946;4(1):70–86.
45. Bozzetti F, Cozzaglio L, Biganzoli E, Chiavenna G, De Cicco M, Donati D, et al. Quality of life and length of survival in advanced cancer patients on home parenteral nutrition. Clin Nutr. 2002;21(4):281–8.
46. Allison SP. The uses and limitations of nutritional support. Clin Nutr [Internet]. 1992;11(6):319–30. Available from: http://linkinghub.elsevier.com/retrieve/pii/0261561492900822.
47. Bozzetti F. Home parenteral nutrition in cancer. In: Bozzetti F, Staun M, van Gossum S, editors. Home parenteral nutrition. 2nd ed. CAB International Nosworthy Way, Wallingford; p. 118–138.
48. Porzio G, Aielli F, Verna L, Galletti B, Shoja E, Razavi G, et al. Can malignant bowel obstruction in advanced cancer patients be treated at home? Support Care Cancer. 2011;19(3):431–3.
49. Mercadante S. Bowel obstruction in home-care cancer patients: 4 years experience. Support Care Cancer. 1995;3(3):190–3.
50. Bozzetti F, Amadori D, Bruera E, Cozzaglio L, Corli O, Filiberti A, et al. Guidelines on artificial nutrition versus hydration in terminal cancer patients. Nutrition. 1996;12(3):163–7.
51. August DA, Huhmann MB, American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. Clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. J Parenter Enter Nutr. 2009;33(5):472–500.
52. Naghibi M, Smith TR, Elia M. A systematic review with meta-analysis of survival, quality of life and cost-effectiveness of home parenteral nutrition in patients with inoperable malignant bowel obstruction. Clin Nutr. 2015;34(5):825–37.
53. Violante G, Alfonsi L, Santarpia L, Cillis MC, Negro G, De Caprio C, et al. Adult home parenteral nutrition: a clinical evaluation after a 3-year experience in a Southern European centre. Eur J Clin Nutr. 2006;60(1):58–61.
54. Bozzetti F, Santarpia L, Pironi L, Thul P, Klek S, Gavazzi C, et al. The prognosis of incurable cachectic cancer patients on home parenteral nutrition: a multi-centre observational study with prospective follow-up of 414 patients. Ann Oncol. 2014;25(2):487–93.
55. August DA, Thorn D, Fisher RL, Welchek CM. Home parenteral nutrition for patients with inoperable malignant bowel obstruction. J Parenter Enter Nutr. 1991;15(3):323–7.
56. Orrevall Y, Tishelman C, Permert J. Home parenteral nutrition: a qualitative interview study of the experiences of advanced cancer patients and their families. Clin Nutr [Internet]. 2005;24(6):961–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16099552.
57. Seys P, Tadmouri A, Senesse P, Radji A, Rotarski M, Balian A, et al. Home parenteral nutrition in elderly patients with cancer: an observational prospective study. Bull Cancer [Internet]. 2014;101(3):243–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24691188.
58. Finocchiaro C, Gervasio S, Agnello E, Appiano S, Bertetto O, Ciuffreda L, et al. Multicentric study on home parenteral nutrition in advanced cancer patients. Riv Ital di Nutr Parenter ed Enterale [Internet]. 2002;20(2):98–107. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=34851343.
59. Girke J, Seipt C, Markowski A, Luettig B, Schettler A, Momma M, et al. Quality of life and nutrition condition of patients improve under home parenteral nutrition. Nutr Clin Pract [Internet]. 2016;31(5):659–65. Available from: http://journals.sagepub.com/doi/10.1177/0884533616637949.
60. Vashi P, Dahlk S, Popiel B, Lammersfeld C, Ireton-Jones C. A longitudinal study investigating quality of life and nutritional outcomes in advanced cancer patients receiving home parenteral nutrition. BMC Cancer [Internet]. 2014;14(1):593.
61. Culine S, Chambrier C, Tadmouri A, Senesse P, Seys P, Radji A, et al. Home parenteral nutrition improves quality of life and nutri-

tional status in patients with cancer: a French observational multicentre study. Support Care Cancer. 2014;22(7):1867–74.
62. Obling SR, Wilson BV, Pfeiffer P, Kjeldsen J. Home parenteral nutrition increases fat free mass in patients with incurable gastrointestinal cancer. Results of a randomized controlled trial. Clin Nutr [Internet]. 2019;38(1):182–90.
63. Bozzetti F, Cozzaglio L, Biganzoli E, Chiavenna G, De Cicco M, Donati D, et al. Quality of life and length of survival in advanced cancer patients on home parenteral nutrition. Clin Nutr [Internet]. 2002;21(4):281–8. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12135587.
64. Bozzetti F, Cotogni P, Lo Vullo S, Pironi L, Giardiello D, Mariani L. Development and validation of a nomogram to predict survival in incurable cachectic cancer patients on home parenteral nutrition. Ann Oncol. 2015;26(11):2335–40.
65. Grassi L, Giraldi T, Messina EG, Magnani K, Valle E, Cartei G. Physicians' attitudes to and problems with truth-telling to cancer patients. Support Care Cancer. 2000;8(1):40–5.
66. Mosconi P, Meyerowitz BE, Liberati MC, Liberati A. Disclosure of breast cancer diagnosis: patient and physician reports. GIVIO (Interdisciplinary Group for Cancer Care Evaluation, Italy). Ann Oncol. 1991;2(4):273–80.
67. Campora E, Pronzato P, Amoroso D, Bertelli GF, Venturini M, Baldini E, et al. Prognostic factors in node positive primary breast cancer patients treated with adjuvant CMF. Anticancer Res. 1992;12(5):1555–8.
68. Centeno-Cortés C, Núñez-Olarte JM. Questioning diagnosis disclosure in terminal cancer patients: a prospective study evaluating patients' responses. Palliat Med. 1994;8(1):39–44.
69. Ruggeri B. Awareness of disease among Italian cancer patients: is there a need for further improvement in patient information? Ann Oncol. 1999;10(9):1095–100.
70. Espinosa E, González Barón M, Poveda J, Ordóñez A, Zamora P. The information given to the terminal patient with cancer. Eur J Cancer. 1993;29(12):1795–6.
71. Costantini A, Grassi L, Picardi A, Brunetti S, Caruso R, Nanni MG, et al. Awareness of cancer, satisfaction with care, emotional distress, and adjustment to illness: an Italian multicenter study. Psychooncology. 2015;24(9):1088–96.
72. Ordine dei Medici. Consenso informato e accanimento terapeutico. Arri del Congresso, Italy. 2001;November-D.
73. Chochinov HM, Tataryn D, Clinch JJ, Dudgeon D. Will to live in the terminally ill. Lancet. 1999;354(9181):816–9.
74. Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer. 1997;79(4):835–42.
75. Coppola KM, Bookwala J, Ditto PH, Lockhart LK, Danks JH, Smucker WD. Elderly adults' preferences for life-sustaining treatments: the role of impairment, prognosis, and pain. Death Stud. 1999;23(7):617–34.
76. Pearlman RA, Cain KC, Starks H, Cole WG, Uhlmann RF, Patrick DL. Preferences for life-sustaining treatments in advance care planning and surrogate decision making. J Palliat Med. 2000;3(1):37–48.
77. Naghibi M. Home parenteral nutrition therapy for patients with incurable malignancy and intestinal failure. 2017.
78. Towse A, Pritchard C. National Institute for Clinical Excellence (NICE): is economic appraisal working? Pharmacoeconomics [Internet]. 2002;20(Suppl 3):95–105. Available from: http://link.springer.com/10.2165/00019053-200220003-00010.
79. Appleby J. Data briefing. Money for health. Heal Serc J. 2002;112(5815):49.
80. Claxton K, Palmer S, Longworth L, Bojke L, Griffin S, McKenna C, et al. Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development. Health Technol Assess (Rockv). 2012;16(46):1–323.
81. Wyers C, Reijven P, Evers S, Willems P, Heyligers I, Verburg A, et al. Cost-effectiveness of nutritional intervention in elderly subjects after hip fracture. A randomized controlled trial. Osteoporos Int [Internet]. 2013;24(1):151–62. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013036627.
82. Richards DM, Irving MH. Cost-utility analysis of home parenteral nutrition. Br J Surg. 1996;83(9):1226–9.
83. Cookson R. Willingness to pay methods in health care: a sceptical view. Health Econ. 2003;12(11):891–4.
84. Mason H, Jones-Lee M, Donaldson C. Modelling the monetary value of a QALY: a new approach based on UK data. Health Econ. 2009;18(8):933–50.

Monitoring of Parenteral Nutrition at Home

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Key Points

1. The haematological and biochemical monitoring of patients receiving parenteral nutrition at home should be individualised and may change with their clinical condition.
2. Routine blood tests include sodium, potassium, chloride, bicarbonate (as a measure of acid-base balance), calcium, magnesium, phosphate, urea or blood urea nitrogen (BUN) /glomerular filtration rate (GFR), creatinine, liver function tests (albumin, bilirubin alanine transaminase (ALT), aspartate tranaminase (AST), alkaline phosphatase, gamma glutamyl tranferase (GGT), international normalised ratio (INR)), glucose, blood count, ferritin and C reactive protein (CRP)) and are performed every 1–4 months depending upon the stability of the patient.
3. At discharge from hospital patients should have their prothrombin time (INR), cholesterol and triglyceride, Haemoglobin A1c, vitamin D & B_{12} and folate concentrations checked. These are rechecked every 6–12 months. If the triglyceride concentration is elevated a fasting level is taken.
4. Baseline vitamins A&E, zinc, copper, manganese and selenium concentrations are checked initially then every 6–12 months.
5. If the CRP is raised (>25 mg/l), transferrin saturation is used as a measure of iron status. In the presence of sepsis or inflammation, do not measure zinc, copper, selenium or vitamins A, D or E.
6. Urine sodium concentration is useful for assessing sodium balance in patients with a jejunostomy and a 24-hour urinary oxalate collection for assessing the risk of renal stone formation in patients with a short bowel and colon in continuity.

Introduction

Home parenteral nutrition (HPN) is a life-saving treatment that allows patients with intestinal failure to return in the community while receiving appropriate nutrition. Monitoring HPN is important for multiple reasons. It ensures that treatment goals are met, it helps to prevent, recognise and treat complications arising from HPN, it allows an audit of outcomes and more importantly it secures and improves patient's quality of life.

Guidelines and Studies on Monitoring

A series of guidelines (1–7) have been published and cover the topic of monitoring patients on HPN. Most of them recommend that a multidisciplinary team with experience with HPN be responsible for the monitoring and that patient care be assigned to a particular person in the group. The core members of the team include a gastroenterologist, a surgeon, specialist nursing, dietitians and pharmacists. The guidelines also emphasize the fact that monitoring should be guided by outcomes that will have been set with the patient prior to initiation of the treatment. In addition to these goals, impact on quality of life, morbidity, anthropometric measures and incidence of complications related to HPN should be considered. A study by Dreesen (8) conducted in an international

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cohort of 300 HPN patients, all with benign disease, showed that the most important outcome indicators for patients were incidence of catheter related infection, survival and quality of life.

The monitoring regimens found in the major international guidelines (1–6) propose different frequency and timing of monitoring based on the consensus reached by their authors. None of these guidelines are based on randomized controlled trials and a study has yet to show the impact of the different regimens on patient outcome.

The current literature (1–6) outlines a similar biochemical monitoring between articles which includes extended electrolytes (sodium, potassium, chloride, phosphate, magnesium, calcium), glucose, HbA1C, liver function test (albumin, bilirubin, aspartate aminotransferase(ALT), alanine aminotransferase (ATL), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT) and International Normalized Ratio (INR)), renal function test (creatinine, glomerular filtration rate (GFR), urea, bicarbonate), complete blood count, trace elements (zinc, copper, manganese, selenium), iron, ferritin, folate, lipid panel (triglycerides, cholesterol), vitamins (vitamin A, B12, D, E) and Dual-energy X-ray absorptiometry bone scan (DEXA) and C-reactive protein (CRP). Regular clinical assessments are also recommended with monitoring of anthropometric measures including weight, height, mid upper arm circumference, triceps skinfold measurement, mid arm muscle circumference and grip strength. Evaluation of fluid status, oral intake, mood and quality of life are recommended to be part of the assessment.

Interestingly, in a study conducted by Smith et al. in 2002 (9), affiliation with organizations that provide patient support and education was a factor that improved HPN patients' outcomes by improving the quality of life index, lowering depression scores and decreasing the cumulative incidence of catheter-related bloodstream infections over 18 months. The authors suggested that contact between these organizations and patients be facilitated by the HPN programs.

When comparing clinical practice to guideline recommendations, Wengler et al. found in 2005 that of 42 studied European centers, most varied from the recommendations found in the literature (10). 92% of the centers had a multidisciplinary HPN team and in most of these centers the main responsibility for monitoring a patient was assigned to one member of the team. After hospital discharge, 81% of centres continued to monitor patients' skills for HPN administration, with 31 centers organizing home visits carried out either by the HPN team, a home care agency, a community nurse or a general practitioner. After more than 1 year of HPN, stable patients continued to be monitored by the discharging hospital in 73% of centers, a local hospital in 12% and a general practitioner in 11%.

From this report (10), 28 centers had written guidelines for monitoring practices and 23 of those had developed their own local guidelines. The interval for clinical assessment of patients ranged from 1 to 6 months with more than half the centers reporting a range of 2–3 months. At each visit body weight and anthropometry were monitored in all centers. Less than half took blood pressure and pulse at every visit; 88% of centers evaluated the state of hydration and 74% inquired about oral intake. 86% checked the mood of their patients at every monitoring visit.

For laboratory tests, between 95 and 81% of centers measured haematology, biochemistry for liver function, creatinine, electrolytes, magnesium, calcium, phosphate and glucose at every visit. 48% of centers also monitored triglycerides, cholesterol and albumin. Trace elements and analysis of vitamins and folic acid took place at every visit in 19% and 14% of centers respectively. Other centers also monitored these variables regularly but not at every visit. In some cases it was only done if a problem arose. More than 60% of the centers requested BMD once or twice a year and quality of life was assessed in 10 of the 42 centers; 6 of which used the SF 36 questionnaire. The other 4 had their own local questionnaire. In case of complications, patients contacted the HPN in 76% of centers and if admission was needed it was arranged in the HPN-teaching hospital in 95% of cases. When distance was an issue patients were directed to the local hospital. In Scotland, the HPN managed clinical network studied the frequency and adequacy of monitoring in their patient group with their results indicating that length of time on HPN was found to be inversely associated with frequency of monitoring without an increase in complication rates (11).

Core Monitoring

Hospital patients need to be metabolically stable on a parenteral nutrition prescription before being discharged home. Based on the previously mentioned literature and clinical experience, core monitoring for HPN patients is summarized in Tables 1 and 2.

After discharging a new HPN patient initially, blood work should be considered every 1–2 weeks for the first 2 months. If stability is achieved, the interval can be lengthened to monthly for 3 months and then every 3 months (see details in Table 1). Assessment of trace element and vitamin status should be done annually in the stable patient and more frequently in situations that require closer monitoring such as in severe malnutrition or increased losses, when deficiencies or toxic levels are suspected or when a deficiency or toxicity has been diagnosed and is being treated. Clinical interpretation of plasma vitamin and trace element results can only be done with knowledge of the patients CRP level. The effects of the acute phase response on micronutrient levels have been well described by Duncan et al. (12). In patients at risk

Table 1 Suggested laboratory monitoring practice for stable Home Parenteral patients

	Baseline	Monthly for 3 months	Every 3 months	Yearly
Electrolytes	X	X	X	–
Glucose	X	X	X	–
Liver function test	X	X	X	–
Albumin	X	X	X	–
INR	X		X	–
Renal function test	X	X	X	–
Complete blood count	X	X	X	–
Lipid panel	X	–	X	–
Iron and ferritin	X	–	–	X
Vitamin D 25-OH and PTH	X	–	–	X
Vitamin A, E, C	X	–	–	X
Vitamin B12 and folate	X	–	–	X
Trace elements	X	–	–	X
DEXA scan	X	–	–	X
24 hr. urine collection for oxalate	X	–	–	X

Suggested core monitoring based on clinical experience and current guidelines (1–6)

Electrolytes include sodium, potassium, chloride, magnesium, phosphate, calcium. Liver function test include aspartate aminotransferase (ALT), alanine aminotransferase (ATL), alkaline phosphatase (ALP), bilirubin. INR = International Normalized Ratio. Renal function test include creatinine, GFR, BUN. Lipid panel includes triglycerides and cholesterol. Trace Elements include zinc, copper, manganese, selenium and chromium. DEXA = Dual-energy X-ray absorptiometry bone scan

Table 2 Suggested clinical monitoring for Home Parenteral patients

	Baseline	Between 1 and 3 months after discharge[a]	Every 3–6 months[a]	Yearly[a]
Anthropometry	X	X	X	X
Calculation of nutritional requirements	X	X	X	X
Vital signs	X	X	X	X
Physical examination	X	X	X	X
Fluid balance and evaluation of fluid status	X	X	X	X
Oral intake	X	X	X	X
Mood	X	X	X	X
Quality of life	X	–	X	–
CVC examination	X	X	X	X

Suggested clinical monitoring based on clinical experience and current guidelines (1–6)

Anthropometry includes weight, height and body mass index calculation. Evaluation of quality of life should be done with recognized and validated tools (see chapter "Home Parenteral Nutrition for Adults"). *CVC* central venous catheter

[a]Evaluation done in person during clinic or with telehealth

of oxaluria and kidney stone such as those who have steatorrhea and colon in continuity, 24-hour urine oxalate should be monitored every 3–6 months initially, and then yearly, while on a low oxalate diet (see chapter "Nephrolithiasis and Nephrocalcinosis"). Bone density should be assessed at baseline and yearly thereafter (see chapter "Bone and Joint Disease").

Clinic visit should be organized within the first 3 months after discharge. After this initial assessment, future appointment schedule will depend on the stability of the patient. The intervals should range between 3–6 months and eventually yearly. If a patient lives far from the center responsible for monitoring it is possible to rely on technology with the use of tele-health for clinical assessments (13). Evaluation of quality of life should also be done yearly with a validated tool (see chapter "Home Parenteral Nutrition for Adults"). At every clinic visit, weight, anthropometric measures, oral intake, fluid status, central line patency, medications, physical signs of nutritional deficiency, the need for continuation of HPN as well as the symptoms linked to the underlying disease which led to the need for HPN should be assessed (Table 2).

Monitoring of Complications Related to HPN

Besides metabolic complications associated with the administration of parenteral nutrition (PN), long term HPN support is associated with central venous catheter complications, parenteral nutrition associated liver disease, and bone disease. Close monitoring of HPN patients as recommended above may reduce this risk. In addition, patients should be provided with information regarding these complications and how to monitor themselves at home.

Monitoring of Blood Glucose

Self-monitoring of blood sugar at home is not a routine practice in non-diabetic patients whose blood glucose is well controlled before hospital discharge if there is no difference between inpatient and home regimen. However, if there is a significant change in the amount of glucose infused and/or cyclic infusion occurs at home or patient relies on PN as the sole source of carbohydrate (e.g. ultra-short bowel), then blood glucose should be monitored 4–6 hourly (14, 15) to assess risks of hyperglycemia and/or rebound hypoglycemia (16). If these occur, reducing infusion rate by half in the first 2 h of infusion and the last 2 h of infusion as well as a diabetic team review should be considered. Monitoring of blood glucose in non-diabetic patient can be discontinued when the results show consistently normal levels although it is important to be aware that previously stable patients may go on to

develop hyperglycaemia (17). On the contrary, in diabetic patients who require either intravenous insulin in PN or subcutaneous insulin injection, the monitoring is indefinite, but frequencies and subsequent managements should be based on clinical judgement.

Monitoring for Catheter Infections

Catheter related blood stream infection (CRBSI) is one of the most serious complications in patients receiving PN. Signs and symptoms of this infection include fever, chills, hypotension, elevated white count, and, sometimes, elevated liver function tests. There are also other catheter related infections with fewer systemic symptoms, which can eventually progress to blood stream infection. Exit site infection is commonly detected by redness and purulent discharge at the exit site of the catheter. Tunnel infection usually present with redness and tenderness along subcutaneous tract of tunnelled catheter. Tenderness, induration and/or necrosis of skin overlying the implanted device are presented in pocket infection (18). HPN patients and their carers must be educated to identify the potential signs of a CRBSI, an exit site infection or a tunnel infection and know the importance of seeking medical advice should symptoms occur. If a blood stream infection is suspected, blood cultures from both catheter and peripheral vein should be obtained immediately. Although the current clinical guideline for catheter related infection does not define how to manage PN in this situation, it is recommended to temporarily discontinue PN when CRBSI is suspected or confirmed, and administered broad spectrum antibiotics (14). The practice of withholding PN is based on one study showing that continuing PN after a positive blood culture resulted in longer hospitalization (19).

For more details on diagnosis and management of catheter complications please refer to chapter "Prevention, Diagnosis and Management of Catheter-Related Blood Stream Infections".

Monitoring for Hepatobiliary Complications

Long-term HPN may result in intestinal failure-associated liver disease, also known as PN-associated liver disease (PNALD). The clinical presentation of PNALD varies from asymptomatic transient elevated liver function tests that improve with modifying PN prescription (e.g. reduction in total parenteral glucose or lipid energy, or a change in lipid emulsion), to cirrhosis (20). Thus, as recommended in Table 1, it is necessary to have serial measurement of liver function tests in every patient on PN to monitor and detect early, any elevations in liver enzymes or bilirubin. Patients who have sudden or persisting elevations should be further investigated with blood cultures to eliminate a central venous line infection and an abdominal ultrasound to assess for hepatobiliary complications, depending on the clinical situation.

For more details on diagnosis and management of hepatobiliary complications please refer to chapter "Intestinal Failure Associated Liver Disease".

Metabolic Bone Disease Monitoring

Long-term HPN increases the risk of bone loss on top of pre-existing individual's risk factors (e.g. lack of exercise, postmenopausal, etc.). Factors associated with intestinal failure and HPN are multiple and include suboptimal vitamin D levels and low calcium absorption or intake, high amino-acid load, electrolyte imbalance, aluminum contamination, and cyclic infusion (21, 22). The prevalence of vitamin D insufficiency and deficiency is well documented in patients on home parenteral nutrition, even in those receiving additional oral and IV supplementation (23, 24). Thus, annual or biannual bone mineral density testing (DEXA Scanning) should be considered and PN modification, high dose vitamin D supplementation and other managements should be addressed accordingly.

For more details on diagnosis and management of metabolic bone disease please refer to chapter "Bone and Joint Disease".

Weaning off Parenteral Nutrition

The fate of the intestinal failure patients is determined by types (acute, prolonged acute, or chronic) and aetiologies (short bowel, dysmotility, fistula, mechanical obstruction, mucosal disease, etc.) and treatments of each individual. In general, it is widely accepted that intestinal adaptation in surgical short bowel syndrome reaches maximum extent within 2 years after the last bowel resection in adult. Prior to the era of novel growth factor therapies, if elimination of PN is not accomplished in the first 2 years, the probability of permanent PN requirement is 94% (25). Several factors influence the success of PN weaning in this group of patients. Length of remaining small bowel, the presence of colon and ileocecal valve in short bowel play important roles in weaning of PN because of the impact on nutrients and fluid absorption. Residual disease in the remaining small bowel also determines the outcome of weaning in patients with inflammatory bowel disease and radiation enteritis. Other factors that may be associated with the success of PN weaning include use of novel medications (Glucagon-like peptide-2 agonist (GLP-2 agonist), recombinant human growth hormone), age of the patient, duration of time on PN, and nutritional status prior to

weaning (26, 27). Weaning will also be more rapid if growth factors are used (e.g. GLP2-agonist), requiring closer monitoring, initially on a weekly basis until patients are more stable in their weight gain and hydration status. Individualized plans to reduce or stop PN should be established in all patients except for those with a predicted short term survival, such as intestinal failure from inoperable malignant bowel obstruction, and patients with ultra-short bowel syndrome. The aim is to provide the minimum amount of parenteral support to maintain an acceptable nutritional status and prevent dehydration.

Transition from PN support to oral and/or enteral nutrition requires the effort from both patient and multidisciplinary team. Patient' motivation and compliance should be assessed. General education about their underlying diseases, physiological changes of remaining small bowel, as well as, dietary and pharmacological therapies should be reinforced. Furthermore, patients have to understand that the process of PN weaning generally requires life style modifications which include increasing daily oral food intake, modification of daily fluid intake, taking more supplements and medications, and switching some intravenous medications to other formulations.

Optimization of diet, fluid intake, and medications is necessary and should be achieved before weaning of PN. Clinicians in PN team should establish caloric requirement of individual patients based on their resting energy expenditure, activity factor and malabsorption factor. Serial measurements of body weight and actual caloric intake by food diary or food recall should be assessed to confirm if nutritional status is optimized. Adequacy of hydration can be addressed by fluid intake and output records. A pragmatic approach to monitor hydration in clinical setting is daily urine more than 1 L. However, if urine output is not easily measured, urine sodium >20 mmol/L and serial measurements of blood urea nitrogen (BUN), serum creatinine and electrolytes are also useful. Enteral balance (oral fluid intake minus stool output) more than 500 mL per days is suggested by the expert (26), however, it is not a good parameter in short bowel with high ostomy output.

Reduction of PN can be done by either decreasing the days of infusion per week or decreasing the daily infusion volume equally throughout the week (10–30%). Most patients prefer the former because of psychosocial benefits and a potential reduction in catheter infections. However an assessment of the patient's fluid dependence needs to be made before this option is discussed. If this method is chosen, in order to maintain adequate hydration, the PN free nights should not be consecutive. Some patients may require intravenous hydration instead of PN on those days, which can be administered during the day, allowing for a good night sleep.

An optimal interval for making PN reduction decision should be also individualized and based on feasibility of monitoring and PN modification by PN team. Once a week reduction is possible but need close monitoring especially from hydration perspective. During the process of weaning, patient should be monitored, as mentioned above, to ensure adequate nutrition and hydration on weekly basis until stable. This interval of laboratories monitoring should be based on reduction regimen. Besides modification of calories and fluid in PN solution, electrolytes especially magnesium, potassium, and phosphate should be of concern. Antidiarrheal medications and oral vitamins plus trace elements should be adjusted and serum levels of trace elements and vitamins closely monitored. 1–6 mg intramuscular or subcutaneous vitamin B12 supplement is required in patients with history of gastrectomy or distal ileal removal when multivitamins is discontinued together with PN (in UK 1 mg hydroxocobalamin is given intramuscularly every 3 months). Some patients will maintain weight with withdrawal of parenteral macronutrients but overtime may develop micronutrient deficiencies despite oral micronutrient supplementation and will need an ongoing plan to support their micronutrient status parenterally.

A trial of PN discontinuation is considered when PN infusion has gradually been reduced to 3 days or less per week. Weaning of PN is not equal to elimination of all parenteral support. Some patients with a high stomal output require intravenous hydration to prevent fluid and electrolyte imbalances when PN is reduced or terminated.

Conclusion

Monitoring of HPN patients is extremely important in order to maximize the benefits of receiving HPN while reducing complications. This requires a multidisciplinary PN team that has the expertise and experience in following these patients as well as protocols to monitor and avoid or treat promptly any complications. Weaning should be attempted in most patients, in order to improve quality of life and reduce HPN associated complications. This also requires continuous monitoring that needs to be more intensive if growth factors like GLP2-agonist are used.

References

1. Messing B, Joly F. Guidelines for management of home parenteral support in adult chronic intestinal failure patients. Gastroenterology. 2006;130:S42–51. https://doi.org/10.1053/j.gastro.2005.09.064.
2. August D, Teitelbaum D, Albina J, Bothe A, Guenter P, Heitkemper M, et al. Guidelines for the use of parenteral and enteral nutrition in adults and pediatric patients. JPEN. 2002;26 1 Suppl:1SA–138SA. https://doi.org/10.1177/0148607102026001011.

3. American Society for Parenteral and Enteral Nutrition (ASPEN) board of Directors. Clinical guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN. 2009;33(3):255–9. https://doi.org/10.1177/0148607109333115.
4. Gillanders L, Angstmann K, Ball P, Chapman-Kiddell C, Hardy G, Hope J, et al. AuSPEN clinical practice guideline for home parenteral nutrition patients in Australian and New Zealand. Nutrition. 2008;24:998–1012. https://doi.org/10.1016/j.nut.2008.06.004.
5. Staun M, Pironi L, Bozzetti F, Baxter J, Forbes A, Joly F, et al. ESPEN guidelines on parenteral nutrition : home parenteral nutrition (HPN) in adult patients. Clin Nutr. 2009;28:467–79. https://doi.org/10.1016/j.clnu.2009.04.001.
6. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure. Clin Nutr. 2016;35:247–307. https://doi.org/10.1016/j.clnu.2016.01.020.
7. Mercer-Smith G, Kirk C, Gemmell L, Mountford C, Nightingale J, Thompson N; the BIFA Committee. British Intestinal Failure Alliance (BIFA) guidance: haematological and biochemical monitoring of adult patients receiving home parenteral nutrition. 2021. https://www.bapen.org.uk/pdfs/bifa/position-statements/position-statement-haematological-biochemical-monitoring-adult-hpn.pdf.
8. Dressen M, Pironi L, Wanten G, Szczepanek K, Foulon V, Willems L, et al. JPEN. 2015;39(7):828–36. https://doi.org/10.1177/0148607114536926.
9. Smith CE, Curta S, Werkowitch M, Kleinbeck SVM, Howard L. Home parenteral nutrition : does affiliation with a national support and educational organization improve patient outcome? JPEN. 2002;26(3):159–63.
10. Wengler A, Micklewright A, Hébuterne X, Bozzetti F, Pertkiewicz P, Moreno J, et al. Monitoring of patiens on home parenteral nutrition (HPN) in Europe: a questionnaire based study on monitoring practice in 42 centers. Clin Nutr. 2006;25:693–700. https://doi.org/10.1016/j.clnu.2006.01.026.
11. Hallum N, Baxter J, O'Reilly D, McKee R. Home parenteral nutrition in Scotland: frequency of monitoring, aqdequacy of review and consequence for complication rates. Nutrition. 2010;26(11–12):1139–45.
12. Duncan A, Talwar D, Mc Millan DC, Stefanowicz F, O'Reilly DS. Quantitative data on the magnitude of the systemic inflammatory response and its effect on micronutrient status based on plasma measurements. Am J Clin Nutr. 2012;95(1):64–71.
13. Saqui O, Chang A, McGonigle S, Purdy B, Fairholm L, Baun M, et al. Telehealth videoconferencing: improving home parenteral nutrition patient care to rural areas of Ontario Canada. JPEN. 2007;31(3):234–9. https://doi.org/10.1177/0148607107031003234.
14. Edakkanambeth Varayil J, DiBaise JK, Hurt RT. Home parenteral nutrition initiation, monitoring, and weaning. In: DiBaise JK, Parrish CR, Thompson JS, editors. Short bowel syndrome: practical approach to management. Boca Raton, FL: CRC press; 2016. p. 321–34.
15. Edakkanambeth Varayil J, Yadav S, Miles JM, Okano A, Kelly DG, Hurt RT, et al. Hyperglycemia during home parenteral nutrition administration in patients without diabetes. JPEN J Parenter Enteral Nutr. 2017;41(4):672–7.
16. Stout SM, Cober MP. Metabolic effects of cyclic parenteral nutrition infusion in adults and children. Nutr Clin Pract. 2010;25(3):277–81.
17. Edakkanambeth Varayil J, Yadav S, Miles J, Okano A, Kelly D, Hurt R, Mundi M. Hyperglycaemia during home parenteral nutrition administration in patients without diabetes. JPEN J Parenter Enteral Nutr. 2017;41(4):672–7.
18. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1–45.
19. Patel V, Liu X, Paul M, Belisle CD. Longer hospitalization of patients with positive blood cultures receiving total parenteral nutrition. Surg Infect. 2014;15(3):227–32.
20. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med. 2000;132(7):525–32.
21. Buchman AL, Moukarzel A. Metabolic bone disease associated with total parenteral nutrition. Clin Nutr. 2000;19(4):217–31.
22. Seidner DL. Parenteral nutrition-associated metabolic bone disease. JPEN J Parenter Enteral Nutr. 2002;26(Suppl 5):S37–42.
23. Tee CT, Milestone AN, Murugananthan AU, Bernardo D, Gabe SM. Hypervitaminosis D in patients on long term parenteral nutrition. Proc Nutr Soc. 2010;69(OCE7):E554.
24. Bharadwaj S, Gohel T, Deen O, Coughlin K, Corrigan M, Fisher J, Lopez R, Shatnawei A, Kirby D. Prevalence and predictors of vitamin D deficiency and response to oral supplementation in patients receiving long-term home parenteral nutrition. Nutr Clin Pract. 2014;29(5):681–5.
25. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology. 1999;117(5):1043–50.
26. DiBaise JK, Matarese LE, Messing B, Steiger E. Strategies for parenteral nutrition weaning in adult patients with short bowel syndrome. J Clin Gastroenterol. 2006;40(Suppl 2):S94–8.
27. Amiot A, Messing B, Corcos O, Panis Y, Joly F. Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome. Clin Nutr. 2013;32(3):368–74.

Quality of Life

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Key Points

1. QoL reflects a complex interplay of physical and psychological health. It is influenced by a person's independence, position within their environment, social relationships and social standings.
2. QoL in IF may relate to the underlying disease, having a short bowel, medication or needing parenteral support.
3. QoL involves a physical and psychological assessment. It also includes assessing how daily activities have been affected (including employment), eating/drinking, socialising and often stoma/wound management.
4. The SF-36, Euroqol, HPN-QOL, SBS-QoL, PNIQ and HPN-PROQ have and still are used to assess quality of life.
5. HPS patients who require the greatest number of nights per week (and greatest volumes of PS) consistently report the worst QoL which may improve when the PS requirements can be reduced.
6. Patients with a short bowel are mainly affected by thirst.
7. Patients with poor social networks and those of working age who had ceased employment are particularly at risk of depression and anxiety.
8. HPS-dependent patients with SBS and their family members, described restrictions on activities of daily living and physical functioning, highlighting that patients' lives were dominated by their condition.
9. Transplant recipients score better than HPS patients in ability to holiday/travel, fatigue, gastrointestinal symptoms, stoma management or bowel movements. However they have more psychological issues which in addition to being post traumatic, partly relate to fear of graft rejection and the consequences of severe immunosuppression.

Introduction

Patients with a reduction in gut function to the point that they require home parenteral support (HPS) are said to have type 3 intestinal failure (IF) [1]. The overarching aim of HPS is to enable long term survival, while also maintaining, wherever possible, quality of life (QoL). There is no doubt that the requirement for HPS can be burdensome and time-consuming, requiring a significant degree of adjustment for patients and their families [2–5]. Thus, not only may activities of daily living be affected, patients can also encounter sleep disturbance as well as emotional reactions of fear, anger, disbelief or depression [6]. Economic and social restraints associated with the need for HPS can lead to a further restriction of leisure activities and employment opportunities, elements of life that many people may take for granted [7–9]. HPS is frequently life long and, whilst preserving life, it is associated with inherent risks of complications such as catheter related bloods stream infection, thrombosis, biochemical instability and liver disease [5, 10–12]. Readmission to hospital with complications associated with HPS can further impair a person's QoL, as can worry over the development of such complications [13]. Frequent hospitalisation is seen in this cohort of patients which in turn will, of course, have a negative impact upon wellbeing [14–16].

Maintaining QOL has been identified to be of key importance to patients when dependent on HPS [2]. The World Health Organization has defined QoL as 'an individual's perception of their position in life in the context of culture and value systems in which they live and in relation to their goals,

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expectations, standards and concerns' [17]. QoL reflects a complex interplay of a person's physical and psychological health and is influenced by an individual's independence, position within their environment, social relationships and social standings. Tools or questionnaires that are used to evaluate QoL can be grouped into generic measures, thus applicable across a wide range of conditions, and disease-specific measures.

QoL Assessment Tools

General

Across the available literature, the generic Short Form-36 (SF-36) has been the most commonly used tool for QoL measurement in clinical trials [2, 18]. An advantage of a generic tool is that it allows for comparisons and summation from a wide range of studies examining different disease types; for example, a comparison between the QoL of those living with chronic IF and those with end-stage renal failure, both of whom require life preserving therapies that impact upon daily activity and also share the need for long term central venous access [2, 19]. The EuroQoL is also frequently utilised to evaluate QoL and cost-utility; this is a relatively simplistic tool that is often used in conjunction with a second measure such as SF-36 [2]. However, neither EuroQoL nor the SF-36 specifically address the unique issues for patients living with chronic IF, such that disease-specific tools have subsequently been developed, particularly given the more recent and evolving need to evaluate the impact of novel therapies such as growth factors on the QoL of HPS-dependent individuals.

HPS Specific

The first attempt to derive a disease specific tool was by Baxter et al., who developed the HPN-QOL after validation in U.K. patients [20]. The questionnaire contains multi and single-item scales for functional and symptomatic assessment. The functional scales cover general health, ability to holiday or travel, physical function, ability to eat and drink, employment and sexual function, amongst others; for these scales, a high score indicates a high level of functioning. The symptom or problem scales, in which a high score represents high severity or more problems, include body image, fatigue, sleep pattern, pain, stoma presence or absence and body weight. Two questions relate to nutrition teams and the availability of specific equipment related to HPN, in which a high score represents a good outcome [20]. The largest study using HPN-QoL included 699 patients across 14 countries and demonstrated that QoL scores were significantly associated with HPN duration (better after longer-term dependency), underlying disease (better in Crohn's disease and mesenteric ischemia) and living status (worse for those living alone) and, after adjusting for the other factors, with the number of HPN infusions per week [20]. A smaller single centred assessment using HPN-QoL analysed 193 patients and their care givers, demonstrating that those with intestinal dysmotility reported the lowest quality of life [21].

The Parenteral Nutrition Impact Questionnaire (PNIQ) was developed and validated in the U.K. to measure patient reported QoL and lived experiences of HPS [9, 13, 22]. An initial series of semi-structured qualitative interviews with HPS-dependent patients were used to identify the impact of HPS on need fulfilment and then to create a needs-based model and item response theory to design the final version of PNIQ. The tool comprises 20 questions, specifically related to the impact of HPS on QoL. Each question has a dichotomous response of 'True' or 'Not true', with scores summated up to give a total score ranging from 0 (good quality of life) to 20 (very poor quality of life). In contrast to HPN-QoL, PNIQ tests patients' response to HPS and QoL independently of the underlying disease. Notably, PNIQ can typically be completed in under 10 min by the patient without assistance, making it a useful tool for QoL assessment in routine day-to-day clinical practice [13, 23].

The HPN patient reported outcome questionnaire (HPN-PROQ) was developed as a disease specific tool in order to allow patients to identify and address lifestyle concerns they may wish to discuss with their clinician and these, in turn, may lead to more in-depth conversation about psychosocial feelings and QoL [24]. HPN-PROQ consists of 23 HPN related questions, each with a 5-point Likert response scale as well as questions from HPN-QoL. This includes items relating the number of HPN nights, medical devices used in the administration of HPN and the organisation of the service delivery in the community. In addition, questions also specifically assess perceived QoL. The HPN-PROQ provides a way to help foster patient-clinician communication about lifestyle adaptation and QoL [24]. The tools are summarised in Table 1.

Short Bowel

More recently, the short bowel syndrome (SBS)-QoL tool was developed primarily for self-administration specifically in those living with SBS, with or without HPS-dependency. The SBS-QoL relies on Visual Analogue Scale assessment with scores summated to a maximum value, with a recall period of the preceding 7 days. Due to its disease specific nature, SBS-QoL has been particularly used to evaluate the impact of growth factor therapies such as glucagon-like peptide-2 (GLP-2) on HPS dependency and SBS-related symptoms [25, 26].

Table 1 Key features of available HPN or CIF specific QoL measurement tools

QoL measurement tool	Key features
HPN-Qol	• Developed using classical test theory • Scales for functional and symptomatic assessment, with questions also relating to nutrition teams • Assessment of nutritional team support and HPN related equipment
SBS-QoL	• Developed using classical test theory • Visual analogue scale assessment • Disease specific tool for short bowel syndrome
PNIQ	• Developed using item response theory • Dichotomous response questions • Evaluates impact of PN on the individual
HPN-PROQ	• 5-point Likert scales and items from HPN-QoL • Aimed at encouraging dialogue with provider

Factors Affecting Quality of Life for HPS-Dependent Patients and Their Family Members

When viewed in isolation, the available disease-specific QoL tools identify a number of factors that influence an HPS-dependent person's QoL, such as the number of infusions per week, underlying disease and mechanism. However, it is important to recognise that, at any one time and for any individual, QoL represents a complex interplay of social, medical and psychological issues. Nonetheless, identifying common influential factors in cohorts of patients with a specific disease can of course be informative both for research and day-to-day clinical practice.

Effect of Infusion Time/Amount

As noted, there is a clear correlation between frequency HPS requirements and duration of infusion and QoL. Patients who require the greatest number of nights per week consistently report the worst QoL, as evidenced in studies using PNIQ and HPN-QoL, which demonstrated an association between worsening QoL with an increasing number of infusion days [13, 16, 20]. Patients have also reported an improvement in their QoL when a reduction in PS requirements is achieved [26], with Nordsten et al. demonstrating an improvement in SBS-QoL with a reduction in daily PS volumes [16].

Effect of Peptide Growth Factors

The associations between PS frequency and duration of infusion and QoL are important since therapeutic strategies, such as GLP-2 analogues, have the potential to reduce requirements and thus improve QoL. While the GLP-2 analogue, Teduglutide, has been shown to effectively reduce PS requirements in a large randomised controlled study [27], it is noteworthy that initial post-hoc analysis of these data did not demonstrate an improvement in SBS-QoL compared to placebo [26, 27]. However, when considering these initial data, it is important to recognise that QoL was not the primary outcome of the studies, which were also of relatively short duration and, as such, may have been underpowered to achieve an effect on QoL. Indeed, more recently, Jeppesen et al. reported that Teduglutide resulted in volume reduction that was significantly associated with improvements in SBS-QoL [28]. The strongest association was observed with 80–100% PN volume reduction and the effect on QoL was particularly notable in the IBD cohort [28]. A study in 2020 reported that those with the highest baseline PS requirements derived the greatest improvements in QoL from the use of teduglutide [25], which may be expected given that patients with the largest PS requirements report the worst baseline QoL [16].

Eating and Amount of HPS

The ability to eat and maintain oral intake has been described as key goal for HPS-dependent patients [29], which is of course relevant when interpreting the effect of enterohormonal therapies such as Teduglutide on QoL. In a similar fashion, the interplay between intestinal anatomy, HPS requirements and QoL likely explain the finding that patients with less than 50 cm of remnant small bowel report a poorer QoL compared to those with longer bowel lengths, even when adjusting for confounders of age, sex, body mass index and education [16]. It must be recognised that those with shorter remnant small bowel are likely to have greater HPS requirements. However, the additional detrimental effect of a high stoma output and voluminous diarrhoea may also play a part in impairing QoL in those with shorter bowel lengths, which may also explain the association between citrulline levels and QoL reported in patients with SBS, with citrulline acting as a surrogate marker for small bowel mass and function, as well as HPS requirements [29].

Duration of Illness and of Receiving HPS

The length of time an individual has received HPS, as well as the duration of any pre-morbid condition can also influence QoL. Thus, it was recognised more than 20 years ago that those with relatively sudden onset intestinal failure, such as following an acute mesenteric ischaemic insult, may experience an abrupt deterioration in QoL, compared to those already suffering with long term chronic conditions such as

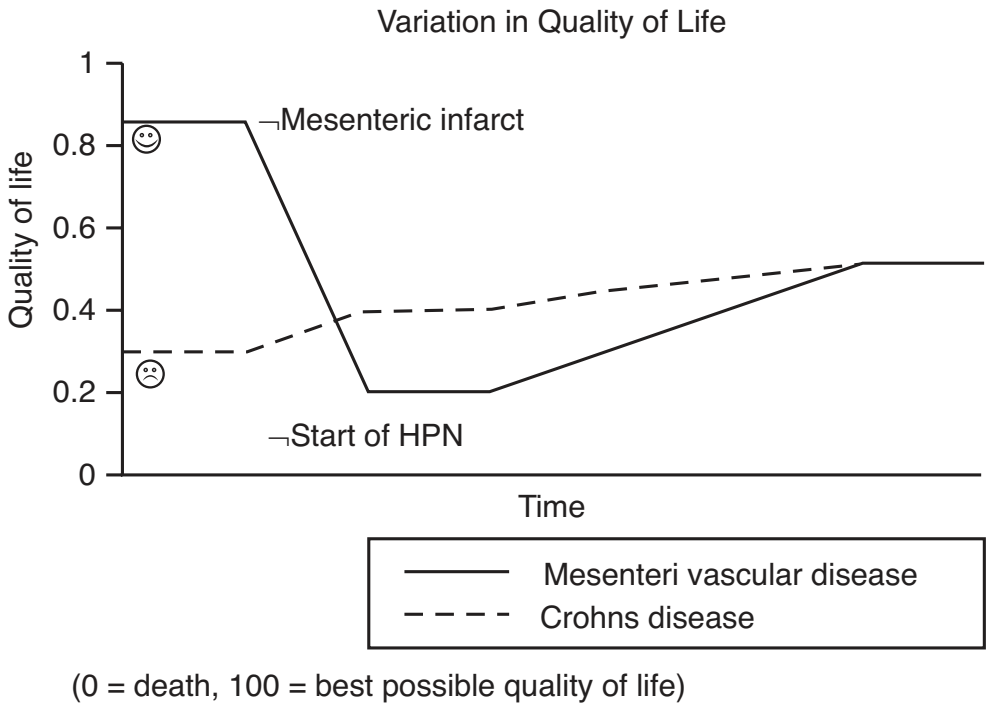

Fig. 1 Quality of life of HPS patient secondary to Crohn's and mesenteric ischaemia and variation with time

Crohn's disease (Fig. 1). In keeping with this, Burden and colleagues more recently demonstrated that those suffering from surgical complications leading to intestinal failure reported a poorer PNIQ score compared to HPS-dependent patients with chronic inflammatory bowel disease [13]; this effect may be explained by the sudden onset of intestinal failure that occurs in patients with surgical complications. Indeed, patients with acute, type 2 IF resultant from surgical complications, typically present after multiple operations and, after prolonged periods of in-patient stay, are discharged home to recuperate on HPN [30, 31] and such patients are often devastated by a relatively rapid deterioration in their QoL [13]. Moreover, better overall HPN-QoL scores were reported in patients with HPN duration longer than 24 months compared to patients with shorter duration [20] and other studies have similarly demonstrated the same pattern of improving QoL with over time [26, 32].

Dysmotility

The reported QoL of HPS-dependent patients resultant from gastrointestinal dysmotility seems to vary according to the tool used. While there has been a report of increased distress secondary to gastrointestinal symptoms and problems with eating in those with underlying dysmotility compared to patients with SBS, this did not seem to have an impact on overall QoL [14, 21]. Baxter et al. used HPN-QoL to demonstrate that patients with GI motility disorders had a lower QoL when directly compared to those with Crohn's or mesenteric ischaemia [20]; however, this was not the case when PNIQ was used to evaluate QoL [13]. This discrepancy may reflect the fact that PNIQ solely evaluates the impact of HPS on QoL, while tools such as HPN-QoL also take into account underlying gastro-intestinal symptoms and patients with gastro-intestinal dysmotility receiving HPS will often continue to have very troublesome symptoms, including pain, nausea and vomiting. Therefore, tools which assess symptom impact as well as HPS impact will likely report lower QoL scores.

Employment

The ability to work and maintain a living will ultimately have a significant impact on an individual's and families' quality of life, as with all chronic conditions. One consistent finding is the positive impact on wellbeing that employment has. Ablett et al. reported patients with poor social networks and those of working age who had ceased employment were particularly risk of depression and anxiety [33]. The number of days per week on HPN and the desire of the patient to return to employment have also been found to be significantly associated with the ability to maintain employment [34]. When compared to HPS-dependent patients receiving an above minimum wage, those paid minimum wage or below had a significantly lower reported QoL [13].

Activities of Daily Living

When using a qualitative, non-interventional interview approach to assess QoL in HPS-dependent patients with SBS-IF, novel themes and drivers can be identified. A recent qualitative assessment of HPS-dependent patients with SBS and their family members, described restrictions on daily life, actives of daily living and physical functioning, highlighting that patients' lives were dominated by their condition. The most burdensome symptoms reported by patients was thirst. In addition, patients described the emotional aspects of living with SBS, specifically with difficulties socialising and maintaining relationships. Patients also described coping mechanisms and adapting their lives around their condition, acknowledging the life sustaining element of the treatment. Family members also described the impact of living with an individual on HPS, reporting that they worried about their relative's condition with some also being affected by the obligations of HPS and the impact it had on QoL. Relatives also reported the importance of achieving a night off from infusions, which is an important consideration for clinicians [35].

Advanced Malignancy

Quantitative and qualitative evaluation of the impact of HPS in those with advanced malignancy and palliative needs have revealed insightful results. Notably, the PNIQ score of patients with advanced cancer was comparable to that of patients with inflammatory bowel disease in a large U.K. study, suggesting that HPS has a similar effect on the QoL of those with benign and malignant conditions [13]. Sowerbutts et al. used longitudinal interviews to assess QoL of patients with ovarian cancer and malignant bowel obstruction, along with their caregivers. Patients considered HPS as an essential element of their condition as a whole. Although it inferred some negative aspects, many considered it as a "lifeline" that allowed them be at home. Negative aspects reported included the loss of normality and the effect it could have on the social aspect of mealtimes. On the whole, many felt HPS was worthwhile because of the extended time they had at home with their relative [36].

Impact on Family Members and Carers

More recent larger studies have further evaluated the impact of HPS on family members and carers. Beursken-Meijerink et al. assessed QoL and distress using the HPN-Qol and the Caregiver Strain Index (CSI) and found that the caregivers of those with dysmotility experienced a higher burden when compared with caregivers of patients with SBS, due to increased demands on time and perceived strain. A multinational, cross-sectional survey from 2021 assessed the impact on caregivers of adult patients receiving parenteral support for short-bowel syndrome. Caregivers reported an overall negative effect, with a reduction in the ability to work full-time. They also reported an impact on daily activities and their ability to participate in recreational activities. When asked about the impact of caregiving on emotions, most caregivers reported worrying about the health of the patient [37]. The health status of the caregiver also appears to be an important factor, with French et al. (unpublished) reporting family members with a poor health status more likely to perceive a moderate to very severe subjective burden when living with an individual dependent on HPS [38].

Intestinal Transplantation

Intestinal transplantation can be considered in patients with unique circumstances of extremely poor QoL (see chapter "Intestinal Transplantation") but, given the risks associated with transplantation, QoL alone should be scrutinised by a multidisciplinary team if used as a single factor indication for transplant [39].

It is difficult to directly compare the QoL of patients of patients receiving HPS with patients who have undergo an intestinal transplant. However, using HPN-QoL as the assessment tool, Pironi et al. made comparisons between people receiving long term HPS for benign disease and those who had undergone intestinal transplant; notably, transplant recipients showed a significantly better score in the domains related to ability to holiday/travel, fatigue, gastrointestinal symptoms, stoma management or bowel movements and the numerical rating scales of quality of life. Furthermore, HPS-dependent patients reported poorer scores for employment and for emotional function [40].

Pither et al. reported QoL scores measured using SF-36 improved in approximately half of the patients compared to their status at listing for transplantation, no change in around one third, and a minority experienced a decline [41]. In a parallel paper, Pither and colleagues evaluated psychiatric disorders in patients pre- and post-transplantation and found that 10 of 14 patients still had a single psychiatric disorder after transplantation and 3 of 14 had also acquired a second psychiatric diagnosis with suicidal ideation in 2 cases. Notably, depression resolved in only 1 patient after transplantation and a further patient without a history of psychiatric issues before being transplanted, developed a double psychiatric diagnosis (anxiety with depression) during the post-operative course [42]. The authors highlighted in their conclusion that the additional stress of transplantation can impact psychological wellbeing, detailing the importance of mental health support during rehabilitation. A further study found that patient personal financial

pressures are greater following intestinal transplant which may affect the morbidity associated with organ graft receipt [43]. A similar effect was reported by Abu-Elmagd et al., whereby a number of domains improved post-transplant, but recipients reported worsening of levels of depression and financial obligation worries [44]. A systematic review published in 2016 reported that post-transplant QoL improved with time since transplant and there is a need for large and longitudinal studies to explore any improvements to QoL and other areas of daily living over time in more detail [45].

When considering QoL as a sole indication for transplantation, it is, of course, important to take survival into account. A prospective 5-year study compared survival of patients with uncomplicated HPN to those with any indication for transplant and found that the probability of survival of individuals considered possible candidates solely on the basis of low acceptance of HPN was 100%; the authors concluded that while desmoids and IF-related liver failure were clear indications for life-saving intestinal transplantation, other indications should be considered on a case-by-case basis [11]. Clearly, the risk: benefit ratio may change as survival following transplantation improves but, for the time being, QoL as a sole indication needs to be carefully considered on an individual basis with the patient and wider multi-disciplinary team, highlighting the risks following any transplant.

References

1. Pironi L, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35:247–307.
2. Baxter JP, Fayers PM, McKinlay AW. A review of the instruments used to assess the quality of life of adult patients with chronic intestinal failure receiving parenteral nutrition at home. Br J Nutr. 2005;94:633–8.
3. Carlson G, et al. Quality of life on home parenteral nutrition: a single centre study of 37 patients. Clin Nutr. 1995;14:219–28.
4. Macritchie KJ. Life without eating or drinking: total parenteral nutrition outside hospital *. Can Psychiatr Assoc J. 1978;23:373–9.
5. Dibb M, et al. Survival and nutritional dependence on home parenteral nutrition: three decades of experience from a single referral centre. Clin Nutr. 2016;16:S0261–5614.
6. Macritchie KJ. Parenteral nutrition outside hospital: psychosocial styles of adaptation. Can J Psychiatr. 1980;25:308–13.
7. Winkler MF, Smith CE. Clinical, social, and economic impacts of home parenteral nutrition dependence in short bowel syndrome. JPEN J Parenter Enteral Nutr. 2014;38:32S–7S.
8. Kumpf VJ. Challenges and obstacles of long-term home parenteral nutrition. Nutr Clin Pract. 2019;34:196–203.
9. Heaney A, et al. The impact of home parenteral nutrition on the lives of adults with type 3 intestinal failure. Clin Nutr ESPEN. 2018;24:35–40.
10. Pironi L, et al. Outcome on home parenteral nutrition for benign intestinal failure: a review of the literature and benchmarking with the European prospective survey of ESPEN. Clin Nutr. 2012;31:831.
11. Pironi L, et al. Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. Gut. 2011;60:17–25.
12. Dibb M, Lal S. Home parenteral nutrition: vascular access and related complications. Nutr Clin Pract. 2017;32(6):769–76. https://doi.org/10.1177/0884533617734788.
13. Burden ST, et al. Needs-based quality of life in adults dependent on home parenteral nutrition. Clin Nutr. 2019;38:1433–8.
14. Sowerbutts AM, Jones D, Lal S, Burden S. Quality of life in patients and in family members of those receiving home parenteral support with intestinal failure: a systematic review. Clin Nutr. 2021;40:3210–20.
15. Persoon A, et al. Impact of long-term HPN on daily life in adults. Clin Nutr. 2005;24:304–13.
16. Nordsten CB, et al. High parenteral support volume is associated with reduced quality of life determined by the short-bowel syndrome quality of life scale in nonmalignant intestinal failure patients. J Parenter Enter Nutr. 2021;45:926–32.
17. World Health Organization. The World Health Organization Quality of Life (WHOQOL); 2012.
18. Scoggins JF, Patrick DL. The use of patient-reported outcomes instruments in registered clinical trials: evidence from ClinicalTrials.gov. Contemp Clin Trials. 2009;30:289–92.
19. Herfindal ET, Bernstein LR, Kudzia K, Wong A. Survey of home nutritional support patients. J Parenter Enter Nutr. 1989;13:255–61.
20. Baxter JP, et al. An international study of the quality of life of adult patients treated with home parenteral nutrition. Clin Nutr. 2019;38:1788–96.
21. Beurskens-Meijerink J, Huisman-de Waal G, Wanten G. Evaluation of quality of life and caregiver burden in home parenteral nutrition patients: a cross sectional study. Clin Nutr ESPEN. 2020;37:50–7.
22. Wilburn J, et al. Development and validation of the parenteral nutrition impact questionnaire (PNIQ), a patient-centric outcome measure for home parenteral nutrition. Clin Nutr. 2018;37:978–83.
23. Baxter JP, Fayers PM, McKinlay AW. The clinical and psychometric validation of a questionnaire to assess the quality of life of adult patients treated with long-term parenteral nutrition. J Parenter Enter Nutr. 2010;34:131–42.
24. Winkler MF, Machan JT, Xue Z, Compher C. Home parenteral nutrition patient-reported outcome questionnaire: sensitive to quality of life differences among chronic and prolonged acute intestinal failure patients. J Parenter Enter Nutr. 2021;45:1475–83.
25. Chen K, et al. Impact of teduglutide on quality of life among patients with short bowel syndrome and intestinal failure. J Parenter Enter Nutr. 2020;44:119–28.
26. Jeppesen P, et al. Quality of life in patients with short bowel syndrome treated with the new glucagon-like peptide-2 analogue teduglutide--analyses from a randomised, placebo-controlled study. Clin Nutr. 2013;32:713–21.
27. Jeppesen PB, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology. 2012;143:1473–1481.e3.
28. Jeppesen P, et al. Impact of teduglutide and parenteral nutrition (PN) volume reduction on quality of life (QoL) in patients with short bowel syndrome and PN dependency. Transplantation. 2017;101:S66.
29. Bednarsch J, et al. Oral intake and plasma citrulline predict quality of life in patients with intestinal failure. Nutrition. 2020;79–80:110855.
30. Lal S, Teubner A, Shaffer JL. Review article: intestinal failure. Aliment Pharmacol Ther. 2006;24:19–31.
31. Klek S, et al. Management of acute intestinal failure: a position paper from the European Society for Clinical Nutrition and Metabolism (ESPEN) Special Interest Group. Clin Nutr. 2016;35:1209–18.
32. Chambers A, Hennessy E, Powell-Tuck J. Longitudinal trends in quality of life after starting home parenteral nutrition: a randomised controlled study of telemedicine. Clin Nutr. 2006;25:505–14.

33. Ablett J, Vasant DH, Taylor M, Cawley C, Lal S. Poor social support and unemployment are associated with negative affect in home parenteral nutrition–dependent patients with chronic intestinal failure. J Parenter Enter Nutr. 2019;43:534–9.
34. Samuel M, et al. Home parenteral nutrition and employment in patients with intestinal failure: factors associated with return to employment. Clin Nutr. 2019;38:1211–4.
35. Sowerbutts AM, et al. Short bowel syndrome and the impact on patients and their families: a qualitative study. J Hum Nutr Diet. 2020;33:767–74.
36. Sowerbutts AM, et al. Palliative home parenteral nutrition in patients with ovarian cancer and malignant bowel obstruction: experiences of women and family caregivers. BMC Palliat Care. 2019;18:120.
37. Jeppesen PB, Chen K, Murphy R, Shahraz S, Goodwin B. Impact on caregivers of adult patients receiving parenteral support for short-bowel syndrome with intestinal failure: a multinational, cross-sectional survey. JPEN J Parenter Enteral Nutr. 2022;46:905–14. https://doi.org/10.1002/jpen.2248.
38. French C, et al. Impact of home parenteral nutrition on family members: a national multi-centre cross-sectional study. Clin Nutr. 2022;41(2):500–7. https://doi.org/10.1016/j.clnu.2021.12.030.
39. Avitzur Y, Miserachs M. Quality of life on long-term parenteral nutrition: can it be an indication for intestinal transplantation? Curr Opin Organ Transplant. 2018;23:199–206.
40. Pironi L, et al. Assessment of quality of life on home parenteral nutrition and after intestinal transplantation using treatment-specific questionnaires: quality of life in intestinal transplantation. Am J Transplant. 2012;12:S60–6.
41. Pither C, et al. Quality of life and performance status before and after small intestinal transplantation. Transplant Proc. 2014;46:2109–13.
42. Pither C, et al. Psychiatric disorders in patients undergoing intestinal transplantation. Transplant Proc. 2014;46:2136–9.
43. Ambrose T, et al. The impact of intestinal transplantation on quality of life. Clin Nutr. 2020;39:1958–67.
44. Abu-Elmagd KM, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg. 2012;256:494–508.
45. Ceulemans LJ, Lomme C, Pirenne J, De Geest S. Systematic literature review on self-reported quality of life in adult intestinal transplantation. Transplant Rev. 2016;30:109–18.

The Patient's Requirements

Carolyn Wheatley, Monika Malickova, Joanne Shepherd, and Steven Brown

Key Points

1. Patients prefer to have their care at home but not all will want to self-care.
2. The patient must feel part of the decision-making processes involving their care.
3. Many have body image issues in addition to physical weakness.
4. While there is feed and ancillaries (equipment and consumables) delivered to the home, the home should not look like a hospital.
5. The patient/carer/parent/guardian needs to understand the underlying medical condition and the reasons for the type of feeding (enteral or parenteral nutrition) and the challenges (including complications) that may occur. It is helpful to have a short medical summary that includes contact details.
6. The aim at home is to be able to return to doing all/most of the activities that were previously done (includes washing/dressing, driving, sport/leisure activities and going on holidays.
7. Patient groups and associations can give very useful support and helpful advice? to common problems.

Introduction

The route to home artificial nutrition is complex and the reasons why it is required are diverse. Navigating this route to successful discharge and home treatment can be challenging. Increasing numbers of patients—both adults and children, are now able to live with varying degrees of independence in their own homes whilst receiving artificial nutrition. Some individuals are immediately dependent on it from birth, whilst for others it is the failure to thrive that subsequently leads to awareness that it is urgently needed. Both adults and children may encounter medical and surgical complications that necessitate artificial feeding during their lifetimes, which then becomes a life-saving home therapy. While many patients are fortunate to have homecare as an option, we know through the network of patient groups, that the availability of homecare varies around the world.

Home is always the goal—it's where people want to be, both those receiving the treatment and their parents, partners and families. For many this will be a welcome relief from long and possible frequent episodes of hospitalisation, but for others it may mean a life of intense routine and isolation. Acceptance that life is dependent upon a specialised treatment, aseptic procedures, complex routines and mechanical equipment can be hard to comprehend. Those able to self-care may find adjusting a little easier, but this should not be assumed. Children will naturally be dependent on their parents/guardians for their care initially.

During treatment, and at intervals along the way, everyone will need the support of family and friends. Whilst they are life-saving treatments, they can be both demanding and a burden [1]. Patients understand these are likely to be needed long-term, and that a desired lifestyle choice may need changing or modifying. An adult may resent being dependent on others for their care and all those involved in home treatment will need to place their trust in the hands of a highly specialised medical team whose skills will allow them to integrate the therapy into their home and personal lives. Additionally, for those who have a homecare service and community support, it will be necessary to determine who is responsible and how this all fits together to provide the necessary support for all concerned.

Patients, parents and carers are fully aware that home nutritional support will not cure their underlying condition, but instead allow them to live with it. In the initial stages, and possibly for the duration of their therapy, both children and

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adults may experience situations and emotions that are psychologically challenging. These experiences can be difficult to explain and are partly due to the subjective effects of both the nutritional support and the underlying illness(es).

There are pros and cons to having hidden conditions and tubes. Invisibility may mean the patient is perceived as 'normal', however, the need for artificial nutrition is often poorly understood by society at large, so many patients can find themselves alienated in a world that does not always comprehend things it cannot see.

Recently, patient groups and associations worldwide have made excellent progress in forging links. It has proved invaluable to learn of the variation in treatment options and homecare. We are now able to appreciate the inequity in both care and services.

Despite difficult, and possibly prolonged periods of hospitalisation, homecare is a natural step for many. However, the journey to going home can be a long one, if it's even an option. There are some patients fighting for their treatment options, parents advocating for their children, and carers, who for a variety of reasons, are also seeking appropriate treatment and choices.

Care in Hospital

Once the decision has been made to commence artificial nutrition, parenteral or enteral, the patient or carers are likely to experience some degree of apprehension. They will be aware that this treatment is only commenced when all other avenues have been exhausted. As the patient may have experienced disappointment following previous treatment failure, doubts may surface. The patient and carers may wonder 'can we afford to place our trust in yet another treatment which may not have a positive outcome?' Often the families and carers involved are juggling work, childcare and education so they want the right decision made for their loved one to expedite improved nutritional status and hopefully discharge.

Weight loss or failure to thrive, has both clinical and physical impacts on the body. People may experience poor body image in addition to the physical weaknesses this imposes. Observing the body wasting away or failing to develop properly, despite all attempts to correct it, can leave the patient with low self-esteem, feeling worthless and defeated. In certain circumstances the individual may lapse into a period of denial, and this state of mind may adversely affect the outcome of their treatment. Parents and carers may feel helpless despite the encouragement and support they provide; their desire to make things better is not always that simple.

Prior to Insertion of Venous Access Device/ Feeding Tube

To support the patient and provide them with all relevant information, it is important to ensure enough time is set aside to discuss all aspects of the process. To facilitate the acceptance of change, the patient needs to feel empowered [2]. Where the parents or carers of a young person are making the decisions, they need equal time and opportunity to discuss it and ask questions. Indeed, the parents/carers will need to explain this to their child and it will be them who they turn to if they have questions. Everyone needs the opportunity to discuss any fears or concerns with the medical team. It is vital that the patient feels part of the decision-making processes [3], as it is their body. Verbal communication needs to be as informal and open as possible. Educational resources, where possible, should be made available in different formats such as film or reading material—as not everyone processes information in the same way.

As soon as the need for a feeding device is identified, the preparation should begin, it should not be rushed nor overlooked. No concern or question should be belittled. Anxieties require discussion and need to be systematically worked through to quell any fears. The patient or carer may benefit from time spent familiarising themselves with the equipment. This juncture is crucial to the acceptance of what will change their life forever—not only will they have a visual and constant reminder that they are now different, but their state of mind may be altered. There are several child-friendly educational resources available, which will certainly aid acceptance for a child. These are also useful for siblings.

At this crucial point of acceptance, the patient and/or their family may need some psychological support to navigate the change. Support should be provided by healthcare professionals who have experience of intestinal failure and artificial nutrition. Some intestinal failure units have acknowledged the benefit of having this support integrated into their service and, as a result, have psychologists as part of the nutritional care team [4].

Dependent upon the patient's state, appropriate anaesthetics should be administered to ensure equanimity during the procedure. For those who have undergone many surgical procedures during their illness, another procedure, no matter how minor, may cause distress. When feeding devices are being replaced, it is important to ask the patient or carer about previous experiences that could impede the smooth operation of the next procedure. They are experts in their own health and procedures. It is important to stress that discomfort and soreness may be present after the insertion. Knowing something is normal and expected can be reassuring.

A positive result for the patient is full acceptance and correct management of their feeding device.

After Venous Access Device/Feeding Tube Insertion

Patients and carers will notice that shortly after nutritional support has commenced the nourishment has a positive impact on the body and mind. Possibly, the initial and most obvious sign of improvement will be a healthier looking patient and weight gain. It may be slow, but the much-needed nutrition will fuel the body. It will become apparent that the patient is more attentive and shows a greater ability to concentrate.

Everyone will be pleased to see the improvements, and this will hopefully contribute to acceptance of the device and the need for artificial nutrition. Patients may previously have been told they looked thin and unwell. Following treatment, it can be satisfying to be told how well you look. Often, it's not until things improve that there is recognition of how bad things were beforehand. However, underlying conditions must not be forgotten during this phase. For parents of tube-fed children weight gain will be welcome, but they will also be keen to know if their child is progressing in other ways too.

For the patient the presence of a feeding device may be both welcomed and feared. It will alter body-image and may not be the only medical attachment they have. Even patients who accepted the need for the device prior to its insertion, may find that the physical presence alters how they feel. They may require support from psychologists with experience of intestinal failure and artificial nutrition; ideally one connected to the nutrition team.

Equipment Management

Tubes and central lines require strict care and observation to ensure they remain patent, safe and infection free. The presence of a feeding device will bring restrictions in terms of clothing, activities and possibly raise questions about sports and swimming. Children may be restricted, and parents may be concerned about normal development milestones that could compromise a feeding device e.g. tummy time, crawling, rolling over and a lot of tossing and turning at night.

All patients have personal feeding regimes, many patients are restricted by feeding tubes and central lines, pumps and equipment—it is unrealistic to assume that all patients stay in bed for the duration of their feed.

For many, as they are starting to regain control of their life, confidence will return and they will be heartened by their improved appearance. A former dislike to weighing scales may vanish as they are now displaying signs that 'this treatment' is working.

Conversely, there are patients who find themselves on artificial nutrition with no time to prepare or adjust; it happens quickly—an accident or sudden health change. For these patients, acceptance takes longer or may not happen. Additionally, not all patients feel better and have complications that add to their medical issues; it's not always a blessing.

A skilled medical team with carefully planned follow-up appointments for the patient, should be in place to not only monitor the clinical parameters but also the psychological aspects of living with home artificial nutrition. They will have seen the 'unexpected' emotions before and their expertise can be used to address these and, if necessary, refer patients, parents and carers for additional support [5].

Training Programme

It is essential that the patient, parents and carers understand the training programme which has been devised for them and appreciate the importance of taking one step at a time. We recognise that the training for parenteral and enteral procedures are different and require different training programmes. Also, there are large variations in training locations. At one time it was always carried out in hospital but in some countries, it's done in the patient's home. There is also variation between the adult and child training.

A training programme should ideally be outlined in advance, providing information on where it will be done and who will be trained. Everyone concerned should be informed; if self-caring is the goal then this should be made clear with goals and clear timelines. For those who will self-care, it will be a one-to-one training progamme. For those who are reliant on parents or carers, an amended programme will be needed. Preferably more than one person will be trained to care for the patient, particularly for children. The best laid plans often need to change, usually at short notice. At no time should day-to-day living cause issues if a sole parent or carer became detained or delayed; feeding and the care of the patient should never be compromised.

Where children transition into adulthood and still require artificial nutrition, transferring skills to create independence and autonomy, should be discussed with the parents and carers as soon as it's considered appropriate. Where possible independence should always be the goal.

Where homecare nursing services are used to train patients, a clear outline of the plan and timescale should be apparent. Sometimes people are eager to take over their own care; whilst others nearing the end of their training may feel uneasy about losing visits from nursing staff. It's essential that no patient, parent or carer should feel that once training ends they are on their own. The availability of a support network must be certain.

Everyone will learn at their own pace; it may be necessary to reiterate certain aspects of the procedures to ensure people understand what they are doing and why. It can be an overwhelming process for some; others will pick it up easily, it's about ensuring the patient is competent and capable of performing the procedures.

Individuals may form a close bond with those who are teaching them; it's a very personal time and during training, people often share their feelings and seek reassurance that it's all going to be okay.

Following initial training, everyone should have the opportunity to ask questions or express their concerns. Also, as new products are introduced, it's preferable if everyone is taught how to use and integrate them. Often basic information is sent out via the homecare companies and patients, but parents and carers are left wondering what to do with them. At all times during the need for artificial nutrition, healthcare professionals should be vigilant to ensure patients, parents and carers are continually reviewed and updated [6].

Life at Home

Going home can be a satisfying feeling, however this may be combined with feelings of anxiety, fear and excitement.

Often, long periods of hospitalisation will have been endured and it may take time to adjust to life on the outside. It will be challenging for all concerned; there will be so much to adjust to; feeding equipment, ancillaries, routines and procedures all to be done in a completely different environment. Home is not a hospital, but it will need to accommodate all the essential elements of the home artificial feeding. Preferably home should not resemble a hospital but the amount of storage required may mean several adjustments need to be made. Some people will dedicate a spare room for this and keep it all stored centrally. Others will need to use every bit of space they can find to fit it all in. The practical aspects of being at home can be a challenge.

Some people receiving home artificial nutrition may have a reduced capacity for oral intake. It will vary between people and for an array of reasons. Adjusting and accepting to this may be difficult for some people and psychological support should be offered to aid the adjustment period. Family life includes food and drink; for being unable to enjoy it or take part has the potential to cause distress, not only to the person receiving artificial feeding but to family and friends. A large portion of social interaction is based around food and drink, birthdays, christenings, weddings and religious events; life with a limited or no oral intake is challenging. Identifying this is important and support should be offered as part of the clinical care. Support groups can help with empathy but often a higher level of care is required.

Babies and young children: For families taking home a baby or small child; while it's exciting, there may be a lack of support from the usual channels, i.e. health visitor, GP, baby clinic and the most natural network of other new families. Home can suddenly feel isolating and lonely. Whilst the goal is to give families the best possible quality of life, the burden of care on the parents is enormous [7]. The only network they may have is medical. It's preferable to balance medical with conventional support.

Children and young adults will start or return to school, college or progress onto university. All aspects of their care and personal needs should be considered; life must go on to provide normal education and development; systems need to be in place to support them on this journey.

Adults at home: Adults may be returning home to find life has carried on without them. How they integrate back into family life, work, friendships and hobbies may be overwhelming depending on how much they are able to participate.

For some people, they are returning home to be on their own, this can be isolating; it's very different to the hustle and bustle of hospital life. Those with partners or other family members at home may find that their loved ones must give up work or education to become full-time carers and the combination of the feeding, medical conditions and daily life may leave little time for activities outside the home. Many people cope extremely well with the immense changes that have occurred. But these coping mechanisms, which partly depend upon the effects of their underlying condition and its treatment, are not automatic and they take time to evolve.

Needs of the carers at home: Consideration should be given to the mental health and emotional needs of the patients; but let us not forget the parents and carers. Everyone will have their own set of challenges, this will fluctuate with health changes and day-to-day living. To make life at home as manageable as possible, focus needs to be on the whole person and not just the feeding.

As we know, patients often return to hospital, it's upsetting when it happens, people truly don't want to be in hospital but often know it's the best place to be. Frequently

admissions cause further emotional turmoil for everyone; once at home it's where people want to stay. Sadly, when life at home starts to settle, fate often dictates that it's time to pack your bags and be re-admitted; often not knowing how long it will be until everyone is back at home.

Feeding

Food is everywhere—television commercials, magazines, advertising hoarding and it is also a key component in celebrating any major event. Eating and drinking are accepted social pastimes and exclusion from these can cause social isolation, leading to depression, social anxieties and loneliness.

Eating and drinking will be advised for each patient depending upon their personal circumstances. Some patients will have upper allowances of what they can consume orally. These allowances should be monitored in the hope that they can be increased, and, for some patients, dietitian involvement can have key benefits. Where limits are set; self-control must be steadfast.

When it comes to the actual process of setting up the feeds, how this affects family or home life will vary from one situation to another. Being part of a normal household may bring unexpected pressures, particularly with timings. Initially, accommodating the feeding into other people's lifestyles may be problematic and adjustments will be required. Those who can self-care will determine how best to accommodate it. If the patient needs a carer to set the feed up, then the timing and availability of their support network will need careful consideration and planning. In some countries, where patients cannot carry out their own procedures, a nursing service may be available. While this is good as the patient can go home, it can be restrictive in terms of rotas and the capacity of the nurses. For example, up to a 2-h window may be given—the nurse will be arriving at some point during that slot. If nursing support is required, sometimes twice a day, then the patient and family may have restricted freedom of movements and feeding time options.

Feeding the patient is the priority; in practice how this works while people juggle their daily commitments can mean a major impact on day-to-day living. In some instances, a child may need more than one parent or an additional carer to assist for logistical reasons; their playfulness, feeling tired or unwell may hamper the parent or carers from being able to perform the procedures safely.

Some people, both adults and children, will need supervision or assistance during the night both in terms of practical help—toilet needs, responding to pump alarms, changing feeding containers/topping up feeds as well as safety needs—for example, failure of equipment, such as tubing leaks, or symptoms of infection requiring immediate hospitalisation. Independent patients may need help with personal hygiene or medication.

The common belief that parenteral feeding at home is administered while the patient is asleep is not necessarily correct. Each patient will have their own sleeping patterns and may not wish to retire to bed early just because it is time to commence feeding. Some patients are electing to feed during the day to try and eliminate frequently disturbed nights due to regular trips to the bathroom. Feeding patterns will not be constant and the time for connecting will fluctuate. As part of the teaching process, the patient should be assured that it will be a natural occurrence for feeding time to vary from those that they have become used to in hospital. Patients, parents and carers should be encouraged to take control of the feeding regimes in terms of timings. Life must go on, families and couples need quality time together, this may be outside the home, so feeding must be adapted to ensure this takes place. Where possible, patients, parents and carers should ensure that the treatment does not rule their lives. The aim of the therapy should be to enable the individual to live life to the fullest and to meet their personal goals.

Equipment

There are various aspects of equipment management that need to be considered for home artificial feeding.

Ancillaries and storage: Initial deliveries of ancillaries may be overwhelming. Patients, parents and carers may not fully appreciate the number of essential items they will be receiving. It may be mentioned that a lot of boxes will be sent but it's not until you see it in the home environment that reality dawns. Storage space may be a significant issue. Ancillaries need to be stored safely yet easily accessible for use, as well as being rotated and used in date order. Keeping curious people out of medical fridges or little people away from interesting medical supplies may be a challenge.

Type of pumps and equipment used in the home: Despite increased awareness of ambulatory feeding pumps, some patients are using hospital-style static pumps in the home environment. These pumps need to be attached to heavy hospital-style cumbersome drip stands. This is across both feeding treatments; enteral and parenteral. However, sadly there are many patients who do not even have a static pump to infuse their feeds. Gravity feeding is still favoured by some countries and healthcare professionals. Mobility is improved where ambulatory equipment is available. This applies within the home—being able to go up and down stairs independently or move freely is a huge confidence

booster. Pumps are evolving which enhance the patient's quality of life; allowing them to feed outside the home and not be dependent upon a power supply to power the pump.

All options should be discussed with the patient, parents and carers. Pumps should be reviewed in line with lifestyles. While we advocate that ambulatory pumps should be considered, backpacks may not be viable for all patients. It will be dependent upon their personal well-being. The development of wheel rucksacks should be welcomed to meet the changing needs of patients, whether that is adults or babies and toddler patients who are learning to crawl or walk and need to be given confidence from an early age [8].

Dedicated parenteral nutrition fridge: There are large variations in how parenteral nutrition is supplied and subsequently stored by the patient. Some feeds are supplied as multi-chamber bags while others are cold-chain bespoke compounded solutions. For those who have cold-chain feeds, the storage facilities should be between 2 and 8° and a dedicated fridge is desirable. Some patients are not given fridges, some need to purchase their own while others have access to anything between domestic fridges and pharmacy quality fridges. Some patients will struggle to accommodate a large fridge and it may need to be 'squeezed' into the home somehow. Ensuring it's not tampered with is also vital, the internal temperature must be maintained to ensure the safety of the parenteral nutrition.

Patients, parents and carers should be asked about their lifestyles and the most appropriate equipment supplied. This should also be reviewed, as they may not necessarily know what the alternatives are. Healthcare professionals need to ensure they support their patients with choices, while being clinically safe, about equipment and ancillaries that could either hamper or enhance their feeding experience.

Deliveries/Supplies to the Home

For the patient to carry out their essential medical treatments they need the relevant ancillaries, and prescribed medication/solutions. There may be various options available to the patient, but some may be time consuming and difficult, especially if we consider that patients are unwell and have varying levels of mobility, particularly when attached to their feed. Gathering supplies from local pharmacies or surgeries and collecting nutritional fluids from hospitals, for example, is less than ideal.

Although homecare companies do not operate in all countries; in an ideal world, all patients should have a reliable service that will minimise stress by delivering complete supplies directly to their home [9]. The delivery times and frequency should be tailored to local resources in conjunction with the instructions from healthcare professionals as they arrange these services for their patients. A desirable goal would be for a homecare company to supply all relevant medical items related to the patient's needs. Centralising contact and distribution would make life much easier for patients, parents and carers. One call, one delivery, one monitoring and checking process.

Where homecare companies operate, there should be a good relationship between the prescribing hospital, the company and the patient. It should be clear how the service will operate, who to contact and how and where the lines of responsibility rest. Where the patient, parent or carer has been given a homecare service, it should meet their expectations and enhance their home feeding regime. They should deliver what's promised, when it's promised and in good condition and be fit for purpose [9]. Ancillaries and fluids should be supplied as expected; any omissions or replacement should be made known to the patient in advance of the delivery. For some patients, it's a struggle to determine what they can have and how many. The lines of approval for ancillaries is often unclear and the importance of a consistent service cannot be underestimated.

This is an area where the patient, carer or parent can feel 'out of control' of the means to sustain their life. They put huge trust in the homecare company and it can be a source of anxiety if errors and mix-ups occur. Whilst a consumer can look at a food and drink item and use their senses of vision, smell, taste etc. to assess the quality, freshness and safety; with medicinal products and ancillaries the consumer is trusting the provider. When errors occur, thoughts as to what other undetectable errors have occurred can be a source of anxiety. Due to the lines of responsibility between the hospital, homecare company and patient, follow-up of errors and ensuring appropriate action is taken can be difficult for the patient themselves to facilitate.

During the COVID 19 pandemic many homecare services were under as much pressure as the hospital services around the world. Homecare services need to be protected and safeguarded to ensure the supply of essential medical nutrition during usual and unexpected crises. Communication with patients/families/careers is vital for reassurance. Information needs to be given to those dependent on homecare deliveries and supplies. Homecare enables people to remain at home unless clinical care is specifically needed in a hospital.

Hospital Follow-Up

All patients, parents and carers understand the need for follow-up and clinic appointments at the hospital. Not only is it necessary to review and monitor their nutritional status but also their on-going underlying condition(s). The frequency

will vary depending on the needs of the individual patient. In addition to follow-up and clinics, some patients may be frequently admitted to hospital to manage various aspects of their needs. While necessary, this is very disruptive to family life, work life, schooling and education. It's upsetting when loved ones are re-admitted, often with no knowledge of how long they will be an in-patient. While the patient is in hospital, life at home doesn't stop; school, work and social occasions continue regardless. Each admission brings familiar emotions, often difficult and painful.

At home, the patient, parent and carer assume the roles of some of the healthcare professionals as they need to monitor and respond to the changing situations at home. Ill-health, raised temperatures, pain, sickness—each need appropriate action. When do you stop trying at home and decide to contact the hospital? Self-diagnosis is common and accepted for those with long-term illness and treatments but knowing when to seek help can be confusing and worrying.

Continual support must be given to the patient, parents and carers, and they must feel secure in the knowledge that advice is available 24 h a day just as it was in the hospital. Contact numbers must be given, but more importantly, where there is an answer machine, they should be checked regularly or provide clear and precise instruction on how to gain access to a person able to provide support. The nurse is generally the team member that the patient turns to in a crisis, therefore their availability and accessibility is paramount to the patient's sense of security.

Unfortunately, many of the problems faced by patients at home appear to occur late in the evening or at weekends. Most patients prefer to deal with their own team members who have knowledge and an understanding about them, which eliminates the need to go over old ground before any help can be offered. Hopefully, the hospital supervising the care will have someone known to the patient on call or at least they can be contacted for expert advice. It's important to realise that most people on home artificial nutrition are experts in their own conditions and care. Many are more than happy to discuss this and work with healthcare professionals to ensure the right treatment options are planned and administered. Patients, parents and carers will be fully aware of all the complications that can arise.

Large units with specialised knowledge in intestinal failure care for many patients receiving home parenteral nutrition. This may pose problems as the distance between home and the hospital may be considerable; requiring the need for a car, for example. However, this does not deter many patients and they elect to stay under their care despite the distance involved. For some a shared care policy can add a reassuring back up for unexpected events.

When a child needs to transition to adult services, there is usually a clear pathway already defined. It's essential that children are not seen as small adults, they have specific needs and when transitioning careful attention must be paid to the emotional and psychological support, not only for the patient but the parents.

Relationships

The need for home artificial nutrition can start at any point in someone's life; unexpectedly—following a trauma or accident or because of a long-term illness which may change over time. As there are various types of artificial nutrition, oral supplements, enteral and parenteral feeding, it is not unusual for some patients to have progressed from one to another based on their personal needs. No matter when artificial nutrition is introduced into a family unit it will have profound effects. If we consider the numerous types of relationships we have in our lives starting from an early age—parents and children, children and siblings/school friends, friends we socialise with, work colleagues, personal relationships—long-term relationships: life evolves as do relationships.

Children should be encouraged to ask questions about relationships as they develop. Altered body image, along with peer pressure, may leave them confused with potential for low self-esteem. As a child approaches puberty and then transitions to adulthood, it can be extremely daunting without the right support.

New personal relationships may be hard to contemplate—long-term ones may be just as difficult to re-establish. Consideration and understanding for all concerned should ease people through these testing times. It often helps to discuss these emotions with either the hospital team or other patients, people who have faced these challenges many times before. Partners and parents often need to adopt the role of the carer, even if this would not be a natural fit for them, which can alter previous relationship frameworks. It's imperative that personal relationships are maintained, but in practice, marriages and partnerships may be put under considerable strain. Other family members will be affected, and their needs may be overlooked. Child and sibling carers' needs are not always met.

Established relationships may be already strained during the diagnosis, admission and treatment phases. Bearing in mind, always, that the underlying condition may still be present and active, the treatment may feel like another set of issues to contend with. All aspects of the need for artificial nutrition will fluctuate and need careful understanding along the way.

In an ideal world we would hope that other people would be more accepting of illness and medical treatments, but sadly we know that this is not always the case. Whilst family and friends may find they can accommodate additional needs such as the use of a wheelchair easily, planning for unseen

conditions and disabilities may not be so easy. For example, strain may be placed on relationships with family and friends who don't make allowances for the need to be home in time to commence feeding. There may be time when activities are planned which the patient finds it difficult to participate in. Feeding regimes can make spontaneity difficult, thereby excluding the patient or adding stress to their life.

When the patient is in hospital, friends and family realise that attendance at social events such as weddings and celebrations is impossible. However, once home, expectations of family and friends might exceed the patient's ability to organise their healthcare needs to attend such events. It might be very difficult for the patient to attend, especially if the event is organised without the patient's needs in mind, but family and friends may not see these difficulties and may view it as the patient being difficult or unreasonable.

Self-confidence can be easily knocked by thoughtlessness or when constant rejections are made, leading to friendship/relationship breakdown. The treatment becomes the obvious obstacle, which can lead to diminished enthusiasm for trying again. Negotiating the relationship maze may be tricky for some, easier for others and it may change throughout the life of the patient.

Talking about sex and relationships should be part of the overall care of the patient, it should be managed by the right people and support offered to those who need it. Sadly, access to psychologists may be patchy. In many places mental health services are not established or funded sufficiently to enable this. However, the mind should be supported as much as the body is; we should never assume patients will just cope [4].

It is assumed that there are fewer psychosocial and sexual problems where low level or implanted feeding devices are used [10]. However, this will vary from patient to patient. Let us not forget that the feeding device may not be the only medical attachment they have, stomas are often present for many, along with scars and dressings.

Education and Work

It can take several weeks, if not months before usual routines or lifestyles can be re-established. The prospect of starting/returning to school or work may need to be reconsidered and based upon feeding regimes and health, adjustments may be required.

School/Education

The safety of the patient, in any setting, must be the priority. For a child at school or in education determining what help they may need, what information needs to be shared and whether any special arrangements need to be put in place, must be discussed and agreed prior to the child returning to school. Obviously, this should be reviewed at frequent intervals. Mainstream school and education should be encouraged unless they have specific needs that cannot be met in these environments.

Work

For those on artificial feeding who will hopefully embark on a career when completing education, their chosen pathway may be already influenced based on their health and feeding. Young adults should be encouraged to grow and prosper and venture into the world with confidence; it goes without saying that support networks should be in place throughout their adventure in life.

For an adult patient, depending upon the type of career the patient has, it may be possible to return with minor or no modifications. For some, the prospect of returning to full-time employment or an established career may not be possible; every effort should be made to ensure the patient has an opportunity to consider all options.

In some instances, partners and parents become a carer for the patient—personal careers and ambitions are set aside to support their loved one. While they often do this freely and unconditionally; it frequently leaves people feeling burdened with the routine and responsibility of home artificial nutrition and the medical needs of the patient.

The perception that ambulatory equipment is a given to easier employment is misleading. We need to consider the many 'health and safety' aspects of offices and companies; they will accommodate medical and special needs much more widely nowadays, but these should not be assumed, just like a child at school, they should be discussed and planned. A recent survey by PINNT showed that adult patients on home artificial nutrition reported that their ability to work was moderately to severely affected [11].

Travelling and Holidays

Planning is key—any time away from home on artificial nutrition requires close attention to detail! Where patients are visiting other countries, it's good to try and establish links for added support, even determining if there is any help in terms of fluids, compounding or healthcare, where possible.

Most patients want to travel, if not for themselves then for the benefit of their friends and family, it's something most people take for granted. Often, it's not the distance you travel but the personal journey you take.

Travelling and holidays are enjoyable and fun; for example, it is often during a holiday that the thought of a fun pas-

time such as swimming is considered. Patients will have at least one feeding device. Currently there is no consensus on swimming.

Travel is also necessary in many aspects of life. For patients who have lifelong artificial nutrition, travel does not just mean a 'week in the sun' but may be required in employment and to visit friends and relatives. At times, travel may be required at short notice, such as the sudden illness or death of a member of the family and the perceived barrier to travel, the artificial nutrition can be especially difficult. Ensuring patients and their parents and carers can travel is crucial to quality of life.

Patients travel via various modes of transport, some find packing the car easier and less stressful, others want to fly. Cruising is becoming increasingly popular with patients, especially no-fly cruises. Several destinations can be enjoyed in one trip, there are medical facilities on-board and storage—especially for parenteral nutrition, and it may be easier to arrange.

Due to heightened security around the world, especially in airports, navigating the strict security systems may be worrying for many. It comes back to planning; making all the right pre-travel arrangements and having the right paperwork should ease the stress and aid a swift and safe transition through the airport.

Where patients have a homecare provider, it's useful to find out what help and assistance they provide with arranging travel or a holiday. There are variations in services, it's always good to ask well in advance of travelling. Some homecare companies have a deadline for requests.

The first trip away can be the most daunting. It is best for the patient to start by talking to their usual healthcare professionals to seek advice. Deciding where to go and when are possibly the most important issues to address. If the chosen destination is warm, the patient may need to consider extra fluids to ensure they do not suffer any effects from dehydration. If the patient is staying in their own country access to their usual support networks should be available to them. However, if they elect to go further afield, there are different aspects to consider. While the basic planning will be the same for both enteral and parenteral patients, for those transporting cold-chain parenteral nutrition it may be more complex.

Patients, parents and carers need to take great caution when travelling, make lists, check and re-check, never forget the basic principles that have been learnt, always take safety stock too. Feeding can be done anywhere providing the procedures and safety aspects are maintained.

Support Groups/Patient Associations

The best support for patients, parents and carers in terms of adapting to life and facing the future on home artificial nutrition, is to meet and talk to others in similar positions. Patient groups and associations have been established in many countries, and often it's a case of locating them and providing information to the patients as part of their discharge planning. For many patients a large proportion of their energy is channelled into maintaining an image of expected well-being. It becomes a natural part of being ill to maintain an outwardly positive facade.

Some groups and associations have been established for many years, others are in the early stages of becoming established. Their remits may vary but fundamentally they all provide a vital support network to patients in their own country or locality as well as setting up International networks. Almost all problems experienced by a new patient have been encountered and resolved by a previous patient. It is reassuring to know that there are others in similar situations who can frequently offer support.

Advice and assistance are tailored to the needs of patients, family and carers. Each group will provide the support and advice they know their members need. Many will campaign for products and services that, if available, would enhance the quality of life for the patient.

Via the patient groups network, we can identify that there is a distinct inequity in both services and products for those on home artificial nutrition. Some patients are fighting for basic care and services, while others don't realise the wealth of choice they have available to them.

In the UK, the patient group PINNT, is a core group and founder member of the British Association for Parenteral and Enteral Nutrition (BAPEN); this well-established relationship has been beneficial for all concerned. If we truly believe all aspects of home artificial nutrition should be managed by multi-professional teams then surely the patients and carers should be part of that. We hope to see this model adopted in more countries.

In addition to groups and associations, modern communication methods provide different models of support via social media. Most are very useful and credible, but caution should always be applied when using social media due to its faceless nature.

Conclusions

Home artificial nutrition provides patients with an essential treatment that can be carried out in their own homes. Often these treatments have saved lives and brought individuals back from the depths of illness, but not provided a cure. All age groups, who receive home artificial nutrition, have been through some very challenging times and no doubt will face further difficulties in the years ahead [12].

Feeds and formulations are continually evolving and feeding lines and tubes are improving all the time. These changes contribute to better outcomes for those receiving the treatments, meaning that many patients are thriving on artifi-

cial nutrition. These improvements also mean that the number of adults who have been on artificial nutrition all their life and have a prognosis of lifelong artificial nutrition is growing. This provides new challenges for healthcare, for example, in a patient with parenteral nutrition, this might mean taking a very conservative approach to preserving venous access, given that the patient will need lifelong access. Many patients, parents and carers develop an inner strength and good coping mechanisms. Life presents its ups and downs and they continually endeavour to overcome each of them in their own unique way. Don't ever assume it's easy; it's an emotional rollercoaster.

Homecare is growing, and we would like to see greater equity for all patients who need these life-saving treatments at home. When faced with illness or trauma, they should not be using their energy to fight for the right to live but channel their energy and personal resources into achieving improved health and an acceptable quality of life.

Patients constantly face the problem of projecting a positive and healthy exterior with no visible signs of the pain and suffering they may be experiencing from their underlying condition(s). Artificial nutrition has enabled patients to manage this, along with their lives to an acceptable standard. The permanent links with hospitals and healthcare professionals are accepted as part of their normal life and the patient becomes an active member of any healthcare team. Their continued support in addition to that of the homecare provider, partners, friends and family is essential to maintain the status quo and it is important for them to remember that each patient is an individual who must be treated accordingly.

Everyone should have access to appropriate healthcare and support that treats them holistically rather than as a sum of their parts.

References

1. Smith CE. Quality of life in long term TPN patients and their family caregivers. J Parenter Enter Nutr. 1993;17:501–6.
2. Patient empowerment – a patient-Centre approach to improve care. Hong Kong Med J. 2002;8(5):372.
3. Liberating the NHS: No decision about me, without me'. 1st edn. London. 2012. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216980/Liberating-the-NHS-No-decision-about-me-without-me-Government-response.pdf. Accessed 29 Sept 2018.
4. Klek S, Forbes A, Gabe S. Management of acute intestinal failure. A position paper from the European Society for Clinical Nutrition and Metabolism (ESPEN) Special Interest Group. Clin Nutr. 2006;35:1209–18.
5. Staun M, Peroni L, Bozzetti F, et al. ESPEN guidelines on parenteral nutrition: home parenteral nutrition (HPN) in adult patients. Clin Nutr. 2009;28(4):467–79.
6. Prioni L, Arends J, Bozzetti F, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35:247–307.
7. Koletzko B, Agonstoni C, Ball P. ESPEN/ESPGHAN guidelines on paediatric parenteral nutrition. J Gastroenterol Nutr. 2006;41:S70–5.
8. Boutin J, Hagan E. Patients' preference regarding portable pumps. J Intravenous Nurs. 1992;15(4):230–2.
9. PINNT. Home parenteral nutrition services in England Patient Charter, 2016. https://pinnt.com/Support/HPN-Patient-Services-in-England-Patient-Charter/Patient-Charter-2016-Final.aspx. Accessed 9 July 2018.
10. Magnay S, Wheatley C, Wood S, Forbes A. Comparison of implanted ports with Broviac/Hickman-style tunnelled catheters for long term home parenteral nutrition: the patient's view. Proc Nutr Soc. 1995;54:103A.
11. PINNT. Short bowel syndrome survey. 2017. https://pinnt.com/getattachment/1862b5f8-7adf-4a5b-94a2-058d7a4002c7/PINNT-Short-Bowel-Syndrome-Survey-2016.pdf.aspx. Accessed 1 July 2018.
12. Farrer K, Cawley C, Page A, Taylor M, and the BIFA Committee. Top tips for discharging a patient on home parenteral support in England. www.bapen.org.uk/pdfs/bifa/bifa-top-tips-series-8.pdf.

Nutritional Support Services

Simon Lal, Simon Gabe, and Jeremy M.D. Nightingale

Key Points

1. Patients with type 1 (short term) intestinal failure (IF) are managed by a hospital multidisciplinary nutrition support team (NST). By keeping careful data a NST should be able to justify itself in terms of quality of care and cost savings.
2. Patients with type 2 (medium term) IF and those re-admitted to hospital with complications associated with type 3 (long term) IF should be managed by a specialised multidisciplinary team on a dedicated Intestinal Failure/Rehabilitation Unit (IF/IRU) in order to achieve an optimal outcome.
3. Core members of the IF multidisciplinary team (MDT) should include gastroenterologists, IF surgeons, specialist nurses, dietitians, pharmacists, interventional radiologists, microbiologists and psychologists/psychiatrists.
4. A ward dedicated solely to the management of patients with type 2 and 3 IF concentrates clinical expertise and can obtain the lowest central venous catheter-related complication rates, while also promoting patient, family and carer support.
5. IF/IRUs should continuously collect data and undertake quality improvement activity on type 2 and 3 IF outcomes, including mortality, surgical and catheter/metabolic complication rates, unplanned re-admissions, waiting times for admission, length of stay and patient quality of life.
6. IF/IRUs should work to national and international guidelines and audit their outcomes.
7. There should be close working relationships between IF/IRUs and intestinal transplant services with regular MDT meetings to overview patient selection and follow-up.
8. The organisation of hospitals specialising in IF/rehabilitation care in a country can be developed into a formal network to harmonise patient care.

Introduction

There are three types of IF [1, 2]. Type I IF (short term) is a common, short-lived and usually self-limiting condition, occurring in approximately 15% of patients in the perioperative setting after abdominal surgery and comprising the vast majority of all cases of IF on general hospital wards [2]. Indeed, more than 90% of patients requiring PN following surgery do so for less than 30 days [3]. Such patients should be managed by hospital NSTs to ensure appropriateness of PN and minimise their risk of PN-related complications [4].

Types 2 (medium term) and 3 (long-term) IF are rarer and more complex conditions [1, 2]. Type 2 IF is a prolonged acute condition, characterised by metabolic instability, whereby patients require intravenous nutrition for weeks or months [1, 2]. Type 3 IF is a chronic condition occurring in metabolically stable patients who require long term, sometimes lifelong, PN; type 3 IF may be reversible or irreversible [1, 2]. Patients with type 2 IF and those re-admitted to hospital with complications associated with type 3 IF should be managed by specialised MDTs on a dedicated IF/IRU in order to achieve optimal outcomes [5, 6].

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Nutrition Support Team

If healthcare staff are not skilled and experienced in giving clinically assisted nutrition and hydration (CANH) serious life threatening complications can occur; with enteral nutrition (EN) aspiration pneumonia and local gastrostomy problems; with PN catheter-related blood stream infection (CRBSI), central vein thrombosis and IF associated liver disease (IFALD).

Many disciplines with different, but essential skills (Table 1), are involved in the safe administration of CANH particularly parenteral support (PS) and these staff need to communicate regularly with each other to give co-ordinated planned care. This is most commonly and effectively done by combining the specialist skills of different disciplines into one NST that works closely together. The composition of a NST team is variable in different hospitals but core members are a clinician, nutrition nurse specialist (NNS), dietitian and pharmacist [7, 8, 11] and they will do a NST inpatient round 2–5 times a week. Gastroenterologists have largely taken on the role of leading an NST because they can achieve access to the gut via endoscopic techniques and they manage patients with intestinal problems. However, some teams are run effectively by a non-gastroenterologist such as a general surgeon, chemical pathologist, anaesthetist or endocrinologist. The most important starting member of a new NST is the NNS who allows safe PN using aseptic techniques [12, 13]. The NNS achieves the administration of safe PN with a low rate of CRBSI initially by personally caring for the central feeding catheters and later by teaching others to put up and take down a PN bag [9]. The techniques used to do this involve strict asepsis (non-touching of key parts) and may be different to the clean techniques used by other disciplines to care for Hickman-type lines. Once PN can be administered safely in a hospital, attention can be directed to the nutritional/fluid requirements with the dietitian and to the composition/compounding of the PN bags with a pharmacist. Thus the traditional NST core membership consists of a clinician, NNS, dietitian and pharmacist though other specialists may be involved particularly when the team works with type 2 and 3 patients (e.g. chemical pathologist, microbiologist, radiologist) (Table 1). A NST improves the quality of patient care largely though education that improves nutritional assessment, appropriate nutrient delivery and reduces mechanical, infective and metabolic complications [9, 14]. The rate of CRBSI should fall to much less than 10/1000 catheter days (ideally nearer to 5/1000 days) after an NST had been formed [13, 15].

Table 1 Members of a nutrition support team [7–10]

Essential member	Roles
Clinician	Overall responsibility, co-ordinated care, may insert enteral and intravenous feeding tubes. Liaises with the patient's primary team. Prescribes the parenteral feeding solution
Nutrition nurse specialist	Teaches and supervises care of tubes and catheters and recognises and manages complications. Places or assists in placement of enteral and parenteral feeding catheters. Acts as the patient's advocate, who also trains patients/carers to manage at home
Dietitian	Nutritional assessment, calculates requirements, designs feeding regimen and monitors nutritional and fluid status. Can also act as a patient advocate
Pharmacist	Responsible for providing enteral feeds and sterile PN nutrition solutions (may include compounding). Optimises composition and advises on compatibility/stability issues and drug/nutrient interactions

NB: the roles may overlap and all are involved in monitoring progress
All the core personnel need cover for all their roles in of case time away (courses, holiday, sickness, etc.)

Other Staff in the Extended NST and Needed for IF/IRUs [10, 16, 17]

Stoma care/tissue viability nurses.
Upper or lower intestinal surgeons (± plastic surgeon).
Social worker.
Physiotherapist.
Occupational therapist.
Psychiatrist/psychologist.
Interventional radiologist.
Microbiologist.
Speech and language therapist.
Other specialists as necessary (e.g. haematologist, urologist, gynaecologist etc).
Community workers (e.g. dietitians and nurses).

Most hospitals in the UK have a NST [18]. While they may be involved with seeing all types of patient needing nutritional support, they are likely to manage many with type 1 IF. Table 2 gives an example of the types of patient referred to the NST for PN.

The overall aim of a multidisciplinary NST team is to provide safe up-to date appropriate nutritional and fluid support to an individual patient, who is malnourished or at risk of

Table 2 Reasons for 117 patients being given PN by an NST in its first year after formation [19]

	n (%)
Short term—type 1	
Ileus	17 (15)
Chemotherapy/GVHD	12 (10)
HIV	4 (3)
Medium term—type 2	
Fistula/anastomotic leak	35 (30)
Small bowel obstruction	28 (24)
Long term—type 3	
High output stoma/short bowel	18 (15)
Other	3 (3)

malnutrition, in a co-ordinated fashion. In many of the patients the care also will involve treating over hydration (usually due to excess intravenous saline) or dehydration (often due to a high output stoma or fistula).

The NST can be "totally responsible (complete autonomy)" in which the team assesses the nutritional and fluid requirements of the patient, established the access for feeding, writes the prescription, monitors progress and manages any complications. It is easier if the team is also responsible for the medical management of the patient but this is not always practical. An alternative way of working is to be "consultative (or supervisory)" and to see patients and advise upon their management. This is more difficult and less efficient as it relies upon good communication with the primary medical team, who need to act upon the advice offered. Often a team will work in a totally responsible way on some wards (e.g. medical gastrointestinal and surgical wards) and in a consultative capacity on others (e.g. ITU, haematology and oncology). At least one member of an NST must see all patients needing PN daily.

The team may perform some procedures itself. Some teams insert all central parenteral lines themselves with or without ultrasound and/or X-ray guidance. Others may insert the peripherally inserted central catheters (PICC) themselves and ask radiologists, surgeons or anaethetists to do other central lines. There is no evidence that the place a central feeding line is inserted relates to the subsequent occurrence of CRBSI providing the insertion is performed using an aseptic technique. Most enteral tubes will be inserted by the gastroenterologists (naso-jejunal (NJ), percutaneous endoscopic gastrostomy (PEG), PEG with a jejunal extension (PEGJ), or percutaneous endoscopic jejunostomy (PEJ)), some will be inserted in a radiology department and others in theatres by surgeons.

An NST needs to establish good links with the local community staff who will care for patients needing enteral feeding. There needs to be clear information/guidelines about the care and contact details if there are problems. When this works well patients will be discharged home more quickly and emergency admissions can be prevented.

The NST is likely to undertake a large educational role both teaching (undergraduates and postgraduates in medicine and nursing, all healthcare workers and many carers/patients) and writing guidelines/policies and setting standards. These are likely to be about nutritional assessment, indications and management of EN and PN. The NNS may teach and establish link nurses on the relevant wards.

The UK NICE guidelines recommend that all hospital trusts have a nutrition steering committee (NSC) to co-ordinate the nutritional care within a hospital and in addition to the NST this includes catering and dietetic services [8] (Fig. 1). In the UK, a freedom of information request in 2017

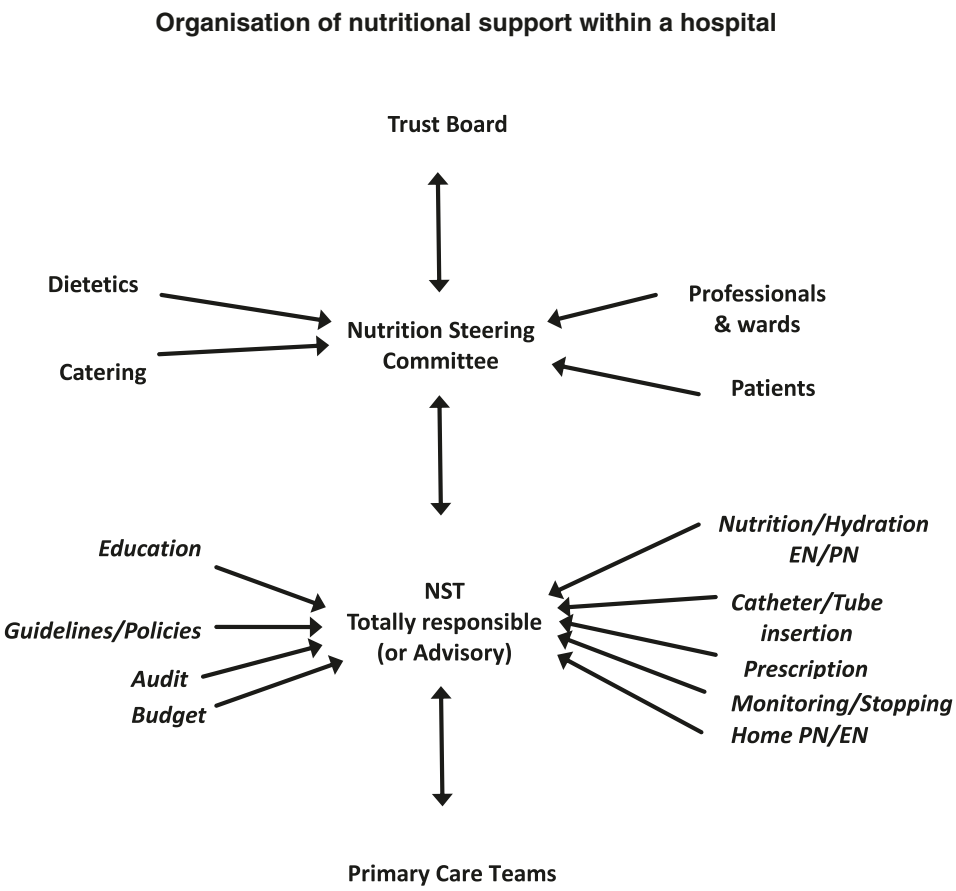

Fig. 1 Organisation of nutritional support within a hospital

showed that 80% of Trusts have a NSC [18]. Core members of the NST are members of and will report to the NSC which oversees their actions and reports directly to the Trust Board (see Fig. 1). Some members of the NST may become involved in the hospital catering.

The Setting Up and the Continuation of a Hospital NST

The process of setting up a team is slow and involves changing the culture of an organisation to one that realises the importance of such a team and questions why it does not have one. This process involves making many presentations to management and healthcare workers. This can be done simply using three questions; where are we now, where do we want to be and how do we get there? In addition a strengths, weaknesses, opportunities and threats analysis may be used (SWOT analysis). In making a business case alternatives need to be proposed and these include doing nothing, having a fully functioning salaried team with backup, or in-between situations (e.g. employing a nutrition support nurse only).

In a hospital with no NST, there is likely to be a problem of unrecognised malnutrition which may be poorly treated with high complication rates and high rates of PS bags being wasted. There may be no or few policies / guidelines and care is likely to be fragmented and uncoordinated. To demonstrate the poor current situation background local data needs to be collected; this may include looking at the prevalence of in-patients who are undernourished or at risk of becoming undernourished and determining how many of these are unrecognised [20] and the staff knowledge of undernutrition and its treatment [21]. The rate of CRS, waiting time for venous access for PN, waiting time for NJ or PEG tube placement, and the number of wasted parenteral feeding bags is relatively easy to obtain. The number of PEGs inserted, their appropriateness and the 30 day mortality rate following placement may also be audited.

The two key steps in setting up a NST are to establish a Nutrition Steering Committee (NSC) which reports directly to the Trust board and to appoint a NNS who can perform and teach the aseptic techniques to safely set up and take down a parenteral feeding bag.

The continuation of the NST at first will depend upon it keeping good audit data. As a minimum it must record details of all patients seen and data about every episode of CRBSI and every other complications of parenteral support (PS) [22]. It should present infection data per 1000 catheter days; percentage of infections is not such a good indicator as it gives no indication of the duration of the feeding before an infection occurred. There should be a clear definition of what a CRBSI is (definite and probable). It may also have data about wasted PN bags, central vein thrombosis and IFALD, and PEGs not inserted and PS not deemed appropriate.

While the employment of a NST involves costs these can be offset by showing quality benefits and cost savings. In terms of PS, the savings come in avoiding giving PS (using EN instead) and in reducing complications especially CRBSI [13]. Additional cost savings can be made by an NST reducing the number of PEGs that are inserted [23] and preventing PN bags from being wasted.

The NST must have plans for backup staff to cover holiday, study leave and sick leave.

Intestinal Failure or Intestinal Rehabilitation?

As described in this book, IF occurs in patients who require nutritional support to survive and there are established types of IF (types 1–3). However, for patients/relatives the feeling that they have a failing organ is not a helpful perception especially if this is a long term or indefinite situation (type 3 IF). Being treated in an IRU by specialists in intestinal rehabilitation implies both hope and specialism. Consequently, some units around the world (England, North America, Columbia and the Middle East) are adopting this terminology that includes rehabilitation (rather than failure) within their names to become an IRU with doctors and other healthcare professionals specialising in the various elements of intestinal rehabilitation. Small changes like this can make a big difference to patients and relatives.

Referral to a Specialised IF/IRU

Specialised units caring for patients with IF are usually called intestinal failure units (IFU). However, the teams offer positive ways of helping patients manage with a life threating condition.

In the U.K., a service specifications outlined referral recommendations for specialised IF care [24] (Table 3). Patients with type 2 IF include those requiring prolonged PN support; the duration of support can vary but, in general, patients needing more than 28 days of PN tend to cross the threshold from having type 1 to 2 IF. However, if the referring team have difficulties managing the patient's medical and/or surgical IF needs prior to 28 days, then earlier referral is appropriate. Intestinal rehabilitation teams should proactively manage patients referred on any waiting list through regular contact with referring teams in order to optimise the patient's condition prior to transfer and to make pre-emptive admission and discharge plans. This may include multidisciplinary contact by a nurse, dietitian and/or physician/surgeon and can involve the use of telemedicine. Any urgent non-IF

Table 3 Referral indications for specialised intestinal rehabilitation care [24]

PN with complications or PN whose duration is causing concern
• More than two episodes of catheter related blood stream infection
• Uncontrolled high output stoma despite standard management
• Central venous thrombosis with associated access problems
• Persistent metabolic complications (e.g. liver or renal dysfunction, diabetes)
• Significant associated psychiatric co-morbidity
IF with intra-abdominal sepsis, fistulation and/or open abdomen
• Recurrent/persistent severe abdominal sepsis
• Complex fistulation requiring surgical reconstruction
• Dehisced abdominal wound or open abdomen needing reconstruction
• High output enterocutaneous fistula despite standard management
• Need for distal limb feeding
• Surgery in a patient with radiation enteritis or inherited connective tissue disorder
• Persistent IF with significant comorbidity
IF occurring in patients requiring intestinal reconstruction
• Surgery for severe intestinal dysmotility
• Intestinal lengthening
Surgical re-appraisal
• Severe intra-abdominal adhesions/potentially hostile abdomen
• IF due to encapsulating peritoneal sclerosis
Establishment on HPN
• Short bowel syndrome
• Uncontrolled high output stoma or fistula
• Severe intestinal dysmotility or mucosal disease leading to malabsorption unable to meet needs via enteral nutrition
• Advanced malignancy with loss of intestinal function

related confounding medical issues should be optimised prior to transfer, where it is safe and appropriate to defer transfer to the IF/IRU. If required, direct transfer to the intensive care may be needed in exceptional circumstances for clinical stabilisation prior to admission to the IF/IRU ward. It is incumbent on the intestinal rehabilitation service to minimise waiting times for transfer where possible; such an approach can mitigate the risk of IF-related morbidity and mortality prior to transfer [25].

IF/IRU Multidisciplinary Team

A broad and experienced MDT (Table 1) is required to manage the complex needs of patients with types 2 and 3 IF. Core clinical members involved in day-to-day patient care include specialist gastroenterologists (with experience in nutrition support), IF surgeons (usually with a colorectal background), specialist nurses, specialist dietitians, specialist pharmacists, interventional radiologists, microbiologists and psychologists/psychiatrists. Patients should be given every opportunity to make informed decisions about their care and treatment, in partnership with their MDT. Subsequent treatment and care should take into account the patients' needs and preferences.

. Depending on the patient's individual requirements, the core MDT may require access to additional specialised services, such as urologists, gynaecologists, pain management teams, plastic surgeons, physiotherapists, clinical biochemists, occupational therapists and social services [1, 5].

Adoption of a cohesive multidisciplinary approach to intestinal rehabilitation care is integral to successful intestinal rehabilitation outcomes. The 'Sepsis-Nutrition-Anatomy-Plan' approach is a tried and tested means to manage the patient with complex IF needs and can form part of the MDT's core standard of care [1, 5].

IFU/IRU Environment

There is a learning curve for the MDT managing patients requiring long term PN, and this affects patient outcomes [26]. Indeed, since then, evidence has confirmed that lack of team experience can have an adverse experience on the survival of patients with type 3 IF [27]. For example, it is clear that the reported incidence of CRBSI rates varies hugely between different centres and that experienced teams with established CVC care protocols achieve the lowest CRBSI rates for both outpatients and inpatients [28, 29]. This was recently further evidence based in a large multinational study of 2194 HPN-dependent patients from 65 centres which demonstrated that the risk of death on HPN and the occurrence of a CVC infection were both negatively associated with the number of patients included in the study by the individual HPN centre; again, the implication of these findings is that centres managing larger cohorts, with therefore likely greater IF experience, can achieve better outcomes [30]. A challenge now is to share best practice between established IFUs and emerging teams in the same and other countries in order to standardise the care delivered so that optimal outcomes can be achieved in all centres.

In the U.K., dedicated IFUs were established in Salford and London in the late 1970s. Both services and the teams' experience have grown over time; the IFUs commenced as small, 4–5 bedded units and have grown to current establishments housing more than 20 beds each. These units have ring-fenced beds within the hospital solely for patients with type 2 or those readmitted with type 3 IF. A clear advantage of such dedicated units includes the ability to concentrate multidisciplinary expertise into one area within the hospital. A key component to day-to-day patient care includes nursing expertise to manage large laparostomy wounds and long term central venous catheters (CVC). Meticulous care is required to achieve wound healing and optimal surgical outcomes, while maintaining a low CVC infection rate, so as not to add to the patient's metabolic

instability with an additional focus of infection. Thus, by concentrating intestinal rehabilitation nursing expertise on one ward within a hospital allows teams to achieve very low in-patient catheter infection rates on such units as compared to patients receiving PN on general hospital wards. While quality improvement measures, including the introduction of a nutrition support team, were shown to reduce the catheter-related infection rates in patients with type 1 IF receiving PN on general hospitals ward to a low level of around 0.7 per 1000 [4], this figure was still greater than 17-fold higher than the 0.04 in-patient catheter-related infection rate reported for patients with type 2 and type 3 IF cared for on a dedicated IFU in the same hospital in Salford [29].

Beyond very tangible clinical outcomes such as catheter infection rates, dedicated IF/IRUs also benefit patients and families by providing an environment for patient-to-patient peer support. Patients can stay in hospital for a number of months, often a significant distance from home and, therefore, appropriate facilities also need to be offered on the IF/IRU to improve patient outcomes and enhance patients' and families' experiences. Access to social areas, overnight accommodation for families and catering facilities help patients and their visitors interact, so promoting the peer support that is fundamental in helping individuals live with chronic and rare conditions. A quiet area or room that allows psychological counselling, along with more specialised facilities such as cold storage for PN and bioelectrical impedance equipment for dietetic assessment, can also help focussed delivery of care by the MDT. In the past, both U.K. units dedicated an area for training patients to administer PN while in-hospital. However, with an increasing service demand and associated pressure on in-patient beds, patients are now trained at home by home care nursing teams with no detriment noted to CRBSI rates [28].

Out-Patient Follow-Up

Patients with type 3 IF require regular review in the outpatient setting by the MDT, not only to ensure safe and tailored delivery of PN support, but also to optimise patient and family psychological wellbeing. Thus, the outpatient MDT largely mirrors that delivering inpatient care, with dietetic and pharmacy review, physician and surgical input, as well as nursing and psychological support. While patients may require regular hospital attendance for physical examination, there has been an increasing desire by patients to avoid long distance travel, such that established IFU MDTs now offer the option of telemedicine (with telephone or video consultations) [31]. Notably, this approach has not only been offered for medical review, but also for dietetic, nursing and psychology review where necessary with positive feedback from patients, particularly through avoiding the need to travel [31]. Following the recent Covid-19 pandemic this has become much easier to perform for both the healthcare staff and patients.

It is also, of course, vital that all intestinal rehabilitation teams offer 24-h access to specialist advice and admission to the dedicated IF/IRU when required. Patient guided self-management using appropriate education material reduces complication rates and anxieties related to HPN complications; both U.K. units have also found that the use of novel personal health records or e-portal systems supports this approach by allowing patients and other hospital teams access to clinical records as well as secure ways of patients interacting with their clinical team while at home [32]. Using these systems patients can ask questions from the team as well as upload images, results or correspondence. In addition, some personal health record systems enable easier communication between different healthcare professionals, especially when transferring information between multiple care providers [33].

As survival improves, an increasing requirement for transition from paediatric to adult centres has been recognised in most countries. Again, considered and early outpatient MDT involvement in these processes is mandatory to manage patient and parent expectation, minimise risk and also, ultimately, achieve autonomy for the patient in managing his/her own long term healthcare needs.

Quality Outcomes

It is the responsibility of all IF/IRUs to collect data on outcomes of type 2 and 3 IF, including mortality, re-fistulation rates, CRBSI rates, CVC thrombosis rates, unplanned re-admissions, waiting times for admission and length of stay. Progressive teams are also encouraged to embrace quality improvement methodology to address any issues that may arise; examples of successes of this approach include practice changes to reduce admission waiting times and in-patient lengths of stay [34], as well as PN wastage [25]. It is now equally incumbent on intestinal rehabilitation teams to evaluate the quality of life of patients with IF. We aim that completion of a needs-based QoL tool that takes patients minutes to complete, will now be routine practice for patients with type 3 IF in the U.K. [35]. While established tools such as the hospital anxiety and depression scale can currently be used for in-patients, a more dedicated patient-reported outcome measure is required for patients with type 2 IF. Ultimately, all recorded clinical and quality of life outcome measures should be part of a national IF registry, allowing continued monitoring of intestinal rehabilitation service provision.

Home HPS Care Providers

In the UK there is a PN framework contract with commercial companies that compound, dispense, and deliver the PS bags. They are responsible for supplying all equipment (fridge, pumps, drip stands, working surface etc) and ancillaries (dressing packs, flushes etc). They have to ensure they meet quality, time, cost and professional standards. In addition, an increasing number of patients have the feed set up and taken down by the companies trained nursing staff.

Intestinal Transplantation

Around the world there are very different approaches to the timing and position of intestinal transplantation in the management of patients with IF. This can relate to the availability and success of HPN and transplant services in different countries and healthcare systems. Both services are costly for any healthcare service and some countries do not offer either service. In countries that offer both long term HPN and intestinal transplantation, there will be established criteria that need to be met for intestinal transplantation (chapter "Intestinal Transplantation").

Unlike heart, lung and kidney transplantation, there is much less awareness of the possibility of intestinal transplantation in the general public, patients and even healthcare workers [36]. The staff working in an IFU/IRU need to be aware of the indications for transplantation and should also be aware of the patient journey undergoing an intestinal transplant in order to start this conversation. At a practical level, this may be easier where an IF/IRU is co-located in the same hospital as an intestinal transplant centre. For IF/IRUs that are not co-located with an intestinal transplant centre, it is important that there are close working relationships with the regional or national transplant service that involves systems for regular MDT meetings to overview patient selection and follow-up.

IF Networks Within and Between Countries

In 2001 a patient survey in the UK by the patient advocacy group PINNT suggested that patients appreciated expert care in specialised centres with high reputations, but found the distances involved in attending these units for routine care, unforeseen problems or emergencies excessive. Patients want care that leads to an improved quality of life. However, in view of the fact that severe IF is a rare condition, there has to be a balance between centralising the expertise required for specialised services and providing more accessible services with potentially less expertise.

Consequently, in 2007 a national review was undertaken by the NHS which resulted in the publication in 2008 of 'A Strategic Framework for Intestinal Failure and Home Parenteral Nutrition Services for Adults in England' [10]. There was significant geographical variation seen in the management and prevalence of both type 2 and type 3 IF. In addition, there was no consistent coding to identify patients with type 2 IF and the costs were high to manage these patients. It was proposed that a network of specialist hospitals differentiated by their skill sets would be best to cater for the population of patients with IF in England. A specialised definition set was also developed which included standards that should be met by the service [24].

Recently, in England a network comprising HPN centres (predominantly care of type 3 IF), Integrated Care (IC) centres (caring for patients with both types 2 and 3 IF) and National Reference Centres has been developed. In 2021 the IC and National Reference Centres were appointed with the HPN centres appointed later in 2021. The whole network (HIFNET—Home parenteral nutrition & Intestinal Failure NETwork) will work to common protocols and standards to help to unify practice across the country to the overall benefit of patients.

This approach to develop a network of units or hospitals within a country by the NHS is unique and we believe that it will help to set a standard globally as well. There is very significant geographical variation in both the prevalence of IF and the management of the condition, which would benefit from harmonisation.

Networks between countries are more difficult to organise but the European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) have been instrumental in helping to facilitate this by developing guidelines for these conditions [5, 6, 37–40]. In addition, ESPEN developed special interest groups in both acute and chronic IF enabling international cooperation, surveys and studies. The BAPEN special interest group (BIFA, the British Intestinal Failure Alliance) has also developed guidance and top tips that have been widely disseminated (www.bapen.org.uk/about-bapen/bapen-special-interest-groups/bifa).

Appendix

Key Education Topics for Members of a NST [41]

1. Understand the role of a hospital nutrition support team (NST) in giving good quality, safe nutritional care.
   - Consists at least of a clinician, nutrition nurse specialist, registered dietitian and pharmacist.
   - Advises and manages the care of patients needing clinically assisted nutrition and hydration.

2. Include nutritional/fluid status into every patient's clinical notes and state where appropriate a nutritional/fluid care plan.

Basic Physiology

3. Understand how appetite/food intake is regulated. This includes neurological, hormonal and psychological mechanisms.
4. Understand the processes of digestion and absorption (for macronutrients, water, minerals and vitamins), including the importance of colonic fermentation. Know the volumes of the gastrointestinal secretions in health. Know the variable length of the 'normal' small intestine.
5. Know how the estimated daily requirements are derived and appreciate that they vary with rest, physical activity, illness and during life.
6. The essential components of a diet are macronutrients (carbohydrate, fat and protein), water, minerals (includes those often referred to as electrolytes (Na, K, Cl, Mg, P) and trace elements (e.g. Se and Zn)) and vitamins. Know the daily requirements for water and key minerals in health and in illness (including post-operatively).
7. Understand how inflammation and specific diseases (including sepsis, trauma, burns and cancer) and their treatments influence nutritional status and needs by affecting:
   - intake, digestion and absorption
   - requirements
   - losses of water and electrolytes (e.g. from the gut or urine)
8. Know the effects of acute and chronic malnutrition on physiological (especially muscle), biochemical, immunological and mental processes.
9. Understand the processes of adaptation (hyperphagia, structural and functional adaptation) that may occur in patients with a short bowel (especially when the colon remains in continuity).

Problems of Malnutrition

10. Be aware of the effect of malnutrition on clinical outcomes (including complications, length of stay and readmission rate) via mechanisms including:
    - muscle strength (thus mobility and respiratory reserve),
    - wound healing and the risk of pressure ulcers
    - resistance to infection

Problems of Under and Over Hydration

11. Dehydration may cause acute and chronic kidney injury and death. Over hydration (especially saline excess in surgical patients) delays recovery, increases mortality, complications and the duration of the hospital admission.

Recognition/Detection of Patients Who Are Malnourished or at Risk of Becoming So

12. Appreciate the methods and importance of formally assessing nutritional status and the limitations of relying on the initial clinical impression alone. The assessments include:
    - Detecting those currently malnourished from the calculation of BMI, percentage weight loss and mid arm muscle circumference. A measure of muscle function (e.g. grip strength or sit up to squat (SUSS) test) may help. Other tools may be used and include subjective global assessment (SGA), malnutrition universal screening tool (MUST) and the global leadership initiative on malnutrition (GLIM).
    - Detecting those at risk of becoming malnourished from the current nutrient intake and the illnesses' predicted course.
13. Recognise intake (oral) failure (inability to get food into the gut) due to poor dentition, poor appetite, head/neck cancer/trauma, neurological disease (e.g. stroke, cerebral palsy, motor neurone disease, multiple sclerosis) and psychological disorders (e.g. dementia, depression and anorexia nervosa).
14. Recognise the symptoms and signs of typical and atypical eating disorders (and other psychological problems) and know how/when to obtain help from eating disorder specialists.
15. Recognise digestive and absorptive (intestinal) failures. Digestive failure is due to gastric or pancreatic disease and absorptive (intestinal) failure due to short gut, intestinal fistula, obstruction, dysfunction or mucosal disease.
16. Identify patients at risk of developing refeeding problems (e.g. low phosphate) when food (especially carbohydrate) is introduced to a malnourished patient. Know the principles to prevent and treat this.

Recognition of Patients Who Are Dehydrated or Overhydrated

17. Recognise the clinical symptoms, signs and observations (e.g. weight, fluid balance, postural blood pressure, urine sodium concentration) of over and under hydration.

Treatment (Nutrition and Fluid)

18. Appreciate that giving nutritional support to malnourished patients improves the quality of life, morbidity and mortality. Some diseases (e.g. COPD, CCF, IBD and

cancer) and surgical procedures have a better outcome if nutritional status is improved or normalised.

19. Know how to calculate fluid requirements (including an intravenous infusion regimen for a patient taking nothing by mouth) and know how to take into account losses (e.g. nasogastric aspirate, small bowel stoma/fistula output). Be able to monitor fluid balance with daily weight and fluid balance charts; and sodium balance with a urinary sodium concentration (especially important in patients' with a small bowel stoma/fistula).
20. Know the indications and goals for nutritional/fluid support. Have knowledge of the routes (oral, enteral and parenteral) of giving nutritional support and the advantages and disadvantages of the different forms of nutrition/fluid support.

Problems of Treatment

21. Have knowledge of the problems that can occur with enteral nutrition (e.g. mal-positioned enteral tube, leakage, blockage or associated diarrhoea) and with parenteral nutrition (e.g. catheter-related blood stream infection, central vein thrombosis/stenosis, intestinal failure associated liver disease and metabolic bone disease).

Ethics

22. Know and understand how to apply the principles of the ethical and legal aspects of providing, withholding or withdrawing nutrition and hydration treatment. This includes autonomy, beneficence, non-maleficence, justice and mental capacity.

References

1. Lal S, Teubner A, Shaffer JL. Intestinal failure: a review. Aliment Pharmacol Ther. 2006;24(1):19–31.
2. Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34:171–80.
3. National Confidential Enquiry into Patient Outcome and Death (2010) Parenteral nutrition: a mixed bag.
4. Hvas C, Farrer K, Donaldson E, Blackett B, Lloyd H, et al. Introduction of a complete nutrition support team increases appropriate parenteral nutrition use and reduces its complications. Eur J Clin Nutr. 2014;68(12):1294–9.
5. Klek S, Forbes A, Gabe S, Holst M, Wanten G, et al. Management of acute intestinal failure: a position paper from the European Society for Clinical Nutrition and Metabolism (ESPEN) Special Interest Group. Clin Nutr. 2016;35:1209–18.
6. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35(2):247–307.
7. Lennard-Jones JE, editor. A positive approach to nutrition as treatment. Report of a working group on the role of enteral and parenteral feeding in hospital and at home. London: Kings Fund Centre; 1992.
8. Nutrition support for adults: oral nutrition support, enteral tube feeding and intestinal failure. Clinical guideline [CG32]; 22 Feb 2006. Last updated August 2017.
9. Nightingale JN. Nutrition support teams: how they work, are set up and maintained. Frontline Gastroenterol. 2010;1:171–7.
10. A Strategic Framework for Intestinal Failure and Home Parenteral Nutrition Services for Adults in England. April 2008.
11. Powell-Tuck J. Organisation of food and nutritional support in hospitals. Redditch: British Association for Parenteral and Enteral Nutrition; 2007.
12. Keohane PP, Jones BJ, Attrill H, Cribb A, Northover J, Frost P, Silk DB. Effect of catheter tunnelling and a nutrition nurse on catheter sepsis during parenteral nutrition. A controlled trial. Lancet. 1983;ii:1388–90.
13. Kennedy JFR, Nightingale JMD. Cost savings of an Adult Hospital Nutrition Support Team. Nutrition. 2005;21:1127–33.
14. Vlug LE, Nagelkerke SCJ, Jonkers-Schuitema CF, Rings EHHM, Tabbers MM. The role of a nutrition support team in the management of intestinal failure patients. Nutrients. 2020;12(1):172.
15. Mughal MM. Complications of intravenous feeding catheters. Br J Surg. 1989;76:15–21.
16. A strategic framework for intestinal failure and home parenteral nutrition Services for Adults in England. Implementation plan; Feb 2009. www.ncg.nhs.uk/?dl_id=330.
17. Puntis J, Beath S, Beattie M et al. Intestinal failure: recommendations for tertiary management of infants and children. A Report by the Intestinal Failure Working Group, British Society of Paediatric Gastroenterology, Hepatology and Nutrition, and the British Association of Paediatric Surgeons. 2007.
18. Hollingworth T, Akbar T, Oke S, McKee R, Smith T, Gabe S. Nutrition Support Teams & Committee's in the UK: the current picture. Gut. 2018;67(Suppl):A174–5.
19. Kennedy JF, Baker ML, Nightingale JMD. Appropriate parenteral nutrition – the role of the hospital nutrition support team. Clin Nutr. 2002;21(Suppl 1):35.
20. Nightingale JMD, Walsh N, Bullock ME, Wicks AC. Three simple methods of detecting malnutrition on medical wards. J Roy Soc Med. 1996;89:144–8.
21. Nightingale JMD, Reeves J. Knowledge about the assessment and management of undernutrition: a pilot questionnaire in a UK teaching hospital. Clin Nutr. 1996;18:23–7.
22. Austin P, Stroud M. Prescribing adult intravenous nutrition. London: Pharmaceutical Press; 2007. p. P222–9.
23. Rakshit RC, Litchfield B, Nightingale JMD. Percutaneous endoscopic gastrostomy (PEG) insertion rate is falling but early mortality remains high. Gastroenterology. 2008;134:A563.
24. Intestinal failure service specification (170077S). https://www.england.nhs.uk/wp-content/uploads/2019/07/170077S-Intestinal-Failure-Service-Specification.pdf.
25. Allan P, Taylor M, Harper L, Ramu A, Guest C, Harris C, Lal S. Application of quality improvement techniques to reduce parenteral nutrition wastage in a national intestinal failure unit. Eur J Hosp Pharm. 2018;25(2):85–91.
26. Messing B, Lemann M, Landais P, Goutebei M, et al. Prognosis of patients with non-malignant chronic intestinal failure receiving long-term home parenteral nutrition. Gastroenterology. 1995;108:1005–10.
27. Pironi L, Goulet O, Buchman A, Messing B, Gabe S, et al. Outcome on home parenteral nutrition for benign intestinal failure: a review of the literature and benchmarking with the European prospective survey of ESPEN. Clin Nutr. 2012;31:831–45.
28. Bond A, Teubner A, Taylor M, Cawley C, Abraham A, et al. Assessing the impact of quality improvement measures on the incidence of catheter related blood stream infections and catheter

salvage in home parenteral nutrition: experience from a national intestinal failure unit. Clin Nutr. 2018;37(6):2097–101.
29. Bond A, Teubner A, Taylor M, Cawley C, Varden J, et al. Catheter-related infections in patients with acute type II intestinal failure admitted to a national Centre: incidence and outcomes. Clin Nutr. 2019;38(4):1828–32.
30. Pironi L, Steiger E, Joly F, Wanten G, Chambrier C, et al. The intravenous supplementation type and volume is associated with one-year outcome and major complications in patients with chronic intestinal failure. Gut. 2020;69:1787. https://doi.org/10.1136/gutjnl-2018-318172.
31. Cloutier A, Bond A, Taylor M, Ablett J, Teubner A, et al. Successful implementation of remote video consultations for patients receiving home parenteral nutrition in a national U.K. Centre. Frontline Gastroenterol. 2019;11:280. https://doi.org/10.1136/flgastro-2019-101257.
32. Ambrose T, Topan R, Small M, Nightingale JM, Gabe SM. Electronic personal health records for patients on home parenteral nutrition: a patient satisfaction survey. Gut. 2014;63(1):A270.
33. Personal health record (PHR) case study St Mark's Hospital. https://www.rcplondon.ac.uk/file/3727/download.
34. Donaldson E, Taylor M, Abraham A, Carlson G, Fletcher O, et al. Improving quality in a National Intestinal Failure Unit: greater efficiency, improved access, reduced mortality. Frontline Gastroenterol. 2014;10:1–12.
35. Burden S, Jones D, Gittins M, Ablett J, Taylor M, et al. Needs-based quality of life in adults dependent on home parenteral nutrition. Clin Nutr. 2019;38(3):1433–8.
36. Rushton SN, Hudson AJ, Collett D, Neuberger JM, Mirza DF. Strategies for expanding the UK pool of potential intestinal transplant donors. Transplantation. 2013;95(1):234–9.
37. Kovacevich DS, et al. ASPEN guidelines for the selection and care of central venous access devices for adult home parenteral nutrition administration. JPEN. 2019;43:15–31.
38. Metha NM, et al. Guidelines for the provision and assessment of nutrition support therapy in the Pediatric critically ill patient. JPEN. 2017;41:706–42.
39. Kumpf VJ, et al. ASPEN-FELANPE clinical guidelines. Nutrition support of adult patients with enterocutaneous fistula. JPEN. 2017;41(1):104–12.
40. McClave SL, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. JPEN. 2016;40(2):159–211.
41. Association for Nutrition. UK undergraduate curriculum in nutrition for medical doctors. Published October 2021.

Ethical and Legal Aspects of Nutritional Support

Andrew Rochford

Key Points

1. Artificial nutrition and hydration constitute medical treatment.
2. Nutrition support should be considered in people who are malnourished or at risk of malnutrition.
3. The first question should be 'what are we trying to achieve'? If in doubt, a trial of clinically assisted nutrition and hydration with clearly agreed objectives may be appropriate.
4. It is essential to consider the pre-existing wishes of the patient and adhere to the core ethical principles of autonomy, non-maleficence, beneficence and justice.
5. Decisions should be made as a multi-professional team and clearly communicated and documented.

Introduction

The number and proportion of people aged 60 years and older in the world population is increasing. In 2019, the number of people aged 60 years and older was one billion. This number will increase to 1.4 billion by 2030 and 2.1 billion by 2050. This increase is occurring at an unprecedented pace and will accelerate in coming decades, particularly in developing countries [1]. It is important to acknowledge that millions of people globally are malnourished and face food insecurity on a daily basis. This represents its own ethical and social challenge but is beyond the scope of this chapter.

Although life expectancy is rising, healthy life expectancy (i.e., the number of years we can expect to live in good health) is declining with increasing incidence and prevalence of conditions such as cancer and dementia. For example, in the United Kingdom (UK) it has been estimated that 1.3 million people aged over 65 are malnourished or at risk of malnutrition. One third of people in this age group are found to be at risk of malnutrition when they are admitted to hospital, and the same proportion are discovered to be at risk on admittance to a care home [2]. The use of a validated nutrition screening tool such as the Malnutrition Universal Screening Tool ('MUST') is essential to identify nutritional risk and enable action to be taken at the earliest opportunity to reverse or delay the progress of malnutrition. There is also an increasing drive to encourage patients to self-screen with clinically validated tools such as the Patients Association Nutrition Checklist [3].

However, it is not simply ageing that challenges the legal and ethical provision of Clinically Assisted Nutrition and Hydration (CANH). The number of patients living with chronic disease and long-term conditions that compromise their nutritional intake is also increasing. The number of patients on home enteral tube feeding (HETF) is on the increase worldwide due to advances in technology, development of percutaneous endoscopic gastrostomy (PEG) techniques, and the shift in care provisions from acute to community settings. For example, in the UK in 2015 72% of HETF patients registered as part of the British Artificial Nutrition Survey (BANS) were living in their own home [4]. While the significance of home enteral nutrition in meeting the nutritional requirements of patients with poor swallowing reflexes and those with poor nutritional status is not in doubt, differences exist in terms of funding, standards, management approaches and the level of infrastructural development across the world [5].

The provision of CANH often presents an ethical challenge to many clinicians; in the context of changing health and social demographics, this challenge is set to increase. The subject is incredibly emotive for patients, relatives and carers, and staff as the provision of food and water represent the most basic requirements for life.

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Ethical Position

Biomedical ethics is underpinned by four main tenets:

1. *Autonomy*—respecting and supporting autonomous decisions
2. *Non-maleficence*—avoiding the causation of harm
3. *Beneficence*—a group of norms pertaining to relieving, lessening, or preventing harm and providing benefits and balancing benefits against risk and costs
4. *Justice*—ensuring fair distribution of benefits, risks and costs [6].

These should not be seen as a set of rules but rather perspectives that should be used to frame and facilitate discussion in order to reach consensus (Fig. 1). Important principles to help guide these discussions are the *sanctity of life* and the preservation of *dignity*. The sanctity of life means that the life of a patient is valuable in itself and does not depend on their social or economic achievements. However, the principle of the sanctity of life does not mean that life should be preserved at all costs. For instance, it need not oppose withdrawal or withholding of treatment in particular cases. Neither does the principle of the sanctity of life mean that a patient's autonomous wish to refuse treatment may be overridden. The preservation of dignity means that, at all times, the patient should be treated with respect [7]. These principles are internationally recognised and underpin all aspects of clinical practice. Furthermore, these principles are interrelated, and this should be taken into account when considering their application.

The principle of autonomy recognises the right and the capacity of a person to make a personal choice. People may refuse support even if the refusal is difficult to understand by others and may change their mind at any time with regard to consent [8]. Autonomy does not mean that a patient has the right to obtain every treatment they wish or request, if this particular treatment would not be medically indicated.

When making decisions about the appropriateness of a medical intervention clinicians must balance the benefits (beneficence) and risks of harm (non-maleficence) from the intervention. It is important to note that potential harm may not only be physical but can also be psychological or involve infringement on a patient's privacy or liberty. In some cases, there will be a conclusion that treatment will not yield or may no longer yield any benefits and/or the risks of harm outweigh the anticipated benefits. In other words, the medical intervention is inappropriate or disproportionate. This situation is described as "therapeutic obstinacy" (or unreasonable obstinacy). In such cases, the clinician may legitimately decide, in their dialogue with the patient, not to implement the treatment or to withdraw it [9].

There is no obvious means of measuring whether medical interventions to provide CANH are disproportionate. Even though there are medical criteria from evidence-based medicine, which can be used to evaluate risks and benefits, whether or not treatment is proportionate will be assessed in the light of the patient's situation as a whole. Clinical decisions are the result of a reconciliation between the will of the patient and the assessment of the situation by a healthcare professional taking into account all the ethical tenets.

Religious and Cultural Context

Eating and drinking are not simply essential for maintaining nutrition and hydration. They are important for pleasure and social interactions – food and mealtimes are a way we connect with others and can often be an expression of our cultural identity.

The provision of oral nutritional support should therefore be the preferred method of choice for any patient with inadequate food and fluid intake to meet requirements, unless they cannot swallow safely, have inadequate gastrointestinal function or if no benefit is anticipated, for example in the last days of end-of-life care [7].

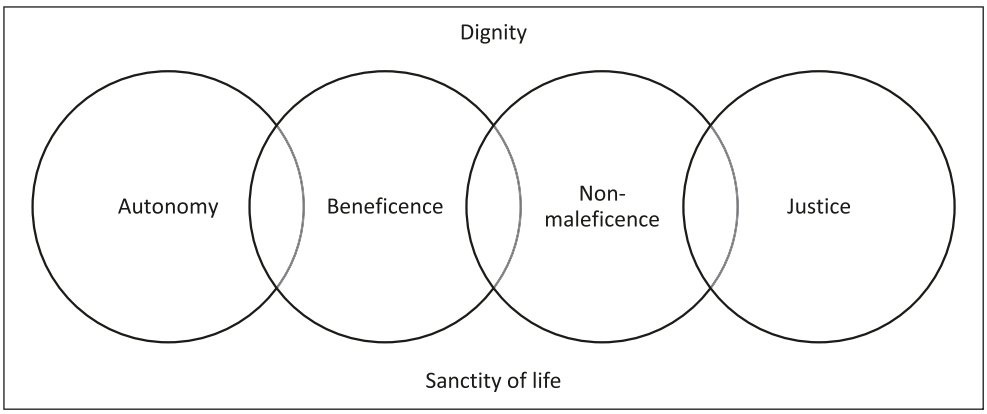

Fig. 1 Ethical considerations for clinical care

Modern society is an amalgam of different religious, ethnic and cultural backgrounds, and beliefs. Attitudes to end-of-life care and the sanctity of life vary widely between different groups. Additionally, medical staff will inevitably judge patients according to their own morals and beliefs. It is beholden on all those involved to respect these views and wherever possible take account of them in a sympathetic and understanding manner [8].

The ethics of refusing or withdrawing nutrition and hydration from sick or dying patients has a substantial history with theological discussions dating back more than 400 years; this suggests that there has always been a significant ethical dilemma to the provision of CANH.

Table 1 Factors encouraging CANH [11]

Party involved	Factors encouraging CANH
Relatives	• Unwillingness to accept terminal prognosis • Belief in cruelty of dying process if ANH not administered • Need to demand interventions to avoid guilt
Clinicians	• Lack of familiarity with palliative care techniques and evidence • Length of time needed to educate families • Desire to avoid controversial decisions • Fears of litigation
Others	• Fear of regulatory sanctions if ANH not provided (nursing homes) • Extra time and staff needed to assist with oral feeding

Legal and Regulatory Position

Generally, in law, the term 'child' is used to refer to people under the age of 18. The law treats a child's consent to treatment differently from a refusal of consent. This is because it assumes that healthcare professionals who propose treatment do so for good reasons [7]. The provision of nutrition and hydration to children and adolescents may differ from adults; in this section we will focus on the legal and regulatory position in adults.

The provision of food and drink by mouth is seen legally as basic care whereas the provision of CANH is considered a medical treatment in many, but not all countries. The competent patient has the right to participate in decision making and to refuse treatment although a doctor is not obliged to give treatment which they consider futile or against the patient's interests. There is often a delicate balance between professional judgement and patients' rights which on occasion has been legally challenged. The ethical principle of autonomy underpins the legal process of consent as it is the patient's consent that makes invasive medical treatment lawful. Clear guidance has been provided by the British Medical Association and the Law Society regarding gaining consent in the UK (see Box 1).

Box 1 Best practice guide for gaining consent [10]

A person should be able to:

- Understand in simple language what the medical treatment (or research intervention) is, its purpose and why it is proposed.
- Understand its principle benefits, risks and alternatives.
- Understand in broad terms what will be the consequences of not receiving the proposed treatment.
- Retain the information for long enough to make an effective decision.
- Make a free choice without pressure.

In the acute setting, the ethical challenges around providing CANH frequently involve patients who lack capacity with increasing pressure for clinicians to prescribe CANH for a number of reasons (see Table 1). However, healthcare professionals should not be tempted to underestimate the patient's capacity to make a decision and should make every attempt to assist this process.

The legal and regulatory position on the provision of CANH varies in different countries and often within different states. It. Is therefore paramount that appropriate advice is sought where there may be doubt or confusion.

Patients Who Lack Capacity

The provision of nutrition and hydration is a basic human right. It is only in circumstances where a person is unable to eat and drink for themselves or adequately maintain their required nutrition and hydration where medical intervention may need to be considered and the principles of biomedical ethics applied.

Someone's capacity may be affected by cognitive impairment which may be permanent (e.g. dementia) or temporary (e.g. delirium), a learning disability, or a mental health problem. There may be other clinical reasons which affect people's capacity, for example sedation or anaesthesia. It is important to recognise therefore that decisions regarding the provision of CANH may need to be assessed over a period of time.

The Mental Capacity Act 2005 (MCA) is a statute in force in England and Wales [11]. It sets out a legal framework for determining mental capacity and making decisions on behalf of people aged 16 and over who lack the capacity to decide for themselves and provides a good reference with which to frame discussion in this section.

The MCA specifies that any act done, or decision made, for a patient who lacks capacity, and does not have a valid

and applicable advance decision to refuse treatment, must be done or made in their best interests. This means that a decision-maker must consider all relevant circumstances, including any wishes, feelings, beliefs and values of the patient. The MCA provides very useful guidance on how to determine capacity (summarised in Box 2).

Box 2 Best Practice Guide for Assessing Capacity

The MCA says that a person has capacity if they are able to:

- Understand the information relevant to the decision.
- Retain that information.
- Use or weigh that information as part of the process of making the decision.
- Communicate their decision (by talking, using sign language or any other means).

The MCA requires that the decision should be that which, objectively, is in the best interests of the patient [12]. Decision-makers must start from the strong presumption that it is in a patient's best interests to receive life-sustaining treatment, but that presumption can be rebutted if there is clear evidence that a patient would not want CANH provided in the circumstances that have arisen.

If the patient does not have capacity and cannot make their own decisions about what to do, then their voice will have to be relayed by others. It is imperative that the collection of information and opinions should be respectful, unhurried and comprehensive, as well as carefully documented. Legally, family members cannot give consent to or refuse treatment on the patient's behalf unless they have been formally appointed as a health and welfare attorney. Although not the decision-maker, they do have a crucial role in providing information about the patient as part of the best interest's assessment [7].

Mental Health

Patients with mental health disorders cannot have treatment imposed on them simply because the treating clinicians think it is medically justified. Patients may have capacity to make some decisions but not others and so the standard of practice around informed consent still applies. Equally, patients with mental health disorders may lack capacity in the same way as anyone else in which case treatment will be deemed legal if it is in the patient's best interest.

Under carefully specified circumstances, CANH may be considered a medical treatment for a mental health disorder. For example, in eating disorders such as Anorexia Nervosa, malnutrition contributes to the psychiatric burden of the illness and in extreme cases CANH may need to be enforced to support treatment of the underlying mental health disorder. However, in all situations the ethical principles of providing CANH should be carefully considered and applied.

Best Interests

In making a best interests decision about giving or continuing life-sustaining treatment, there is always a strong legal presumption that it will be in the patient's best interests to prolong their life. This presumption can be nullified if there is sufficient evidence to suggest that the patient would not want to have the treatment proposed in the given circumstance, the treatment itself would be overly burdensome for the patient, or the treatment would not provide the patient with an acceptable quality of life. However, it is imperative to highlight that these judgements must be made from the patient's perspective and not those of healthcare professionals.

There have been a number of high profile cases relating to CANH (see Table 2) that provide insight into the legal challenges that exist around best interest decisions.

Legal proceedings in England have highlighted that best interests means more than 'best medical interests.' Healthcare professionals making decisions must look at a patient's welfare in the widest sense—not just medical but social and psychological. They must consider the nature of the medical treatment, what it involves and its prospects of success. They must ask what the patient's attitude to the treatment is or would be likely to be; and they must consult others for their view of what his or her attitude would be. [1]

[1] *Aintree University Hospitals NHS Foundation Trust v James* [2013] UKSC 67 at paragraph 39.

Table 2 Examples of high profile court cases relating to CANH

Legal case (country)	Background	Outcome
Tony Bland (England)[a]	Tony Bland was a football supporter who was crushed in the Hillsborough disaster which reduced him to a persistent vegetative state. He had been in this state for three years. His brain stem was still functioning, so technically he was still alive but he was not conscious and had no hope of recovery The hospital with the consent of his parents applied to the courts to discontinue all life-sustaining treatment and medical support measures, including the termination of CANH	The court ruled that there was no duty to treat if treatment was not in the best interests of the patient. Since there was no prospect of the treatment improving the patient's condition the treatment was deemed futile and there was no interest for Tony Bland in continuing the process of artificially feeding him upon which the prolongation of his life depended
Vincent Lambert (France)[b]	Vincent Lambert sustained serious head injuries in a road-traffic accident in 2008, which left him tetraplegic and in a state of complete dependency In 2011 his condition was characterised as minimally conscious and in 2014 as vegetative He received CANH via a gastrostomy In 2012 his carers observed increasing signs of what they believed to be resistance on his part to daily care In early 2013 the medical team initiated a procedure provided for by French law on patients' rights and end-of-life issues (known as the "Leonetti Act"). The patient's wife Rachel Lambert was involved in the procedure, which resulted in a decision by his doctor to withdraw CANH. The courts ruled this as appropriate in April 2013. However, the parents and other family members appealed and won an injunction ordering the hospital to resume CANH In January 2014, there was a further application to discontinue CANH which was upheld but family members appealed to the European Court of Human Rights in Strasbourg	The Grand Chamber of the Strasbourg Court upheld the right of to die with dignity by ruling that there would be no violation of Article 2 (right to life) of the European Convention on Human Rights if artificial nutrition and hydration were to be withdrawn from a patient in a persistent vegetative state
Terri Schiavo (USA)[c]	At the age of 26 Terri Schiavo had an out of hospital cardiac arrest and suffered a hypoxic brain injury. After almost three months without recovery, she was declared to be in a permanent vegetative state. Her clinical condition remained unchanged despite intensive rehabilitation effort over the next two years Schiavo's husband and legal guardian argued that Schiavo would not have wanted prolonged artificial life support without the prospect of recovery, and in 1998 elected to remove the gastrostomy tube. Schiavo's parents disputed her husband's assertions and challenged Schiavo's medical diagnosis, arguing in favour of continuing CANH There then followed a prolonged series of legal challenges presented by her parents, which ultimately involved state and federal politicians up to the level of President George W. Bush After a a seven-year (1998 to 2005) period Schiavo's gastrostomy tube was finally removed	The "Terri Schiavo case" actually refers to a series of cases. Fundamentally, the case involved a dispute between family members over what the patient's wishes would have been for such a situation The Schiavo case involved 14 appeals and numerous motions, petitions, and hearings in the Florida courts; five suits in federal district court; extensive political intervention at the levels of the Florida state legislature, Governor Jeb Bush, the U.S. Congress, and President George W. Bush; and four judicial reviews in the Supreme Court of the United States

[a]*Airedale N.H.S. Trust v Bland* [1993] A.C. 789 House of Lords (see also *All Engl Law Rep* 1993;1:821–96)
[b]Lambert and Others v. France (application no. 46043/14) http://hudoc.echr.coe.int/eng?i=001-155352
[c]See Caplan AL Ed. (2006) *The case of Terri Schiavo: Ethics at the End of Life*. Amherst, NY: Prometheus books

The MCA has outlined a helpful checklist (see Box 3) that can be used to help decision making when determining best interests.

Box 3 A Proposed Checklist for Determining Best Interests [13]

- Do not discriminate or make assumptions on the basis of the person's age, appearance, condition or behaviour
- Consider whether the person will at some time regain capacity, and if this is likely, whether the decision could be postponed
- Encourage participation by doing whatever is possible to permit or encourage the person to take part
- Cannot be motivated by a desire to bring about the person's death where the decision relates to life-sustaining treatment
- Consider all the relevant circumstances by trying to identify the things the person lacking capacity would take into account if they were making the decision themselves
- Find out the person's views, including their past and present wishes and feelings, and any beliefs or values that might influence their decision if they had capacity. This should include consulting family, carers and anyone granted a lasting power of attorney.

Advance Decisions

An advance decision is a decision by a person to refuse particular medical treatments at a time in the future when they may be unable to make such a decision. It is sometimes referred to as a living will or advance directive. It might say, for example, that an individual would not want to be given CANH if they were ever in a permanent vegetative state.

An advance decision is legally binding in English law and can be applied to adults who wish to refuse life-sustaining treatment. It is therefore considered a surrogate for the patient's autonomy should they not be able to express their own wish. An advance decision only applies where it is in writing, witnessed, and verified by a statement by the person to the effect that it is to apply to that treatment even if life is at risk [7]. However, even if not all the legal criteria are followed, an advanced decision can be considered as an expression of a patient's feelings and should be taken into consideration when making best interest decisions.

In England the MCA recognises that some patients may also have appointed a Lasting Power of Attorney, who can make decisions relating to personal health, financial and property matters when the patient becomes incapacitated. If the patient has no relatives and lacks capacity, consideration should be given to appointing an Independent Mental Capacity Advocate, particularly if Deprivation of Liberty Safeguards are being considered [13].

Oral Feeding Dilemmas

If possible, the provision of adequate food and water taken by mouth should be the aim for all patients. When considering the provision of CANH the first question should be 'what are we trying to achieve?' If there is any doubt it is recommended that a trial of treatment is provided. A good example would be in the case of an acute stroke where the prognosis may be uncertain in the short term; however, without the provision of CANH the recovery and outcomes would be poorer. In contrast, for patients in an advanced stage of a progressive neurological disease such as Alzheimer's dementia it has been shown that tube feeding does not prolong life and causes more complications than benefits.

For many patients maintaining independence with eating and drinking for as long as possible remains important; and mealtimes continue to provide a key opportunity for social interaction and enjoyment as well as nutritional intake. Unintentional weight loss in the frail elderly is associated with higher rates of mortality, institutionalisation, adverse health outcomes, decline in functional status, and overall poorer quality of life. A careful weight history is therefore paramount when considering the provision of CANH. The mechanisms of weight loss are multi-factorial, but the prevalence of malnutrition often increases with disease progression; for example, in the later stages of dementia more than two thirds of all those living with dementia are likely to be at risk of malnutrition [14]. There is evidence that meal-time adaptations such as providing assistance and an appropriate environment for eating can slow the rate of unintentional weight loss, however, as disease progresses it is unlikely that malnutrition can be reversed and simply slowing nutritional deterioration through adapted oral intake should be seen as a positive outcome.

Many patients with oral feeding difficulties have communication or cognitive disabilities which affect understanding, retention and processing of verbal and written information and communication of needs. It is therefore imperative that appropriate measures have been taken to enable participation in discussions and decision making around long term nutrition and hydration. Ideally, discussions and decisions about the provision of CANH for patients with progressive conditions should be made in advance of the point of clinical deterioration where CANH is being considered. It is recommended that decisions to provide CANH should be reviewed every

6 months (or every 12 months where the patient has been in a stable condition over a long period of time) and more often if the clinical situation has changed significantly [7].

The term 'feeding at risk' or 'risk-feeding' is currently used to refer to oral feeding when people continue to eat and drink despite a perceived risk of aspiration. This approach is appropriate for patients unsuitable for tube feeding who have an unsafe swallow that is unlikely to improve and is often seen as a strategy that affords comfort, dignity and autonomy for patients [15].

Many patients will require assistance to eat and drink. The majority of carers prepare all the meals for the person that they care for and 60% of carers express worry about the nutrition of the person they support [16]. Carers may need training and support to ensure that they are using the correct techniques and are complying with guidance regarding preparation of consistency and the modification of food and fluid. If an individual is 'feeding at risk' then this decision needs to be documented with clear guidance for carers and healthcare professionals on how to assist the person with eating and drinking.

Enteral Nutrition

All clinicians have a morale and professional duty to monitor and review the nutrition and hydration needs of their patients. For example, in the UK the General Medical Council states:

> *Malnutrition and dehydration can be both a cause and consequence of ill health, so maintaining a healthy level of nutrition and hydration can help to prevent or treat illness and symptoms and improve treatment outcomes for patients. You must keep the nutrition and hydration status of your patients under review….. If you are concerned that a patient is not receiving adequate nutrition or hydration by mouth, even with support, you must carry out an assessment of their condition and their individual requirements. You must assess their needs for nutrition and hydration separately and consider what forms of clinically assisted nutrition or hydration may be required to meet their needs* [17].

When patients fail to meet or maintain their nutrition and hydration needs orally other routes of administration should be considered. Enteral nutrition is commonly provided temporarily via Nasogastric tubes (NGT) and over a longer period via gastrostomy tubes placed either endoscopically (PEG) or radiologically (RIG). The placement of a gastrostomy tube has recognised risks of mortality and morbidity but there is a lack of high quality clinical evidence in the benefit of gastrostomy feeding in certain population groups. A Cochrane Systematic Review of PEG versus NGT feeding demonstrated no significant difference in mortality rates between the two groups. Furthermore, there was no significant difference between risk of aspiration although there was a lower risk of reflux oesophagitis in patients with a PEG. There was also no significant difference in outcomes relating quality of life, patient satisfaction, inconvenience of maintaining the intervention by nurses, and functional ability [18].

Decision making in these circumstances is often complex and involves many steps; decisions may evolve as the patient's condition changes requiring re-referral and re-assessment. It is often appropriate to seek a second opinion from members of the nutrition support team regarding the most appropriate long-term course of action.

It is important that clinicians consider all the ethical perspectives outlined in Fig. 1 for each individual patient. There may well be conflicting views held within the multi-professional team as well as between patients, relatives and care givers. Particular care needs to be taken for patients with functional gastrointestinal disorders where additional psychological and/or psychiatric evaluation may be required to explore the principles of non-maleficence and beneficence in more detail. Similarly care should be taken for patients with learning disabilities. It has been estimated that approximately 36% of patients with learning disabilities in the UK living in community settings have swallowing difficulties [19]. In many countries it is illegal to discriminate against patients with learning disabilities on the basis of that disability. It would also be considered ethically inappropriate to insert a gastrostomy tube for the convenience of the caregiver. Where there is doubt about clinical outcome and/or long-term nutrition and hydration requirements a trial period of feeding via NGT is recommended.

When tube feeding is continued outside hospital there is an ethical duty to ensure that the patient, carergivers and the community health team are adequately instructed in the technique and possible complications.

Parenteral Nutrition

Home parenteral support (HPS) is arguably more accessible than ever before. For example, the National Framework Agreement for Home Parenteral Nutrition in England allows suitable patients to be discharged within 5 working days once they are stable on their HPS regime; acknowledging that gaining clinical stability may take several weeks in hospital. Over the last 5 years there has been a greater than 200% increase in new HPS patients. In 2015, the major underlying diagnosis for new patients with 'gastrointestinal obstruction' treated with HPS was malignancy (69%) [20].

For most patients requiring HPS the ethical considerations are identical to other forms of clinical nutrition support and the decision making process should be similarly robust. Although it should be highlighted that HPS is an expensive healthcare intervention, and its provision may place a significant economic burden on healthcare services

where resources are limited. This does, therefore, raise a question surrounding the ethical position of justice and resource allocation in such cases.

It is generally accepted that the significant risks and burdens of HPS outweigh the benefits in patients who have an expected survival of less than 2 months. However, it is often extremely difficult to predict the length of survival and quality of life for patients being considered for HPS and there may be palliative benefits in providing HPS to patients with a shorter prognosis but with a good performance status. It is therefore paramount that informed decisions are made regarding prognosis and performance status. It is recommended that a recognised measure such as the Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) performance status is used.

Feeding at the End of Life

There is limited evidence for recommendations regarding nutrition in end-of-life care due to the challenges in undertaking intervention studies in this population. However, in the terminal phase of illness the inability or unwillingness to eat often creates significant anxieties for relatives and carers. It is important for healthcare professionals to support understanding that both the social significance of eating and the atmosphere created around eating may be more important at the end of life than the nutritional content of the food itself [21].

In the dying phase, a patient's desire for food and drink lessens. Good mouth care rather than attempting to feed a patient becomes a more appropriate intervention. It is important at this stage to consider the appropriateness of continuing either enteral or parenteral nutrition and attention to patient comfort and dignity should take precedence. The discontinuation of intravenous fluids must also be considered, as at this late stage it may only serve to exacerbate pulmonary oedema, peripheral oedema and increase secretions, which the semi-conscious patient is unable to manage. Clear reasons should be identified and recorded for withdrawal of nutrition and hydration and good communication between healthcare staff, relatives and carers is essential.

In end-of-life situations, the assessment of "overall benefit" plays a particularly important role in determining the suitability of a treatment whose purpose may change (shifting from a curative to a palliative purpose for example). In these situations, the prolonging of life must not in itself be the sole aim of medical practice, which should attempt just as much to relieve suffering. The difficulty of any medical decision at the end of life is to ensure that the patient's autonomy and dignity are respected and that a balance is struck between the protection of life and the person's right to be relieved of suffering if possible [22].

Withholding and Withdrawing Treatment

People with preserved cognitive function who are unable to eat or drink must be involved in decision making (with all the necessary support). Their perception of the process resulting from absence of food will be different from those with impaired cognitive function. It is commonly believed that death from lack of nutrition or hydration is distressing or painful for the patient. This may be true for some, especially those with better cognitive function. However, appetite is often severely reduced in terminal disease and the sensations of hunger and thirst are suppressed. For those who are severely cognitively impaired, there is little evidence that hunger or thirst are perceived significantly. Indeed, patients may resist efforts by carers to offer food or fluids. These rejections may be no more than reflex responses. The dilemma of whether to 'force feed' such patients by mouth or with clinical assistance then arises [7].

In England the law regards withholding and withdrawing treatment as the same. There is no requirement for decisions to withdraw CANH to be approved by the court, as long as there is agreement upon what is in the best interests of the patient, the provisions of the Mental Capacity Act 2005 have been followed, and the relevant professional guidance has been observed [23]. There are, however, certain situations e.g. persistent vegetative state or when there is conflict between professional judgement and the wishes of legal guardian or family, when the courts need to be involved before any action is taken (see Table 2 for some examples).

There is legal guidance that can be helpful in supporting decision making about the provision of CANH in patients who are not imminently dying (see Box 4).

Box 4 Suggested Questions to Support Decision Making Regarding the Provision of CANH [24]

- What is his/her current condition?
- What is the quality of his/her life at present (from his or her perspective)?
- What is his/her awareness of the world around him/her?
- Is there any (or any significant) enjoyment in his/her life? If so, how can this be maximised?
- Does he/she experience pain and/or distress and if so, is it appropriately managed?
- What is his/her prognosis, if CANH were to be continued?
- Is there any real prospect of recovery of any functions or improvement to a quality of life that he/she would value?
- What is the prognosis if CANH were to be discontinued?
- What end-of-life care would be provided?

The General Medical Council's guidance states that a second clinical opinion should be sought where it is proposed, in the patient's best interests, to stop or not start CANH and the patient is not within hours or days of death [25]. There is sufficient evidence that the provision of parenteral nutrition is best provided by specialist nutrition teams and there is some evidence that the provision of enteral tube feeding support has less complications and better outcomes if managed through a specialist nutrition team. It is therefore appropriate that the opinion of nutrition support teams may be sought to assist in decision making around the provision of CANH.

It is important to highlight that in some countries CANH does not constitute treatment but is considered a form of care meeting the patient's basic needs, which cannot be withdrawn unless the patient, in the terminal phase of an end-of-life situation, has expressed a wish to that effect.

Multi-Professional Working and Best Practice

Communication and decision making surrounding CANH often takes time and requires considerable skill. A multi-professional approach is essential but within a multi-professional team there may well be differing moral, ethical, religious and cultural opinions and beliefs. A study of the dynamic challenges facing a multi-professional team discussing the provision of CANH has shown that decision making is not a singular decision but frequently involves many steps with the potential for anonymity of decision-making to emerge [26]. Decisions are rarely made in a single meeting and are constantly evaluated in different settings and clinical situations. Decisions are frequently made across at least four inter-dependent axes (as shown in Fig. 2).

The Royal College of Physicians (RCP) has published guidance to support conversations for ethically complex care [27]. The College recommends six guiding principles for ethical decision making which are:

- Respect for patients
- Duty of care
- Equity of care
- Accountability and transparency
- Inclusivity
- Reasonableness

Furthermore, the guidance recommends a stepwise, question-based approach to ethical decision making that is founded on the work of Jonsen, Siegler and Winslade [28] (shown in Fig. 3).

For more complex situations, the RCP recommends using the Ethical Care Decision-Making Record (ECDMR) which is available to download at https://www.rcplondon.ac.uk/projects/outputs/conversations-ethically-complex-care. This provides an excellent framework that will ensure robust and appropriate documentation of the decisions made.

Fig. 2 An illustrative model of the decision-making axes upon which clinical information can be weighted to make decisions [26]

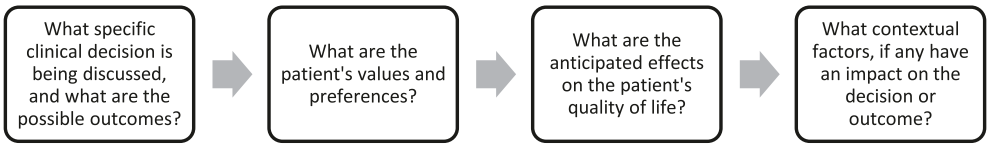

Fig. 3 A four-question approach to facilitate and support conversations for ethically complex care

Conclusions and Recommendations

In many countries CANH is regarded in law as medical treatment and should therefore be considered in the same way as any other medical intervention. The application of the principles of biomedical ethics is paramount. Patients, relatives and carers cannot demand treatment, but patients can refuse treatment. For patients who lack capacity there is clear guidance for healthcare professionals to support best interest decision making. There is a lack of high-quality clinical evidence, but it is recommended that decisions are made on a case-by-case basis involving a multi-professional team with experience of providing CANH. As patients approach the end-of-life priority should be given to supporting quality of life over and above nutritional intake and may involve supporting patients, relatives and carers to 'feed at risk' in preference to the provision of CANH.

References

1. https://www.who.int/health-topics/ageing#tab=tab_1. Accessed 3 Apr 2021.
2. Stratton R, Smith T, Gabe S. Managing malnutrition to improve lives and save money. BAPEN October 2018. https://www.bapen.org.uk/pdfs/reports/mag/managing-malnutrition.pdf.
3. Murphy JL, Burrow A, Guestinin R, et al. Identifying older people at risk of malnutrition and treatment in the community: prevalence and concurrent validation of the Patients Association Nutrition Checklist with 'MIUST'. J Hum Nutr Diet. 2019;33(1):31–7.
4. Stratton R, Evill R, Smith T. Home Enteral Tube Feeding (HETF) in Adults (2010-2015). BAPEN BANS Report 2018. https://www.bapen.org.uk/pdfs/reports/bans/bans-report-2018.pdf.
5. Ojo O. The challenges of home enteral tube feeding: a global perspective. Nutrients. 2015;7(4):2524–38.
6. Beauchamp TL, Childress JF. Principles of biomedical ethics. 5th ed. Oxford: Oxford University Press; 2001. ISBN-13: 978e0195143324.
7. Royal College of Physicians. Supporting people who have eating and drinking difficulties. A guide to practical care and clinical assistance, particularly towards the end of life. Report of a working party. London: RCP; 2021.
8. Druml C, Ballmer P, Druml W, et al. ESPEN guideline on ethical aspects of artificial nutrition and hydration. Clin Nutr. 2016;35:545–56. https://doi.org/10.1016/j.clnu.2016.02.006.
9. Council of Europe issues guide to end-of-life care. http://www.coe.int/en/web/bioethics/end-of-life. Accessed 4 Apr 2021.
10. The British Medical Association and the Law Society. Assessment of mental capacity. 4th ed. London: General Editor Alex Ruck Keene. Law Society; 2015.
11. The Mental Capacity Act 2005. https://www.legislation.gov.uk/ukpga/2005/9/contents. Accessed 5 Jun 2021.
12. Salford Royal NHS Foundation Trust v Mrs P [2017] EWCOP 23. https://www.bailii.org/ew/cases/EWCOP/2017/23.html.
13. Mental Capacity Act Code of Practice. www.gov.uk. Published 2007 ISBN 9780117037465. Updated 2016.
14. Franx BA, Arnoldussen IA, Kiliaan AJ, et al. Weight loss in patients with dementia: considering the potential impact of pharmacotherapy. Drugs Aging. 2017;34(6):425–36.
15. Palecek EJ, Teno JM, Casarett DJ, et al. Comfort feeding only: a proposal to bring clarity to decision-making regarding difficulty with eating for persons with advanced dementia. J Am Geriatr Soc. 2010;58:580–4.
16. Carers UK. Malnutrition and caring. London: Carers UK; 2012.
17. General Medical Council. Treatment and care towards the end of life: good practice in decision making. Manchester: The General Medical Council; 2020.
18. Gomes CAR Jr, Andriolo RB, Bennett C, et al. Percutaneous endoscopic gastrostomy versus nasogastric tube feeding for adults with swallowing disturbances. Cochrane Database Syst Rev. 2015;2015(5):CD008096.
19. Leslie P, Crawford H, Wilkinson H. People with a learning disability and dysphagia: a Cinderella population? Dysphagia. 2009;24(1):103–4.
20. Smith T, Ngabi M. Artificial nutrition support in the UK 2005–2015. Adult home parenteral nutrition & home intravenous fluids. BAPEN BANS Report 2016. https://www.bapen.org.uk/images/pdfs/reports/bans-report-2016.pdf.
21. Hopkinson JB, Wright D, Foster CL. The emotional aspects of cancer anorexia. Curr Opin Support Palliat Care. 2010;4(4):4254–8.
22. Council of Europe Issues Guide to End-of-Life Care. http://www.coe.int/en/web/bioethics/end-of-life. Accessed 4 Apr 2021.
23. An NHS Trust v Y [2018] UKSC 46. https://www.bailii.org/uk/cases/UKSC/2018/46.html.
24. PL v Sutton Clinical Commissioning Group & Anor [2017] EWCOP 22. p. 29. http://www.bailii.org/ew/cases/EWCOP/2017/22.html.
25. General Medical Council. Treatment and care towards the end of life: good practice in decision making. London: GMC; 2010.
26. Clarke G, Galbraith S, Woodward J, et al. Eating and drinking interventions for people at risk of lacking decision-making capacity: who decides and how? BMC Med Ethics. 2005;16:41.
27. Royal College of Physicians. Conversations for ethically complex care: a framework to support discussion and documentation of decision making for levels of care in clinical practice. London: RCP; 2021. www.rcplondon.ac.uk/ethically-complex-care
28. Jonsen AR, Siegler M, Winslade WJ. Clinical ethics: a practical approach to ethical decisions in clinical medicine. 8th ed. New York: McGraw-Hill; 2015.

Part VII

Problems of Treatment

Enteral Nutrition

Timothy Bowling

Key Points

1. Enteral nutrition is most commonly given to patients with "intake (oral) failure" (inability to get food into the gut) due to poor dentition, poor appetite, head/neck cancer/trauma, neurological disease (e.g. stroke, cerebral palsy, motor neurone disease, multiple sclerosis) and psychological disorders (e.g. dementia, depression and anorexia nervosa).
2. Enteral tubes are used for patients with inadequate or unsafe oral intake, and a functional, accessible gastrointestinal tract.
3. Complications of enteral tube feeding may be mechanical (tube insertion, the tube blockage/displacement etc), feed delivery, metabolic/biochemical or gastrointestinal related.
4. The risk of aspiration of the feed from an enteral feeding tube may be reduced by elevating the head of the bed to 30° or more, feeding for less than 24 h a day, using a lower osmolality feed and considering a tube with its tip beyond the duodeno-jejunal flexure.
5. There is always a risk of a naso-gastric feeding tube being inserted inadvertently into the lung. In patients with reduced conscious level or reduced oro-pharyngeal sensation a post procedure chest X-ray may be done in addition to testing the pH of aspirate.
6. Diarrhoea with enteral tube feeding is most commonly due to medication (especially anti-biotics).

Introduction

Undernutrition is common in the hospitalized patient, as has been described elsewhere. When a patient is unable to meet their nutritional requirements by oral intake with or without oral nutritional supplements, enteral feeding will be required, providing there is a functioning and accessible gastrointestinal tract. The management should be by a multi-professional nutrition team, including (as a minimum) a doctor, dietitian and nutrition nurse specialist. Indications for enteral tube feeding are listed in Table 1. Access to the gastrointestinal tract can either be via a nasogastric or nasojejunal tube or by an enterostomy. This chapter will mention the routes and feed delivery; but mainly deals with the complications of enteral feeding.

Table 1 Indication for enteral feeding

Patients with a functioning stomach and/or intestine
• Impaired swallow, e.g. stroke, motor neurone disease, Parkinson's disease
• Altered level of consciousness, making oral feeding impossible
• Ventilated patients
• Dysphagia with oro-pharyngeal/oesophageal obstruction, i.e. head and neck and oesophageal cancer
• Gastric outlet obstruction: Mechanical (tumour, pyloric stricture) or functional (stasis). These situations will require jejunal feeding (see below)
• Severe pancreatitis (gastric or jejunal)
Supplement inadequate oral intake
• Cystic fibrosis
• Hyper-catabolic states, e.g. burn injury, decompensated liver disease
• Facial injury
• HIV wasting
• Psychological/psychiatric reasons, e.g. anorexia nervosa

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Routes for Enteral Feeding

The following options are available:

1. Nasogastric tube (NGT)
2. Nasojejunal tube (NJT)
3. Gastrostomy
   (a) Percutaneous Endoscopic Gastrostomy (PEG)
   (b) Radiological Inserted Gastrostomy (RIG)
   (c) Surgical
4. Jejunostomy
   (a) Endoscopic (PEJ or PEGJ)
   (b) Radiological (RIGJ)
   (c) Surgical

Nasogastric Tubes

NGT are recommended for those requiring tube feeding for no longer than 4–6 weeks. They are safe, cost effective and less invasive than alternatives. There are two types of NGT: Fine bore tubes designed for administration of feed; and wide bore tubes (e.g. Ryles) designed for aspiration. The latter can cause oesophageal damage, such as ulceration and stricture, if left in for a prolonged period, and should not normally be used for feeding. Fine bore tubes are usually easy to insert and safe, even in patients with oesophageal varices. They should not be inserted in patients with obstructive pathology in the nasopharynx or oesophagus, or in patients with basal skull fractures.

NHS Improvement issued guidance in 2016 for safe placement and position checking of nasogastric tubes [1]. The guidance highlighted the unreliability of certain tests—such as the "whoosh" test and testing for acidity with litmus paper - and instead recommended testing with pH indicator paper as the first line check (pH $\leq$ 5.5). Higher pH suggests either the position could be wrong, i.e. in the respiratory tract, or the patient could be on acid suppressing therapies, such as a proton pump inhibitor. It recommended checking X-ray images as the second line test, although not for routine use. The single greatest cause of harm resulted from misinterpretation of X-ray images. The National Patient Safety Agency (NPSA) issued a safety alert in March 2011 focusing on safe interpretation of X-ray images [2]. Tube placements should be checked at least once daily and before administering each feed or medication. However, there has to be an element of pragmatism in this. Provided that the initial placement was appropriately confirmed and no other signs of dislodgement (such as retching or coughing) are present, repeat radiography would not usually be needed as long as the external length of tube remains unchanged [3].

Nasojejunal Tubes

These are most commonly placed endoscopically. However, specifically designed self-propelling nasojejunal tubes will spontaneously cross the pylorus in 70–80% of patients with normal gastroduodenal motility, especially with a concurrent intravenous bolus of metoclopramide [4]. If the stomach is atonic, nasojejunal tubes usually require endoscopic placement. The distal end must be placed beyond the duodenojejunal flexure or it will invariably pass retrogradely back into the stomach. There are other systems that can facilitate transpyloric passage, for example an electromagnetic device on the end of the tube can be tracked by a bedside imaging system to help ensure correct placement [5]. Plain abdominal X-ray is required to verify placement, unless placed under screening. NJT come as single, double or triple lumen. Double or triple lumen tubes are recommended for patients who require simultaneous gastric decompression and small bowel feeding.

Gastrostomy

A gastrostomy is usually preferred if tube feeding is likely to be required for greater than 4–6 weeks. It can be placed endoscopically (PEG); radiologically (RIG); or occasionally surgically. There are a number of different types of PEG/RIG tubes in terms of size (9 FG–30 FG); internal fixator (flange, balloon) and material, including more cosmetically acceptable "button" gastrostomies. If the anatomy prevents insertion by one method then other methods will often be limited by the same problem.

PEG insertion is usually straightforward. Although not a sterile procedure, antibiotic prophylaxis 30 min prior to the procedure is recommended [6]. Table 2 lists the contraindications to PEG insertion. It should be noted that many of

Table 2 Contraindications to PEG insertion

Absolute	Relative
• Inability to pass endoscope due to obstructing pathology in oro-pharynx or oesophagus[a] • Obstructing gastric outflow pathology • Significant ascites • Gastric varices	• Severe obesity (due to technical difficulties accessing the stomach)[a] • Uncorrected coagulopathy • Portal hypertension/ascites • Active gastric ulceration/malignancy • Gastroparesis • Gastrectomy (total or partial)[a] • Severe kyphoscoliosis (may be difficult to access stomach)[a] • Impaired respiratory reserve, e.g. motor neurone disease • Current peritoneal dialysis

[a]May be achievable if done under radiological guidance to locate stomach

the "relative contraindications" to endoscopic placement can be overcome if insertion is done under radiological guidance.

PEG's and RIG's can be easily taken out, but care is required. If removed within 2–3 weeks of insertion a formal tract may not have formed, with consequent risk of spillage of gastric contents into the peritoneal cavity leading to peritonitis. This also means that it is not possible to re-insert a feeding tube down the same track, as it will not find its way into the gastric lumen. Therefore if the PEG/RIG does come out in the first few weeks of insertion the stoma site should be covered, antibiotic cover instituted and, if nutritional support is still required, an alternative, e.g. NGT, used until the wound has healed. After 2–3 weeks removal presents little risk of peritonitis or sepsis. However, closure is rapid, so if replacement is required this must be done within 4–6 h using a fresh PEG/RIG or, temporarily, a balloon gastrostomy or Foley catheter. Elective removal is usually undertaken endoscopically. Alternatively, the tube can be cut close to the skin allowing the internal fixator to pass spontaneously through the gastrointestinal tract. There are a few reported incidents of obstruction, e.g. at the ileocaecal junction, and therefore some experts are wary of this method of removal [7]. This should not be undertaken if there is known small intestinal pathology, such as strictures.

Jejunostomy

Percutaneous endoscopic gastrojejunostomy (PEGJ) are "extensions" that attach to a PEG and can be passed endoscopically beyond the duodeno-jejunal flexure. PEJ is similar to PEG but requires a direct puncture into the small intestine. Insertion techniques are not straightforward, but in expert hands successful placement can be achieved in 70–80% [8]. For most hospitals, where such expertise may not be available, and where post-pyloric feeding is required, a surgically-placed jejunostomy for post-pyloric feeding is often preferred, except in a patient too unfit for a general anaesthetic.

Removal of PEGJ/PEJ's have similar cautions as those described for PEGs.

Surgical jejunostomies are most commonly needle catheter jejunostomies inserted subserosally to reduce the risk of leakage, but tend to be fine bore, and prone to block if poorly managed. Other tubes such as Foley catheters can be used but are not recommended because of leakage and difficulties in connecting with feeding equipment. Increasingly, jejunostomies are inserted per-operatively to allow for early post-operative feeding, especially in those whose nutritional status is sub-optimal at the time of surgery. Although complications can occur, the advantages of improved post-operative nutrition usually out-weigh the risks [9].

Delivery of Enteral Feed

Feed can be administered as a bolus or continuously. Continuous feeding is usually over 16–18 h; bolus feeds are typically 100-500mls of feed over 15–60 min at 3–6 h intervals. Bolus feeding into the stomach is more physiological. Although there is a perception that it predisposes to aspiration, diarrhoea, bloating and dumping syndrome compared to continuous feeding, there is no clinical evidence to indicate that this is the case. With jejunal feeding, the loss of the stomach reservoir means patients with post pyloric tubes should be fed continuously. Further detail on delivery and formulation of enteral feeds is dealt with elsewhere.

Complications of Enteral Feeding

Complications of enteral feeding can be divided into mechanical, ie related to the tube; gastrointestinal, ie related to the delivery of the feed; and biochemical/metabolic, ie related to the content of the feed. Table 3 lists these.

Mechanical Complications

Naso-Enteric Feeding Tubes

Inadvertent Removal

The most commonly encountered problem with NGT is inadvertent removal, either by the patient or by accident, e.g. snagged on clothing, vomiting. If this is a recurring problem and feeding is still required, either a PEG can be considered

Table 3 Complications of enteral tube feeding

Mechanical	Insertion	Nasoenteral—nasal damage, intra-cranial insertion, pharyngeal/oesophageal pouch perforation, bronchial placement
		Enterostomy—bleeding, pain, peritonitis, pneumoperitoneum, intestinal/colonic perforation, gastrocolic fistula
	Post-insertion	Nasoenteral—tube displacement/removal, blockage, bronchial administration of feed, erosions, strictures Enterostomy—stoma infection, blockage, displacement, leakage, over-granulation, buried bumper
Feed delivery	Gastrointestinal	Nausea, fullness, diarrhoea, constipation
	Pulmonary	Aspiration, pneumonia
Metabolic		Refeeding syndrome, hyperglycaemia, fluid overload, electrolyte disturbance

or a "nasal loop" or bridle can be attached, thereby making accidental removal far less likely—18% for bridled tubes compared to 63% for non-bridled tubes in one study—with the bridled group more likely to meet their recommended nutritional requirements [10]. Bridle systems are commercially available and although their unit cost is relatively high, this is more than offset by the avoidance of repeated NGT placements +/− X-rays to verify placement.

Tube Blockage

Tube blockage may occur if crushed medication is inserted into fine-bore tubes, if the tube is not flushed adequately, or if there is precipitation of protein in the enteral feed. Precipitation of enteral feed occurs because the iso-electric point of protein is between pH 4.5 and 5.3, and at this pH, protein precipitates causing tube blockage [11]. Many elixir medications have a pH of 5 or less [12] and thus may cause protein precipitation and tube blockage.

To prevent tube blockage a feeding tube should be flushed with sterile or boiled water at least before and after a feed or medication. Obstructed tubes may be unblocked with water, a variety of solutions including fizzy drinks, pineapple or cranberry juice, alcohol or powdered pancreatic enzymes. If enteric-coated pancreatic enzymes are used they need to be dissolved in a sodium bicarbonate solution before being administered (e.g. the contents of one Creon® capsule can be dissolved in 10 ml of 8.4% sodium bicarbonate).

Malposition

Malposition of a naso-enteric feeding tube, especially when inserted blind, occurs in about 2% of insertions. When placed into the airways, with subsequent intrapulmonary infusion of an enteral diet, this can be fatal if not recognized. Intracranial placement has also been reported. Other complications arising from tube malposition include pneumothorax, intrapleural infusion of enteral diet and oesophageal perforation [13].

Localised Trauma

Physical complications of naso-enteric tubes may be due to the size, material and pliability of the tube used. Polyurethane naso-enteric feeding tubes are preferable to polyvinylchloride naso-enteric feeding tubes, as they are softer, less traumatic and easier to aspirate the gastric contents. Intubation with a naso-enteric tube can cause discomfort for patients, and depends to some extent on the type and size of tube used. In general, the larger the tube the greater the discomfort [14].

Although many problems are less common with the softer, more flexible fine-bore tubes, complications due to the physical presence of the feeding tube can occur. Nasopharyngeal discomfort persisting after intubation may be due to reduced saliva production, due to mouth breathing and absence of chewing. Patients can develop a sore mouth, difficulty with swallowing, and a sensation of thirst and dry mucous membranes. Simple measures such as mouthwashes, sucking ice cubes or using artificial saliva may help alleviate discomfort. Nasal erosions and occasionally an abscess can occur from pressure of the naso-enteric tube on the nasal alae. If the sinus tracts or Eustachian tubes are blocked by the naso-enteric tube, acute sinusitis or secondary otitis media infection respectively may occur. The mucous membranes of the larynx can be irritated causing hoarseness. Excessive pressure against the oesophageal wall may cause ulceration with subsequent stenosis. The risk of oesophageal ulceration is increased in the presence of severe gastro-oesophageal reflux and oesophagitis. Fine bore tubes do not appear to jeopardise the integrity of oesophageal varices. However, large bore tubes should be avoided where varices are known to exist. Rarely, tracheo-oesophageal fistula may develop with large-bore naso-enteric tubes as a result of pressure necrosis of the oesophagus and trachea.

Enterostomy Feeding Tubes

Complications can arise from the insertion procedure itself or related to the enterostomy. A more detailed review can be found elsewhere [15].

Insertion Related Complications

- Complications of endoscopy, such as cardiopulmonary compromise resulting from sedation, hypoxia, arrhythmias and hypotension; upper gastrointestinal haemorrhage and oesophageal perforation all have similar rates of occurrence as with other diagnostic and therapeutic endoscopies. The risk of pulmonary aspiration and subsequent chest infection is greater, as a result of the case mix of those requiring a PEG, who are often older, more frail and have, by the definition of needing a PEG, significant co-morbidity, usually affecting the ability to swallow and gag. Further detail of endoscopic complications can be found elsewhere [16].
- **Pain:** This is common within the first 24 h. If severe, it is important to exclude peritonitis or tube displacement into the anterior abdominal wall.
- **Haemorrhage**: This is unusual if the clotting screen is within normal limits. As malnutrition can lead to vitamin K deficiency, the prothrombin time/INR should always be checked prior to procedure, and corrected if necessary.
- **Peritonitis**: This can develop from infection introduced during the insertion process. Pre-procedure antibiotics mitigate against this complication [6].
- **Pneumoperitoneum**: There will always be some free air after PEG insertion Pneumoperitoneum is usually self-limiting. It only needs to be a cause of concern when intra-abdominal air is worsening or when it is found in the presence of signs of peritonitis, portal and/or mesenteric venous gas, systemic inflammatory response and/or sepsis.

- **Gastrocolic fistula** due to the interposition of the colon between the anterior abdominal wall and stomach is a rare complication. It is often not clinically apparent and can be found by chance, for example during a colonoscopy. Measurement of the anterior abdominal wall thickness on the PEG after insertion can be an indicator. For example measurements over 3 cm in a thin individual should raise concern of interposed tissue between the stomach and anterior abdominal wall.
- **Injuries** to small and large intestine, spleen and liver have all been documented. They are rare, but should be considered when there is otherwise unexplained haemodynamic compromise or signs of peritonitis following insertion.
- Surgical or anaesthetic complications need to be considered in surgically placed enterostomies or those placed under a general anaesthetic. Further discussion on these issues is beyond the remit of this chapter.

Tube-Related Complications

- **Stoma infection:** This is a common complication, and even with prophylactic antibiotics occurs in up to 5% in the first 30 days after insertion [6]. The risk is increased both from insertion factors, eg excessive traction on the internal bumper, and host factors such as diabetes, malnutrition and underlying malignancy. It usually resolves with appropriate antibiotics and proper stoma care. It is not usually necessary to remove the enterostomy or stop feeding unless severe ulceration or wound breakdown occurs.
- Less commonly an abscess in the anterior abdominal wall can develop, especially if there is spillage of feed and gastric contents through an immature stoma tract. This will cause localized pain. The management is usually to stop the feed and give antibiotics.
- Necrotising fasciitis is a very rare complication, and more likely when there is systemic compromise, for example poorly controlled diabetes. This usually requires surgical debridement.
- **Tube blockage:** This is a common problem, and arises either because of thick consistency of feed or medication. It can be minimized if flushed with water before and after each feed/medication. The management is the same as for a blocked nasoenteral tube (see above).
- **Peristomal leakage and tube displacement**: Although the reported incidence of peristomal leakage is 1–2% [17], this complication is probably much more common, especially early after PEG placement. Tube displacement through the gastric wall in the immature stoma tract is a common precipitant to peristomal leakage. This is more likely to occur in a confused patient who may pull on the enterostomy. Correct siting of the internal end should be checked either radiologically or endoscopically, and corrected if necessary. There should not be excessive traction on the external bolster compressing the abdominal wall too tightly, and this should be loosened if necessary. Barrier creams and skin protectants should be applied. Antisecretory therapy, such as proton pump inhibitors, to reduce gastric acid secretion can help. Replacing the original PEG tube with a larger one should be avoided as this may cause the tract to enlarge and exacerbate the leakage. If leakage persists, it is often necessary to remove the PEG and resite a new one elsewhere.
- Displacement of a PEJ or PEGJ back into the stomach is a common problem, and this should be suspected if the patient complains of the symptoms that led to the need for post-pyloric feeding in the first place, including fullness and vomiting with feed.
- **Buried bumper**: This is migration of the internal fixator into the gastric/anterior abdominal wall leading to tube blockage. It is a late complication, usually months or years after placement, and diagnosed when the enterostomy cannot be rotated or pushed inwards. Removal can often be done endoscopically, but on occasions requires surgery.
- **Tumour tract seeding**: There are some case reports of PEG's inserted where there are oesophageal or oropharyngeal tumours, with neoplastic seeding in stoma tracks [18]. Where the PEG is inserted as part of palliative care, this is unlikely to be of relevance in the patient's lifetime. Where an enterostomy is required as a bridge for definitive treatment, a radiological procedure avoids the risk of tract seeding, and some experts advocate this.
- **Overgranuation**: Can occur at the stoma site and bleed and/or become painful. This is treated with steroid cream or silver nitrate.
- **Mortality**: There is a 30 day mortality of about 10% following PEG insertion, and 40% following a RIG. The difference is explained by the case mix for the two procedures, with the sicker and more co-morbid individuals more likely to have a RIG [19]. Careful case selection can minimise these figures.

Complications Relating to Feed Delivery

Gastrointestinal Problems

Nausea and Fullness

Nausea and fullness can occur in 10–20% of patients, with the pathogenesis being multifactorial, including smell, diet osmolality, altered gastric emptying, rapid infusion of feed and psychological factors [20]. Management has to be individualised, depending on the circumstances of the particular patient.

Diarrhoea

Diarrhoea occurring in the enterally-fed patient is a common problem, with a reported incidence ranging from 6–60%, more frequent in the critical care setting. This huge variability is a reflection of the heterogeneity of patients and case-mix in the various studies and of the definitions used for diarrhoea. Patients range from critical care to community-based elderly, all with varying degrees of comorbidity and polypharmacy. The definitions of diarrhoea are even more variable—at least 33 quoted in the literature [21]. Many studies utilise consistency, frequency, stool volume and stool weights either alone or in many different combinations. Some studies have developed diarrhoea scores; others just cite "inconvenient" bowel activity and several have no definition at all. What this all means is that it is difficult to truly determine from the literature how much of a problem there is with diarrhoea in the enterally-fed patient.

Contaminated feeds and feeding equipment can lead to the introduction of exogenous pathogens into the gastrointestinal tract. Enteral feed provides an excellent growth medium for bacteria, and once contaminated bacteria will rapidly multiply. A variety of micro-organisms have been cultured from enteral feeds including *Enterobacter* spp., *E. coli*, *Klebsiella* spp., *Proteus mirabilis*, *Salmonella enteriditis*, *Pseudomonas* spp., *Staphylococcus aureus* and *epidermidis*, *Streptococcus faecalis*, *Acinobacter* spp., *Citrobacter* spp. and yeasts. Although enteral feeds are sterilized, as soon as the bottles or cans are opened, there is a risk of bacterial colonization of the feed, through a variety of routes, which is exacerbated by handling, type of delivery system, prolonged hanging time and ascending spread of bacteria up the giving set [22]. Contaminated feeds reportedly cause not only diarrhoea, but also sepsis, pneumonia and urinary tract infections [23]. Gastric acid is an important protection against infused exogenous pathogens, and therefore inhibiting gastric acid secretion allows bacterial overgrowth. Those on antacid medication are therefore at an increased risk of infected enteral feeds and the clinical consequences that can follow. To mitigate risk, containers and giving sets should be changed at least every 24 h [23].

Many gastrointestinal diseases may cause diarrhoea, and these need to be considered, investigated for and dealt with where appropriate. Also to be considered are metabolic causes, such diabetes and thyroid dysfunction. Medications are frequently implicated in causing diarrhoea. The most common are antibiotics, probably due to their effects on colonic flora and short chain fatty acids. Antibiotic usage therefore should be scrutinised and stopped if possible. Other drugs include osmotically-active medications, primarily relating to sorbitol, which is present in many elixirs, and which is frequently given to many patients on enteral feeding for ease of swallowing. There are many other medications which list diarrhoea as a potential side effect. Therefore all medication, prescription and otherwise, should be considered and, if appropriate, stopped [24].

Other aetiological factors have been proposed as relevant to enteral feeding related diarrhoea [25]. Hypo-albuminaemia has been associated but is probably only as a surrogate for a sick patient with a sick and leaky gut. There is no evidence to implicate lactose intolerance or diet osmolality, both of which have been proposed in the literature. It has been suggested from healthy volunteer studies that intragastric feeding is more likely to lead to diarrhoea than post-pyloric feeding, because of different neurohumoral responses resulting from the two methods of feeding, with consequent effects on colonic water flows [26]. However, no clinical studies have been undertaken to test this hypothesis.

Diarrhoea is distressing for patients and their relatives, time-consuming for nursing staff and can add to potential problems such as infected pressure sores and altered fluid and electrolyte balance. It may also delay patient discharge and increase hospital costs. Loperamide at standard dosage (2-4 mg once to three times daily) is often very effective. The addition of codeine phosphate (30–60 mg up to four times daily) can also be of benefit [27].

The role of colonic flora, short chain fatty acids, fibre and pre/probiotics in relation to enteral feeding diarrhoea remains unclear. There are a lot of interesting data on the analysis of colonic flora and the changes observed during enteral feeding. However, the true clinical relevance of such manipulations remains unresolved [26]. There are some clinical data to suggest that including fibre in enteral diets reduces diarrhoea [28]. Therefore, a trial of a fibre-containing feed is worth trying, especially when enteral feeding related diarrhoea is not responding to anti-diarrhoeal medication [29].

Enteral feeding is unphysiological. Bolus feeding is better in this regard than continuous feeding for gastric feeding, but unless the bolus is substantial (more than 500 kcals over 20–30 min) the normal post-prandial neurohumoral responses do not get activated, and this may be of relevance to enteral feeding diarrhoea [30]. There are practical arguments for and against these two forms of feeding, such as ease of administration, patient comfort and convenience and staffing input, which often take precedence over clinical applications. If diarrhoea is a significant problem and is not responding to anti-diarrhoeal medication, then a critical look at the method of feeding is advised. Post-pyloric continuous feeding is more physiological and could be considered, although there are no clinical studies comparing this with gastric feeding and the incidence of diarrhoea. Very occasionally, when diarrhoea is incapacitating and cannot be eased by any of the above, parenteral feeding can be started.

Constipation

Constipation, often with resulting overflow diarrhoea, can be a problem with enteral feeding, although is much less

common that enteral feeding related diarrhoea. It has been suggested that constipation is due to a lack of dietary fibre in many enteral feeds. There is currently, however, little conclusive evidence that using fibre-enriched enteral feeds increase stool frequency and weight. The lack of improvement in constipation by adding fibre to enteral diets may be partly due to the manufacturing process which alters the physicochemical properties of the added fibre. The viscosity of the feed is kept low by using fine rather than coarse fibre. However this reduces the water holding and bulking properties of the feed. Furthermore, due to the requirement of having a small particle size renders the fibre highly fermentable, reducing the amount of fibre available to bulk faeces. A recent meta-analysis has not demonstrated a clear benefit of fibre supplementation in the treatment of either constipation or diarrhoea [29]. However, given the theoretical benefits of fibre and the intuitive view that it should be part of a nutritional regime, many experts would use a fibre-enriched enteral feed in patients with constipation.

Pulmonary Complications

Reflux of feed is almost invariable. Many studies have identified evidence of this, for example pepsin in alveolar aspirates is found in more than 90% of patients being nasoenterally fed [31]. The development of aspiration pneumonia is therefore a potential complication in all patients being tube fed into the stomach or small bowel. Aspiration of feed can occur without obvious evidence of vomiting, particularly in those patients with poor mental status and an absent swallow reflex. Such regurgitation is often a clinically silent event until signs of pneumonia develop. Those at particular risk are the elderly, those with dementia or neurological disease affecting their swallow and gag reflux, and those in critical care on ventilators and with impaired consciousness.

To reducing the risk of pulmonary aspiration, elevating the head of the bed to 30° or more, to help aboral progression of feed by gravity, and feeding for less than 24 h a day, for example over 18–20 h, have been shown to improve aspiration risk [32]. High osmolality feeds of 560 milliosmoles or greater can significantly delay gastric emptying, and so it is probably preferable to use iso-osmotic feeds in patients at risk from aspiration.

There has been much interest in gastric residual volumes for patients primarily in the critical care setting and a presumed association with risk of aspiration. On critical evaluation, there is no clear link between amount of residual and aspiration risk, and 500 mL residuals appear to be no more hazardous than smaller amounts [33, 34]. Current evidence would therefore not support review of residuals only if these are less than 500 mL per 6 h [35].

As with gastric residuals it has also been presumed that bolus feeding increases the risk of aspiration compared to continuous pump feeding. Studies have given mixed results, with some demonstrating benefit with pump feeding [36] and others showing no difference [37].

There is no evidence that enterostomy feeding has any less risk than nasoenteral feeding. There have been a number of controlled trials comparing postpyloric to pre-pyloric feeding, with meta-analyses giving conflicting results [38–40]. It is commonly the case that nasoduodenal tubes can reflux back into the stomach, so to minimise risk of retrograde displacement and aspiration risk, postpyloric tubes should be placed beyond the duodenojejunal flexure (Ligament of Treitz). Pro-motility drugs (e.g. metoclopramide or erythromycin) can be tried to reduce the chances of aspiration in those patients most at risk, although evidence of benefit from meta-analysis is weak [41].

In terms of evidence, the only strategy clearly demonstrated to improve aspiration risk is feeding for no more than 20 h per day and with patients propped up by 30° or more [31].

Metabolic/Biochemical Complications

Artificial feeding of patients may cause a variety of metabolic problems, including deficiencies or excess of fluid, electrolytes, vitamins and trace elements. Over-hydration occurs frequently, particularly if enterally-fed patients are also receiving supplementary intravenous nutrition or fluids.

Hyponatraemia is a common problem when enteral nutrition is given to sick patients. It is often accompanied by the development of oedema and is usually due to a combination of enteral tube feeding and excessive use of IV fluids along with the adverse effects from malnutrition and severe illness. Patients end up with excess body water and a very high total body sodium (the low plasma levels being due to dilution effect). As a consequence, rather than administering further sodium in feeds or IV fluids, treatment should usually entail fluid restriction. Generous amounts of potassium to encourage cell membrane sodium exchange may be helpful. Hypernatraemia can also occur but is usually due to dehydration and/or excess water loss, e.g. through diuresis, rather than as a direct consequence of enteral tube feeding.

Between 10–30% of tube fed patients are hyperglycaemic and may need oral anti-diabetic agents or insulin, before and during feeding. Rebound hypoglycaemia may also occur in tube-fed patients if feeding is stopped abruptly, especially if they are on anti-diabetic therapy.

Deficiencies or excesses of many other electrolytes, vitamins and trace elements can occur but which can usually be avoided by careful monitoring. Basic haematological and biochemical parameters should be measured before starting

nutritional support, and then monitored regularly during such support, with appropriate supplementation given when necessary, especially for those on prolonged enteral feeding.

Refeeding Syndrome

The refeeding syndrome was reported among those released from concentration camps following the Second World War. Oral feeding of these grossly malnourished individuals often resulted in fatal diarrhoea, heart failure and neurological complications including coma and convulsions. Milder symptoms were later reported by Keys et al. during the refeeding of healthy volunteers with a mean weight loss of 23% after starvation [42].

Severely malnourished patients appear to be at particular risk of developing the refeeding syndrome (chapter "Refeeding Problems"), who's features include:

- Salt and water retention leading to oedema and heart failure, which may be exacerbated by cardiac atrophy,
- Hypokalaemia due to rapid cellular uptake of potassium as glucose and amino acids are taken up during cellular synthesis of glycogen and protein,
- Hypophosphataemia due to increased phosphorylation of glucose,
- Rapid depletion of thiamine, a cofactor in glycolysis, leading to Wernicke's encephalopathy and/or cardiomyopathy, and
- Hypomagnesaemia due to cellular uptake of this mineral.

In severe nutritional depletion, atrophy of the gut mucosa and impairment of pancreatic function may predispose to severe diarrhoea following oral or enteral refeeding, precipitating further electrolyte and mineral imbalance.

It is difficult to give a precise definition for the refeeding syndrome since many otherwise well-nourished patients, refed after only a few days starvation, will show a modest change in biochemical values, e.g. a fall in serum potassium and phosphate concentrations, without displaying any symptoms. There is a spectrum or gradation in the features of this condition from such asymptomatic cases to those with severe malnutrition who are at risk of overt and even life-threatening symptoms. The cut-off point at which the 'refeeding syndrome' can be said to be present is, therefore, somewhat arbitrary. The full blown syndrome should be defined by the presence of symptoms, but that biochemical changes of sufficient degree to pose a potential risk should be acted upon without delay in order to prevent the clinical features developing.

Common factors involved with the pathogenesis of the refeeding syndrome include the severity of the underlying malnutrition, overaggressive nutritional support in the early stages without adequate supplements of phosphate, thiamine, potassium and magnesium, and associated conditions that exacerbate micronutrient, electrolyte and mineral deficiencies, e.g. alcoholism, gastrointestinal disorders, and poor or eccentric diets.

Although phosphate is just one of the components affected, hypophosphataemia has far reaching consequences on the functioning of various organ systems. During starvation, phosphate and potassium are lost from the cell in proportion to the breakdown of glycogen and protein, potassium being the main intracellular cation balancing the negative charges on proteins. There is, therefore, no clinical deficiency of these electrolytes until catabolism is abruptly reversed and resynthesis of glycogen and protein begins, creating a sudden demand for inorganic phosphate for phosphorylation and ATP synthesis and for potassium to balance the negative charges on protein and glycogen. Magnesium, being involved in ATP synthesis, is also taken up by the cells. Upon the introduction of carbohydrate, insulin is released into the blood stream and there is a shift of metabolism from fat to carbohydrate. Acute thiamine deficiency may be precipitated, especially in patients suffering from chronic alcoholism, since diminished thiamine reserves are rapidly used up, as carbohydrate metabolism is accelerated. Excessive infusion of glucose may also cause hyperglycaemia leading to osmotic diuresis, dehydratation and hyperosmolar non-ketotic coma. The production of fat from glucose due to lipogenesis can result in hypertriglyceridaemia and/or a fatty liver.

Refeeding problems primarily occur after feeding commences, and can be regarded as an iatrogenic condition. With awareness of its existence and careful management, its development is usually preventable. NICE and other authorities recommend that generous amounts of potassium, magnesium and phosphate supplements should be given alongside initiation of feeding, which should start at around 10 kcal/kg/day in very high risk groups [42, 43]. Thiamine and other B vitamins must also be given intravenously starting before any feed is commenced, and continuing for at least the first 3 days of feeding. Feeding rates can then be gradually increased over the next few days to full calorie requirements by day 8. Thereafter, regular monitoring, especially of the refeeding electrolytes (phosphate, potassium and magnesium) is essential, although the frequency required will depend on the stability of the patient. A more in depth description of the management of refeeding syndrome can be found in reference [43] and chapter "Refeeding Problems".

References

1. Initial placement checks for nasogastric and orogastric tubes. 2016. https://improvement.nhs.uk/resources/resource-set-initial-placement-checks-nasogastric-and-orogastric-tubes/.
2. National Patient Safety Agency. Reducing the harm caused by misplaced nasogastric feeding tubes in adults, children and infants. (Patient Safety Alert 2011). 2011. www.nrls.npsa.nhs.uk/alerts/?entryid45=129640.
3. Milsom SA, Sweeting JA, Sheahan H, Haemmerle E, Windsor JA. Naso-enteric tube placement: a review of methods to confirm tip location, global applicability and requirements. World J Surg.

2015;39(9):2243–52. www.ncbi.nlm.nih.gov/pubmed/25900711. https://doi.org/10.1007/s00268-015-3077-6.
4. Puiggròs C, Molinos R, Ortiz MD, Ribas M, Romero C, Vázquez C, Segurola H, Burgos R. Experience in bedside placement, clinical validity, and cost-efficacy of a self-propelled nasojejunal feeding tube. Nutr Clin Pract. 2015;30(6):815–23. Epub 2015 Jul 24. https://doi.org/10.1177/0884533615592954.
5. Gerritsen A, Duflou A, Ramali M, Busch OR, Gouma DJ, van Gulik TM, Nieveen van Dijkum EJ, Mathus-Vliegen EM, Besselink MG. Electromagnetic-guided versus endoscopic placement of nasojejunal feeding tubes after pancreatoduodenectomy: a prospective pilot study. Pancreas. 2016;45(2):254–9. https://doi.org/10.1097/MPA.0000000000000448.
6. Lipp A, Lusardi G. Systemic antimicrobial prophylaxis for percutaneous endoscopic gastrostomy. Cochrane Database Syst Rev. 2013;(11):CD005571. https://doi.org/10.1002/14651858.CD005571.pub3.
7. Pratt J, Green S. Removal of percutaneous endoscopic gastrostomy tubes in adults using the "cut and push" method: a systematic review. Clin Nutr ESPEN. 2017;21:59–65. Epub 2017 Jun 26. https://doi.org/10.1016/j.clnesp.2017.05.004.
8. Rumalla A, Baron TH. Results of direct percutaneous endoscopic jejunostomy, an alternative method for providing jejunal feeding. Mayo Clin Proc. 2000;75:807–10.
9. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN guideline: clinical nutrition in surgery. Clin Nutr. 2017;36:623–50.
10. Seder CW, Stockdale W, Hale L, Janczyk RJ. Nasal bridling decreases feeding tube dislodgment and may increase caloric intake in the surgical intensive care unit: a randomized, controlled trial. Crit Care Med. 2010;38:797–801.
11. Marcaud SP, Perkins AM. Clogging of feeding tubes. J Parenter Enter Nutr. 1988;12:403–5.
12. Altman E, Cutie A. Compatability of enteral products with commonly employed drug additives. Nutr Support Serv. 1984;4:8–17.
13. Taylor S. Confirming nasogastric feeding tube position versus the need to feed. Intensive Crit Care Nurs. 2013;29(2):59–69.
14. Blumenstein I, Shastri YM, Stein J. Gastroenteric tube feeding: techniques, problems and solutions. World J Gastroenterol. 2014;20(26):8505–24.
15. Schrag SP, Sharma R, Jaik NP, Seamon MJ, Lukaszczyk JJ, Martin ND, et al. Complications related to percutaneous endoscopic gastrostomy (PEG) tubes. a comprehensive clinical review. J Gastrointestin Liver Dis. 2007;16(4):407–18.
16. Levy I, Gralnek IM. Complications of diagnostic colonoscopy, upper endoscopy, and enteroscopy. Best Pract Res Clin Gastroenterol. 2016;30(5):705–18.
17. Lin JS, Ibrahim HZ, Kheng JW, Fee WE, Terris DJ. Percutaneous endoscopic gastrostomy: strategies for prevention and management of complications. Laryngoscope. 2001;111:1847–52.
18. Cruz I, Mamel JJ, Brady PG, Cass-Garcia M. Incidence of abdominal wall metastasis complicating PEG tube placement is untreated head and neck cancer. Gastrointest Endosc. 2005;62:708–11.
19. Laskaratos FM, Walker M, Walker M, Gowribalan J, Gkotsi D, Wojciechowska V, et al. Predictive factors for early mortality after percutaneous endoscopic and radiologically-inserted gastrostomy. Dig Dis Sci. 2013;58(12):3558–65.
20. Heitkemper MM, Martin MN, Hansen BC, Hanson R, Vanderburg V. Rate and volume of intermittent feeding. J Parenter Enter Nutr. 1981;5:125–9.
21. Lebak KJ, Bliss DZ, Savik K, et al. What's new on defining diarrhea in tube-feeding studies? Clin Nurs Res. 2003;12:174–204.
22. Payne-James JJ, Rana SK, Bray MJ, McSwiggan DA, Silk DB. Retrograde (ascending) bacterial contamination of enteral diet administration systems. J Parenter Enter Nutr. 1992;16:369–73.
23. Anderson K, Norris D, Godfrey L, Avent C, Butterworth C. Bacterial contamination of tube-feeding formulas. J Parenter Enter Nutr. 1984;8:673–8.
24. Barbut F, Meynard JL. Managing antibiotic-associated diarrhoea. Br Med J. 2002;324:1345–6.
25. Bowling TE. Diarrhoea in the enterally fed patient. Frontline Gastroenterol. 2010;1:140–3.
26. Bowling TE, Raimundo AH, Silk DBA. Colonic secretory effect in response to enteral feeding in man. Gut. 1994;35:1734–41.
27. Whelan K, Schneider SM. Mechanisms, prevention, and management of diarrhea in enteral nutrition. Curr Opin Gastroenterol. 2011;27(2):152–9.
28. Whelan K, Judd PA, Tuohy KM, et al. Fecal microbiota in patients receiving enteral feeding are highly variable and may be altered in those who develop diarrhea. Am J Clin Nutr. 2009;89:240–7.
29. Elia M, Engfer MB, Green CJ, et al. Systematic review and meta-analysis: the clinical and physiological effects of fibre-containing enteral formulae. Aliment Pharmacol Ther. 2008;27:120–45.
30. Meier R, Gassull M. Consensus recommendations on the effects and benefits of fibre in clinical practice. Clin Nutr. 2004;10:73–80.
31. Metheny NA. Strategies to prevent aspiration-related pneumonia in tube-fed patients. Respir Care Clin N Am. 2006;12(4):603–17.
32. Jacobs S, Chang RWS, Lee B, Bartlett FW. Continuous enteral feeding: A major cause of pneumonia among ventilated intensive care unit patients. J Parenter Enter Nutr. 1990;14:353–6.
33. McClave SA, Lukan JK, Stefater JA, et al. Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. Crit Care Med. 2005;33:324–30.
34. Montejo JC, Minambres E, Bordeje L, Mesejo A, Acosta J, Heras A, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. Intensive Care Med. 2010;36:1386–93.
35. DeLegge MH. Managing gastric residual volumes in the critically ill patient. Curr Opin Clin Nutr Metab Care. 2011;14:193–6.
36. Shang E, Geiger N, Sturm JW, et al. Pump-assisted enteral nutrition can prevent aspiration in bedridden percutaneous endoscopic gastrostomy patients. JPEN J Parenter Enteral Nutr. 2004;28:180–3.
37. Lee JS, Kwok T, Chui P, Ko F, Ko W, Kam W, et al. Can continuous pump feeding reduce the incidence of pneumonia in nasogastric tube-fed patients? A randomised controlled trial. Clin Nutr. 2010;29:453–8.
38. Marik PE, Zaloga GP. Gastric versus post-pyloric feeding: a systematic review. Crit Care. 2003;7:R46–51.
39. Ho KM, Dobb GJ, Webb SA. A comparison of early gastric and post-pyloric feeding in critically ill patients: a meta-analysis. Intensive Care Med. 2006;32:639–49.
40. Alkhawaja S, Martin C, Butler RJ, Gwadry-Sridhar F. Post-pyloric versus gastric tube feeding for preventing pneumonia and improving nutritional outcomes in critically ill adults. Cochrane Database Syst Rev. 2015;(8):CD008875. https://doi.org/10.1002/14651858.CD008875.pub2.
41. Lewis K, Alqahtani Z, Mcintyre L, Almenawer S, Alshamsi F, Rhodes A, Evans L, Angus DC, Alhazzani W. The efficacy and safety of prokinetic agents in critically ill patients receiving enteral nutrition: a systematic review and meta-analysis of randomized trials. Crit Care. 2016;20(1):259. https://doi.org/10.1186/s13054-016-1441-z.
42. Keys A, Brožek J, Henschel A, Mickelsen O, Taylor H. The biology of human starvation. Minneapolis, MN: University of Minnesota Press; 1950. Nutrition Support in Adults: oral nutrition support, enteral tube feeding and parenteral nutrition, CG32. London, National Institute for Health and Clinical Excellence, 2006. http://www.nice.org.uk/nicemedia/live/10978/29981/29981.pdf.
43. Friedli N, Stanga Z, Sobotka L, Culkin A, Kondrup J, Laviano A, et al. Revisiting the refeeding syndrome: results of a systematic review. Nutrition. 2017;35:151–60.

Prevention, Diagnosis and Management of Catheter-Related Blood Stream Infections

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Key Points

1. Catheter-related bloodstream infections (CRBSI) represent the most common serious and life-threatening complication for patients receiving home parenteral support (HPS).
2. Development of CRBSIs occurs mostly following microbial migration along the contaminated or colonized central venous catheter (CVC) surface into the bloodstream (usually from the hub).
3. Skin-derived flora causes most catheter related infections; therefore adequate hand hygiene and aseptic catheter handling techniques are most important for CRBSI prevention.
4. CRBSI should be suspected when patients receiving HPS present with fever (especially if within an hour of setting up an infusion), are unwell or have been involved in events that may be associated with a catheter infection (e.g. catheter fracture, attempts at restoring patency, etc.).
5. Paired qualitative (using differential time to positivity (DTP) or paired quantitative (using pour plates)) blood cultures from a peripheral vein and from the catheter are required for the diagnosis of a definite CRBSI.
6. When central blood cultures are positive and no peripheral cultures can be taken (or vice versa), this can be classified as a probable CRBSI providing the symptoms and clinical picture is suggestive of a CRBSI.
7. For uncomplicated CRBSIs it is recommended that an attempt to salvage the CVC is made, by means of treatment with antibiotics since repeated catheter loss ultimately will lead to a failure to obtain adequate and reliable central venous access. Catheter salvage is not recommended for candida infection.
8. Once a CRBSI is suspected and while blood cultures results are awaited, empirical therapy should be commenced with a CVC antibiotic lock plus a systemic antibiotic, adjusted thereafter according to microbial sensitivity.
9. If salvage fails or the patient has recurrent CRBSI, the CVC should be removed and other sources of infection should be considered.
10. Fluid (or parenteral nutrition) during salvage is given by a different catheter (often into a peripheral vein).
11. After a CRBSI the aseptic techniques in setting up/taking down an infusion should be reassessed, and possible environmental contributors identified.
12. Central blood cultures should be taken at least 48 h after completion of therapy to confirm successful treatment.

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Introduction

Patients with chronic intestinal failure depend on parenteral nutrition to maintain health and preserve life. Catheter related complications, particularly blood stream infections, are a significant cause of morbidity and mortality in patients on HPS. Dedicated intravenous catheters managed with rigorous aseptic protocols are vital in preventing complications and obtaining good long-term outcomes in patients dependent on HPS. Similarly, robust arrangements for the early recognition and treatment of catheter-related complications, including catheter-related blood stream

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infection (CRBSI), help to prevent progressive loss of venous access.

Pathogenesis of CRBSI

The use of a central venous catheter (CVC) is associated with the risk for microbial colonization and subsequent serious infections, including CRBSI. Several factors have been implicated in the pathogenesis of CRBSI:

Colonization and Contamination of the Central Venous Catheter

The catheter itself can be involved through several potential routes [1]:

- Colonization of the catheter tip and/or extraluminal subcutaneous tract by skin-derived flora
- Colonization of the catheter lumen through microbial contamination
- Hematogenous spread of microbes onto the catheter surface from other foci of infection
- Colonization of the catheter lumen through contaminated infusate.

The most common routes for contamination of CVCs are migration of skin-derived flora from the insertion or exit-site of the catheter into the cutaneous catheter tract, and along the extraluminal surface of the catheter with subsequent colonization of the catheter tip, or via direct contamination of the catheter hub by contact with hands, contaminated fluids or devices. Less common causes of CRBSI are hematogenous seeding or infusate contamination [2]. Microbial contamination, colonization and subsequently biofilm formation on catheter surfaces can occur within 24 h after insertion [3].

Biofilm Formation

Microbial contamination of the catheter leads to the development of microbial consortia associated with the CVC surface and surrounded by a self-produced polymer matrix, termed a 'biofilm'. Biofilms typically consist of 3 components: the biofilm-growing microorganisms, the planktonically (nonaggregated) growing organisms and the integrated host component, such as fibrin, platelets or immunoglobulins [4]. Biofilms have the capability to seize and concentrate a number of environmental nutrients in their extracellular matrix. In addition, biofilms facilitate the resistance to antimicrobial factors by several mechanisms, such as down-regulation of cell division and by acting as a diffusion barrier. Finally, there is a potential for dispersion through detachment, allowing for an enduring bacterial source population [5]. When harbored within a biofilm, pathogenic bacteria are, to some degree, protected against host defenses and antimicrobial compounds. The stability of this environment allows the bacteria to grow on the surfaces of indwelling medical implants or devices such as catheters or infusion ports [3, 6]. Since these devices are in direct contact with the bloodstream, the surface becomes coated with bloodstream components that act as a conditioning film to which microbes can attach [7]. Within days of adherence to the catheter cell wall, multiple bacterial layers are usually formed and microcolony aggregation occurs. An extracellular matrix of exopolysaccharide (EPS) forms an antimicrobial glycocalyx or "slime" layer [8]. Bacteria in a biofilm communicate cell-to-cell through molecular signals, a phenomenon that is termed 'quorum sensing' (QS) [9]. Many proteins and virulence factors are produced by bacteria in response to QS and thereby create a chronic, low-grade immune response [8]. A substantial proportion of the intimately connected microbial population lives in a down-regulated state because of the low nutrient and oxygen content within the biofilm. In addition, host responses that comprise the actions of granulocytes, immunoglobulins and antimicrobial therapy will likely have diminished effects since they fail to penetrate the biofilm [10].

Infection Prevention

Type, Choice and Site of Central Venous Access Device

The choice, type and exit-site location of the central venous catheter (CVC) plays an important role in occurrence of catheter colonization and the risk for developing CRBSI and is best determined by a multidisciplinary HPS team, where the opinion of the patient or his/her caregiver should also be taken into consideration [11]. The first choice for placing the CVC is in the upper caval vein with the tip placed as near as possible to the level of the right atrial-superior vena cava junction, via the internal jugular or subclavian vein and preferably on the right side. A left-sided approach, with a more intimate contact between the venous vascular lining and the catheter, is associated with a higher risk for thrombotic complications [12]. Femoral vein access routes potentially have more risk for catheter colonization, bloodstream infections and symptomatic thrombosis, though this has only been proven in the case of short-term and non-tunnelled catheterization [13, 14]. Subcutaneously tunnelled or totally implanted devices are preferred above non-tunnelled devices because of the lower rate of infections due to the specific protection from extraluminal contamination and fewer complications related to self-administration of HPS [15]. If pos-

sible, a single lumen is device is preferred over a multiple lumen catheter because of the lower infection rate. Also, infection treatment itself is more complicated in the multi-lumen situation [16, 17]. In selected patients, for example for those with recurrent CRBSI, the creation of an arteriovenous fistula has been proposed as a valuable alternative [18].

HPS Training

Careful management of CVCs, that are dedicated solely for HPS administration according to a well-established protocol, is key for the prevention of CRBSI. As such, CRBSI rates are the main quality indicator for any HPS support program. To establish this optimal care, the patient and caregiver need to be well trained and educated in all fields of CVC care. Since adequate training in this respect is of major importance for the prevention of CRBSI, training programs in many centres have been intensified in recent years. Attention is more focused on the teaching of patients and their caregivers on how to manage their CVC themselves and encompasses more rigorous aseptic protocols that are performed at the patients' home instead of in the hospital environment, thus reducing length of hospital stay [19–21]. However, so far, CRBSI rates remain the lowest whenever the care is under control of a highly trained nurse [21]. More modern forms of training programs that include video education of both staff and patients may be another measure that lowers catheter related infection rates and improves problem-solving capacities and quality of life [22]. On the other hand, a recent study was more pessimistic and suggested that, when compared with usual care, video education may lead to an increased number of patient calls without improvements in CRBSI rates [23].

Hand Hygiene, Antiseptics and Central Line Care

Adequate hand hygiene with appropriate use of disinfectants before and after touching the CVC (and non-touching of any key parts) by those who perform the HPS care is the cornerstone for preventing healthcare related infections in general [24]. The preferred antiseptic for catheter exit site and certain parts of the catheter (hubs, stopcocks and sampling ports) is chlorhexidine 2% [25]. Intravenous administration sets should be changed every 24 h when parenteral nutrition (PN) is used [15]. In general, the use of in-line filters, needle free connectors and routine replacement of catheters are not advised as infection prevention measures since there is no definitive proof that these measures reduce the incidence of CRBSI [26]. Antimicrobial-coated access devices only seem a valuable option in short-term PN care [15].

Dental Care

The various medications and therapies that are being used by patients with intestinal failure receiving HPN may affect their oral health status. Concerns exist that some CRBSIs arise from poor oral health or recent dental treatment and for this reason some experts recommend parenteral antibiotic prophylaxis prior to dental care according to the infective endocarditis (IE) dental prophylaxis guidelines [27]. However, further study is needed to establish whether there is a true relation between dental treatment and CRBSI and clear guidelines on appropriate prescription of antibiotic prophylaxis specific for patients on HPN are required.

Catheter Lock Solutions

Catheter lock therapy is a technique for disinfecting the catheter lumen and involves the dispension of locking solutions in the catheter lumen for extended periods of time while the catheter is not in use. Several lock-solutions have been developed and are being used for the prevention of CRBSIs, while others primarily serve to prevent occlusions. Unfortunately, although this strategy may seem promising, several of these catheter lock-solutions carry some associated risks and special attention should be given to problems that can arise, such as the development of side effects based on toxicity and allergies, as well as antimicrobial resistance. An overview of the most commonly researched or used catheter lock solutions is provided below:

Anticoagulant and Fibrinolytic Lock Solutions

These types of catheter-lock solutions are especially relevant in the setting of haemodialysis, since in these patients blood is aspirated through the catheter and anticoagulants are required to prevent catheter clotting and occlusion. However, this does not apply to the HPS setting, since blood is only withdrawn from the catheter in cases of a severe infection. There is some evidence that heparin and citrate may promote catheter colonization and biofilm formation [28]. Therefore, the use of anticoagulants as a catheter lock therapy to prevent CRBSI is not advised in the HPS setting.

Ethanol

Although ethanol lock therapy (ELT) is relatively inexpensive, readily available and seems to reduce the rate of CRBSI in high-risk HPN patients (i.e. patients with a history of prior CRBSI), the reduced CRBSI rate cannot be generalized to all HPS patients [29–31]. Therefore, and due to the concerns that exist, particularly the effect of ethanol on catheter structure, integrity and systemic toxicity, use of ELT is currently not advised [26, 32].

Antibiotic Locks

Results from in vitro studies demonstrate stability of antibiotic locks while maintaining high concentrations for prolonged periods of time [33–35]. However, evidence is lacking that prophylactic use of such antibiotic locks reduce the incidence of CRBSIs in HPS patients, while this strategy is associated with an increased risk for the development of microbial resistance, especially in the case of long-term HPS requirement [15]. Additionally, the biofilm that develops on the intravascular catheter is relative resistant to antibiotic penetration and this necessitates much higher blood levels of antibiotics to reach sufficient therapeutic efficacy than can be achieved by antibiotic lock therapy [36].

Taurolidine

Taurolidine, a derivative of the amino acid taurine, is non-toxic for humans and is rapidly metabolized into the amino acid taurine, water and carbon oxide. An irreversible reaction of its downstream methylol metabolites with the bacterial cell wall leads to diminished microbial adhesion to catheter surfaces, and hence, biofilm formation. Taurolidine displays a broad spectrum of antimicrobial activity against Gram positive and Gram negative microbes as well as yeasts and also neutralizes bacterial endo- and exotoxins [37, 38]. Experience with taurolidine as a catheter lock therapy is growing and the use of this compound as part of diverse available formulations has become common practice in several centres over the last years. Several randomized controlled trials (RCTs) have been conducted and all of them showed that the use of taurolidine locks is significantly associated with a lower incidence of CRBSIs without obvious adverse effects and development of bacterial resistance when compared to heparin locks [39]. Since the previous trials cold not discriminate between the beneficial effects of taurolidine and/or detrimental effects of heparin, more recently a European multicenter RCT was conducted that compared taurolidine 2% to sodium chloride 0.9% as a catheter lock solution in HPS patients. In this study, use of taurolidine resulted in a decreased CRBSI risk by more than four times with a favourable safety profile as compared to saline, without adversely influencing microbial susceptibility [40]. Whether taurolidine as a catheter-lock solution should be considered in all patients or only those with a high infection risk is still a matter of debate, not least because of the financial implications of this strategy.

Novel Preventive Strategies

Staphylococcus aureus Eradication

Although not new, strategies focussing on the eradication of the skin bacterium *Staphylococcus aureus* are currently under research in the HPN population [41]. It is known that eradicating *S. aureus* with mupirocin ointment in nasal carriers results in a statistically significant reduction in *S. aureus* infections (RR 0.55, 95% CI 0.43–0.70). Nevertheless, there is a wide variety between centers and the prevalence and clinical outcomes of CRBSIs caused by *S. aureus* in the HPN population appears in some centers not as poor as in other patient groups [21, 42–45]. Hopefully, in the near future it will become clearer if the benefits also outweigh the potential risks for eradicating *S. aureus* in the HPN population.

Novel Catheter Lock Solutions

The inhibition of biofilm formation still appears the most attractive strategy to prevent catheter-associated infections. In recent years, the emphasis has been on the development of non-toxic and preferably antibiotic-free antiseptic agents that disrupt the biofilm, like taurolidine; these rely on matrix degradation, destabilization or anti-virulence compounds that target the most tolerant microbes inside the biofilm. For example, a recently developed novel non-antibiotic, heparin-free solution containing nitroglycerin (NTG) demonstrated *in vitro* activity against a broad spectrum of microbes with high efficacy and ability to eradicate biofilm formation, with a potency similar to that of heparin. This compound appeared safe and well-tolerated when administered in cancer patients who had peripherally inserted central catheters (PICCs) [46–48]. Altogether, a better understanding of biofilm formation at the molecular level may help to develop novel approaches for the prevention of CRBSI.

Diagnosis

There is a wide variation in the incidence of reported CBRSI rates, even amongst internationally-recognised HPN centres, with a systematic review published in 2013 reporting a range of 0.38–4.58 per 1000 catheter days amongst 39 studies reviewed [44]. Since the publication of this systematic review, a case series from the U.S.A. reported a much higher CRBSI rate of 11.5 per 1000 catheter days occurring in 101 adults newly discharged home on PN [49], while a much larger series from the U.K. published in 2017 reported the lowest published CRBSI rate of 0.22 per 1000 catheter days in 279 patients newly discharged on home parenteral nutrition (HPN) [21]. This variation in CRBSI rates between different international centres may, to a limited degree, reflect differences in patient cohorts studied since a number of patient-related factors, such as the presence of a stoma and/or opiate use, have been associated with CRBSI occurrence [45]; however, differences in catheter care protocols between centres is likely the most significant factor accounting for the extremes in CRBSI rates.

Another factor that may influence reported CRBSI rates is the criteria used for CRBSI diagnosis. A number of organisations have proposed criteria for the diagnosis of bacteremia affecting patients with indwelling venous catheters,

including the Centre for Disease Control and Prevention (CDC), Infectious Disease Society of America (IDSA) and the European Society of Enteral and Parenteral Nutrition (European Society of Clinical Nutrition and Metabolism) (ESPEN) [15, 50, 51]. The current ESPEN guidelines are based upon the CDC criteria and recommend that a CRBSI is diagnosed by a 'positive culture of the catheter (on removal), or paired blood cultures from a peripheral vein and the catheter (when left in place) with isolation of identical organisms (both species and antibiograms) from cultures of catheter segments and blood drawn from a peripheral vein in a patient with clinical symptoms of sepsis and the absence of another source of infection.' Once drawn, international guidelines further recommend that blood samples from central and peripheral veins undergo quantitative and/or qualitative analysis in the laboratory. Quantitative methods, such as pour plates, are thought to have the best diagnostic accuracy and are recommended by international organisations, but may not be widely used [50, 52–55]; if quantitative methods are used, then the diagnosis of a CRBSI should be made if the colony count of microbes grown from the catheter hub blood sample is at least threefold greater than the colony count from the peripheral blood [50]. Qualitative methods include assessment of differential time to positivity (DTP), which has reasonable accuracy and is more widely available in most hospitals; a positive CRBSI is diagnosed if the growth of microbes from the catheter hub blood sample occurs at least 2 h before any microbial growth is detected in the peripheral blood sample [56]. Quantitative and qualitative blood cultures rely upon careful sample labelling, with equal volumes of blood instilled into blood culture bottles (within 10 min) and that the samples are then handled identically. The samples require prompt transport to and processing within the laboratory (within 4 h of being collected).

Failure to follow standardised guidelines utilising quantitative or qualitative paired cultures can lead to CRBSI misdiagnosis, inappropriate antibiotic usage and potentially unnecessary catheter removal. Indeed, a retrospective study from Denmark demonstrated that simply adopting a clinically-based approach to diagnose CRBSI (for example, based on the presence of clinical symptoms, elevation of biochemical blood tests and a positive peripheral or central blood culture) rather than using quantitative or qualitative methods may lead to significant over-diagnosis by 46% [57]. Thus, consistent approaches to the CRBSI diagnosis are clearly important to allow meaningful comparisons between different centres, not least because CRBSI rate is deemed a surrogate marker of the quality of care provided by HPS centres and the outcome indicator considered to be the most important by HPN-dependent patients [58].

New methods to diagnose CRBSI have been evaluated but have not yet proven to be of clinical benefit. For example, plasma immunoglobulin levels against flagellin and lipopolysaccharide were not found to differentiate between non-bacterial febrile illnesses and CRBSIs in a small study of children with intestinal failure [59] while other methods aimed at making a rapid diagnosis, including real time PCR, have been explored but currently do not appear to be adequately sensitive to be used in this setting [60]. Further work is required to develop and evaluate the role of novel techniques aimed at rapidly diagnosing CRBSIs, while ensuring consistent methodology so that meaningful comparisons of CRBSI rates can be made between different IF centres.

Management

Current international guidelines recommend that infected CVCs are salvaged wherever possible because repeated catheter loss can ultimately lead to failed venous access which, currently, can be an indication for a small bowel transplant [26]. Thus, once diagnosed, attempts should be considered to treat the CRBSI with antibiotics without resorting to CVC removal. Of course, salvage should be only attempted if deemed clinically appropriate such that immediate CVC removal is recommended if the patient is at clinical risk with septic shock, where any attempt at CVC salvage may be felt to compromise the safety of the patient [21, 26, 45]. In addition, if patients have a CVC tunnel infection, a metastatic infection (e.g. endocarditis, osteomyelitis) or a septic thrombosis associated with the CRBSI, salvage is also not generally recommended because of the relatively low chance of success and, in these circumstances, CVC removal is advised [26, 45]. While tunnelled catheters can be readily salvaged, some experts also describe successful salvage of infected implanted ports; however, in the authors' experience and according to European guidelines [26], successful salvage of these devices is rare and most implanted ports have to be removed if infected [16, 26]. If removed, reinsertion of any long term CVC should not take place until after completion of a course of appropriate systemic antibiotics and, thereafter, once repeat blood cultures are negative [26].

For uncomplicated CRBSIs, current guidelines advise that systemic antibiotics with appropriate microbial sensitivity based on blood culture results, alongside antibiotic CVC lock therapy, should be used for 2 weeks [26]. Two recent papers evaluating very large series since the 1990s, from Salford in the U.K. and the Mayo Clinic in the U.S.A., have demonstrated high CVC salvage rates of HPS-associated CRBSIs of 72.5% (180 CVCs salvaged of 248 CRBSIs) and 70% (325 CVCs salvaged of 465 CRBSIs) respectively, with low associated mortality (U.K. 1.7% inpatient episodes of CRBSI and U.S.A. 3.5% overall mortality from CRBSI in the HPN population) [45, 61]. Coagulase negative staphylococci were the most frequent isolate in both series and had the greatest successful salvage rate of 79.8% in the U.K. paper and 77.8% in the U.S.A. paper [45, 61]. CVCs infected

with Gram negative or polymicrobial bacteria could also be salvaged at high rates [45, 61]. Notably both papers demonstrated that more than half of all CVCs infected with potentially highly pathogenic organisms, such as *S. aureus,* could also be safely salvaged [45, 61]. This is despite guidance from the Infectious Disease Society of America (IDSA) recommending that CVCs infected with *S. aureus* should be removed [62]. Most international authorities recommend that CVCs infected with fungi should be removed [15, 26, 50, 51] and this was the practice in recently published papers from the U.K. [21, 45]; the Mayo group actually reported successful treatment of fungal CRBSIs, albeit at a very low rate (14.2%) [61]. An ECHO should be performed if there is a prosthetic heart valve, pacemaker/ICD, persistent bacteraemia and/or pyrexia 72 h after initiation of appropriate antibiotic therapy and/or with S aureus infection.

There remain some methodological differences between institutions in CVC salvage protocols. For example, some [21, 45] but not all [61] centres advocate routine use of thrombolytics within the CVC salvage protocol theoretically to remove any associated intraluminal thrombus, although the evidence-base for this approach is limited [26]. Furthermore, the duration of antibiotic therapy has varied according to the underlying organism and according to institution protocol. Although international guidelines recommend a course of 14-days antibiotic treatment for all organisms, recent evidence suggests that 10-days [21] or even 7-days [61] may be equally effective for less virulent organisms such as Coagulase negative staphylococci [21]. Similarly, methods used to confirm salvage success have varied between different institutions. The Mayo group defined catheter salvage 'as the process of treating an occurrence of CRBSI appropriately with antibiotics without removing the central venous catheter', while the Salford group confirmed salvage success through negative repeated sets of peripheral and central blood cultures and pour plates 48 h after completion of antibiotic therapy [45]. The latter approach supported in a subsequent publication from the same group which revealed that negative cultures following antibiotic salvage could predict the absence of re-infection in 96% of patients over the following 1-year [21].

Current guidelines do not recommend the routine screening for CRBSI occurrence in the absence of suspicion of a catheter-related infection. However, clinicians may have a low index of suspicion for a CVC infection or colonisation if patients are transferred from general hospital wards with a high incidence of infection to a dedicated IFU. Indeed, a recent study screened a large number of patients newly diagnosed with type 2 IF with central and peripheral blood cultures on admission to an intestinal failure unit and found that 19% of had a colonised or infected catheter that had been contracted but not recognised in the referring hospital [21]. A successful CVC salvage rate of 91% was achieved in this cohort after antibiotic therapy and the subsequent in-patient catheter-related BSI rate for those admitted with a CVC on the IFU was very low at 0.042 per 1000 catheter days, over a total of 23,548 in-patient catheter days [21]. Thus, since there is a risk that continued PN infusion may serve as an infective milieu, identification of central venous catheter infection or colonisation is clearly important in patients with acute IF to attempt to reduce the risk of the associated morbidity resultant from subsequent CRBSI development in already metabolically-unstable individuals [21].

After a CRBSI the patient/carer's aseptic technique in handling should be reassessed. If recurrent CRBSI another source of infection should be sought (e.g. teeth, wounds, nails, urine etc). 70% Isopropyl alcohol port protectors may be used. The prophylactic use of antimicrobial locks (e.g. taurolidine) can be used for recurrent CRBSI, but ethanol locks are not recommended. For all (especially nursed) patients a root cause analysis is recommended to try and identify possible contributory factors.

References

1. Gahlot R, Nigam C, Kumar V, Yadav G, Anupurba S. Catheter-related bloodstream infections. Int J Crit Illn Inj Sci. 2014;4(2):162–7.
2. Dobbins BM, Catton JA, Kite P, McMahon MJ, Wilcox MH. Each lumen is a potential source of central venous catheter-related bloodstream infection. Crit Care Med. 2003;31(6):1688–90.
3. Donlan RM. Biofilms and device-associated infections. Emerg Infect Dis. 2001;7(2):277–81.
4. Donlan RM. Biofilms: microbial life on surfaces. Emerg Infect Dis. 2002;8(9):881–90.
5. Gompelman M, van Asten SA, Peters EJ. Update on the role of infection and biofilms in wound healing: pathophysiology and treatment. Plast Reconstr Surg. 2016;138(3 Suppl):61s–70s.
6. Rohrich RJ, Monheit G, Nguyen AT, Brown SA, Fagien S. Soft-tissue filler complications: the important role of biofilms. Plast Reconstr Surg. 2010;125(4):1250–6.
7. Yousif A, Jamal MA, Raad I. Biofilm-based central line-associated bloodstream infections. Adv Exp Med Biol. 2015;830:157–79.
8. Frei E, Hodgkiss-Harlow K, Rossi PJ, Edmiston CE Jr, Bandyk DF. Microbial pathogenesis of bacterial biofilms: a causative factor of vascular surgical site infection. Vasc Endovascular Surg. 2011;45(8):688–96.
9. Schuster M, Lostroh CP, Ogi T, Greenberg EP. Identification, timing, and signal specificity of Pseudomonas aeruginosa quorum-controlled genes: a transcriptome analysis. J Bacteriol. 2003;185(7):2066–79.
10. Balaban N, Stoodley P, Fux CA, Wilson S, Costerton JW, Dell'Acqua G. Prevention of staphylococcal biofilm-associated infections by the quorum sensing inhibitor RIP. Clin Orthop Relat Res. 2005;437:48–54.
11. Schneider PJ. Nutrition support teams: an evidence-based practice. Nutr Clin Pract. 2006;21(1):62–7.
12. Ge X, Cavallazzi R, Li C, Pan SM, Wang YW, Wang FL. Central venous access sites for the prevention of venous thrombosis, stenosis and infection. Cochrane Database Syst Rev. 2012;(3):Cd004084.
13. Merrer J, De Jonghe B, Golliot F, Lefrant JY, Raffy B, Barre E, et al. Complications of femoral and subclavian venous catheterization

in critically ill patients: a randomized controlled trial. JAMA. 2001;286(6):700–7.
14. Parienti JJ, Mongardon N, Megarbane B, Mira JP, Kalfon P, Gros A, et al. Intravascular complications of central venous catheterization by insertion site. N Engl J Med. 2015;373(13):1220–9.
15. Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN guidelines on parenteral nutrition: central venous catheters (access, care, diagnosis and therapy of complications). Clin Nutr. 2009;28(4):365–77.
16. Kuizon D, Gordon SM, Dolmatch BL. Single-lumen subcutaneous ports inserted by interventional radiologists in patients undergoing chemotherapy: incidence of infection and outcome of attempted catheter salvage. Arch Intern Med. 2001;161(3):406–10.
17. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control. 2011;39(4, Supplement):S1–S34.
18. Versleijen MW, Huisman-de Waal GJ, Kock MC, Elferink AJ, van Rossum LG, Feuth T, et al. Arteriovenous fistulae as an alternative to central venous catheters for delivery of long-term home parenteral nutrition. Gastroenterology. 2009;136(5):1577–84.
19. Buchman A, Opilla M, Kwasny M, Okamoto RJ, Diamantidis TG. Risk factors for catheter-related blood stream infections (CRBI) in adults with intestinal failure. Gastroenterology. 2013;1:S749.
20. Donaldson E, Taylor M, Abraham A, Carlson G, Fletcher O, Varden J, et al. Improving quality in a national intestinal failure unit: greater efficiency, improved access and reduced mortality. Frontline Gastroenterol. 2015;6(3):182–93.
21. Bond A, Teubner A, Taylor M, Cawley C, Abraham A, Dibb M, et al. Assessing the impact of quality improvement measures on catheter related blood stream infections and catheter salvage: experience from a national intestinal failure unit. Clin Nutr. 2017;37(6 Pt A):2097.
22. Smith CE, Curtas S, Kleinbeck SV, Werkowitch M, Mosier M, Seidner DL, Steiger E. Clinical trial of interactive and videotaped educational interventions reduce infection, reactive depression, and rehospitalizations for sepsis in patients on home parenteral nutrition. J Parenter Enter Nutr. 2003;27(2):137–45.
23. Emery D, Pearson A, Lopez R, Hamilton C, Albert NM. Voiceover interactive powerpoint catheter care education for home parenteral nutrition. Nutr Clin Pract. 2015;30(5):714–9.
24. Marcia R. Evidence-based practice in the management of vascular access devices for home parenteral nutrition therapy. J Parenter Enteral Nutr. 2006;30(1S):S82–93.
25. Chaiyakunapruk N, Veenstra DL, Lipsky BA, Saint S. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. Ann Intern Med. 2002;136(11):792–801.
26. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35(2):247–307.
27. Lee AM, Gabe SM, Nightingale JM, Burke M. Oral health, dental prophylaxis and catheter related bloodstream infections in home parenteral nutrition patients: results of a UK survey and cohort study. Br Dent J. 2012;212(2):E4.
28. Shanks RM, Donegan NP, Graber ML, Buckingham SE, Zegans ME, Cheung AL, et al. Heparin stimulates Staphylococcus aureus biofilm formation. Infect Immun. 2005;73(8):4596–606.
29. John BK, Khan MA, Speerhas R, Rhoda K, Hamilton C, et al. Ethanol lock therapy in reducing catheter-related bloodstream infections in adult home parenteral nutrition patients. J Parenter Enteral Nutr. 2012;36(5):603–10.
30. Salonen BR, Bonnes SL, Vallumsetla N, Varayil JE, Mundi MS, Hurt RT. A prospective double blind randomized controlled study on the use of ethanol locks in HPN patients. Clin Nutr. 2017;37(4):1181.
31. Opilla MT, Kirby DF, Edmond MB. Use of ethanol lock therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients. JPEN J Parenter Enteral Nutr. 2007;31(4):302–5.
32. Mermel LA, Alang N. Adverse effects associated with ethanol catheter lock solutions: a systematic review. J Antimicrob Chemother. 2014;69(10):2611–9.
33. Droste JC, Jeraj HA, MacDonald A, Farrington K. Stability and in vitro efficacy of antibiotic–heparin lock solutions potentially useful for treatment of central venous catheter-related sepsis. J Antimicrob Chemother. 2003;51(4):849–55.
34. Messing B, Peitra-Cohen S, Debure A, Beliah M, Bernier J, Messing B, et al. Antibiotic-lock technique: a new approach to optimal therapy for catheter-related sepsis in home-parenteral nutrition patients. J Parenter Enteral Nutr. 1988;12(2):185–9.
35. Henrickson KJ, Powell KR, Schwartz CL. A dilute solution of vancomycin and heparin retains antibacterial and anticoagulant activities. J Infect Dis. 1988;157(3):600–1.
36. Donlan RM. Biofilm elimination on intravascular catheters: important considerations for the infectious disease practitioner. Clin Infect Dis. 2011;52(8):1038–45.
37. Watson RW, Redmond HP, McCarthy J, Bouchier-Hayes D. Taurolidine, an antilipopolysaccharide agent, has immunoregulatory properties that are mediated by the amino acid taurine. J Leukoc Biol. 1995;58(3):299–306.
38. Shah CB, Mittelman MW, Costerton JW, Parenteau S, Pelak M, Arsenault R, et al. Antimicrobial activity of a novel catheter lock solution. Antimicrob Agents Chemother. 2002;46(6):1674–9.
39. Liu Y, Zhang AQ, Cao L, Xia HT, Ma JJ. Taurolidine lock solutions for the prevention of catheter-related bloodstream infections: a systematic review and meta-analysis of randomized controlled trials. PloS One. 2013;8(11):e79417.
40. Wouters Y, Theilla M, Singer P, Tribler S, Jeppesen P, Pironi L, et al. Taurolidine prevents catheter-related bloodstream infections in patients on home parenteral nutrition-a randomized controlled trial. United Eur Gastroenterol J. 2017;5(5 Supplement 1):A834. http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/008/CN-01439008/frame.html.
41. Gompelman M, Wouters Y, Kievit W, Hopman J, Wertheim HF, Bleeker-Rovers CP, et al. Long-term Staphylococcus aureus decolonization in patients on home parenteral nutrition: study protocol for a randomized multicenter trial. Trials. 2018;19(1):346.
42. Kaasch AJ, Barlow G, Edgeworth JD, Fowler VG Jr, Hellmich M, Hopkins S, et al. Staphylococcus aureus bloodstream infection: a pooled analysis of five prospective, observational studies. J Infect. 2014;68(3):242–51.
43. Thwaites GE, Scarborough M, Szubert A, Nsutebu E, Tilley R, Greig J, et al. Adjunctive rifampicin for Staphylococcus aureus bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391(10121):668–78.
44. Dreesen M, Foulon V, Spriet I, Goossens GA, Hiele M, De Pourcq L, et al. Epidemiology of catheter-related infections in adult patients receiving home parenteral nutrition: a systematic review. Clin Nutr. 2013;32(1):16–26.
45. Dibb MJ, Abraham A, Chadwick PR, Shaffer JL, Teubner A, Carlson GL, et al. Central venous catheter salvage in home parenteral nutrition catheter-related bloodstream infections: long-term safety and efficacy data. J Parenter Enteral Nutr. 2016;40(5):699–704.
46. Raad II, Fang X, Keutgen XM, Jiang Y, Sherertz R, Hachem R. The role of chelators in preventing biofilm formation and catheter-related bloodstream infections. Curr Opin Infect Dis. 2008;21(4):385–92.
47. Reitzel RA, Rosenblatt J, Hirsh-Ginsberg C, Murray K, Chaftari AM, Hachem R, et al. In vitro assessment of the antimicrobial efficacy of optimized nitroglycerin-citrate-ethanol as a nonantibiotic, antimicrobial catheter lock solution for prevention of central line-associated bloodstream infections. Antimicrob Agents Chemother. 2016;60(9):5175–81.

48. Chaftari AM, Hachem R, Szvalb A, Taremi M, Granwehr B, Viola GM, et al. A novel nonantibiotic nitroglycerin-based catheter lock solution for prevention of intraluminal central venous catheter infections in cancer patients. Antimicrob Agents Chemother. 2017;61(7):e00091.
49. Zhao VM, Griffith DP, Blumberg HM, Dave NJ, Battey CH, McNally TA, et al. Characterization of post-hospital infections in adults requiring home parenteral nutrition. Nutrition. 2013;29(1):52–9.
50. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1–45.
51. Liang SY, Marschall J. Update on emerging infections: news from the Centers for Disease Control and Prevention. Vital signs: central line-associated blood stream infections—United States, 2001, 2008, and 2009. Ann Emerg Med. 2011;58(5):447–51.
52. Catton JA, Dobbins BM, Wood JM, Kite P, Burke D, McMahon MJ. The routine microbiological screening of central venous catheters in home parenteral nutrition patients. Clin Nutr. 2004;23(2):171–5.
53. Planes AM, Calleja R, Bernet A, Campins-Marti M, Almirante B, Pumarola T, et al. Evaluation of the usefulness of a quantitative blood culture in the diagnosis of catheter-related bloodstream infection: Comparative analysis of two periods (2002 and 2012). Enferm Infecc Microbiol Clin. 2016;34(8):484–9.
54. Capdevila JA, Planes AM, Palomar M, Gasser I, Almirante B, Pahissa A, et al. Value of differential quantitative blood cultures in the diagnosis of catheter-related sepsis. Eur J Clin Microbiol Infect Dis. 1992;11(5):403–7.
55. Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular device-related bloodstream infection. Ann Intern Med. 2005;142(6):451–66.
56. Beekmann SE, Diekema DJ, Huskins WC, Herwaldt L, Boyce JM, Sherertz RJ, et al. Diagnosing and reporting of central line-associated bloodstream infections. Infect Control Hosp Epidemiol. 2012;33(9):875–82.
57. Tribler S, Brandt CF, Hvistendahl M, Staun M, Brobech P, Moser CE, et al. Catheter-related bloodstream infections in adults receiving home parenteral nutrition: substantial differences in incidence comparing a strict microbiological to a clinically based diagnosis. JPEN J Parenter Enteral Nutr. 2018;42(2):393–402.
58. Dreesen M, Pironi L, Wanten G, Szczepanek K, Foulon V, Willems L, et al. Outcome indicators for home parenteral nutrition care: point of view from adult patients with benign disease. J Parenter Enteral Nutr. 2015;39(7):828–36.
59. Galloway DP, Troutt ML, Kocoshis SA, Gewirtz AT, Ziegler TR, Cole CR. Increased anti-flagellin and anti-lipopolysaccharide immunoglobulins in pediatric intestinal failure: associations with fever and central line-associated bloodstream infections. J Parenter Enteral Nutr. 2015;39(5):562–8.
60. Warhurst G, Maddi S, Dunn G, Ghrew M, Chadwick P, Alexander P, et al. Diagnostic accuracy of SeptiFast multi-pathogen real-time PCR in the setting of suspected healthcare-associated bloodstream infection. Intensive Care Med. 2015;41(1):86–93.
61. Edakkanambeth Varayil J, Whitaker JA, Okano A, Carnell JJ, Davidson JB, Enzler MJ, et al. Catheter salvage after catheter-related bloodstream infection during home parenteral nutrition. J Parenter Enteral Nutr. 2017;41(3):481–8.
62. van Rijen M, Bonten M, Wenzel R, Kluytmans J. Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. Cochrane Database Syst Rev. 2008;(4):Cd006216.

Central Vein Thrombosis

Cristina Cuerda and Yaser Naji

Key Points

1. Acute central vein thrombosis is a medical emergency requiring an urgent Doppler ultrasound and/or venogram.
2. Thrombolysis can be given directly into the clot.
3. Early treatment may prevent later venous stenosis/occlusion.
4. Chronic venous stenosis can be treated with angioplasty and stenting.
5. The cause of the thrombosis should be determined.
6. When 2 of the 4 major supra-diaphragmatic veins have been lost there should be consideration for a small bowel transplant.

Introduction

Home parenteral support (HPS) is administered through central catheters of different type (tunneled, ports, peripheral inserted central catheters (PICCs)). Even though thrombotic complications of the catheter are less frequent than catheter-related infections, they cause a significant burden in these patients and may lead to catheter replacement and loss of venous access that may compromise the administration of parenteral nutrition in the long-term.

In this chapter we will review the incidence, etiology, diagnosis and the strategies for the prevention and treatment of this complication.

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Incidence and Etiology

Thrombotic complications of the catheter are a dynamic process with varying severity from the appearance of the fibrin sheath at the tip of the catheter, intraluminal blood clot, mural thrombosis to venous thrombosis [1].

The fibrin sheath does not usually affect catheter function and can occur within 24 h after catheter placement and often develops within two weeks. Intraluminal clots usually cause catheter occlusion. Mural thrombosis is a blood clot that adheres to the vessel wall and can occlude the tip of the catheter but does not completely occlude the vein. Central venous thrombosis (CVT) occludes the vein and is the most significant thrombotic complication.

CVT is a severe complication that is responsible for the loss of central venous accesses in patients on home parenteral support (HPS) and may be an indication for small bowel transplantation if it affects two or more of the central venous vessels (subclavian, jugular or femoral) [2].

The pathogenesis of CVT is multifactorial and includes the following: (a) vessel injury during the procedure of insertion, (b) venous stasis due to indwelling of the device and damage to the endothelium caused by infusion of parenteral nutrition with a high osmolality, and (c) mechanical rubbing of the catheter against the vessel wall.

Venous thrombosis can develop soon after catheter insertion or delayed in patients with long-term catheterization. The former cause is probably related to the damage to the endothelium of the vein during the insertion and may be decreased using ultrasound guidance [3]. Other important factors are the proper selection of the vein (the right internal jugular vein is the preferred one due to its direct direction to the right atrium *vs.* the left-sided catheters), the catheter (less thrombogenic material, lowest calibre and single-lumen), and the correct location of the tip of the catheter (in the lower third of the superior vena cava, at the atrio-caval junction, or in the upper portion of the right atrium) [3–6]. PICCs are associated with a higher risk of CVT than tunneled or chest ports in some studies [7, 8], but not in others [9, 10]. The risk

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Table 1 Risk factors for venous thrombosis

Catheter
• Material (polyvinylchloride and polyethylene are more thrombogenic than silicone and polyurethane)
• Number of lumens
• Diameter of the catheter
• Location of the tip of the catheter
• Traumatic insertion (previous catheterizations)
• Infection
• Ethanol lock (pediatric patients)
• Type of catheter (PICC associated with more thrombosis than tunneled or chest ports)
Patient
• Underlying disease (cancer)
• Thrombotic diathesis
• Previous thrombosis
• HPS, chemotherapy, thoracic radiation
• Immobilization

for thrombosis is also higher in patients with cancer, thrombotic diathesis, previous thrombosis, multiple catheterizations, catheter infection, or treatment with chemotherapy [11, 12]. In recent studies it has been described an increased risk for thrombosis associated with ethanol lock therapy in the pediatric HPN population [13, 14]. In children with intestinal failure on long-term HPS low levels of anticoagulant proteins (antithrombin, protein C and S) and elevated factor FVIII activity have been described, likely reflecting liver insufficiency and chronic inflammation [15]. The main risk factors for venous thrombosis are summarized in (Table 1).

CVT may be clinically manifest or subclinical. Most of the data on the incidence of CVT in patients receiving home parenteral nutrition (HPN) comes from retrospective series with large patient numbers but only report clinically manifest thrombosis. In these studies, the incidence of CVT is around 0.02–0.09 cases/catheter/yr. or 0.06–0.12/1000 catheter-days [16–23]. Some retrospective cohort studies have shown a decrease in the incidence of this complication over the years, probably due to changes in the catheter management and patient selection [12]. Paediatric patients seem to have higher incidence of CVT than adults [15, 24].

The incidence of subclinical CVT with a routine diagnostic imaging in patients on HPS is much more unknown. In a cross-sectional study in 42 adult patients on HPN with a mean dwelling time of 37 weeks, the authors reported 26% of clinical obstruction of the upper venous system, 51% of radiologic thrombotic changes of the vessels wall and/or catheter tip and 66% of catheter dislocation from the original place, although this study is quite old and probably does not reflect the current practise [25]. In a prospective study including 30 consecutive patients receiving intravenous feeding (16 of whom had cancer), venography was performed in the 24-h period prior to catheter removal. The percentage of thrombosis found was 33%, but only one patient had symptoms [26].

However, in a recent prospective study of the HAN-CIF ESPEN group in 62 patients, the incidence of CVT with serial Color Doppler Duplex Sonography evaluations for 12 months after catheter insertion was 0.045/catheter/year, quite like that referred in retrospective studies [27]. In this study all the catheters were inserted with ultrasound guide or radiologic control and the catheter tip was in the atrio-caval junction or in the lower third of the superior cava vein in all the subjects.

Diagnosis

The diagnosis of venous thrombosis may be suspected in patients with symptoms due to interrupted venous return (pain, swelling, erythema, positional headache; patients often say they have a sensation of having a swollen head and neck) and signs (oedema, non-pulsatile raised jugular venous pulse and if chronic visible collateral vessels usually on the upper anterior chest wall) in the territory drained by the vein in which the catheter is located. Due to its low specificity (14%), the D-dimer test is not a useful method in screening for deep vein thrombosis of upper extremities [11]. The gold standard method for diagnosis is venography, but it is invasive and requires exposure to intravenous contrast and radiation (Fig. 1). The preferred method for screening is Doppler ultrasonography, which may be employed in both symptomatic and asymptomatic thrombosis as it is a non-invasive method with high sensitivity (97%) and specificity (96%)

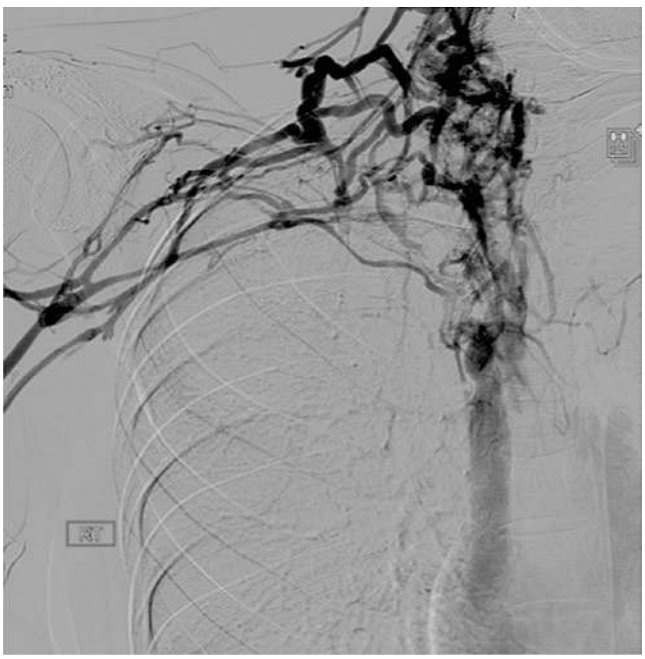

Fig. 1 Right upper limb venography showing occluded right brachiocephalic vein with extensive collaterals

compared to venography in upper extremity deep venous thrombosis [4]. Duplex ultrasound can accurately detect CVT involving the jugular, axillary, distal subclavian and the arm veins. Constrast venographic imaging is required for indeterminate duplex findings and to evaluate the deep central veins and pulmonary arteries.

Alternative strategies such as serially performed ultrasound, spiral CT or MRI may be useful and of potential interest, but are not yet validated [28].

Complications

The main complications of venous thrombosis are infection, pulmonary thromboembolism and post-thrombotic syndrome [1, 11]. Also, intracardiac thrombus has been described in patients on HPS [29].

The infection of the thrombus leads to a septic thrombophlebitis that is a serious complication that requires catheter removal. On the other hand, catheter infection facilitates the development of thrombosis due to the adherence of the components of the thrombus to the *biofilm*. Pulmonary thromboembolism is symptomatic in 4–14% of patients with venous thrombosis of the upper limbs and is asymptomatic in 15–36%, sometimes delayed months or years after catheter withdrawal. Although the post-thrombotic syndrome has been described only in 5% of patients with deep thrombosis of the upper limbs, it may be more frequent in patients on HPN. In the study of Barco et al., 20.7% of the HPN patients with venous thrombosis developed vena cava syndrome [12]. In a retrospective study of 527 patients, including 138 children found an incidence of superior vena cava or inferior vena cava syndrome of 0.02/catheter/year [16]. Moreover, CVT causes loss of central venous accesses and may compromise the administration of HPS in the long-term in these patients.

Prevention

To prevent CVT it is very important to minimize the damage to the vein wall during catheter insertion, recommending using ultrasound guided catheterization, choosing a catheter with the smallest caliber compatible with the infusion therapy, and placing the tip of the catheter at or near to the atriocaval junction [3, 5]. All the risk factors relating to the patient and catheter, previously discussed, should be considered. A thrombophilia screen may be done.

Several drugs have been used in the prevention of CVT, including heparin (in the catheter lock, inside the HPN bag, or administered subcutaneously) and oral anticoagulation (vitamin K antagonists). Also, these studies may be done in primary and secondary prevention of CVT. They have been summarized in several meta-analysis and systematic reviews, but the results are difficult to analyze as they often include a mixed population (cancer and benign disease), hospitalized and at home, different types of catheters, and there are differences in the diagnosis of thrombotic complications (with routine diagnostic imaging or with clinical endpoints) [30–38]. Based on the current evidence the use of routine prophylactic anticoagulation is not recommended in patients with central catheters in different guidelines [39, 40]. In the same direction, ESPEN guidelines do not recommend routine thromboprophylaxis with drugs (heparin, warfarin) for all adults on HPS based on the risk/benefit balance (grade of evidence low) [5].

At least 5 old, randomized studies in patients receiving parenteral nutrition (none receiving HPN) used unfractionated heparin in various doses added in the bag or intravenously and found a trend through less thrombotic events in the venogram [41–45]. However, the safety of heparin prophylaxis due to the risk of bleeding, thrombocytopenia, bone disease, among others, presumably outweighs the risk of thrombosis in many cases.

Regarding HPS adult patients, there are only retrospective and prospective studies, but no large, randomized, controlled clinical trial that evaluates the role of thromboprophylaxis.

Studies on the effectiveness of warfarin in preventing thrombosis in HPN patients are limited and most have used low-dose warfarin (1 or 2 mg/day), which does not increase the INR. One of the factors that may influence the effectiveness of warfarin prophylaxis is vitamin K intake in these patients [46]. Three studies evaluated warfarin prophylaxis in HPN adults. In a prospective non-randomized trial of 2 mg of warfarin given to 23 HPN patients, the incidence of venous thrombosis was 1 in 1617 catheter days compared with 1 in 251 days prior to the study [47]. In a retrospective review of 47 HPN patients with HIV/AIDS, the thrombosis rate was 0.016 per patient per month in 9 patients receiving 1 mg/day warfarin compared with a rate of 0.09 thromboses per patient per month in 38 patients on no prophylaxis [48]. Finally, in a retrospective review of HPN patients who already had 1 thrombotic event, the use of therapeutic warfarin resulted in a significantly decreased thrombosis rate (1 in 18 patient months vs. 1 in 184 patient months) [49].

In a retrospective study in children on HPN, prophylactic anticoagulation with low molecular weight heparin or warfarin significantly decreased catheter-related thrombosis and occlusion [50].

In general, therapeutic warfarin has been associated with a 0.4%–2% annual risk of non-intracranial hemorrhage and an annual intracranial hemorrhage risk of 0.1–0.9%, depending on the INR target range [51]. In a study with patients on HPN the annual incidence of major bleeding was 4.3% for patients on anticoagulants versus 1.8% for those off anticoagulants, heparin-induced thrombocytopenia occurred in 0.6% and heparin hypersensitivity in 2.5% of the patients [12].

In two recent surveys on the current practice of experienced centers on HPN (one in UK, and the other one in the HAN-CIF ESPEN group) most of the centers used warfarin for the prevention of CVT only in patients with previous CVT or other venous thrombotic events [52, 53].

Based on current evidence, the decision to use anticoagulation therapy to prevent venous thrombosis requires an assessment of the risk of thrombosis, bleeding risk with anticoagulation therapy and patient compliance, on an individual basis.

Treatment

Treatment of CVT depends on the chronicity of the condition, the underlying cause, and the clinical presentation [54]. Acute CVT is a medical emergency and its adequate treatment can prevent loss of venous access. BAPEN has recently pubished guidance papers for the appropriate treatment of this relevant catheter complication [55, 56].

The treatment will include thrombolysis if within 14 days of onset of symptoms followed by anticoagulation; otherwise anticoagulation only will be used. There should be an early discussion of the patient with the vascular radiological team. It is important not to remove CVC immediately, as it may be dangerous. However, it may be necessary if thrombolysis is not successful. If there is a residual central venous stenosis then balloon venoplasty can be considered (with or without stenting) and subsequently antiplatelet therapy should be given for 3–6 months, with anticoagulation after this. Figure 2 summarizes the treatment of acute CVT.

Anticoagulation

This is the mainstay of treatment for acute CVT in addition to endovascular procedures as catheter-directed thrombolysis (CDT), pharmacomechanical catheter-directed thrombolysis (PCDT), or percutaneous mechanical thrombectomy (PMT). Endovascular procedures have proven to be effective in improving patient's outcomes [57].

Anticoagulation will prevent progression of the thrombus and preserve patency of the collaterals. Unfractionated heparin is used initially as a bridge until full anticoagulation with warfarin is achieved, with a target INR between 2.0 and 3.0. Unfractionated heparin can be replaced with low molecular weight heparin which is helpful for those patients who can be managed in an outpatient setting [58].

Anticoagulation does not lyse an already existing clot that has formed after CVT. The residual thrombus will impede blood flow and the inflammatory reaction to the thrombus can cause significant narrowing or occlusion [59].

The time on anticoagulant treatment should be individualized, and long-term anticoagulation must be considered, with any decision to cease determined on a case-by-case basis involving discussions with an expert in intestinal failure/parenteral support.

Thrombolysis

Systemic thrombolysis has been proven to cause partial clot removal in randomized clinical trials but is associated with 3–4 times increased risk of major bleeding when compared with anticoagulation alone [60–62].

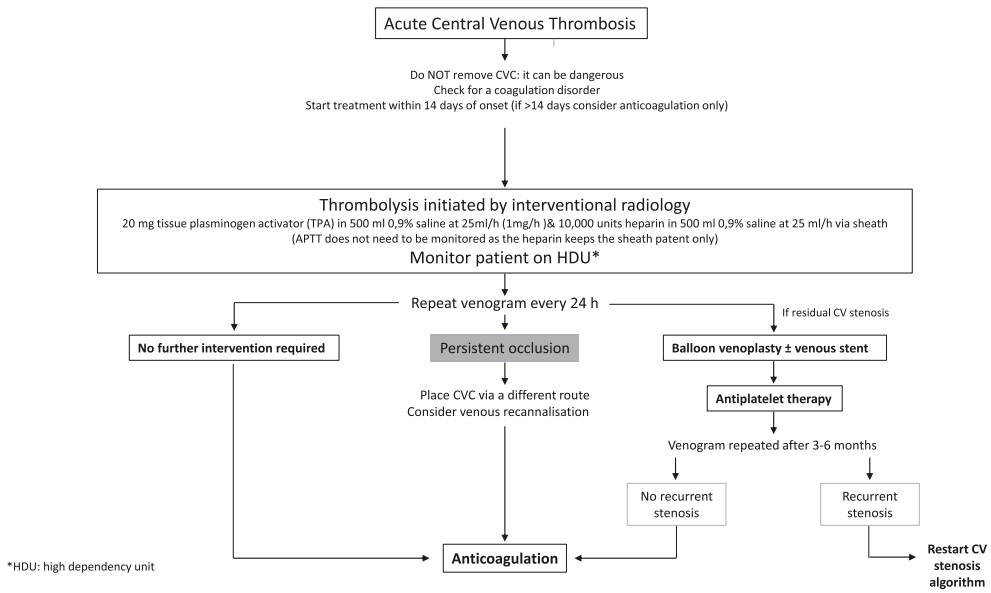

Fig. 2 Algorithm of acute central venous thrombosis treatment. (Modified from [56])

Catheter-directed thrombolysis (CDT) is a procedure where a fibrinolytic drug is infused, over 6–24 h, directly into the thrombus using a catheter with many side holes, that is positioned directly into the clot under fluoroscopy guidance. This ensures that a smaller dose of the fibrinolytic drug achieves a higher intra-thrombus concentration of the fibrinolytic drug, when compared with systemic administration of the drug. This will result in reduced treatment time and hospital stay as well as less bleeding complications. Underlying venous strictures, which might be the precipitating factor for CVT, can be identified and treated at the same time after dissolving the clot [63, 64] (Fig. 3a–d). Heparin is

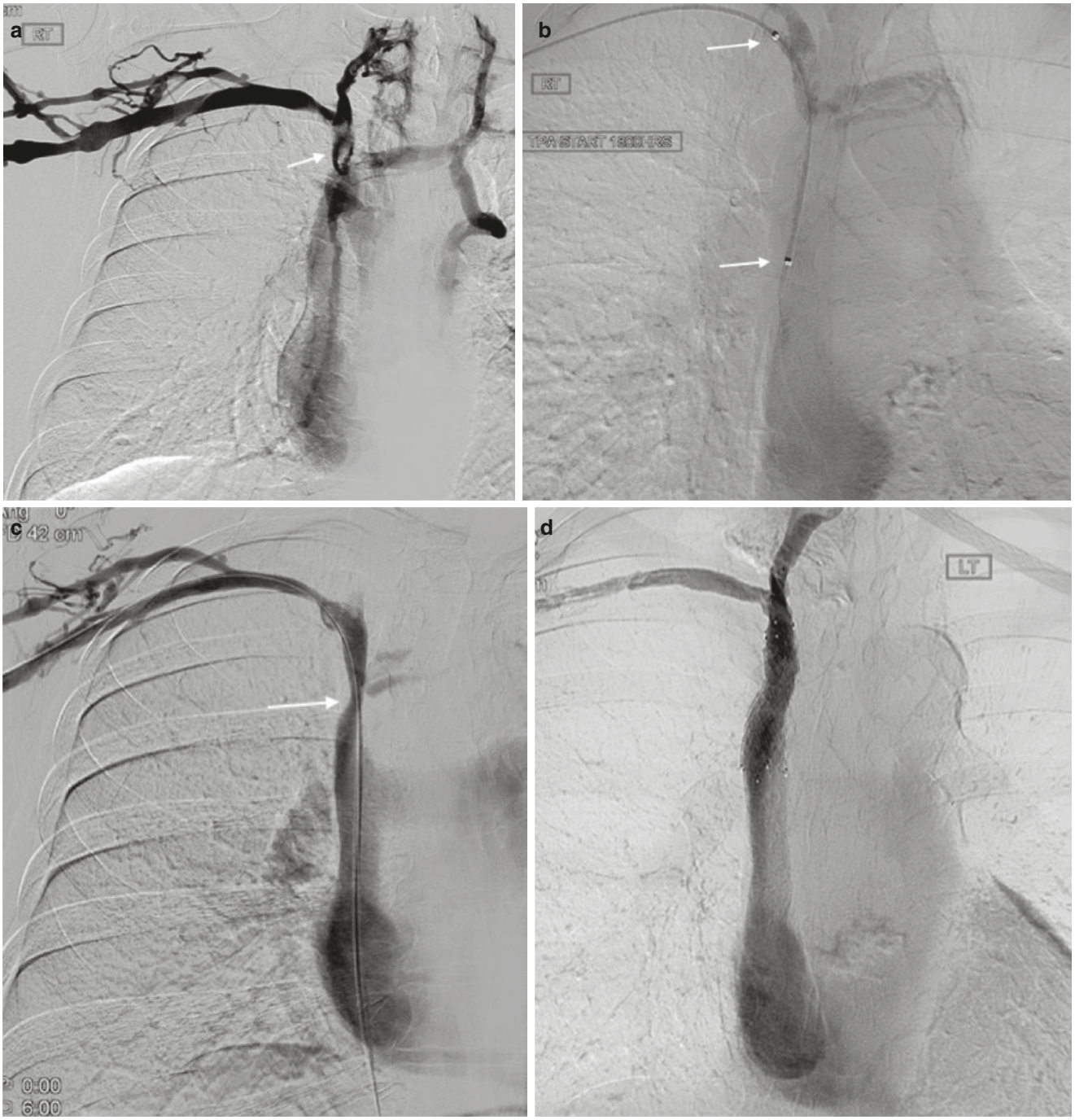

Fig. 3 (**a**) Right upper limb venography showing a thrombus in the form of filling defect in the right brachiocephalic vein (arrow). (**b**) Catheter-directed thrombolysis. A catheter with multiple side holes (identified by two radio-opaque markers on the catheter "arrows") is introduced so that the holes are present within the thrombus. (**c**) Thrombolysis check venography 24 h post initiation of catheter-directed thrombolysis shows complete resolution of the thrombus and an underlying significant stenosis at upper SVC (arrow). (**d**) Self expanding metal stent deployed at site of stenosis

infused at the same time, through the side arm of the vascular sheath, to prevent venous thrombosis around the sheath and the catheter [58].

A successful rate of clot lysis is expected in 80–90% of patients after 1–3 days of the thrombolytic treatment if the thrombus is less than 2 weeks old [64].

Cases should be individually assessed to address the factors that might increase the risk of bleeding, which is a potential serious side effect of CDT. Those factors include active or recent bleeding, recent major surgery or trauma, recent haemorrhagic stroke, or bleeding-prone lesions in critical areas like the central nervous system, and uncontrolled hypertension [65, 66].

The incidence of major bleeding is estimated to be 2–4% only with infusions of recombinant tissue plasminogen activator at low doses (0.5–1.0 mg/h) [67–69].

The addition of a mechanical thrombectomy device to intrathrombus administration of the fibrinolytic drug is called pharmacomechanical CDT (PCDT). Devices like AngioJet (Possis Medical Inc) and Aspirex (Straub Medical) have been widely used. Retrospective studies have suggested that PCDT can further reduce the dose of fibrinolytic therapy needed to lyse the clot as well as treatment time [70, 71].

Thrombolysis restores venous flow early on, prevent endothelial damage and subsequent long-term complications like stenosis and occlusions which are detrimental to patients on parenteral nutrition [72–74].

When thrombolysis restores venous patency, and if there is an underlying significant venous narrowing, endovascular treatment options include percutaneous transluminal angioplasty (PTA) and bare metal stents (BMS). Several studies have demonstrated variable success rates for all these procedures [75–79].

The most common complication of thrombolysis is puncture site oozing or bleeding. This is usually responsive to manual compression or extrinsic compression using bandages. Allergic reaction to the fibrinolytic drug can occur and is more likely to happen with Streptokinase.

Balloon Angioplasty

Balloon angioplasty is usually performed for chronic venous narrowing/occlusion. Noncompliant high-pressure balloons with diameters from 8–16 are needed to dilate the narrowing or occlusion in the central veins. These balloons have a higher rated bursting pressure (up to 18 atm.) compared with the standard balloons. If a significant residual narrowing (>30%) is still present post balloon angioplasty with persistent filling of the collaterals, insertion of a bare metal stent is advised to prevent recurrence of CVT [80].

PTA for central venous disease has a technical success rate of 70–90% [75, 78, 79, 81–83]. One of the largest studies for PTA demonstrated a cumulative patency rate of 76% at 3 months, 62% at 6 months, and 53% at 12 months [84].

Repeated interventions with PTA might be needed for central venous disease to maintain patency for a long duration [82, 83].

Stenting

Bare metal stents (BMS) will provide mechanical support and are indicated if the following conditions: (1) significant residual stenosis (>30%) after PTA (2) dissections or circumscribed perforations after PTA (3) post recanalization of venous occlusions. Stents can migrate, shorten, fracture, or get luminal instent narrowing due to intimal hyperplasia, which will require frequent ballooning. As no proven advantage has been noticed in BMS over PTA, stent deployment should be restricted to the above-mentioned indications [82–84]. Primary and cumulative patency rates of BMS at 3 months are 63–100% and 72–100% respectively, 42–89% and 55–100% at 6 months, and 14–73% and 31–91% at 12 months [78, 79, 82–93]. Flexible, self-expandable bare-metal stents are preferred as they can conform with the tortuosity of the veins and enough radial strength for most venous occlusions [94]. In patients with Paget-Schroetter syndrome (venous thoracic outlet syndrome), stent insertion across the first rib/clavicle is a contraindicated due to high rate of stent fracture and occlusion [95].

Covered stents (CSs) might have the advantage of reduced endothelialisation and in-stent stenosis while still provide the mechanical effect of the BMS. The disadvantages of CSc are occlusion of collateral veins, accidental cover of nearby veins like the internal jugular or the contralateral brachiocephalic vein and the high cost [96].

In cases with chronic occlusion of the central veins, the combination of catheters and glide wires is tried first to cross the occlusion. This is followed by prolonged ballooning with or with stent insertion. If conventional wire manipulation was unsuccessful in crossing the lesion, sharp recanalization using the back of a stiff wire, or a thin-gauge needle can be attempted [95]. If the occlusion could not be crossed with this technique, a longer sheath is advanced as close as possible to the occlusion and angled or straight glide wires (Terumo) with glide catheters are usually successful in crossing the occlusion [96]. If not, a second venous access in performed from the right common femoral vein under US guidance and a glide catheter and wire are used to negotiate the occlusion from below. More aggressive techniques like using the back end of a stiff wire or a thin trocar needle and trocar cannula can be used to cross tough and fibrotic lesions [58] (Fig. 4a–e).

Cases with complete occlusion of the central veins, including those who will require access from brachial / subclavian and femoral veins, and even those in whom thin needles are needed to cross the occlusions are not associated with higher complication rates [97].

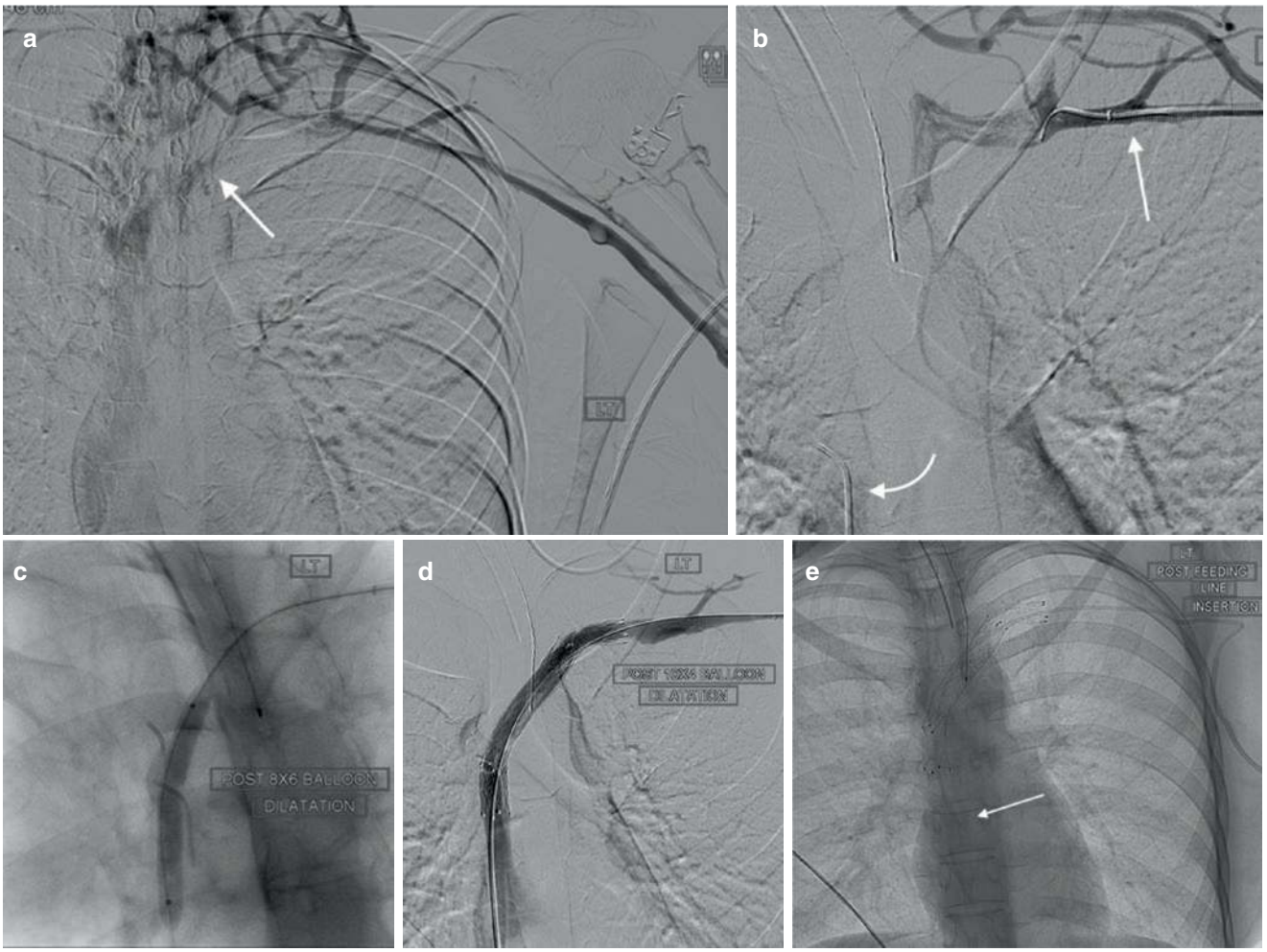

Fig. 4 (**a**) Left upper limb venography confirms an occluded left brachiocephalic vein (arrow) with multiple bridging collaterals. Crossing the lesion with an angled glide wire was unsuccessful. (**b**) A long sheath with an angled glide wire were advanced form the left upper limb venography puncture site (straight arrow) and a curved catheter (curved arrow) was introduced into the upper SVC for a right common femoral vein puncture to help in crossing the occlusion. (**c**) The occlusion was crossed, and an 8 mm diameter balloon is used to dilate the track before stent deployment. (**d**) Two self-expanding metal stents deployed at site of occlusion and dilated using a 10 mm diameter balloon. (**e**) A feeding line was inserted from a separate left subclavian vein puncture and through the stents. Note that the tip of the feeding line was kept at lower SVC / upper part of right atrium to reduce the risk of catheter-induced venous narrowing (arrow)

Complications of Balloon Dilatation and Stenting

PTA and stent insertion for venous narrowing or occlusions are considered safe procedures [83, 97–100]. Puncture site bleeding, which is usually mild even in patients who are anticoagulated, can be easily managed with manual compression. Venous perforation, which can happen during sharp recanalization is not associated with serious comorbidities and serious bleeding is rate, as there is low or zero flow at the site of perforation [82, 83, 100].

Recanalization and stenting for chronic venous occlusion is associated with severe pain and adequate pain management is needed. Most of the cases will be performed under general anaesthesia but the pain might persist for few days after stent insertion [82, 83].

Stent can migrate especially if under-sized. If they migrate to the heart or the pulmonary circulation, they should be removed as soon as possible [100]. Increased venous return that can occur after venous recanalization of major central veins has been reported to cause pulmonary oedema [101]. Stent thrombosis can happen, which can be treated with thrombolysis or anticoagulation. In stent stenosis, due to endothelial hyperplasia can be treated with repeated balloon angioplasty rather than an additional stent insertion [100]. Over dilatation of the SVC can cause arrhythmia or even cardiac arrest [102].

Surgery

Extrinsic venous compression causing chest outlet syndrome (Paget-Schroetter syndrome) can be surgically treated with resection of the anterior part of the first rib or clavicle. After successful thrombolysis, if a residual narrowing over the anterior part of the first rib is seen, a venogram in neutral and abducted positions should be performed. If venous flow is imbedded in abducted position only, this would confirm a chest outlet syndrome, and surgical treatment should be considered before balloon venoplasty or stent insertion. This approach will ensure long term patency of the treated vein [74, 102–105].

Surgical thrombectomy is an invasive procedure, needs general anaesthesia and can be complicated with pneumothorax, brachial plexus injury, and is usually attempted in thrombolysis refractory cases [72].

References

1. Baskin JL, Pui C-H, Reiss U, Wilimas JA, Metzger ML, Ribeiro RC, Howard SC. Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. Lancet. 2009;374:159–69.
2. Abu-Elmagd KM. Intestinal transplantation for short bowel syndrome and gastrointestinal failure: current consensus, rewarding outcomes, and practical guidelines. Gastroenterology. 2006;130:S132–7.
3. Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). Clin Nutr. 2009;28:365–77.
4. Di Nisio M, Van Sluis GL, Bossuyt PMM, Buller HR, Porreca E, Rutjes AWS. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. J Thromb Haemost. 2010;8:684–92.
5. Pironi L, Arends J, Bozzetti F, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35:247–307.
6. Cadman A, Lawrance JA, Fitzsimmons L, Spencer-Shaw A, Swindell R. To clot or not to clot? That is the question in central venous catheters. Clin Radiol. 2004;59:349–55.
7. Moureau N, Poole S, Murdock MA, Gray SM, Semba CP. Central venous catheters in home infusion care: outcomes analysis in 50,470 patients. J Vasc Interv Radiol. 2002;13:1009–16.
8. Toure A, Duchamp A, Peraldi C, Barnoud D, Lauverjat M, Gelas P, Chambrier C. A comparative study of peripherally-inserted and Broviac catheter complications in home parenteral nutrition patients. Clin Nutr. 2015;34:49–52.
9. Cotogni P, Barbero C, Garrino C, Degiorgis C, Mussa B, De Francesco A, Pittiruti M. Peripherally inserted central catheters in non-hospitalized cancer patients: 5-year results of a prospective study. Support Care Cancer. 2015;23:403–9.
10. Christensen LD, Rasmussen HH, Vinter-Jensen L. Peripherally inserted central catheter for use in home parenteral nutrition: a 4-year follow-up study. JPEN J Parenter Enteral Nutr. 2014;38:1003–6.
11. Kucher N. Clinical practice. Deep-vein thrombosis of the upper extremities. N Engl J Med. 2011;364:861–9.
12. Barco S, Heuschen CBBCM, Salman B, Brekelmans MPA, Serlie MJ, Middeldorp S, Coppens M. Home parenteral nutrition-associated thromboembolic and bleeding events: results of a cohort study of 236 individuals. J Thromb Haemost. 2016;14:1364–73.
13. Wong T, Clifford V, McCallum Z, Shalley H, Peterkin M, Paxton G, Bines JE. Central venous catheter thrombosis associated with 70% ethanol locks in pediatric intestinal failure patients on home parenteral nutrition: a case series. JPEN J Parenter Enteral Nutr. 2012;36:358–60.
14. Wales PW, Kosar C, Carricato M, de Silva N, Lang K, Avitzur Y. Ethanol lock therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients with intestinal failure: preliminary experience. J Pediatr Surg. 2011;46:951–6.
15. Gonzalez-Hernandez J, Daoud Y, Styers J, Journeycake JM, Channabasappa N, Piper HG. Central venous thrombosis in children with intestinal failure on long-term parenteral nutrition. J Pediatr Surg. 2016;51:790–3.
16. Buchman AL, Misra S, Moukarzel A, Ament ME. Catheter thrombosis and superior/inferior vena cava syndrome are rare complications of long term parenteral nutrition. Clin Nutr. 1994;13:356–60.
17. Pironi L, Goulet O, Buchman A, et al. Outcome on home parenteral nutrition for benign intestinal failure: a review of the literature and benchmarking with the European prospective survey of ESPEN. Clin Nutr. 2012;31:831–45.
18. Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term parenteral nutrition. Aliment Pharmacol Ther. 2013;37:587–603.
19. Puiggros C, Cuerda C, Virgili N, Chicharro ML, Martinez C, Garde C, de Luis D. Catheter occlusion and venous thrombosis prevention and incidence in adult home parenteral nutrition (HPN) programme patients. Nutr Hosp. 2012;27:256–61.
20. Pironi L, Paganelli F, Labate AMM, Merli C, Guidetti C, Spinucci G, Miglioli M. Safety and efficacy of home parenteral nutrition for chronic intestinal failure: a 16-year experience at a single centre. Dig Liver Dis. 2003;35:314–24.
21. Brandt CF, Tribler S, Hvistendahl M, Naimi RM, Brobech P, Staun M, Jeppesen PB. Home parenteral nutrition in adult patients with chronic intestinal failure: catheter-related complications over 4 decades at the Main Danish Tertiary Referral Center. JPEN J Parenter Enteral Nutr. 2018;42:95–103.
22. Cotogni P, Pittiruti M, Barbero C, Monge T, Palmo A, Boggio Bertinet D. Catheter-related complications in cancer patients on home parenteral nutrition: a prospective study of over 51,000 catheter days. JPEN J Parenter Enteral Nutr. 2013;37:375–83.
23. Green CJ, Mountford V, Hamilton H, Kettlewell MGW, Travis SPL. A 15-year audit of home parenteral nutrition provision at the John Radcliffe Hospital, Oxford. QJM. 2008;101:365–9.
24. Diamanti A, Basso MS, Castro M, Calce A, Pietrobattista A, Gambarara M. Prevalence of life-threatening complications in pediatric patients affected by intestinal failure. Transplant Proc. 2007;39:1632–3.
25. Hofmann-Preiss K, Becker A, Sailer S. Radiologic and clinical follow-up of central venous indwelling catheters in home parenteral nutrition. Infusionstherapie. 1991;18:292–5.
26. Valerio D, Hussey JK, Smith FW. Central vein thrombosis associated with intravenous feeding—a prospective study. JPEN J Parenter Enteral Nutr. 1981;5:240–2.
27. Cuerda C, Joly F, Corcos O, Concejo J, Puiggros C, Gil C, Pironi L. Prospective study of catheter-related central vein thrombosis in home parenteral nutrition patients with benign disease using serial venous Doppler ultrasound. Clin Nutr. 2016;35:153–7.
28. Rooden CJ, Tesselaar MET, Osanto S, Rosendaal FR, Huisman MV. Deep vein thrombosis associated with central venous catheters—a review. J Thromb Haemost. 2005;3:2409–19.
29. McCulloch I, Pennington CR. Intracardiac thrombus complicating prolonged parenteral nutrition in an adult. JPEN J Parenter Enteral Nutr. 1989;13:557–9.
30. Randolph AG, Cook DJ, Gonzales CA, Andrew M. Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials. Chest. 1998;113:165–71.

31. Klerk CPW, Smorenburg SM, Buller HR. Thrombosis prophylaxis in patient populations with a central venous catheter: a systematic review. Arch Intern Med. 2003;163:1913–21.
32. Cunningham MS, White B, Hollywood D, O'Donnell J. Primary thromboprophylaxis for cancer patients with central venous catheters—a reappraisal of the evidence. Br J Cancer. 2006;94:189–94.
33. Kirkpatrick A, Rathbun S, Whitsett T, Raskob G. Prevention of central venous catheter-associated thrombosis: a meta-analysis. Am J Med. 2007;120:901.e1–13.
34. Rawson KM, Newburn-Cook CV. The use of low-dose warfarin as prophylaxis for central venous catheter thrombosis in patients with cancer: a meta-analysis. Oncol Nurs Forum. 2007;34:1037–43.
35. Chaukiyal P, Nautiyal A, Radhakrishnan S, Singh S, Navaneethan SD. Thromboprophylaxis in cancer patients with central venous catheters. A systematic review and meta-analysis. Thromb Haemost. 2008;99:38–43.
36. Akl EA, Kamath G, Yosuico V, Kim SY, Barba M, Sperati F, Cook DJ, Schunemann HJ. Thromboprophylaxis for patients with cancer and central venous catheters: a systematic review and a meta-analysis. Cancer. 2008;112:2483–92.
37. Yacopetti N. Central venous catheter-related thrombosis: a systematic review. J Infus Nurs. 2008;31:241–8.
38. Akl EA, Vasireddi SR, Gunukula S, Yosuico VED, Barba M, Sperati F, Cook D, Schunemann H. Anticoagulation for patients with cancer and central venous catheters. Cochrane Database Syst Rev. 2011;6(6):CD006468.
39. Debourdeau P, Farge D, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. J Thromb Haemost. 2013;11:71–80.
40. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e195S–226S.
41. Brismar B, Hardstedt C, Jacobson S, Kager L, Malmborg AS. Reduction of catheter-associated thrombosis in parenteral nutrition by intravenous heparin therapy. Arch Surg. 1982;117:1196–9.
42. Macoviak JA, Melnik G, McLean G, Lunderquist A, Singer R, Forlaw L, Rombeau JL. The effect of low-dose heparin on the prevention of venous thrombosis in patients receiving short-term parenteral nutrition. Curr Surg. 1984;41:98–100.
43. Ruggiero RP, Aisenstein TJ. Central catheter fibrin sleeve—heparin effect. JPEN J Parenter Enteral Nutr. 1983;7:270–3.
44. Fabri PJ, Mirtallo JM, Ruberg RL, Kudsk KA, Denning DA, Ellison EC, Schaffer P. Incidence and prevention of thrombosis of the subclavian vein during total parenteral nutrition. Surg Gynecol Obstet. 1982;155:238–40.
45. Fabri PJ, Mirtallo JM, Ebbert ML, Kudsk KA, Powell C, Ruberg RL. Clinical effect of nonthrombotic total parenteral nutrition catheters. JPEN J Parenter Enteral Nutr. 1984;8:705–7.
46. Duerksen DR. Central venous thrombosis in patients receiving long-term parenteral nutrition. Appl Physiol Nutr Metab. 2008;33:32–8.
47. Bern MM, Bothe AJ, Bistrian B, Champagne CD, Keane MS, Blackburn GL. Prophylaxis against central vein thrombosis with low-dose warfarin. Surgery. 1986;99:216–21.
48. Duerksen DR, Ahmad A, Doweiko J, Bistrian BR, Mascioli EA. Risk of symptomatic central venous thrombotic complications in AIDS patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr. 1996;20:302–5.
49. Veerabagu MP, Tuttle-Newhall J, Maliakkal R, Champagne C, Mascioli EA. Warfarin and reduced central venous thrombosis in home total parenteral nutrition patients. Nutrition. 1995;11:142–4.
50. Vegting IL, Tabbers MM, Benninga MA, Wilde JC, Serlie MJ, Tas TA, Jonkers CF, van Ommen CH. Prophylactic anticoagulation decreases catheter-related thrombosis and occlusion in children with home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2012;36:456–62.
51. Hylek EM. Complications of oral anticoagulant therapy: bleeding and nonbleeding, rates and risk factors. Semin Vasc Med. 2003;3:271–8.
52. Cuerda C, Joly F, Baxter J, Szczepanek K, Gillanders L, Wanten G, Staun M, Singer P, Pironi L, On Behalf of EH-C Group. Survey on current practice of managing catheter related venous thrombosis in patients on long-term home parenteral nutrition for benign chronic intestinal failure. Clin Nutr. 2014;33:S208–9.
53. Macdougall L, Hanley J, Mountford C, Thompson NP. UK practice in the prevention of central venous catheter-associated thrombosis in adults on home parenteral nutrition. Frontline Gastroenterol. 2017;8:163–6.
54. Flinterman LE, Van Der Meer FJM, Rosendaal FR, Doggen CJM. Current perspective of venous thrombosis in the upper extremity. J Thromb Haemost. 2008;6:1262–6.
55. Nightingale J, Lal S, Gabe S and the BIFA Committee. Top tips for managing central vein thrombosis in patients receiving parenteral support. The Britisth Intestinal Failure Alliance (BIFA) top tips articles series. https://www.bapen.org.uk/.
56. Gabe S, Willsmore J, Oke S, Nightingale J and the BIFA Committee. British Intestinal Failure Alliance (BIFA) Guidelines. Detection and treatment of catheter-related thrombosis in patients receiving home parenteral support. September 2021. https://www.bapen.org.uk/.
57. Vedantham S. Venous clot lysis and stenting. Hematology. 2015;2015:210–4.
58. Joffe HV, Goldhaber SZ. Upper-extremity deep vein thrombosis. Circulation. 2002;106:1874–80.
59. Prandoni P, Frulla M, Sartor D, Concolato A, Girolami A. Vein abnormalities and the post-thrombotic syndrome. J Thromb Haemost. 2005;3:401–2.
60. Goldhaber SZ, Buring JE, Lipnick RJ, Hennekens CH. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. Am J Med. 1984;76:393–7.
61. Elliot MS, Immelman EJ, Jeffery P, et al. A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial. Br J Surg. 1979;66:838–43.
62. Arnesen H, Høiseth A, Ly B. Streptokinase of heparin in the treatment of deep vein thrombosis. Follow-up results of a prospective study. Acta Med Scand. 1982;211:65–8.
63. Semba CP, Dake MD. Iliofemoral deep venous thrombosis: aggressive therapy with catheter-directed thrombolysis. Radiology. 1994;191:487–94.
64. Mewissen MW, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. Radiology. 1999;211:39–49.
65. Vedantham S, Sista AK, Klein SJ, et al. Quality improvement guidelines for the treatment of lower-extremity deep vein thrombosis with use of endovascular thrombus removal. J Vasc Interv Radiol. 2014;25:1317–25.
66. Vedantham S, Thorpe PE, Cardella JF, et al. Quality improvement guidelines for the treatment of lower extremity deep vein thrombosis with use of endovascular thrombus removal. J Vasc Interv Radiol. 2006;17:435–47; quiz 448.
67. Shortell CK, Queiroz R, Johansson M, Waldman D, Illig KA, Ouriel K, Green RM. Safety and efficacy of limited-dose tissue plasminogen activator in acute vascular occlusion. J Vasc Surg. 2001;34:854–9.
68. Sugimoto K, Hofmann LV, Razavi MK, Kee ST, Sze DY, Dake MD, Semba CP. The safety, efficacy, and pharmacoeconomics of low-dose alteplase compared with urokinase for catheter-directed thrombolysis of arterial and venous occlusions. J Vasc Surg. 2003;37:512–7.

69. Grunwald MR, Hofmann LV. Comparison of urokinase, alteplase, and reteplase for catheter-directed thrombolysis of deep venous thrombosis. J Vasc Interv Radiol. 2004;15:347–52.
70. Kim HS, Patra A, Paxton BE, Khan J, Streiff MB. Adjunctive percutaneous mechanical thrombectomy for lower-extremity deep vein thrombosis: clinical and economic outcomes. J Vasc Interv Radiol. 2006;17:1099–104.
71. Dyer J, Rosa J, Chachlani M, Nicholas J. Aspirex thrombectomy in occluded dialysis access: a retrospective study. Cardiovasc Intervent Radiol. 2016;39:1484–90.
72. Hicken GJ, Ameli FM. Management of subclavian-axillary vein thrombosis: a review. Can J Surg. 1998;41:13–25.
73. Aburahma AF, Sadler DL, Robinson PA. Axillary subclavian vein thrombosis. Changing patterns of etiology, diagnostic, and therapeutic modalities. Am Surg. 1991;57:101–7.
74. Urschel HCJ, Razzuk MA. Paget-Schroetter syndrome: what is the best management? Ann Thorac Surg. 2000;69:1663–9.
75. Beathard GA. Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. Kidney Int. 1992;42:1390–7.
76. Glanz S, Gordon D, Butt KM, Hong J, Adamson R, Sclafani SJ. Dialysis access fistulas: treatment of stenoses by transluminal angioplasty. Radiology. 1984;152:637–42.
77. Trerotola SO, McLean GK, Burke DRMS. Treatment of subclavian venous stenoses by percutaneous transluminal angioplasty. J Vasc Interv Radiol. 1986;1:15–8.
78. Kovalik EC, Newman GE, Suhocki P, Knelson M, Schwab SJ. Correction of central venous stenoses: use of angioplasty and vascular wallstents. Kidney Int. 1994;45:1177–81.
79. Quinn SF, Schuman ES, Demlow TA, Standage BA, Ragsdale JW, Green GS, Sheley RC. Percutaneous transluminal angioplasty versus endovascular stent placement in the treatment of venous stenoses in patients undergoing hemodialysis: intermediate results. J Vasc Interv Radiol. 1995;6:851–5.
80. Rajan DK, Clark TI, Baumann DS. Central venous interventions. In: Rajan D, editor. Essentials of percutaneous dialysis interventions. New York: Springer; 2011. p. 357–78.
81. Glanz S, Gordon DH, Lipkowitz GS, Butt KM, Hong J, Sclafani SJ. Axillary and subclavian vein stenosis: percutaneous angioplasty. Radiology. 1988;168:371–3.
82. Dammers R, de Haan MW, Planken NR, van der Sande FM, Tordoir JH. Central vein obstruction in hemodialysis patients: results of radiological and surgical intervention. Eur J Vasc Endovasc Surg. 2003;26:317–21.
83. Surowiec SM, Fegley AJ, Tanski WJ, Sivamurthy N, Illig KA, Lee DE, Waldman DL, Green RM, Davies MG. Endovascular management of central venous stenoses in the hemodialysis patient: results of percutaneous therapy. Vasc Endovascular Surg. 2004;38:349–54.
84. Bakken AM, Protack CD, Saad WE, Lee DE, Waldman DL, Davies MG. Long-term outcomes of primary angioplasty and primary stenting of central venous stenosis in hemodialysis patients. J Vasc Surg. 2007;45:776–83.
85. Nayak L, Hildebolt CF, Vedantham S. Postthrombotic syndrome: feasibility of a strategy of imaging-guided endovascular intervention. J Vasc Interv Radiol. 2012;23:1165–73.
86. Raju S, Neglen P. Percutaneous recanalization of total occlusions of the iliac vein. J Vasc Surg. 2009;50:360–8.
87. Vogel PM, Parise C. SMART stent for salvage of hemodialysis access grafts. J Vasc Interv Radiol. 2004;15:1051–60.
88. Aytekin C, Boyvat F, Yagmurdur MC, Moray G, Haberal M. Endovascular stent placement in the treatment of upper extremity central venous obstruction in hemodialysis patients. Eur J Radiol. 2004;49:81–5.
89. Chen C-Y, Liang H-L, Pan H-B, Chung H-M, Chen W-L, Fang H-C, Lo A, Chen CKH, Lai P-H, Yang C-F. Metallic stenting for treatment of central venous obstruction in hemodialysis patients. J Chin Med Assoc. 2003;66:166–72.
90. Oderich GS, Treiman GS, Schneider P, Bhirangi K. Stent placement for treatment of central and peripheral venous obstruction: a long-term multi-institutional experience. J Vasc Surg. 2000;32:760–9.
91. Haage P, Vorwerk D, Piroth W, Schuermann K, Guenther RW. Treatment of hemodialysis-related central venous stenosis or occlusion: results of primary wallstent placement and follow-up in 50 patients. Radiology. 1999;212:175–80.
92. Vesely TM, Hovsepian DM, Pilgram TK, Coyne DW, Shenoy S. Upper extremity central venous obstruction in hemodialysis patients: treatment with wallstents. Radiology. 1997;204:343–8.
93. Gray RJ, Horton KM, Dolmatch BL, Rundback JH, Anaise D, Aquino AO, Currier CB, Light JA, Sasaki TM. Use of wallstents for hemodialysis access-related venous stenoses and occlusions untreatable with balloon angioplasty. Radiology. 1995;195:479–84.
94. Vorwerk D, Guenther RW, Mann H, Bohndorf K, Keulers P, Alzen G, Sohn M, Kistler D. Venous stenosis and occlusion in hemodialysis shunts: follow-up results of stent placement in 65 patients. Radiology. 1995;195:140–6.
95. Bjarnason H. Handbook of angioplasty and stenting procedures; 2010. p. 303–15.
96. Kundu S, Modabber M, You JM, Tam P, Nagai G, Ting R. Use of PTFE stent grafts for hemodialysis-related central venous occlusions: intermediate-term results. Cardiovasc Intervent Radiol. 2011;34:949–57.
97. Tzifa A, Marshall AC, McElhinney DB, Lock JE, Geggel RL. Endovascular treatment for superior vena cava occlusion or obstruction in a pediatric and young adult population: a 22-year experience. J Am Coll Cardiol. 2007;49:1003–9.
98. Raju S. Long-term outcomes of stent placement for symptomatic nonthrombotic iliac vein compression lesions in chronic venous disease. J Vasc Interv Radiol. 2012;23:502–3.
99. Neglen P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. J Vasc Surg. 2007;46:979–90.
100. Warren P, Burke C. Endovascular management of chronic upper extremity deep vein thrombosis and superior vena cava syndrome. Semin Intervent Radiol. 2011;28:32–8.
101. Rosch J, Uchida BT, Hall LD, Antonovic R, Petersen BD, Ivancev K, Barton RE, Keller FS. Gianturco-Rosch expandable Z-stents in the treatment of superior vena cava syndrome. Cardiovasc Intervent Radiol. 1992;15:319–27.
102. Dondelinger R. Chronic upper extremity/superior vena cava venous occlusive disease. In: Image guided interventions. Philadelphia: Saunders Elsevier; 2008. https://doi.org/10.1016/B978-1-4160-2964-9.50105-8.
103. Machleder HI. Evaluation of a new treatment strategy for Paget-Schroetter syndrome: spontaneous thrombosis of the axillary-subclavian vein. J Vasc Surg. 1993;17:305–7.
104. Adelman MA, Stone DH, Riles TS, Lamparello PJ, Giangola G, Rosen RJ. A multidisciplinary approach to the treatment of Paget-Schroetter syndrome. Ann Vasc Surg. 1997;11:149–54.
105. Kreienberg PB, Chang BB, Darling RC 3rd, Roddy SP, Paty PS, Lloyd WE, Cohen D, Stainken B, Shah DM. Long-term results in patients treated with thrombolysis, thoracic inlet decompression, and subclavian vein stenting for Paget-Schroetter syndrome. J Vasc Surg. 2001;33:S100–5.

Part VIII

Surgical Treatment of Chronic Intestinal Failure

Surgery for Patients with a Short Bowel and Tissue Engineering

Mattias Soop, Laween Meran, Jeremy M.D. Nightingale, and Jon S. Thompson

Key Points

1. Surgery for patients with a short bowel is either to manage the complications resulting from the resection (e.g. abdominal wound, gallstones or renal stones) or to use surgical procedures to maximize the function of the existing intestine.
2. The vast majority of surgical procedures to improve absorption involve standard techniques such as recruiting additional intestine into continuity, relieving obstruction or tapering massively dilated segments.
3. Less common surgical techniques involve lengthening and tapering the bowel or slowing the passage of chyme through the small intestine.
4. Various procedures to slow intestinal transit have been attempted but long term efficacy and benefit have not been demonstrated.
5. The longitudinal intestinal lengthening and tapering (LILT or Bianchi) procedure may increase the absorption surface of the remnant bowel, but can only be performed on a dilated small bowel and is rarely technically possible in adults.
6. The serial transverse enteroplasty (STEP) procedure is technically less challenging than the LILT procedure, and is now more used in both children and adults.
7. Small bowel mucosa may be grown and placed in a synthetic or biological scaffold; however, work continues to form a neural network. In future a tissue engineered graft may be an option to small bowel transplantation.

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Introduction

There are two important roles for surgical procedures in the management of patients with a short bowel. One is the management of complications related to the massive intestinal resection and the resulting pathophysiology. The other is to employ surgical procedures therapeutically to maximize the function of existing intestine.

Surgical Management of Complications

Approximately 50% of patients with a short bowel will require re-operation after their initial time in hospital [1]. These procedures are most frequently required for intestinal problems and cholelithiasis. Gastric acid hypersecretion is no longer a commonly encountered, probably [2] as most patients are given proton pump inhibitors. The important aspects of management are shown in Table 1.

Table 1 Surgical management of complications

Intestinal problems
• Preserve intestinal remnant length
Cholelithiasis
• Early diagnosis
• Prophylactic cholecystectomy
Abdominal wall protection
• Convert enterocutaneous and enteroatmospheric fistulas to conventional stoma
• Reduce chronic abdominal wall sepsis

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Intestinal Problems

Two-thirds of re-operations in patients with a short bowel are for intestinal problems. Many are related to the underlying intestinal disease or to mechanical challenges to the intestine from adhesions or hernias, requiring further resection or management of obstruction or fistula. During these procedures an important goal is to preserve as much of the intestinal remnant as possible. There are several strategies that can be used to preserve intestinal length when further intestinal disease occurs in patients with short intestinal remnants. These include employing intestinal tapering for dilated segments, stricturoplasty for strictures and serosal patches for strictures and perforations to avoid resection [3] (Fig. 1). If resection is necessary, minimal resections should be performed whenever possible. An end-to-end anastomosis is preferred when maintaining length is the goal.

Whereas normally a surgeon might discard a few inches of intestine to avoid another anastomosis, this should be given careful consideration in patients with a short bowel where each additional centimetre of bowel becomes important. Such consideration will take into account the length of bowel already in continuity, the relative gain of the additional segment(s) as well as the type of bowel under consideration: jejunum, ileum or colon. The colon is often thought of as an organ absorbing only water and sodium. However, the colon and rectum also absorb energy in the form of short-chain fatty acids resulting from the microbial metabolism of polysaccharides [5].

Cholelithiasis

As discussed in chapter "Gallstones in Intestinal Failure" cholelithiasis eventually occurs in approximately half of patients (adults and children) with a short bowel requiring parenteral support [3, 5–15]. These patients have a significantly increased risk of developing cholelithiasis (about 75%) when the remnant length is less than 120 cm, total parenteral nutrition (TPN) is required and the terminal ileum is resected [14, 15]. Furthermore, these patients have more complicated biliary tract disease and increased postoperative morbidity and mortality rates [11, 14]. In one study, 40% of these procedures were performed as an emergency, with a complication rate of 54% and mortality of 11% [11]. Delay in diagnosis may contribute to this poor outcome, particularly because of the confounding effect of Intestinal failure associated liver disease (IFALD). Thus, the diagnosis should be suspected and ultrasonography performed liberally to permit early diagnosis. The significant morbidity of symptomatic cholelithiasis in these patients has led to recommendation of prophylactic cholecystectomy, even before cholelithiasis develops [11, 14]. This is particularly appropriate in patients with benign conditions and anticipated long-term survival. While cholecystectomy may not be advisable at the time of the initial massive resection, it should be considered at the time of other abdominal operations in those patients who have developed gallstones [15].

Abdominal Wall Protection

Many enterocutaneous and, even more so, enteroatmospheric, fistulas severely worsen a patient's quality of life [16] by causing frequent leakages under the skin appliance of the fistula bag, destruction of the surrounding skin with associated chronic pain, and the requirement for very lengthy and frequent procedures for fistula dressings. Resection of the fistula is sometimes indicated on the basis of this indication alone, even in cases where there is no scope for a significant increase in absorptive capacity. A clinical observation is that the improvement in quality of life when such a fistula is resected and converted into a conventional stoma, even if high-volume, is very significant.

Occasionally, patients with fistulas develop chronic cavities in the abdominal wall, resulting in accumulation of infected fluid. When it is not possible to control such cavities by drainage procedures, the patient may need to stay nil by mouth. Resecting such fistulas, or diverting them proximally, will often resolve the chronic abdominal wall sepsis and allow patients to resume an oral diet.

Surgical Therapy for Patients with a Short Bowel

The goal of surgical therapy is to increase intestinal absorptive capacity by either improving absorption by existing intestine or by increasing the area of absorption (Table 2). Absorption can often be improved by recruiting additional intestine into continuity, relieving obstruction, or slowing intestinal transit. Intestinal lengthening is feasible in selected patients but obviously the most significant increase in length is achieved by intestinal transplantation (chapter "Intestinal Transplantation").

Adjunctive procedures for surgical therapy of patients with a short bowel should not be performed at the time of initial resection [17, 18]. They add potential morbidity in patients who are already quite ill. Furthermore, intestinal adaptation, in patients with retained ileum and/or colon, will often result in sufficient improvement in absorption to obviate the need for additional therapy. This is particularly true in children, where additional growth occurs. Adaptation may avoid the need for PN in almost half of patients [19, 20].

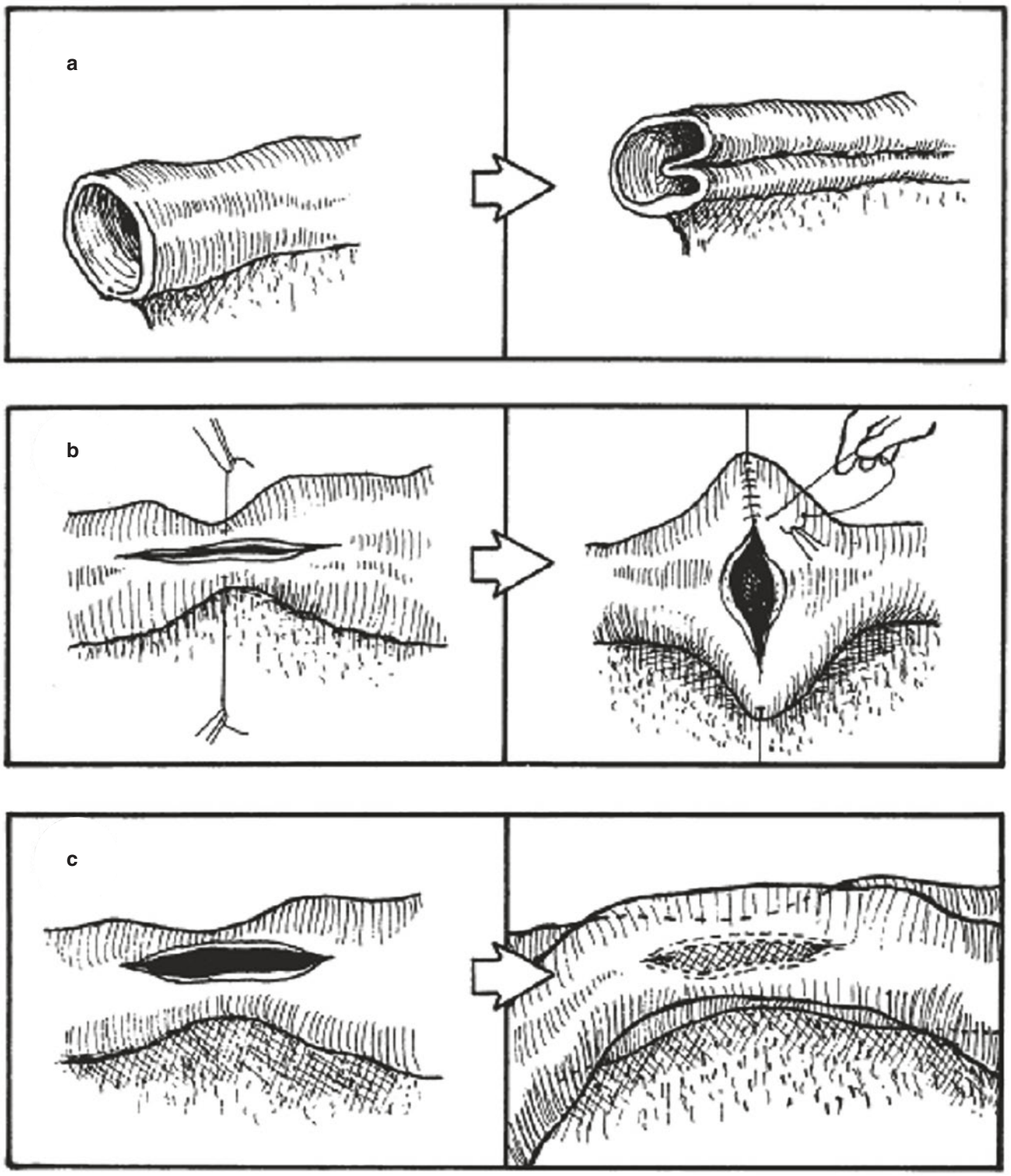

Fig. 1 Techniques for preserving intestinal length include tapering of dilated segments rather than resection (**a**), stricturoplasty for strictures (**b**), and serosal patches for strictures and perforations (**c**). (Reproduced with permission from Thompson [4])

Such adaptation may take longer than previously thought; a substantial proportion of patients continue the adaptive process beyond 10 years [20].

Moreover, there is evidence to suggest that performing such procedures (e.g. colon interposition and serosal patching), at the initial resection may diminish the degree of adap-

Table 2 Surgical therapy for patients with a short bowel

Optimize intestinal function
• Restore continuity
• Relieve obstruction
• Taper dilated bowel
Slow intestinal transit
• Reversed intestinal segment
• Artificial valve
• Colon interposition
Increase intestinal length
• Intestinal lengthening

tation that occurs [19, 21]. Thus, surgical therapy for patients with a short bowel should only be undertaken after the initial adaptive period and even then with specific objectives.

The nature of nutritional support is the primary factor to be considered when surgical therapy for patients with a short bowel is contemplated. Patients supported by enteral nutrition (EN) alone should be considered for operation only if they demonstrate worsening malabsorption, are at risk for receiving parenteral nutrition (PN) or have other symptoms related to malabsorption. Patients who are stable on PN should undergo surgical therapy only if this would permit them to discontinue or significantly reduce PN. Patients who develop significant complications from PN will eventually require either combined liver–intestine or solitary intestine transplantation.

Optimising Intestinal Function

Recruiting any additional intestine into continuity with the gastrointestinal tract is an important objective in managing patients with a short bowel. Intestinal absorptive capacity can be increased and transit time prolonged. Recruiting downstream intestine may simply entail exchanging a more proximal jejunostomy for a more distal colostomy or actually closing a stoma. However, occasionally other intestinal segments are available. For example, continuity has been restored using an ileal segment previously used as a urinary conduit in a patient with a short bowel; this ameliorated diarrhoea and steatorrhoea [22].

Many patients have stomas created at the time of massive resection [23]. Whether or not intestinal continuity should be restored at a later time will depend on several factors, including length of intestinal remnant, status of the ileocaecal valve and colon and the overall condition of the patient. While some patients function well with very short intestinal remnants, generally at least a metre of small intestine is required to prevent severe diarrhoea and perianal complications [23, 24]. Only 20% of the patients with an initial stoma had intestinal continuity restored at a later time [23]. Moreover, only one-third of the patients in whom continuity was maintained at initial resection had a satisfactory long-term outcome. In addition to improving absorption, maintaining intestinal continuity eliminates the inconvenience of the stoma. This has more than psychological advantages since patients with a stoma are more likely to have catheter-related blood stream infections (CRBSI) [25]. Furthermore, malabsorbed carbohydrates that reach the colon are metabolized to short-chain fatty acids by colonic bacteria [26]. Short-chain fatty acids improve fluid and electrolyte absorption, are absorbed as additional energy and may be trophic to the intestinal remnant [26, 27].

There are also a number of potential risks inherent in restoring intestinal continuity. Bile acids cause secretion of fluid in the colon and may exacerbate diarrhea. Thus, there may be more perianal complications and resultant dietary restrictions. 60% of patients in one study had dietary restrictions with intestinal continuity compared to 33% with a stoma [23]. Also, calcium oxalate kidney stones occur more frequently because of absorption of unbound oxalate from the colon (chapter “Nephrolithiasis and Nephrocalcinosis”). In another study no patients with a jejunostomy had nephrolithiasis compared to one-fourth of patients with a short bowel and an intact colon [13].

Predicting the functional outcome after restoring intestinal continuity in individual patients with short remnants is difficult. In general, Carbonnel et al. [28], found that a jejuno-ileal anastomosis is equivalent to adding 80 cm of small bowel and a jejuno-colic anastomosis equivalent to 25 cm of small bowel in terms of improved energy absorptive function compared to a jejunostomy. Patients with a marked increase in stomal output in response to feeding will not do well unless a significant amount of small intestine is recruited distally. As adaptation to a short bowel is a process that continues for several years, sometimes beyond a decade [20], it is not necessary to await completion of this process until surgery to restore intestinal continuity is undertaken.

Assessing the effect of the distal bowel on absorption has been evaluated by using an external reinfusion apparatus [29] (chapter “Distal Feeding and Hydration”). This technique is somewhat cumbersome and requires access to the distal remnant. A smaller reinfusion device that resides in the stoma bag itself has been introduced with favorable results [30]. The potential roles of chyme reinfusion are in evolution, and include evaluation of the effects of restoration of continuity on bowel absorption and function; trophic feeding of the distal gut to prepare this for re-anastomosis and improved recovery; and in some cases a replacement of parenteral support altogether.

The proximal intestine may become markedly dilated secondary to chronic obstruction and/or structural adaptation in patients with a short bowel. In adults this is usually due to obstruction secondary to stenosis. A useful approach in these

patients is simply to relieve the obstruction. Stricturoplasty may be efficacious [19]. Dilated bowel is less frequently due to obstruction in children and may be a variant of intestinal pseudo-obstruction. The resultant stasis and bacterial overgrowth further aggravates malabsorption. These large diameter segments of intestine have low contraction pressures that result in poor propulsion [31]. Therefore, tapering dilated segments should improve motility in these patients.

Intestinal Tapering

Intestinal tapering has been reported in at least 27 children with a short bowel and dilated intestine [19, 31, 32]. Absorptive function, growth and development improved in all cases. Patients had bacterial overgrowth but only one-fourth had an associated mechanical obstruction [19]. All had transient functional improvement but 2 of 11 required further procedures for recurrent malabsorption. Many patients experienced a prolonged postoperative ileus. Segments ranging from 15 to 35 cm in length were tapered on the antimesenteric border. Tapering can be accomplished by either resection or simply turning in the redundant tissue. Overlapping the redundant intestine results in more normal intestinal structure and function than tapering by longitudinal transection and is the preferred approach [33].

Slowing Intestinal Transit

The earliest surgical therapeutic attempts for patients with a short bowel involved using techniques to retard intestinal transit [34]. These have included antiperistaltic segments, artificial valves, colon interposition and other approaches (Fig. 2). These procedures are most appropriate in patients with sufficient intestinal surface area but rapid intestinal transit. Massive intestinal resection results in markedly shortened intestinal transit time, which contributes to malabsorption and diarrhoea. The evolution of pharmacological agents that slow gastrointestinal transit, including glucagon-like peptide analogues (chapter "Pro-adaptive Hormones in the Rehabilitation of Adult SBS Patients"), has reduced the role of these operations.

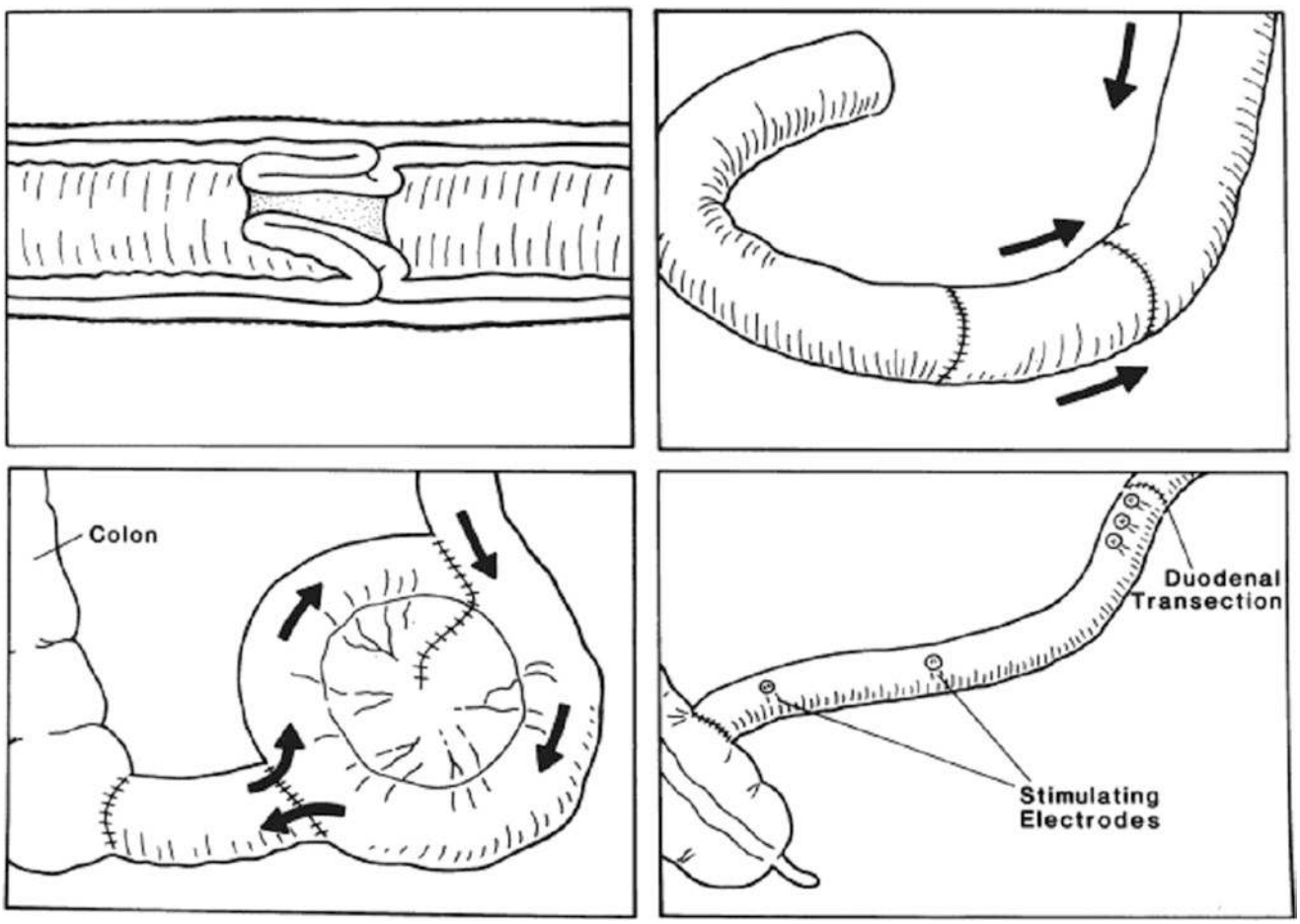

Fig. 2 Techniques for slowing intestinal transit: intestinal valve (upper left), antiperistaltic segment (upper right), recirculating loop (lower left) and intestinal pacing (lower right). (Reproduced with permission from Thompson [4])

Antiperistaltic Segments

Reversing segments of intestine to slow intestinal transit has been studied extensively. The antiperistaltic segment acts as a 'physiologic valve' by causing retrograde peristalsis and disrupting the motility of the proximal intestine. The disruption of the intrinsic nerve plexus slows distal myoelectrical activity [35]. Although retrograde peristalsis has been demonstrated radiologically, this finding does not always correlate with improved function [36]. Antiperistaltic segments slow intestinal transit, improve absorption, reduce weight loss and prolong survival after intestinal resection in some experimental studies but others report no beneficial effect [37–39].

These conflicting results may be partly explained by the different lengths of antiperistaltic segments used. While the ideal length of the antiperistaltic segment is not clear, lengthy segments may produce significant obstruction and short segments may be ineffective. In one study an intestinal valve was more effective than an antiperistaltic segment in prolonging transit time after resection, but neither procedure improved absorption [40].

Antiperistaltic segments have been used clinically in more than 80 patients, the majority being adults [19, 41–46]. Slowed intestinal transit and increased absorption occurs [45]. They benefit half of the selected patients with a short bowel who have rapid transit but adequate remnant length. The outcome in individual patients is difficult to predict and subsequent surgery was frequently required [44]. Transient obstructive symptoms and anastomotic leak are potential problems [39, 42]. While the length of the segment has varied from 5 to 15 cm in these reports, the ideal length of the reversed segment seems to be approximately 10 cm in adults and 3 cm in children. In one study a reversed segment that initially increased absorption could not be demonstrated radiologically 6 months later [45]. Furthermore, initial manometric abnormalities in the proximal intestine may resolve with time which may explain loss of function over the long term this procedure [46]. Another limitation of this procedure is that patients with shorter intestinal remnants may not be able to afford to sacrifice a 10-cm segment for reversal.

Intestinal Valves and Sphincters

The terminal ileum and ileocaecal valve may be important in retarding intestinal transit of nutrients and preventing reflux of colonic contents. The presence of colonic contents in the small intestine may alter motility and may contribute to bacterial colonization of the small intestine and further malabsorption. An intact ileocaecal valve permits survival in children with only 11 cm of small intestine remaining, whereas those who lost their ileocaecal valve required at least 25 cm of small intestine for survival without PN [47].

Intestinal valves and sphincters have been created by a variety of different techniques. These include constricting the intestine externally, denervating segments of intestine and increasing intraluminal pressure by intussuscepting intestinal segments [48–55]. Thompson et al. generally creates a sphincter similar to that employed in the continent ileostomy procedure but only 2 cm in length [19]. The effect of valves and sphincters on intestinal motility is complex, involving several different mechanisms. They create a partial mechanical obstruction, prevent retrograde reflux of colonic contents and disrupt the normal motor pattern of the small intestine, converting jejunal motor activity to a pattern more similar to the ileum [51, 54, 55]. While intestinal valves and sphincters have been shown to lengthen transit time, increase absorptive capacity and prolong survival in several experimental studies, results have been inconsistent [49, 50, 52, 54, 55]. Effective valves usually cause some dilation of the proximal intestine and may result in obstructive symptoms. Necrosis of the valve, complete obstruction and intussusception are potential complications. Valves may lose the sphincter function with time [49].

Clinical experience with intestinal valves and sphincters has been limited with approximately 25 cases reported [19, 48, 51, 56]. Intussuscepted valves have been reported in six patients with a short bowel [19, 48, 51]. Four patients improved markedly, one remained unchanged and the other had an obstruction necessitating take down of the valve. However, in one long-term study ileocolic nipple valves were lost in one-third of patients followed for more than 5 years [56]. As described below, nipple valves have recently been utilized to cause dilation of the intestine to permit subsequent intestinal lengthening [57].

Colon Interposition

Isoperistaltic and antiperistaltic colon interposition will retard intestinal transit. Isoperistaltic transposition is performed proximally and functions by slowing down the rate at which nutrients are delivered to the distal small intestine [21, 58]. The antiperistaltic colon interposition is placed distally, similar to the reversed small intestinal segment, but has the advantage that none of the small intestine remnant is used. In addition to the effect on transit time, interposed segments absorb water, electrolytes and nutrients [59]. Experimental studies demonstrate that isoperistaltic colon interposition, either proximal or distal to the small intestinal remnant, resulted in slower transit time, less weight loss and increased survival without producing intestinal obstruction [58–60]. While one investigator also demonstrated prolonged transit time with isoperistaltic colon interposition, no significant improvement in body weight or intestinal absorption was found [21]. The length of colon interposed seems to be less critical than with reversed segments. However, results with antiperistaltic colon interposition have been less consistent [61, 62].

The use of colon interposition has been reported in ten patients. Isoperistaltic interposition was performed in nine of these patients, of whom eight were infants less than 1 year of age [63–67]. The length of colon interposed varied between 8 and 24 cm. All patients were dependent on PN and had intestinal remnants ranging from 15 to 63 cm in length. Four infants were weaned off PN within 4 months and survived. Diarrhoea improved in one infant who subsequently died of pneumonia. Three patients did not improve and subsequently died of sepsis or hepatic failure. An adult patient had transit time prolonged from 10 to 25 min and a 50% reduction in PN [65]. Thus, isoperistaltic colon interposition has shown some promise as a therapeutic alternative. In a single report of antiperistaltic colon interposition, an infant eventually died after initial increase in weight and slowing of intestinal transit time [67].

Recirculating Loops

Theoretically, intestinal pouches and recirculating loops would prolong transit time by permitting repeated or prolonged exposure of luminal nutrients to the intestinal absorptive surface [68, 69]. However, these procedures have been associated with high morbidity and mortality rates in experimental studies and do not clearly improve absorption or survival rates after massive resection [70, 71]. The results of few anecdotal clinical reports using recirculating loops have not demonstrated clear benefit [72–74]. The three adults were followed for 7, 10 and 24 months. Two died and increased absorption was not clearly demonstrated. Cywes [75] previously created a proximal jejunal pouch with a distal 4-cm antiperistaltic segment in an infant. After 3 months transit time was prolonged, but improved absorption was not demonstrated.

Retrograde Electrical Pacing

Retrograde electrical pacing has also been investigated as a means of prolonging transit time [76–78]. This promotes peristalsis in a reverse direction and also alters the motility of non-paced intestine, presumably through a hormonal mechanism [78]. In experimental studies, postcibal retrograde pacing improved absorption of water and minerals after intestinal resection [76, 77]. In addition, weight loss and faecal fat and nitrogen excretion were decreased. Intestinal pacing has been used clinically in only one patient with a short bowel, but the pacemaker failed to stimulate the intestine [79]. In humans, the natural pacemaker potential frequency is similar throughout the length of the small intestine. Intestinal transection does not alter the pacemaker frequency of the distal intestine [80]. Because the pacemaker frequency cannot be increased above the natural rate in the intact intestine, it may not, in fact, be feasible to entrain the intestine to achieve retrograde pacing in humans [81].

Increasing Intestinal Length

Longitudinal intestinal tapering and lengthening (*LILT*), which has the attraction of not only tapering the dilated intestine but also using the redundant intestine for additional length, was initially described by Bianchi in 1984 [82]. Dissection is performed longitudinally between the blood vessels on the mesenteric border of the intestine, allocating vessels to either side of the intestinal wall (Fig. 3). A relatively avascular plane can be developed because these vessels enter the intestine from either side of midline. The intestine is then transected longitudinally with clamps or a

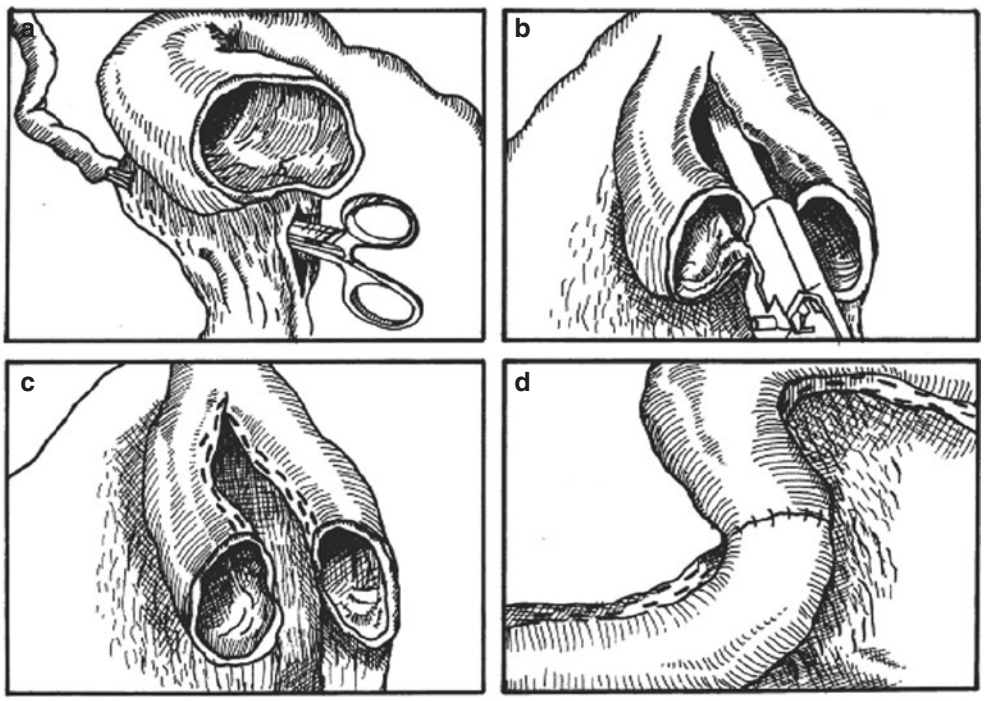

Fig. 3 Longitudinal intestinal tapering and lengthening (LILT). Dissection longitudinally between the blood vessels on the mesenteric border (**a**) permits the stapler to be used to divide the bowel longitudinally (**b**, **c**). The two parallel segments are then anastomosed end-to-end (**d**). (Reproduced with permission from Thompson [4])

stapler. The resultant parallel intestinal segments are then anastomosed end-to-end so that the initial dilated segment becomes a segment of one-half the diameter and twice the length. In the short-term this procedure disrupts motor activity and alters the hormonal response to resection [83]. However, long-term patency and function of divided segments has been demonstrated with resultant improved absorption.

The Bianchi procedure has been reported in more than 50 children ranging in age from 1 day to 19 years [57, 83–85]. Bacterial overgrowth and complications of TPN were present frequently. Significant improvement in nutritional status occurred in approximately 90% of patients in these reports. Segments as long as 55 cm have been tapered and lengthened. Complications have been reported in 20% of cases. In one patient in whom a 25-cm segment of proximal intestine was divided longitudinally, one-half of the divided segment became ischaemic and required resection. Intestinal motility is slow to return in these patients and gastrostomy tubes are frequently used. Death is rare but has occurred in the youngest (days/weeks old) and may be due to sepsis related to an anastomotic leak. Thus, although intestinal lengthening is beneficial in selected patients with a short bowel, the procedure should be applied cautiously because there is the risk of jeopardizing the divided segments. The vascular anatomy must be favourable and the intestinal diameter of the segment to be tapered should be at least 4 cm.

The serial transverse enteroplasty (STEP) procedure was described by Kim et al. in 2003 [86]. This procedure does not require separation of the leaves of the mesentery, and can therefore also be applied to adults. Instead, the dilated intestine is lengthened by partially dividing the bowel from alternate sides with a cutting stapler instrument (Fig. 4), leaving a channel 2.5 cm in diameter and some 70% longer than the original segment.

At least 111 children have undergone the STEP procedure [87]. Of 97 children with long-term follow-up, 11 died and 5 had an intestinal transplant. Thirty-seven achieved nutritional autonomy [88].

Data on outcomes of STEP in adults are scarce. The Nebraska group published a detailed case series in 2010, reporting outcomes in 20 adults who had bowel lengthening, of whom 15 had the STEP procedure [87]. Overall, mortality was nil and four patients (20%) required a reoperation, in all cases for obstruction. At long-term follow-up, 59% had regained nutritional autonomy. Cleveland Clinic reported overall outcomes of 420 cases of autologous gastrointestinal reconstruction for intestinal failure, 14 of whom were children [89]. Among the 420, 68 underwent the STEP procedure. Interestingly, 12 of those also underwent STEP on their colon. Nutritional autonomy was regained by 44 (72%) of 61 long-term survivors [89].

At present intestinal lengthening can only be applied to a fairly select group of patients. They must have a short remnant and an intestinal diameter greater than 4 cm. Thus, there has been recent interest in sequential procedures, first employing a distal valve or sphincter to dilate the proximal bowel and then performing the lengthening procedure [57]. Alternative methods to increase blood supply to isolated seg-

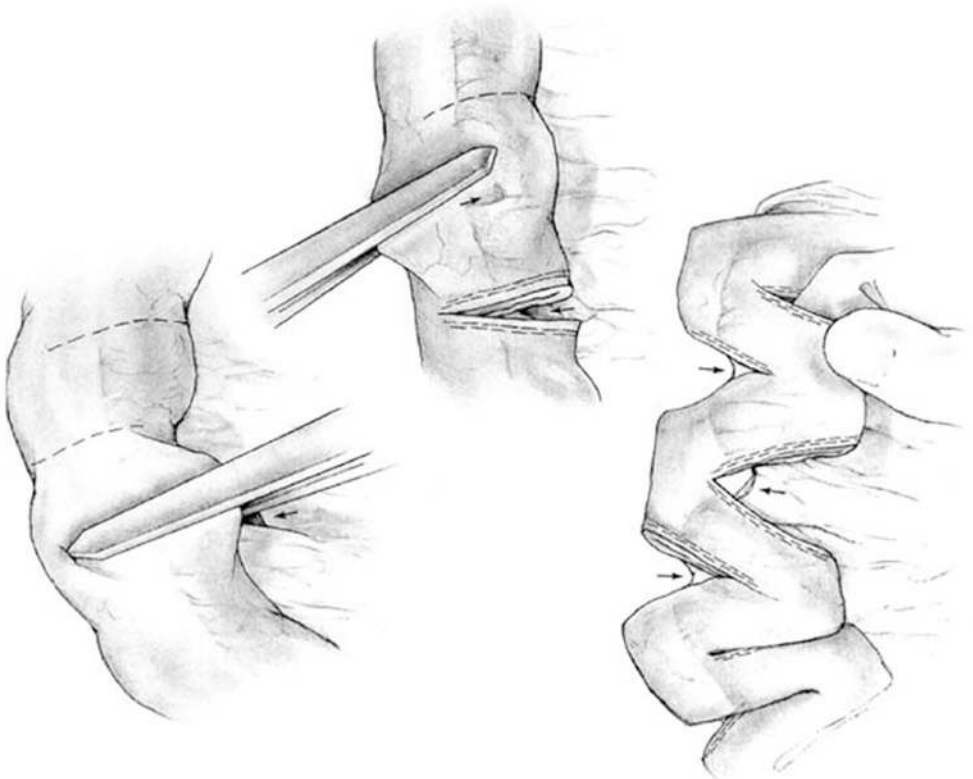

Fig. 4 Serial transverse enteroplasty procedure (STEP). Direction of insertion of the cutting stapler instrument indicated by smaller arrows. (Reproduced by permission from Kim et al. [86])

ments (e.g. from liver or omentum) and thus, permit repeated lengthening have also been investigated [90].

The STEP and LILT procedures are both accepted procedures for non-transplant surgical management of children with a short bowel, and the outcome of the STEP procedure may be more favourable [91, 92]. Long-term outcomes were recently compared in a systematic review of studies including 782 children, reporting nutritional autonomy in 52% of patients following LILT, and 48% following STEP [93].

Spiral intestinal lengthening and tailoring (SILT) is a novel technique described in children by Morabito, which requires less manipulation of the mesentery than the LILT procedure, and does not alter the orientation of the muscle fibers as with the STEP procedure [94–96]. In brief, incisions are made in the dilated bowel at 45–60° to the longitudinal axis. The bowel segment is then stretched longitudinally over a wide catheter with the same diameter as the desired new lumen. The incisions are now closed with bowel in its new, narrowed configuration. This promising technique awaits validation in other centres.

Other Techniques

While the surgical techniques are summarised in Table 3, there are other potential techniques for expanding the intestinal surface area take advantage of the regenerative capability of the intestine.

Intestinal regeneration will occur in full thickness intestinal defects patched with a variety of surfaces, including adjacent serosal surfaces. Whether or not sufficient mucosa can be produced by intestinal patching to significantly increase intestinal absorption remains unclear [18]. Further experimental study is necessary to assess the safety and efficacy of this approach. Clinical experience with intestinal patching to increase absorptive surface in patients with a short bowel has not been reported. This remains a useful technique, however, for managing intestinal defects and strictures when it is desirable to avoid resection.

Table 3 Surgical options for patients with a short bowel

Remnant length	Clinical condition	Surgical options
Remnant >120 cm	Normal diameter	Optimize intestinal function
	Enteral nutrition	
	Dilated bowel with bacterial overgrowth, stasis	Treat obstruction
		Intestinal tapering
Remnant >90 cm	Rapid transit	Recruit additional length
	Need for PN	Reversed intestinal segment
		Artificial valve
		Colon interposition
Remnant 60–90 cm	Normal diameter	Optimize intestinal function
	Dilated bowel	Intestinal lengthening
	Need for PN	
Remnant <60 cm	Complications of PN	Intestinal transplantation

Intestinal Tissue Engineering

Introduction

Tissue engineering is an evolving scientific discipline that combines stem cell biology and biomaterials science to construct human organs. The unifying philosophy within the field of tissue engineering is that the human body's innate regenerative responses can be applied and induced in the laboratory, to reconstruct functional human tissue for transplantation. Bioengineering of tissues with simpler functions such as the skin and cornea are established in clinical practice [97, 98]. Successful clinical applications of more complex organs have also been demonstrated in a few case reports of trachea and bladder reconstruction [99, 100]. There have been great advances in pre-clinical studies of bioengineering organs including oesophagus, skeletal muscle, liver and lung [101–106]. Tissue engineering of small bowel is particularly relevant for patients with a short bowel. Here we discuss the recent advances and strategies in development for intestinal tissue engineering solutions in short bowel syndrome.

Intestinal Stem Cells

The intestinal mucosa has one of the fastest self-regenerating rates of all mammalian tissues. Self-renewal is driven by intestinal stem cells (ISCs), positioned at the base of intestinal crypts. As ISCs divide, they give rise to daughter cells which then proliferate and migrate upwards towards the crypt-villus junction. Here, they terminally differentiate into the absorptive or secretory lineages before reaching the villus tip, where they are shed into the lumen [107].

Early attempts to establish the in vitro expansion of ISCs were extremely difficult without first inducing genetic transformations, which limited their clinical translation potential. In 1992, Evans et al., first demonstrated primary adult intestinal crypt cultures that consisted of both epithelial and mesenchymal cells [108]. However, only short-term cultures lasting up to 2 weeks were possible using this method and multipotency was somewhat variable. In 2007, Barker et al., made the landmark discovery that ISCs were marked by the Wnt target gene *Lgr5* [107]. The increasing knowledge in ISC biology paved the way for the establishment of intestinal organoids in vitro (Fig. 5) [109]. Sato et al., showed that both mouse and human intestinal organoids could be cultured in a

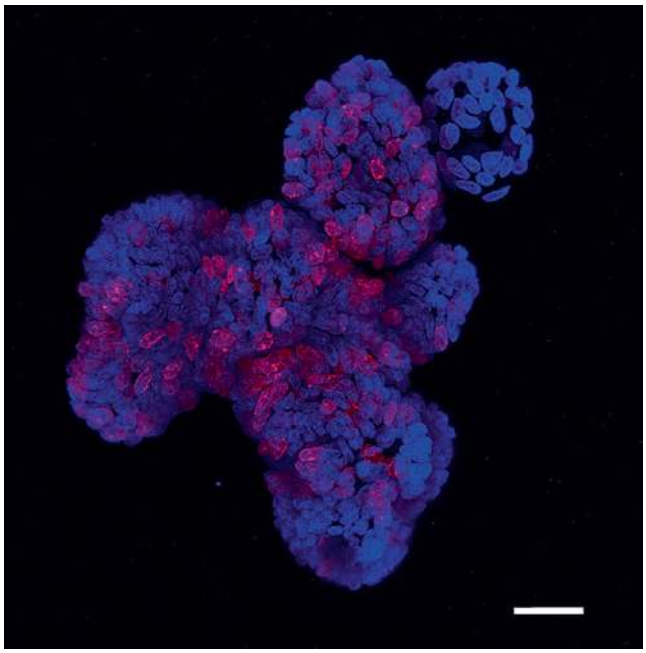

Fig. 5 Whole mount immunofluorescence staining of a human jejunal organoid. Proliferative cells are marked in magenta by 5-ethynyl-2′-deoxyuridine (EdU), whilst non-proliferating cells are marked in blue by 4,6-diamidino-2-phenylindole (DAPI)

three-dimensional matrix with an unlimited expansion potential whilst maintaining multipotency of all differentiated intestinal epithelial cell types [109, 110]. This was a key milestone in the field with significant research applications, particularly for intestinal tissue engineering [111, 112].

Sources of intestinal cells include induced pluripotent stem cells (iPSCs) and embryonic derived stem cells (ESCs). iPSCs are generated by forced expression of genes in differentiated adult cells such as fibroblasts [113], and have been used to generate intestinal epithelium of all lineages in vitro [114, 115]. Furthermore, they have been used in pre-clinical intestinal tissue engineering studies where human iPSCs grafts were transplanted in rats to demonstrate both structural and digestive functional competence in vivo [116]. An advantage is that donor cells can be non-invasively obtained from autologous sources such as skin biopsies, rather than requiring endoscopy.

In contrast, ESCs are derived from totipotent cells of the blastocyst stage of the early mammalian embryo (i.e. less than 8 weeks after fertilization) and are capable of unlimited, undifferentiated proliferation in vitro [117]. Human ES cell lines (commercially available) have also been used to form intestinal tissue when engrafted in the kidney capsule of NSG mice. After 6 weeks in vivo, the cellular grafts contained most of the intestinal epithelial, mesenchymal and smooth muscle cell types found in the developing gut [115]. However, the derivation of ESCs from human embryos is associated with substantial ethical impediments, which may hinder their translation into clinical studies.

Scaffold Biomaterials

Scaffolds are an essential component in tissue engineering as they act as a physical platform and support network, guiding three-dimensional cell growth. Scaffold composition should ideally mimic the natural extracellular matrix (ECM) that exists in vivo as closely as possible [103, 118–120]. Biodegradability of the scaffold is also an important consideration to ensure structural competence once anastomosed to native structures. Both synthetic and biological scaffolds have shown promising results in pre-clinical animal studies.

Synthetic intestinal scaffolds have been derived from biodegradable polymers and are moulded or printed into the intestinal shape. The great advantage of synthetic scaffolds is the potential to develop an "off the shelf" product that is widely available and can be manufactured in large scale production lines. However, these polymers do not retain any of the natural nanotopography of the native intestine, nor any bioactivity, which in turn affects cell behaviour such as loss of pluripotency [120].

Biological scaffolds are derived directly from the ECM of native organs through a process of decellularization, which describes the process whereby an organ is perfused with a series of chemical and biological solutions to remove all cellular and immunogenic material [112, 118]. Bioactivity of important growth factors (such as vascular endothelial growth factor) is maintained after decellularization [121]. Most promisingly, human intestinal decellularized scaffolds (Fig. 6) have been formed and are shown to have preserved microarchitecture of the crypt-villus axis and retained biological activity, therefore offering the most biomimetic substrate for intestinal tissue engineering [112]. Whilst this

Fig. 6 False coloured scanning electron micrograph of human small intestinal decellularized scaffold. Epithelial cells have been stripped off to reveal the underlying extracellular matrix. Crypts are present as depressions on the mucosal surface, whilst villi protrude upwards (coloured in violet/grey at their tips)

strategy still relies on the availability of donor organs, the study also showed it was possible to use colon scaffolds as substrates for jejunal mucosal reconstruction which would provide an alternative source of tissue [112].

Bioengineering Human Intestinal Grafts

There is great momentum in the research field to define the optimal combination of human intestinal cells and scaffolds for transplantation studies [116, 119, 122–126]. Most recently, patient derived jejunal ISCs were expanded and combined with human decellularized small intestine and colon scaffolds to form intestinal grafts which demonstrated digestive and absorptive function in vitro. When transplanted ectopically in mice, the human jejunal mucosal grafts survived and differentiate appropriately, maintained structural competence in vivo and demonstrated evidence of neovascularization [112]. These data support ongoing studies into larger animal transplantation studies using ISCs/iPSCs and biological scaffolds. A second evolving unique strategy being explored by Sugimoto et al., is to transplant small intestinal organoids into a segment of denuded colon, in order to repurpose it into functional small intestinal tissue. This strategy offers a scaffold-free technique of creating small bowel for patients with short bowel syndrome with promising results in small animal models [127].

In the next 10–15 years, tissue engineering advances will enable us to adapt engineering strategies and personalise grafts for an individual patient's needs. The most significant hurdle will be ensuring that intestinal grafts display enteric nervous function post-transplantation. It is likely that a combination of iPSC and ISCs based approaches, together with hybrid biological and synthetic scaffolds will offer the best strategy for first-in-man studies using this technology.

References

1. Thompson JS. Reoperation in patients with the short bowel syndrome. Am J Surg. 1992;164:453–7.
2. Tilson DM. Pathophysiology and treatment of short bowel syndrome. Surg Clinic North Am. 1980;60:1273–84.
3. Thompson JS. Strategies for preserving intestinal length in the short bowel syndrome. Dis Col Rectum. 1987;30:208–13.
4. Thompson JS. Recent advances in the surgical treatment of the short-bowel syndrome. Surg Annu. 1990;22:107–27.
5. McNeil NI. The contribution of the large intestine to energy supplies in man. Am J Clin Nutr. 1984;39:338–42.
6. Colomb V, Goulet O, Rambaud C, De Potter S, Sadoun E, Ben Hariz M, Jan D, Brousse N, Ricour C. Long-term parenteral nutrition in children: liver and gallbladder disease. Transplant Proc. 1982;24:1054–5.
7. Roslyn JJ, Pitt HA, Mann LL, Ament ME, Den Besten L. Gallbladder disease in patients on long-term parenteral nutrition. Gastroenterology. 1983;84:148–54.
8. Roslyn JJ, Berquist WE, Pitt HA, Mann LL, Kangarloo H, DenBesten L, Ament ME. Increased risk of gallstones in children on total parenteral nutrition. Paediatrics. 1983;71:784–9.
9. Messing B, Bories C, Kunstlinger F, Bernier J. Does total parenteral nutrition induce gallbladder sludge formation and lithiasis? Gastroenterology. 1983;84:1012–9.
10. Pitt HA, King W, Mann LL, Roslyn JJ, Berquist WE, Ament ME, DenBesten L. Increased risk of cholelithiasis with prolonged total parenteral nutrition. Am J Surg. 1983;145:106–12.
11. Roslyn JJ, Pitt HA, Mann LL, Fonkalsrud EW, Den Besten L. Parenteral nutrition-induced gallbladder disease: a reason for early cholecystectomy. Am J Surg. 1984;148:58–63.
12. Manji N, Bistrian BR, Mascioloi EA, Benotti PA, Blackburn GL. Gallstone disease in patients with severe short bowel syndrome dependent on parenteral nutrition. J Parenter Enter Nutr. 1989;12:461–4.
13. Nightingale JMD, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces need of parenteral therapy, increases incidence of renal stones, but does not change high prevalence of gallstones in patients with a short bowel. Gut. 1992;33:1493–7.
14. Thompson JS. The role of prophylactic cholecystectomy in the short bowel syndrome. Arch Surg. 1996;131:556–60.
15. Appleton ND, Lal S, Carlson GL, Shaw S, Stevens P, Peristerakis I, Soop M. Cholelithiasis and related morbidity in chronic intestinal failure: a longitudinal cohort study from a National Specialized Centre. J Gastrointest Surg. 2019;23(10):2002–6.
16. Wilburn J, McKenna SP, Heaney A, Rouse M, Taylor M, Culkin A, Gabe S, Burden S, Lal S. Development and validation of the Parenteral Nutrition Impact Questionnaire (PNIQ), a patient-centric outcome measure for Home Parenteral Nutrition. Clin Nutr. 2018;37(3):978–83.
17. Burrington JD. Surgery after massive bowel resection. Am J Surg. 1971;121:213–4.
18. Thompson JS, Harty RJ, Saigh JA, Giger DK. Morphological and nutritional responses to intestinal patching following intestinal resection. Surgery. 1988;103:79–86.
19. Thompson JS, Langnas AN, Pinch LW, Kaufman S, Quigley EMM, Vanderhoof JA. Surgical approach to the short bowel syndrome: experience in a population of 160 patients. Ann Surg. 1995;222:600–7.
20. Dibb M, Soop M, Teubner A, Shaffer J, Abraham A, Carlson G, Lal S. Survival and nutritional dependence on home parenteral nutrition: three decades of experience from a single referral centre. Clin Nutr. 2017;36(2):570–6.
21. Lloyd PA. Colonic interposition between the jejunum and ileum after massive small bowel resection in rats. Prog Pediatr Surg. 1978;12:51–106.
22. Kaveggia FF, Thompson JS, Taylor RJ. Placement of an ileal loop urinary diversion back into continuity with the intestinal tract. Surgery. 1991;110:557–60.
23. Nguyen BT, Blatchford GJ, Thompson JS, Bragg LE. Should intestinal continuity be restored after massive intestinal resection. Am J Surg. 1989;158:577–80.
24. Gouttebel MC, Saint-Aubert B, Astre C, Joyeux H. Total parenteral nutrition needs in different types of short bowel syndromes. Dig Dis Sci. 1986;31:718–23.
25. O'Keefe SJD, Burnes JU, Thompson RL. Recurrent sepsis in home parenteral nutrition patients: an analysis of risk factors. J Parenter Enter Nutr. 1994;18:256–63.
26. Rombeau JL, Kripke SA. Metabolic and intestinal effects of short chain fatty acids. J Parenter Enter Nutr. 1990;14:181S–5S.
27. Koruda MJ, Rolandelli RH, Settle RG, Saul SH, Rombeau JL. The effect of a pectin-supplemented elemental diet on intestinal adaptation to massive small bowel resection. J Parenter Enter Nutr. 1986;10:343–50.

28. Carbonnel F, Cosnes J, Chevret S, et al. The role of anatomic factors in nutritional autonomy after extensive small bowel resection. J Parenter Enter Nutr. 1996;20:275–80.
29. Levy E, Frileux P, Sandrucci S, et al. Continuous enteral nutrition during the early adaptive stage of the short bowel syndrome. Br J Surg. 1988;75:549–53.
30. Sharma P, Davidson R, Davidson J, Keane C, Liu C, Ritchie SR, Chu K, Sutherland G, Bissett IP, O'Grady G. Novel chyme reinfusion device for gastrointestinal fistulas and stomas: feasibility study. Br J Surg. 2020;107(9):1199–210.
31. Weber TR, Vane DW, Grosfield JL. Tapering enteroplasty in infants with bowel atresia and short gut. Arch Surg. 1982;117:684–8.
32. Borgstein ES, Munro A, Youngson GG. Intestinal plication: an alternative to tapered jejunostomy in functional small bowel obstruction. Br J Surg. 1991;78:1075–6.
33. Ramanujan TM. Functional capability of blind small loops after intestinal remodeling techniques. Aust NZ J Surg. 1986;54:145–50.
34. Mall F. Reversal of the intestine. Johns Hopkins Hosp. 1896;1:93–110.
35. Thompson JS, Quigley EMM, Adrian TE. Effect of reversed intestinal segments on intestinal structure and function. J Surg Res. 1995;58:19–27.
36. Persemlidis D, Kark AE. Antiperistaltic segments for the treatment of short bowel syndrome. Am J Gastroent. 1974;62:526–30.
37. Stahlgren LH, Umana G, Roy R, Donnelly J. A study of intestinal absorption in dogs following massive small intestinal resection and insertion of an antiperistaltic segment. Ann Surg. 1962;156(3):483–92.
38. Delany HM, Parker JG, Gliedman ML. Experimental massive intestinal resection: comparison of surgical measures and spontaneous adaptation. Arch Surg. 1970;101:599–604.
39. Barros D'Sa AAB. An experimental evaluation of segmental reversal after massive small bowel resection. Br J Surg. 1979;66:493–500.
40. Williams NS, King RFG. The effect of reversed ileal segments and artificial valve on intestinal transit and absorption following colectomy and low ileorectal anastomosis in the dog. Br J Surg. 1985;72:169–74.
41. Kurz R, Sauer H. Treatment and metabolic finding in extreme short bowel syndrome with 11 cm jejunal remnant. J Pediatr Surg. 1983;18:257–63.
42. Pigot F, Messing B, Shaussade S, Pfeiffer A, Pouliguen Y, Jiau R. Severe short bowel syndrome with a surgically reversed small bowel segment. Dig Dis Sci. 1990;35:137–44.
43. Panis Y, Messing B, Rivet P, et al. Segment reversal of the small bowel as an alternative to intestinal transplantation in patients with short bowel syndrome. Ann Surg. 1997;225:401–7.
44. Thompson JS. Reversed intestinal segment revisited. Transplant Proc. 2016;48:453–6.
45. Wilmore DW, Johnson DJ. Metabolic effect of small bowel reversal in treatment of the short bowel syndrome. Arch Surg. 1968;97:784–91.
46. Richards WO, Golzarian J, Wasuder N, Sawyers JL. Reverse phasic contractions are present in antiperistaltic jejunal limbs up to 21 years postoperatively. J Am Coll Surg. 1994;178:557–63.
47. Dorney SF, Ament ME, Berquist WE. Improved survival in very short small bowel of infancy with use of long-term parenteral nutrition. J Pediatr. 1985;107:521–5.
48. Waddell WR, Kern F, Halgrimson CF, Woodbury JJ. A simple jejunocolic valve for relief of rapid transit and the short bowel syndrome. Arch Surg. 1970;100:438–44.
49. Lopes-Perez GA, Martinez AJ, Machcua J, Lopez S, Unda A, Rodriguez M, Miguelez C. Experimental antireflux intestinal valve. Am J Surg. 1981;141:597–600.
50. Careskey J, Weber TR, Grosfield JL. Ileocecal valve replacement: its effect on transit time, survival and weight change after massive intestinal resection. Arch Surg. 1981;116:618–22.
51. Ricotta J, Zuidema FD, Gadacz RT, Sadri D. Construction of an ileocecal valve and its role in massive resection of the small intestine. Surg Gynecol Obstet. 1981;152:310–4.
52. Stacchini A, DiDo LJ, Primo ML, Borelli V, Andretto R. Artificial sphincter as surgical treatment for experimental massive resection of small intestine. Am J Surg. 1982;143:721–6.
53. Chardovoyne R, Isenberg H, Tindel M, Stein T, Wise L. Efficacy of a surgically constructed nipple valve following massive small bowel resection. Gastroenterology. 1983;84:1122.
54. Sawchuk A, Goto S, Yount J, Grosfield JA, Lohmuller J, Grosfield MD. Chemically induced bowel denervation improved survival in short bowel syndrome. J Pediatr Surg. 1987;22:492–6.
55. Quigley EMM, Thompson JS. Effects of an artificial ileocolonic sphincter on motility in the intestinal remnant following subtotal small intestinal resection. Dig Dis Sci. 1994;39:1222–9.
56. Smedh K, Olaison G, Sjodahl R. Ileocolic nipple valve anastomosis for preventing recurrence of surgically treated Crohn's disease. Dis Colon Rectum. 1990;33:987–90.
57. Georgeson K, Halpin D, Figuera R, Vincente Y, Hardin W. Sequential intestinal lengthening procedures for refractory short bowel syndrome. J Pediatr Surg. 1994;29:316–21.
58. Hutcher NE, Mendez-Picon G, Salzberg AM. Prejejunal transposition of colon to prevent the development of the short bowel in puppies with 90% small intestine resection. J Pediatr Surg. 1973;8:771–7.
59. Sidhu GS, Narasimharao V, Rani V, Sarkar AK, Chakravarti RN, Mitra SK. Morphological and functional changes in the gut after massive small bowel resection and colon interposition in Rhesus monkeys. Digestion. 1984;129:47–54.
60. Hutcher NE, Salzberg AM. Pre-ileal transposition of colon to prevent the development of the short bowel syndrome in puppies with 90% small intestinal resection. Surgery. 1971;70:189–97.
61. Sidhu GS, Narasimharao V, Rani V, Sarkar AK, Mitra SK. Absorptive studies after massive small bowel resection and antiperistaltic colon interposition in Rhesus monkeys. Dig Dis Sci. 1985;30:483–8.
62. Carner DV, Raju S. Failure of antiperistalsis colon interposition to ameliorate short bowel syndrome. Am Surg. 1981;47:538–40.
63. Belin RP, Richardson JD, Medley ES. Transit time and bacterial overgrowth as determinants of absorptive capacity. J Surg Res. 1972;3:185–92.
64. Garcia VF, Templeton JM, Eichelberger MR, Koop CE, Vinograd I. Colon interposition for the short bowel syndrome. J Pediatr Surg. 1981;16:994–5.
65. Glick PL, de Lorimier AA, Adzick NS, Harrision MR. Colon interposition: an adjuvant operation for short gut syndrome. J Pediatr Surg. 1984;19:719–25.
66. Brolin RE. Colon interposition for extreme short bowel syndrome: a case report. Surgery. 1986;100:576–80.
67. Trinkle JK, Bryant LR. Reversed colon segment in an infant with massive small bowel resection. A case report. J Ky Med Assoc. 1967;65:1090–1.
68. Davis HC, Wolcott W, Colder HK, Blum AS. Intestinal recirculation as an aid to absorption: an experimental study. Arch Surg. 1959;29:597–9.
69. Redmond DC, Muraki T, Singleton AO. Effects of recirculating jejunal loops on absorption and transit after massive bowel resection in dogs. Surg Forum. 1964;15(29):1–2.
70. Altman DP, Ellison EH. Massive intestinal resection: inadequacies of the recirculating loop. Surg Forum. 1965:16.
71. Budding J, Smith CG. Role of recirculating loops in the management of massive resection of the small intestine. Surg Gynecol Ostet. 1967;125:213–49.
72. Camprodon R, Guerrero JA, Salva JA, Jornet J. Shortened small bowel syndrome: Mackby's operation. Am J Surg. 1975;129:585–6.

73. Poth EJ. Use of gastrointestinal reversal in surgical procedures. Am J Surg. 1969;118:893–9.
74. Mackby MJ, Richards V, Gilfillan RS, Floridia R. Methods of increasing the efficiency of residual small bowel segments. Am J Surg. 1965;109:32–8.
75. Cywes S. The surgical management of massive bowel resection. J Pediatr Surg. 1968;3:740–8.
76. Gladen HE, Kelly KA. Enhancing absorption in the canine short bowel syndrome by intestinal pacing. Surgery. 1980;88:281–6.
77. Layzell T, Collin J. Retrograde electrical pacing of the small intestine: a new treatment for the short bowel syndrome? Br J Surg. 1981;68:711–3.
78. Bjored WS, Phillips SF, Kelly KA. Mechanisms of enhanced intestinal absorption with electrical pacing. Gastroenterology. 1984;86:1029.
79. Devine RM, Kelly KA. Surgical therapy for the short bowel syndrome. Gastroenterol Clin N Am. 1989;18:603–17.
80. O'Connell PR, Kelly KA. Enteric transit and absorption after canine ileostomy: effect of pacing. Arch Surg. 1987;122:1011–7.
81. Soper NJ, Sarr MG, Kelly KA. Human duodenal myo-electric activity after operation and with pacing. Surgery. 1990;107:63–8.
82. Bianchi A. Intestinal lengthening: an experimental and clinical review. J R Soc Med. 1984;77:35–41.
83. Thompson JS, Quigley EMM, Adrian TE. Effect of intestinal tapering and lengthening on intestinal structure and function. Am J Surg. 1995;169:111–9.
84. Thompson JS, Pinch LW, Murray N, Vanderhoof JA, Schultz LR. Initial experience with lengthening for the short bowel syndrome. J Pediatr Surg. 1991;26:721–4.
85. Pokorny WJ, Fowler CL. Isoperistaltic intestinal lengthening for short bowel syndrome. Surg Gynecol Obstet. 1991;173:39–43.
86. Kim HB, Fauza D, Garza J, Oh JT, Nurko S, Jaksic T. Serial transverse enteroplasty (STEP): a novel bowel lengthening procedure. J Pediatr Surg. 2003 Mar;38(3):425–9.
87. Yannam GR, Sudan DL, Grant W, Botha J, Langnas A, Thompson JS. Intestinal lengthening in adult patients with short bowel syndrome. J Gastrointest Surg. 2010;14(12):1931–6.
88. Jones BA, Hull MA, Potanos KM, Zurakowski D, Fitzgibbons SC, Ching YA, Duggan C, Jaksic T, Kim HB, International STEP Data Registry. Report of 111 consecutive patients enrolled in the International Serial Transverse Enteroplasty (STEP) data registry: a retrospective observational study. J Am Coll Surg. 2013;216(3):438–46.
89. Abu-Elmagd KM, Armanyous SR, Fujiki M, Parekh NR, Osman M, Scalish M, Newhouse E, Fouda Y, Lennon E, Shatnawei A, Kirby D, Steiger E, Khanna A, Radhakrishnan K, Quintini C, Hashimoto K, Barnes J, Costa G. Management of five hundred patients with gut failure at a single center: surgical innovation versus transplantation with a novel predictive model. Ann Surg. 2019;270(4):656–74.
90. Kimura K, Soper RT. A new bowel elongation technique for the short bowel syndrome using the isolated bowel segment Iowa models. J Pediatr Surg. 1993;28:792–4.
91. Frongia G, Kessler M, Weih S, Nickkholgh A, Mehrabi A, Holland-Cunz S. Comparison of LILT and STEP procedures in children with short bowel syndrome—a systematic review of the literature. J Pediatr Surg. 2013;48:1794–805.
92. Mercer DF, Hobson BD, Gerhardt BK, Grant WJ, Vargas LM, Langnas AN, Quiros-Tejeira RE. Serial transverse enteroplasty allows children with short bowel to wean from parenteral nutrition. J Pediatr. 2014;164:93–8.
93. Nagelkerke SCJ, Poelgeest MYV, Wessel LM, Mutanen A, Langeveld HR, Hill S, Benninga MA, Tabbers MM, Bakx R. Bowel lengthening procedures in children with short bowel syndrome: a systematic review. Eur J Pediatr Surg. 2022;32(4):301–9. https://doi.org/10.1055/s-0041-1725187.
94. Cserni T, Biszku B, Guthy I, Dicso F, Szaloki L, Folaranmi S, Murphy F, Rakoczy G, Bianchi A, Morabito A. The first clinical application of the spiral intestinal lengthening and tailoring (silt) in extreme short bowel syndrome. J Gastrointest Surg. 2014;18:1852–7.
95. Alberti D, Boroni G, Giannotti G, Parolini F, Armellini A, Morabito A, Bianchi A. "Spiral intestinal lenghtening and tailoring (SILT)" for a child with severely short bowel. Pediatr Surg Int. 2014;30:1169–72.
96. Coletta R, Aldeiri B, Morabito A. Institutional experience with spiral intestinal lengthening and tailoring. Eur J Pediatr Surg. 2019;29(5):412–6.
97. Rama P, et al. Limbal stem-cell therapy and long-term corneal regeneration. N Engl J Med. 2010;363:147–55.
98. Hirsch T, et al. Regeneration of the entire human epidermis using transgenic stem cells. Nature. 2017;551:327–32.
99. Elliott MJ, et al. Stem-cell-based, tissue engineered tracheal replacement in a child: a 2-year follow-up study. Lancet. 2012;380:994–1000.
100. Atala A, Bauer SB, Soker S, Yoo JJ, Retik AB. Tissue-engineered autologous bladders for patients needing cystoplasty. Lancet. 2006;367:1241–6.
101. Quarta M, et al. Bioengineered constructs combined with exercise enhance stem cell-mediated treatment of volumetric muscle loss. Nat Commun. 2017;8:15613.
102. Jank BJ, et al. Engineered composite tissue as a bioartificial limb graft. Biomaterials. 2015;61:246–56.
103. Uygun BE, et al. Organ reengineering through development of a transplantable recellularized liver graft using decellularized liver matrix. Nat Med. 2010;16:814–20.
104. Zhou H, et al. Bioengineering human lung grafts on porcine matrix. Ann Surg. 2018;267:590–8.
105. Ott HC, et al. Regeneration and orthotopic transplantation of a bioartificial lung. Nat Med. 2010;16:927–33.
106. Urbani L, et al. Multi-stage bioengineering of a layered oesophagus with in vitro expanded muscle and epithelial adult progenitors. Nat Commun. 2018;9:4286.
107. Barker N, et al. Identification of stem cells in small intestine and colon by marker gene Lgr5. Nature. 2007;449:1003–7.
108. Evans GS, Flint N, Somers AS, Eyden B, Potten CS. The development of a method for the preparation of rat intestinal epithelial cell primary cultures. J Cell Sci. 1992;101(Pt 1):219–31.
109. Sato T, et al. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. Nature. 2009;459:262–5.
110. Sato T, et al. Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium. Gastroenterology. 2011;141:1762–72.
111. Sato T, Clevers H. Growing self-organizing mini-guts from a single intestinal stem cell: mechanism and applications. Science. 2013;340:1190–4.
112. Meran L, et al. Engineering transplantable jejunal mucosal grafts using patient-derived organoids from children with intestinal failure. Nat Med. 2020;26:1593–601.
113. Takahashi K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131:861–72.
114. Spence JR, et al. Directed differentiation of human pluripotent stem cells into intestinal tissue in vitro. Nature. 2011;470:105–9.
115. Watson CL, et al. An in vivo model of human small intestine using pluripotent stem cells. Nat Med. 2014;20:1310–4.
116. Kitano K, et al. Bioengineering of functional human induced pluripotent stem cell-derived intestinal grafts. Nat Commun. 2017;8:765.
117. Evans MJ, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. Nature. 1981;292:154–6.
118. Totonelli G, et al. A rat decellularized small bowel scaffold that preserves villus-crypt architecture for intestinal regeneration. Biomaterials. 2012;33:3401–10.

119. Chen Y, et al. Robust bioengineered 3D functional human intestinal epithelium. Sci Rep. 2015;5:13708.
120. Finkbeiner SR, et al. Generation of tissue-engineered small intestine using embryonic stem cell-derived human intestinal organoids. Biol Open. 2015;4:1462–72.
121. Hodde JP, Record RD, Liang HA, Badylak SF. Vascular endothelial growth factor in porcine-derived extracellular matrix. Endothelium. 2001;8:11–24.
122. Grant CN, et al. Human and mouse tissue-engineered small intestine both demonstrate digestive and absorptive function. Am J Physiol. 2015;308:G664–77.
123. Ladd MR, et al. Development of intestinal scaffolds that mimic native mammalian intestinal tissue. Tissue Eng Part A. 2019;25(17-18):1225–41.
124. Schweinlin M, et al. Development of an advanced primary human in vitro model of the small intestine. Tissue Eng Part C Methods. 2016;22:873–83.
125. Shaffiey SA, et al. Intestinal stem cell growth and differentiation on a tubular scaffold with evaluation in small and large animals. Regen Med. 2016;11:45–61.
126. Costello CM, et al. Synthetic small intestinal scaffolds for improved studies of intestinal differentiation. Biotechnol Bioeng. 2014;111:1222–32.
127. Sugimoto S, et al. An organoid-based organ-repurposing approach to treat short bowel syndrome. Nature. 2021;592:99–104.

Intestinal Transplantation

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Key Points

1. There are 4 types of intestine-containing transplant (often these are all grouped under the umbrella term of 'intestinal transplant')—isolated intestinal graft, liver plus intestine, modified multivisceral (stomach, pancreaticoduodenal complex and intestine) and Multivisceral (includes stomach, pancreaticoduodenal complex, liver and intestine).
2. An intestinal transplant is considered for the complications of intestinal failure/parenteral nutrition (e.g. liver disease), or in the context of extensive evisceration for desmoid or other benign abdominal tumours.
3. For an isolated small bowel graft the 5 year patient survival is as high as 80% in some centres and the chance of these patients being off parenteral support is 93%.
4. Problems of immunosuppression include increased risk of infection, nephrotoxicity, neurological side effects and increased risk of malignancy
5. Rejection occurs in 30% and graft-versus-host-disease in 10%.

Historical Perspective

Transplantation of the small intestine, either alone or as part of a cluster of organs has been undertaken for more than a century, but patient survival for more than a few days was not achieved until the late 1980s when Grant *et al.* reported what is accepted to be the first example of a successful small bowel transplant [1]. This group made the observation that this success was associated with the presence of a chimeric population of immunocompetent cells in this patient which led to the proposal that engagement of the host and donor immune systems promotes a degree of tolerance by the recipient for the graft. Other centres have reported evidence of graft tolerance such as the observation of regulatory T cells in the transplanted intestinal lamina propria [2].

Under normal circumstances, lymphocytes circulate between the peripheral lymphatic tissues such as the spleen, lymph nodes and the gut. This process continues after small bowel transplantation but there is interplay between host and transplanted lymphocytes which cycle through the transplanted and host trafficking sites [3–5]. Under suitable immunosuppression this can be a benign process where tolerance prevails. However, inadequate immunosuppression can lead to proinflammatory lymphocyte behaviour and graft rejection or less commonly GVHD [6, 7]. Efficacy of lymphocyte-depleting agents may arise at least in part from the generation of "prope-tolerance" encouraged by the replacement of depleted host immunocytes with a new population that emerges in the environment consisting of both host and donor tissues such that there is an enhanced degree of tolerance of donor tissues as self. In 1995 Campath 1H, a monoclonal anti-CD 52 antibody, was first used for a multivisceral transplantation in Cambridge, UK. This depletes both T and B lymphocytes and seems to promote a greater degree of tolerance which, together with the advent of the more potent calcineurin inhibitors such as Tacrolimus in the early 1990s, led to a decade when the use of intestinal transplantation became exponential. An increase in serious infections tempered enthusiasm and highlighted the delicate balance between preventing rejection and avoiding infection. Attempts to improve tolerance and reduce infections by concurrent splenic transplantation gained some traction for a brief period but has not stood the test of time.

Over the last decade there has been a more cautious policy in most transplant centres and in general survival figures

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are now reasonable with a few centres still achieving results similar to those of liver transplantation. The incorporation of a liver in the cluster of transplanted organs was initially believed to be largely responsible for inducing graft tolerance. It is now clear that it greatly increases the overall risk of the procedure and is associated with a reduced survival compared with that associated with procedures that do not contain a liver. Consequently, patients on parenteral nutrition, particularly if they have a very short small bowel remnant, should be carefully monitored and referred early to a transplant centre before significant liver disease develops.

Indications and When to Refer for Intestinal Transplantation

The current indications for intestinal transplantation in the UK as published by NHS blood transfusion and transplantation are summarized in Table 1. These have gradually broadened over the last 15 years as the risks and benefits of these procedures have become more understood and the survival chance a little more predictable. However, there remains a need for a fully validated system to estimate survival chance of patients who are considered as candidates, both with their existing problems and in the event of transplantation. The same applies to the effect of transplantation on quality of life. Some patients find their quality of life enhanced after intestinal transplantation, but others do not, and may even find a reduction. Currently it is not possible to predict which patients will do well from this perspective. Attention should be given to the likely impact of transplantation on aspects of life that the patient considers of greatest importance to them, but always in the context of the other effects of their likely post-transplant condition. This area remains very challenging.

As seen in Table 1, loss of central access sites for parenteral nutrition is an indication for IT. However, it is critical that the patient has sufficient venous access to allow adequate operative and post-operative support. For example, many patients will require temporary renal replacement therapy, intravenous nutrition, management of complex sepsis, multiple surgical procedures and other invasive procedures during their post-operative recovery. They will therefore require suitable venous access sites to be available over a long period of time and continued attrition of these is to be expected. Even after hospital discharge it is usual for patients to require intermittent re-admission [8], over the long term, with serious intercurrent illness when they require good central access to receive appropriate treatment.

Others may have recurrent sepsis or inadequate nutritional support resulting in a steady decline, and slow growing tumours such as desmoids can present a particular timing difficulty due to their unpredictable growth rate and tendency to be more advanced than indicated on cross sectional imaging.

Table 1 Current indications for intestinal transplantation in the UK (Source: NHS blood and transplant, https://www.odt.nhs.uk/transplantation/small-bowel/

Irreversible intestinal failure, plus
1. Life-threatening complications of parenteral nutrition (a) Progressive intestinal failure-associated liver disease (IFALD) or non-IFALD • Assessed by biochemistry and biopsy • Combined intestinal and liver transplant is best considered in the presence of advanced liver disease (portal hypertension or advanced fibrosis)
(b) Severe sepsis • More than one life-threatening episode of catheter-related sepsis for which no remediable cause can be identified • Endocarditis or other metastatic infection
(c) Limited central venous access • Venous access limited to three major conventional sites in adults (above and below the diaphragm) and two major conventional sites above the diaphragm in children • Conventional central venous sites are defined as internal jugular, subclavian and femoral veins
2. Very poor quality of life thought likely to be correctable by transplantation
Patients with indications for extensive surgery involving partial or complete evisceration
1. Surgery to remove a large proportion of the abdominal viscera considered untenable without associated multi-visceral transplantation (e.g. extensive desmoid disease, extensive critical mesenteric arterial disease)
2. Localised malignancy considered amenable to curative resection requiring extensive evisceration (e.g. localised neuroendocrine tumours). Particular caution should be exercised in this group and patients should be discussed in a multidisciplinary multicentre forum (e.g. National adult small intestinal transplant forum, NASIT)
Patients requiring transplantation of other organs where exclusion of simultaneous intestinal transplantation would adversely affect patient survival
1. Where the transplantation procedure is expected to preclude the possibility of future intestinal transplantation (e.g. loss of venous access or further human leukocyte antigen sensitisation)
2. Where the need for subsequent intestinal transplantation is considered likely and the risk of death is increased by excluding the intestine from the graft
Examples include predictable problems related to administering immunosuppression (e.g. line sepsis), or continuing severe intestinal disease such as diabetic visceral neuropathy, or ultra-short bowel syndrome, which may cause fluid, electrolyte and acid base balance problems that would damage an existing or planned renal graft
Special considerations
Transplantation of additional organs for feasibility reasons Renal transplantation Adults and children with corrected GFR of <45 mL/min/m^2 are evaluated for the possibility of simultaneous renal transplantation

In addition to these factors, consideration should be given to the escalation of surgical complexity. If transplanted early enough, liver disease associated with intestinal failure often resolves. The requirement of a liver as part of the cluster of transplanted organs is associated with a much lower survival rate than non-liver containing grafts. Unfortunately, intestinal failure associated liver disease can develop insidiously and reach an advanced stage with few if any signs for the attending clinician to become alerted to its presence (see below).

Therefore, it is necessary to avoid premature listing for transplantation when the patient does not fulfil criteria and would be exposed to the risks of transplantation unnecessarily, but also avoid undue delay when the patient's condition has deteriorated to a point which significantly reduces his/her chances of survival.

Assessing the Potential Transplant Recipient

The importance of the patients' pre-operative condition and the adverse effect of comorbidity on operative and post-operative survival are now well established. Not only must patients be in a suitable physical condition but their mental state is also of critical importance. Many patients already have mental illness arising in the context of their protracted physical morbidity and the additional burden of the transplant process often deepens any existing tendency toward depression and anxiety. Patients frequently spend several months in hospital after the transplant and have long periods on the intensive care unit. These stresses are often associated with loss or reduction in their support network of friends and family, due to geographical constraints.

There needs to be careful multi-disciplinary consideration as to the suitability of each patient in the broader context of their general condition and likelihood of surviving what is one of the most challenging medical procedures performed in the modern era. Some centres achieve this with multidisciplinary meetings, and in the UK there is a National Adult Small Intestinal Transplantation forum (NASIT) at which all potential candidates are reviewed prior to listing for transplantation. This has also proven to be a valuable opportunity for the exchange of ideas and experiences between centres and is attended by representatives from intestinal failure units as well as transplant centres.

Medical Assessment

The majority of candidates have experienced multiple thrombotic events, either causing bowel loss or complications of vascular access. A comprehensive thrombophilia screen is necessary but even if no defined pro-coagulant condition is identified these patients should be considered as functionally pro-thrombotic.

Some patients will have developed anti-human leucocyte antigen (HLA) antibodies, as a consequence of pregnancies, blood transfusions or previous transplants and are described as "sensitised". Knowledge of previous of sensitising events is mandatory and a full tissue type and HLA antibody screen performed. If there are anti HLA antibodies this will influence waiting time for organs [9] and may preclude transplantation. Once listed it is important to avoid unnecessary sensitising events (e.g. blood transfusions).

Details of the immune status of the host to infections such as Cytomegalovirus, Epstein Barr Virus, Toxoplasmosis, Varicella Zoster, Herpes simplex, HIV, Hepatitis B, C and E and Mycobacterium tuberculosis are important for the heavily immunosuppressed post-operative environment. Knowledge of previous infections particularly if multi-drug resistant will allow better selection of anti-microbial therapy and patients should receive appropriate vaccination against the endemic infections they are likely to be exposed to during and after transplantation. Knowledge of the immune status to CMV and EBV can influence donor and recipient matching and prophylaxis after transplantation.

Assessment of liver pathology in patients with IF is critical. Normal liver function tests do not exclude underlying fibrosis or cirrhosis, and features of portal hypertension can be absent even in the presence of cirrhosis, due to reduced splanchnic blood flow. Patients at particular risk for advanced fibrosis are those who are 'ultra-short' [10] (residual SB length less than 20 cm), or those with a second hepatic insult (alcohol, viral hepatitis, previous non-alcoholic fatty liver disease). Transient Elastography (Fibroscan®) has not been validated in this group of patients and may be misleading. Liver biopsy is currently the gold standard for liver assessment in this context. It is important that the biopsy is of sufficient size and length and is interpreted by an experienced liver pathologist.

Patients with moderate or moderate to severe fibrosis would not necessarily require a liver as part of their graft. Patients with established cirrhosis will usually require a combined intestine/liver graft, even in the absence of portal hypertension as patients often do not manifest the clinical or radiological stigmata of chronic liver disease. Timing of transplantation may be informed by the patient's United Kingdom model for end stage liver disease (UKELD) or model for end stage liver disease (MELD) scores but these have not been validated in IFALD. In any case with IFALD, careful and nuanced judgement by an experienced transplant centre is required.

Surgical Assessment

At referral, knowledge of the current anatomy including a detailed appraisal of the vasculature and previous surgical

history is needed. Previous histopathology can be helpful, particularly if liver pathology (e.g. IFALD) or dysmotility is expected.

Examination focuses on stomata, enterocutaneous fistulae, surgical incisions, drain sites and anthropometrics. Abdominal wall scarring results in reduced compliance and abdominal domain, limiting the size of potential donors. Ascites increases the size of the abdominal cavity and therefore the availability of potential donors.

Assessment for peripheral vascular disease is essential in any transplant; if present it is a marker of reduced long-term survival.

Radiological Assessment

Interpretation of current and previous images with a dedicated radiologist experienced in the challenges of intestinal transplantation is essential.

The corner stone of radiological assessment is triple phase CT. This is the most useful modality to assess gastrointestinal and vascular anatomy. Assessment of the arterial supply to the remaining abdominal organs, degree of aortic calcification and patency of venous structures within and outside the abdomen are essential.

Many patients will have compromised central venous access which impacts per-i and post-operative care. Ultrasound, CT, MRI and/or conventional venography are used for venous mapping. Venous reconstruction (using interventional radiology or surgery) may be required to allow transplantation.

Nuclear medicine EDTA GFR (nGFR) can be performed to determine the need for simultaneous kidney transplantation in borderline cases [11]. DEXA scanning is necessary given the high incidence of pre-existing metabolic bone disease in this cohort.

These are the minimum tests that all potential candidates require, individual circumstances may dictate further testing such as MRCP, CT chest and head.

Anaesthetic Assessment

Cardiopulmonary testing in our institution involves ECG, lung function test, trans-thoracic echocardiography and some form of cardiac stress test in higher risk patients (those with 1 or more cardiac risk factors).

Assessment by an anaesthetist experienced with the operation is essential. Consideration of the peri and post-operative morbidity and mortality and the projected long-term survival is fundamental [12].

Many candidates are considered for transplant because of impaired vascular access. For liver containing grafts vascular access above and below the diaphragm is required. For non-liver containing grafts two central veins are adequate. Limitation of access to a single central vein considerably increases the peri and post-operative risk, but does not necessarily exclude the patient from consideration.

The functional status of the patient is of great importance as many are deconditioned. A program of prehabilitation is desirable to improve post-transplant morbidity.

Psychological Assessment

The pre-operative psychiatric and psychological assessment of patients deserves special mention. A number of patients have died as a consequence of the development or deterioration of mental health disorders. The engagement of patients with the appropriate mental health support in the preoperative period is of critical importance. Not only for post-operative management but to be as certain as possible that patients have the mental capacity to provide fully informed consent. Institutionalised behaviour including chronic opiate use and poor social support impact on outcomes and in extreme cases may preclude listing. A supervised pre-transplant opiate reduction plan will have a positive effect on post-operative pain management and graft function.

Nutritional Assessment

Weight loss (and loss of lean body mass) is frequently seen in the first 3–6 months post-operatively. In our series 90% of patients lost weight, which was ≥20% of their pre-transplant weight in one third [13]. In paediatric recipients, height and weight parameters improve over the first year post transplant [14, 15]. Therefore, attention should be given to the optimization of both the lean body mass and energy stores of the patients with appropriate involvement of the nutrition team. The presence of sarcopenia can be judged by CT scans of the abdomen, from measurements of psoas muscle mass, or total abdominal muscle mass. Bedside anthropometric measurements (including mid-arm muscle circumference, triceps skinfold thickness and handgrip strength) are useful as they can be performed serially to monitor progress.

Table 2 Example assessment checklist

System being assessed	Minimum measurement tools	Additional testing/intervention needed in some	Cut off criteria[a]
Cardiac	12 lead ECG, echocardiogram, stress testing (dobutamine stress echo or MPS scan)	Angiography	– Inducible ischaemia not correctable by intervention – Moderate to severe impairment of LV systolic function
Respiratory	Pulmonary function tests including transfer factor	CPEX	– FEV1 < 1.5 L – TLCO <50% predicted – AT <8 mL/kg/min
Renal	eGFR If eGFR <60 mL/min for Nuclear medicine EDTA GFR	MAG3 renogram (split function)	GFR <45 requires consideration for concurrent renal graft
Psychiatric	At least one assessment by a psychiatry consultant experienced in transplant assessment	Intervention with CBT or other therapy and reassessment	Psychiatric opinion regarding suitability for Tx
Drug and alcohol	Active use of recreational drugs		– Equivalent total morphine dose per day <100 mg – Any alcohol intake (for liver-containing grafts) in past 6 months
Dietetic	Basic anthropometrics (BMI, MAMC, TSF, HGS)		BMI <18
Anaesthetic	At least one assessment by an anaesthetic consultant experienced in transplant assessment	Prehabilitation plan (strength, aerobic and respiratory capacity)	

MPS myocardial perfusion scan, *CPEX* cardio-pulmonary exercise testing, *FEV1* forced expiratory volume in 1 s, *TLCO* total lung transfer factor measured by carbon monoxide exchange, *AT* anaerobic threshold, *CBT* cognitive behavioural therapy, *BMI* body mass index, *MAMC* mid-arm muscle circumference, *TSF* triceps skinfold thickness, *HGS* handgrip strength
[a]Not prohibitive, requires MDT discussion of overall risk

Treatment for reduced bone density should be promptly initiated and managed by a metabolic bone disease specialist.

Summary of the Assessment Process

Patients who are selected as candidates for transplantation will in most cases have already undergone a rigorous multidisciplinary review as part of the selection process. The subsequent preparation for transplantation should be thorough and provide a convenient summary of all comorbidity which should be quantified and monitored. This involves a comprehensive and sequential evaluation of each body system and should include a careful psychiatric and psychological review. Any abnormality should be fully investigated and corrected if possible and irreversible comorbidity or other risk factors these should be detailed in a special preoperative summary to allow them to be appropriately factored into the management of the patients during and after transplantation. Even minor disorders that would under normal circumstances pose little risk to patients or challenge for clinicians can develop into serious life-threatening complications during the operative and post-operative period. An example checklist for listing is shown in Table 2.

The death of patients can often be traced back, with root cause analysis, to a relatively minor disorder which led to a sequence of ever increasing morbidity. The under appreciation of this phenomenon is probably the commonest mistake made by clinicians when assessing patients for intestinal and in particular multi-visceral transplantation.

Types of Intestinal Containing Grafts

There are a variety of different intestinal containing grafts and the most commonly performed examples are described below and in further detail in Table 3 and Figs. 1, 2, 3 and 4: Any transplant that contains a transplant intestine meets the definition of ‘intestinal transplant’.

Table 3 Types of intestine-containing grafts

Type of graft	Organs transplanted	Proximal enteric anastomosis	Advantages/disadvantages	Impact of graft failure
Isolated small bowel transplant	Small bowel (+/− pancreatico-duodenal complex, colon)	Jejuno-jejunal Duodeno-jejunal	Limited exenteration Splenic preservation	Return to PN, potential retransplant at a later date
Modified multivisceral	Stomach, pancreatico-duodenal complex, small bowel (+/−colon)	Gastro-gastric Oesophago-gastric	More extensive evisceration including splenectomy Stomach inclusion with increased risk of aspiration, gastroparesis and anastomotic leak	Urgent re-transplant
Liver small bowel	Liver, pancreatico-duodenal complex, small bowel (+/−colon)	Jejuno-jejunal Duodeno-jejunal	Splenic and gastric preservation	Urgent re-transplant
Multivisceral	Liver, Stomach, pancreatico-duodenal complex, small bowel (+/− colon)	Gastro-gastric Oesophago-gastric	Extensive evisceration with loss of stomach and spleen	Urgent re-transplant

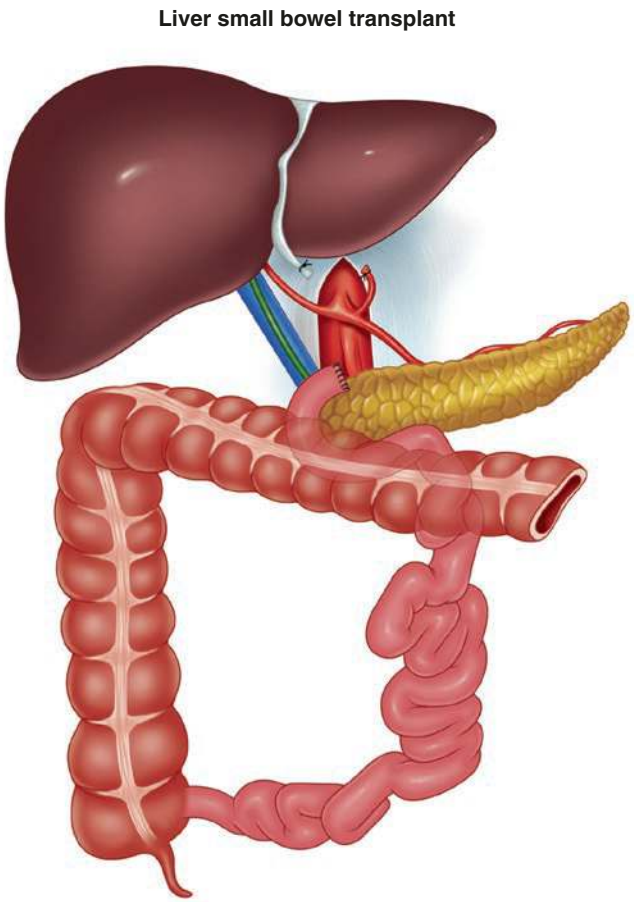

Fig. 1 Combined liver/intestinal transplant (native stomach and pancreatico-duodeno-splenic complex left in situ)

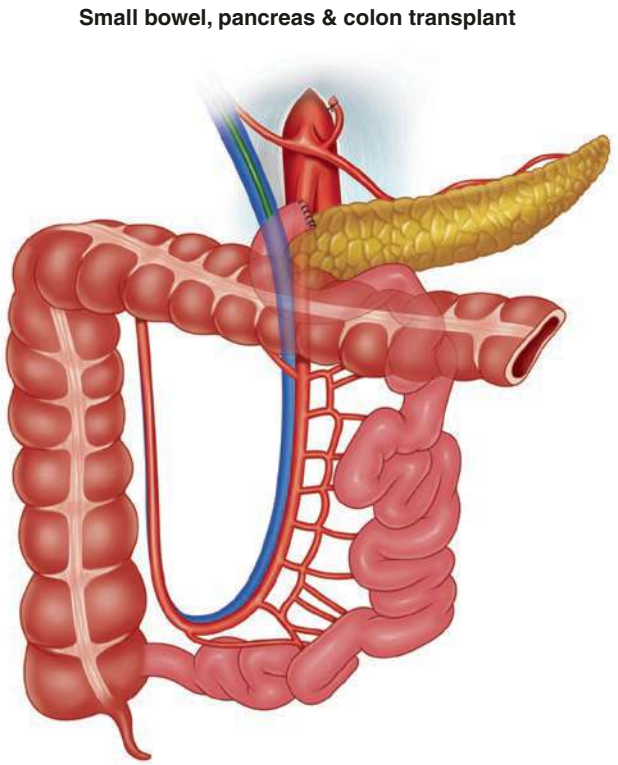

Fig. 2 'Isolated' intestinal transplant (which usually includes small bowel, pancreas and colon)

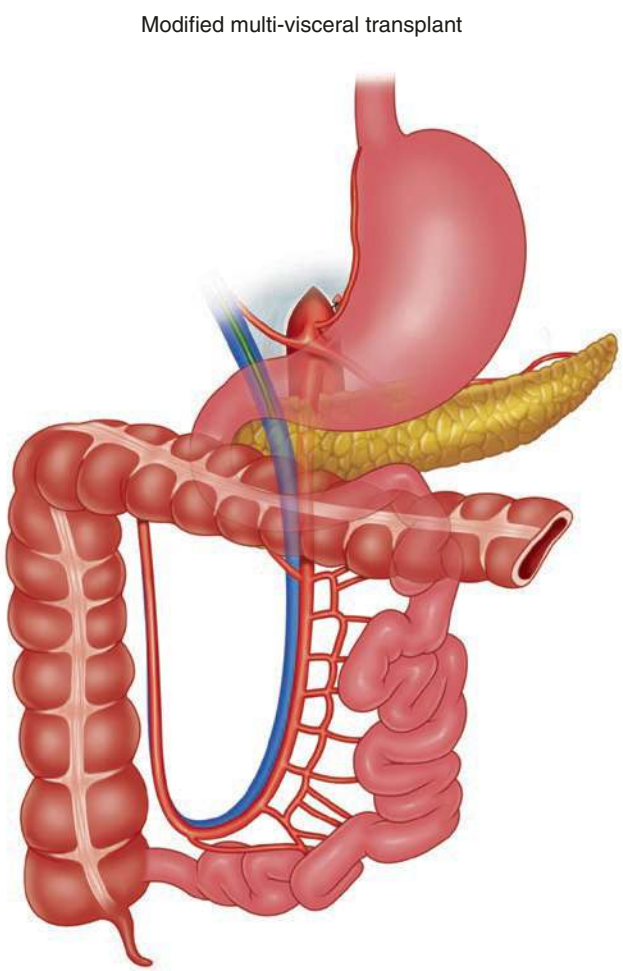

Fig. 3 Modified multivisceral transplant (graft includes stomach, pancreaticoduodenal complex, small bowel and colon with native liver left in situ)

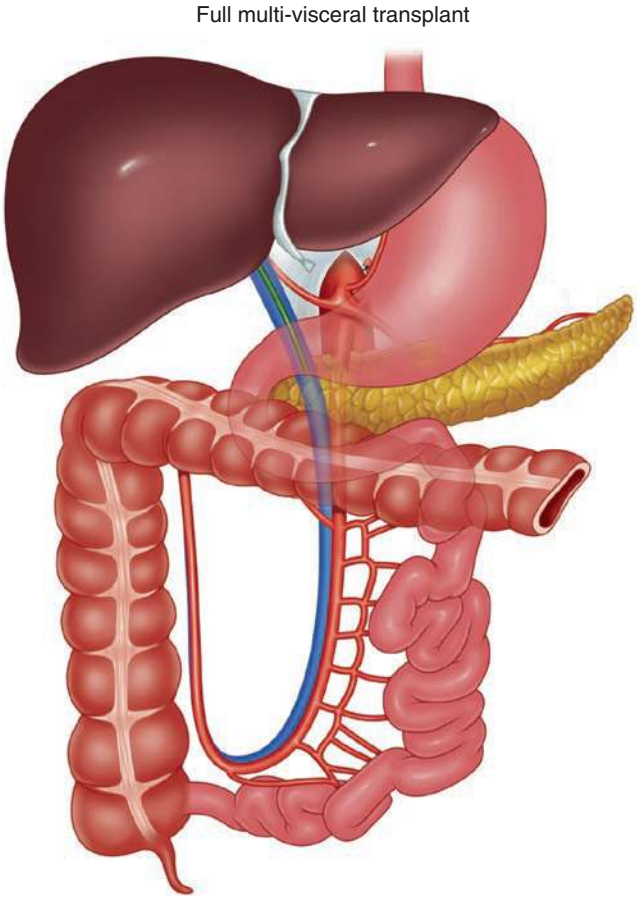

Fig. 4 'Full' multivisceral transplant: replacement of stomach, pancreatico-duodenal complex, small bowel, colon and liver

The Transplant Procedure

The intestine is particularly sensitive to ischaemia reperfusion injury. In order to minimise the cold ischaemia time (<6 hours) the donor and recipient procedures are performed simultaneously.

Donor Selection

Most donors are DBD (donation after brain death) and are selected on the basis of blood group, HLA type, size, viral status and logistics. A small number of living donor intestinal transplants have been performed.

Blood group compatibility is necessary. If the donor and recipient blood groups are compatible but not identical there may be a period of passenger lymphocyte syndrome with haemolysis for up to 6 months [16]. This is addressed by using donor blood group blood when transfusion is necessary post-op. HLA matching is not routinely undertaken, as there is not yet good published evidence to suggest it affects graft survival, but avoidance of donors to which recipients have pre-existing high level anti HLA antibodies is desirable. In some centres donors and recipients are matched according to CMV and EBV serological status to attempt to reduce CMV disease [17] and possibly EBV driven PTLD.

Organ Retrieval (Procurement) Procedure

After an appropriate organ donor has been identified and prior to arrival of the retrieval team the donor bowel is pretreated with anti-fungal and anti-bacterial agents to reduce the number of resident luminal micro-organisms It is not current practice to pre-treat the donor with lymphocyte depleting agents although this has been undertaken by some centres in the past, with no obvious benefit observed.

After the donor procedure has started the organs are assessed for anatomical anomalies and other pathology that would make the organs unsuitable. Once the organs are

deemed appropriate this is communicated to the implanting team and the recipient is anaesthetised and the explant procedure is started.

The specific extent of dissection is dictated by the nature of the graft required [18]. In the situation where a full multivisceral graft is required then the liver, stomach, pancreas, small bowel and colon are prepared in such a way that the donor organs can be removed *en bloc* with a common vascular pedicle. In circumstances where the liver is not required as part of the graft then the block is dissected in such a way that it can be split readily and quickly after cross clamp, thus minimising the cold ischaemia time involved [19]. When no further dissection is necessary this is communicated to the implanting team. If the implanting team are not sufficiently advanced the donor team will delay cross clamp until the recipient operation has progressed further. For this reason the duration of the donor procedure is very unpredictable. It is critical that the other transplanting teams (thoracic and abdominal) need to be aware that there may be delays.

At cross clamp the organs are flushed with preservation solution at 4 °C and rapidly removed and packed in more of this solution. Removal of the thoracic and abdominal organs is undertaken simultaneously. As a result of the extensive dissection prior to cross clamp in these retrievals the intestinal block is often the first to be explanted.

At this point the organs are transported to the recipient centre.

The Recipient Procedure

The recipient procedure involves the removal of the diseased native organs, preparation for implantation of the graft, graft implantation and reperfusion and abdominal closure.

Once the recipient is anaesthetised, central venous access is established to facilitate anaesthesia, for veno-venous bypass (to allow inferior vena cava (IVC) cross clamping or reduce haemorrhage) and allow intra-operative haemofiltration (for metabolic stability). For patients with severe portal hypertension requiring a liver containing graft, very substantial blood loss is expected. Embolisation of the recipient superior mesenteric artery (SMA) and or the coeliac artery (CA) prior to starting the explant procedure results in reduced blood loss and improved haemodynamic stability [20, 21].

The technical challenges of the explant procedure can be very variable. In rare circumstances there is little dissection required to prepare for implantation, most of the native organs having been previously explanted. In most circumstances the recipient will have had multiple previous laparotomies resulting in unclear intra-abdominal anatomy, dense adhesions, enterocutaneous fistulae, intra-abdominal collections and various stomata. Explanting desmoid tumours and other slow growing neoplasms present a particular set of issues including involvement of the abdominal wall and other organs (including the liver and ureters). The involvement of neighbouring organs may require complex strategies (e.g. ureteric reconstruction or auto-transplantation of the native kidney).

Once the necessary native organs have been explanted the vascular inflow and outflow for the graft are prepared. Usually this involves dissection of the infra renal aorta in preparation either for suturing of the Carrel patch or aortic conduit. The venous outflow is either via the IVC or native portal vein or Superior mesenteric vein (SMV).

Isolated Intestinal Transplant (IT)

An isolated small intestinal transplant (not including pancreas or colon) allows the donor pancreas to be utilised as part of a simultaneous pancreas and kidney transplant or pancreas alone transplant. In this situation the arterial inflow is via the SMA and venous drainage is via the superior mesenteric vein (SMV). This may necessitate vascular reconstruction (often using donor iliac vessels) with a potential increased risk of vascular complications. For this reason many units favour inclusion of the pancreas in intestinal grafts.

This facilitates colon inclusion and often negates the need for vascular reconstruction.

Under these circumstances, arterial inflow is via the CA and SMA on a single Carrel patch. This is either sutured directly to the abdominal aorta of the recipient or via an aortic conduit (donor thoracic aorta). Venous outflow is via the portal vein (PV), anastomosed to the recipient PV or SMV (portal drainage) or recipient IVC (systemic drainage). Pancreas inclusion preserves the middle colic vessels and may reduce vascular complications. The proximal enteric anastomosis is to the most distal part of the native foregut. Many units routinely include the colon as part of the graft in order to improve fluid balance and potentially minimise deterioration in renal function [22, 23].

Modified Multivisceral Transplant

A modified multivisceral (MMV) graft requires a larger explant procedure and includes resection of residual small bowel, pancreas, spleen, duodenum and part or all of the stomach. It is essential that the hepatic artery is preserved and if possible, the left gastric artery (allowing a pouch of native stomach to remain). This allows a gastric-to-gastric

proximal anastomosis (a lower risk anastomosis than oesophago-gastric).

As part of the implant procedure a pyloroplasty is necessary to allow gastric emptying. Some transplant centres perform simultaneous gastric fundoplication to reduce the risks of reflux and aspiration pneumonia. Arterial inflow and venous outflow is as for IT.

Liver Small Bowel Transplant and Full Multivisceral Transplant

Liver containing grafts include either a full multi-visceral transplant (including a stomach) (MVT) or a liver small bowel transplant (LSB).

If there are concerns that either the arterial supply/venous drainage of the native stomach (before or after explant) is inadequate or there is compromised gastric motility then a full MVT will be required.

Preservation of the native stomach reduces the magnitude of the explant procedure and also facilitates splenic preservation This is associated with a reduction in sepsis and (anecdotally) the risk of GVHD. For both LSB and MVT the arterial inflow is via the CA and SMA on a single Carrel patch and venous outflow via the hepatic veins. Where the native stomach and native pancreatico-duodenal complex are preserved, the venous outflow from these organs is achieved by a portocaval shunt (either spontaneous, e.g. lienorenal shunt, or constructed at the time of transplant).

At reperfusion extreme fluxes in potassium (from the preservation solution) may cause cardiac arrhythmias and even cardiac arrest. This is usually reversible with CPR.

After completion of the implant and immediately prior to closure most units form a stoma to facilitate graft monitoring. The type of stoma used is variable (and some units choose to avoid a stoma [24]). Our preferred option is a Bishop Koop stoma. This allows access to the graft ileum and colon for surveillance biopsies and keeps the transplant colon in continuity to improve fluid balance. It allows stoma reversal avoiding a full laparotomy.

Abdominal Closure

Abdominal closure must be achieved without causing abdominal compartment syndrome. This is particularly important immediately after transplant because of graft oedema from ischaemia reperfusion injury. If the abdominal domain of the recipient is adequate primary closure is undertaken, if not other techniques may be required:

Use of Prosthetic Materials

Biological and non-biological meshes have been used. They are readily available but have a number of disadvantages.

Abdominal Wall Transplantation (Composite Tissue Allograft)

These are vascularised composite allografts with a number of important considerations in their use [25, 26].

- At implantation the graft is vascularised using microsurgical techniques either directly to the recipient inferior epigastric vessels or indirectly to the arm vessels in a temporary manner
- The teams using this technique have suggested that the donor skin can act as a marker for rejection (a rash) which may help with patient management.

Rectus Abdominus Fascial Grafts

Some centres have used rectus abdominus fascia as a non-vascularised graft [27, 28] (Fig. 1).

Tissue Expansion

Pre-operative insertion of tissue expanders has been described. There are a number of issues that have limited their use.

The Postoperative Course

Post-operative care is frequented by medical and surgical challenges. Some of these are common to all solid organ transplant recipients, however many of these occur with greater frequency in recipients of intestinal transplants. In addition, these patients can present/demonstrate almost unique pathologies that challenge diagnosis and management. The resolution of these conditions, which occur in most areas of specialist medicine, usually require resort to basic principles of the underpinning medical sciences [29].

Induction immunosuppression is given at the time of reperfusion of the graft and may consists of a lymphocyte-depleting antibody and methylprednisolone. Our practice is to give Alemtuzumab (Campath-1H), but some centres use anti-thymocyte globulin, a polyclonal preparation of lytic anti-lymphocyte antibodies or IL-2 receptor blocking antibodies, such as Basiliximab. Maintenance immunosuppression is initially with tacrolimus and a reducing course of steroids, with the introduction of an antimetabolite (usually Mycophenolate mofetil) within the first 2–3 months, depending on individual circumstances.

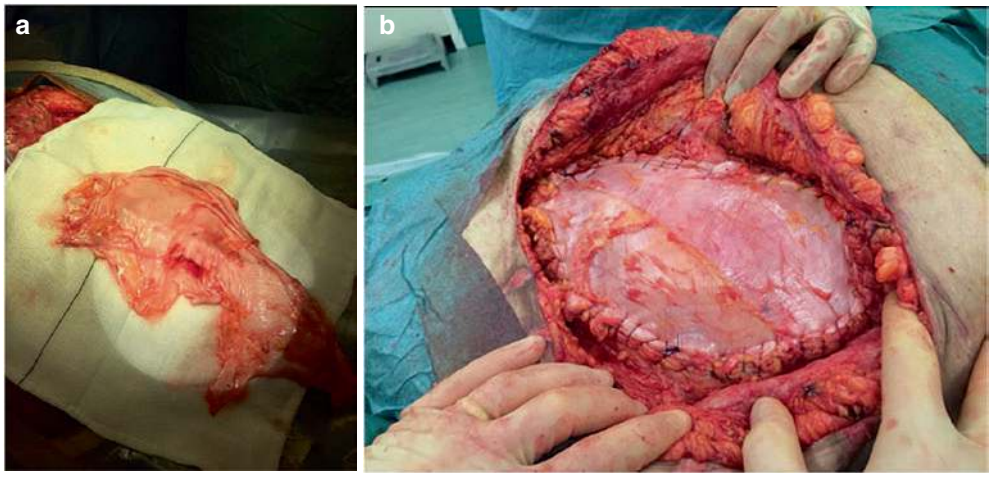

Fig. 5 Donor abdominal wall fascia—pre- (**a**) and post-implantation (**b**)

Mucosal integrity can be compromised in the early phase by ischaemia-reperfusion injury, so broad spectrum antibiotic cover is given for at least the first week, then as necessary for infectious complications. Antifungal and antiviral prophylaxis are given for variable durations post-transplant, depending on the transplanting centre and patient's overall risk.

Most intestinal transplant units have their own protocols for monitoring and management. Key aspects of this include graft surveillance for rejection, monitoring and treatment of infections, nutritional rehabilitation, psychological care and a supported discharge. A wide range of team members are involved, but the transplant specialist nurses are vital for patient support. It is a mistake to try and operate this type of facility without adequate staffing and it is often difficult for those not directly involved to appreciate the number of staff required to provide adequate care for such a brittle and complex group of patients.

The median length of stay in Cambridge is 57 days, the US transplant centres report an overall median length of stay of 49 days (adults and paediatrics). Initially patients are on ICU or high-dependency units and may need to return to a level 2 or 1 unit if complications develop. It is important that patients are advised of this possibility; to avoid feeling this is a 'backwards step'.

All patients will be on parenteral nutrition immediately post-transplant. Nutritional requirements at this stage are very high due to an intense catabolic state and the PN script will reflect this. A feeding jejunostomy tube is often placed at the time of surgery, and this can be used for feeding once the stoma starts working (usually within the first week). Over 90% of patients are weaned off PN by the time of discharge and over 95% are free of this long term.

The international intestinal transplant registry (ITR) last presented their data in 2019. In this report, just over 4100 patients had received an intestine-containing graft worldwide. Patient survival curves for adult and paediatric transplant recipients are depicted in Fig. 5. UK-specific results are published annually at https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/

Post Transplant Complications: Surgical

The usual range of surgical complications occur after transplantation but in addition there are some that require particular consideration.

Vascular Complications

Some patients have a history of arterial or venous thromboses [30] and will have an ongoing need for anticoagulation post-op. Despite this, some still develop thrombotic complications, in the most severe circumstances this can results in graft loss or the need for retransplant.

Management of thrombosis may be surgical (thrombectomy) or conservative.

The balance between bleeding and thrombosis in these patients is challenging. From a surgical perspective, bleeding is preferable to graft thrombosis and loss but it can have catastrophic consequences e.g. intracerebral haemorrhage. In intestinal transplantation the vascular anastomoses are wide with limited risk of stenosis. Vessel 'kinking' and extrinsic compression occur more frequently. In our series this particularly affects the donor SMA presenting with ischaemic enteritis [31].

The development of a mycotic aneurysm is a very unusual but potentially catastrophic vascular complication [32] (Fig. 6). The patient usually exhibits a fever with no obvious

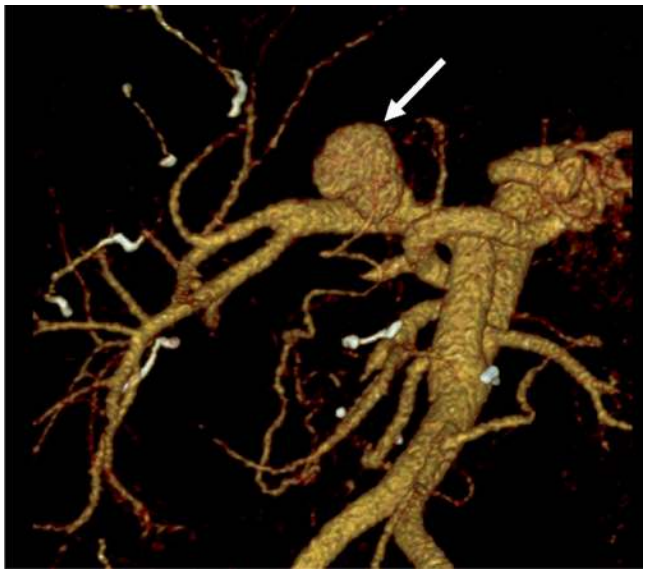

Fig. 6 Mycotic aneurysm of donor aortic conduit (arrow)

cause and a contrast enhanced CT demonstrates an aneurysm. Management is difficult and involves appropriate antimicrobial agents, interventional radiology [33] and may require surgery to excise the infected tissue and replacement with a vascular homograft.

Enteric Complications

Enteric Leaks

Enteric leaks can be either anastomotic or non-anastomotic. Diagnosis can be difficult in immunosuppressed patients. Prompt diagnosis relies upon a high index of suspicion and appropriate use of imaging (oral and iv contrast enhanced CT).

The oesophago-gastric anastomosis is at particular risk of leak and may be associated with Candidal infection. Management has traditionally been surgical (revision of the anastomosis) but successful use of endoscopic 'vac sponge' has been recently described [34].

The aetiology of spontaneous perforations is less clear. They happen relatively early after the transplant and may be associated with unrecognised ischaemic reperfusion injury.

Enterocutaneous Fistulae

These may be either iatrogenic (associated with surgical or radiological interventions) or 'spontaneous'. Iatrogenic fistulae may follow enterotomies at laparotomy. Surgical intervention early after transplantation is extremely challenging. The transplanted bowel is oedematous and friable and densely adherent to itself and the surrounding tissues.

Radiological placement of drains to treat post-operative collections is helpful but may result in perforation. Particular care is needed to avoid the pleural cavity as this may result in empyema and the potentiation of an enteric fistula.

'Spontaneous' entereocutaneous fistulae may also occur. These have been associated with intraperitoneal sepsis (often fungal) and graft ischaemia.

Volvulus

The transplanted small bowel has relatively few peritoneal attachments to the retroperitoneum and this may result in internal herniation and the potential for volvulus and subsequent infarction.

Stoma Complications

Endoscopic graft surveillance early after transplant *may* contribute to the development of stomal prolapse. Parastomal hernias are common. Immunosuppression and poor nutrition result in poor wound healing. The transplanted bowel is oedematous at the time of stoma formation and this may require the use of a larger fascial defect. Stoma reversal is usually undertaken at 6 months to 1 year but may not be possible if there is insufficient distal colon or the patient has a history of anorectal dysfunction [35].

Chyle Leaks

Chyle leaks may present following commencement of enteral feeding. Diagnosis is made by inspection of drain contents and confirmed by measurement of triglyceride concentration. Resolution is achieved with conversion to a medium chain triglyceride (MCT) diet as MCTs are absorbed directly into the portal bloodstream, rather than via the (disrupted) lymphatics [36], and/or bowel rest with parenteral nutrition.

Post Transplant Complications: Medical

Whilst most of the medical complications occurring in the post-transplant period are not unique to these types of grafts, many occur at higher rates than in other solid organ transplants. Of particular concern due to the morbidity and mortality incurred, and therefore discussed in detail here, are acute cellular rejection, graft versus host disease, post-transplant lymphoproliferative disorder (PTLD) and infections. Other significant complications including haematological, neurological and psychiatric, are outlined in brief. The typical medication list of a post-transplant patient is seen in Table 4.

Overall graft and patient survival has been improving over time. Data is collected from all centres for an international registry and the latest output from this registry is shown in Fig. 7.

Table 4 List of typical medication a post-transplant patient will be taking

Medication	Reason for taking	Duration
Tacrolimus[a]	Immunosuppression	Lifelong
Mycophenolate mofetil	Immunosuppression	Lifelong
Prednisolone	Immunosuppression	Reducing course, some may need to continue low dose lifelong
PPI	Gastric protection	6 months
Magnesium supplement	Manage hypomagnesaemia	Often only for 6–12 months
Fluconazole	Fungal prophylaxis	1 year
Valganciclovir/Aciclovir[b]	Viral prophyalxis	12 months/3 months
Penicillin	Splenectomy prophylaxis for some patients	Lifelong
Co-trimoxazole[c]	PCP prophyalxis	Lifelong
Anticoagulation	If pre or post-transplant thrombosis	Lifelong
Loperamide, codeine	Reduce stomal output	According to symptoms

PPI proton pump inhibitor, *PCP Pneumocystis jirovecii* pneumonia
[a]May be converted to ciclosporin or sirolimus
[b]Aciclovir if both donor and recipient CMV seronegative, otherwise valganciclovir given
[c]Alternatives are atovaquone, dapsone or pentamidine

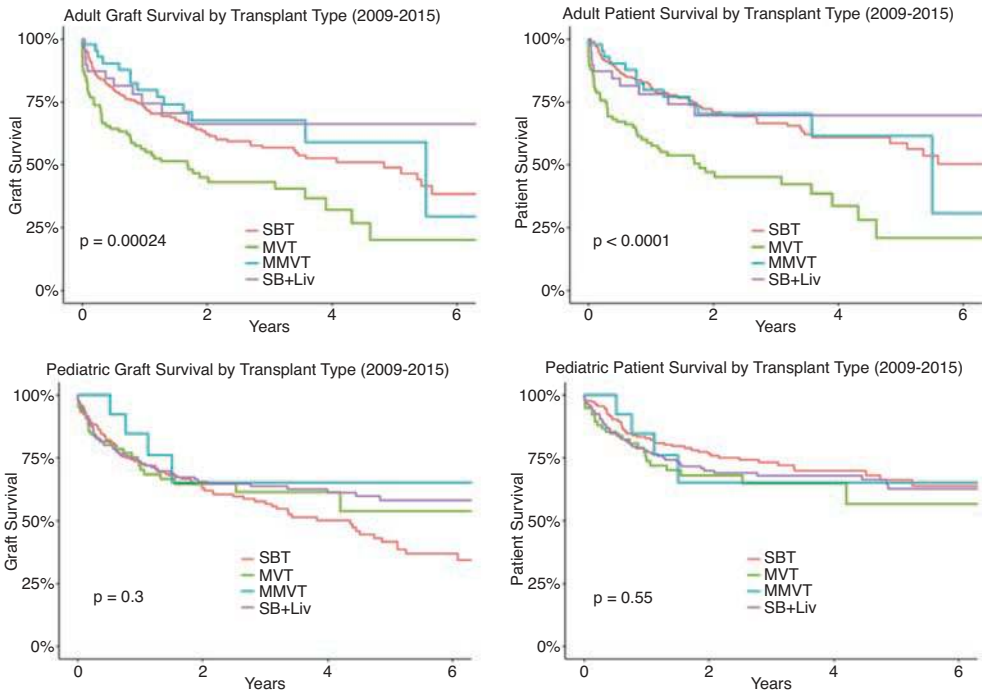

Fig. 7 Adult and paediatric patient and graft survival. Reproduced from the International intestinal transplant registry with permission

Acute Cellular Rejection

This is the most common type of rejection in intestinal transplant recipients and affects 30–40% in the first year [37]. In brief, the mechanisms involve donor antigen presentation to recipient CD4+ T cells, with co-stimulatory signals, resulting in activation of the CD4+ T cells. This results in IL-2 secretion which activates CD8+ (cytotoxic) T cells. These infiltrate the graft and cause tissue damage.

The intestine is more likely to reject, due to the increased numbers of antigen-presenting cells in the gut (intestinal epithelial cells express MHC Class II molecules, in addition to gut-resident 'professional' antigen-presenting cells such as dendritic cells and macrophages in mucosal layer). The classical presentation is with abdominal pain, fever and increased stomal output. However, it can rapidly progress to bacteraemia and septic shock as the damage to the mucosal layer disrupts the usual barrier function. Bacterial translocation can readily occur from the gut lumen into the bloodstream so concurrent broad-spectrum antimicrobials are usually given in addition to augmented immunosuppression.

Diagnosis is by endoscopic evaluation of the graft and histopathology. The early endoscopic findings are mucosal oedema (leading to loss of normal vascular pattern), progressing to ulceration and areas of mucosal/villous loss (Fig. 8). The histological criteria for diagnosis were defined

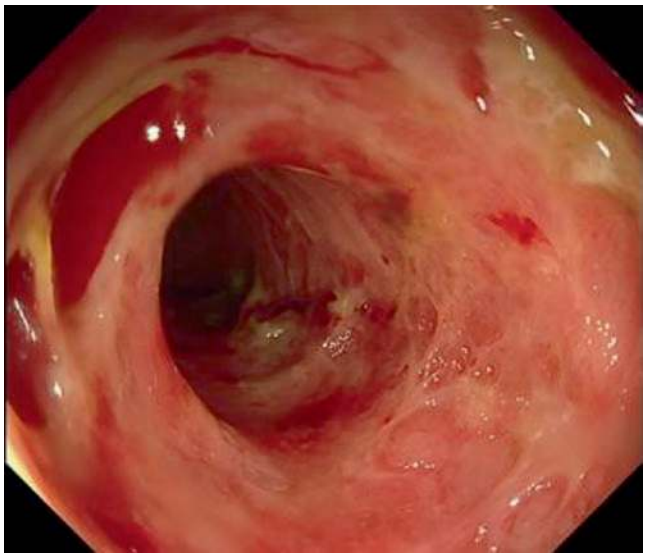

Fig. 8 Endoscopic appearance of severe rejection of the ileum, with mucosal loss, contact bleeding and reduced motility

at the VIII International Small Bowel Transplant Symposium in 2003 [38]. Histologically the early findings are of an increase in the number of apoptotic bodies in the crypts (expressed as the number of bodies per 10 adjacent crypts). With increasing severity, lamina propria inflammation is seen, then architectural distortion and mucosal ulceration. Infections can mimic the symptoms and early histological findings of ACR so it is important to screen all patients for bacterial pathogens and viruses (particularly adenovirus, rotavirus, CMV).

First line treatment of ACR is with pulsed methylprednisolone (500 mg–1 g per day for 3–5 days). Following this it can be difficult to determine the patient's trajectory. Endoscopic and histological features can take 2–3 weeks to improve. It is critical that escalation to second line treatment is timed appropriately. The authors' view is that if a patient is clinically well and a repeat endoscopy 1 week after the index scope does not appear to be worsening, then first line care should be continued. If the patient is deteriorating or the endoscopic appearances are clearly worsening, escalation to a second line agent is needed (Alemtuzumab, Anti-thymocyte globulin, Basiliximab). Graft removal may be necessary in refractory cases, followed by immediate or delayed relisting depending on the patient's clinical state and graft type [39].

Graft Versus Host Disease

Graft versus host disease (GVHD) after solid organ transplant is mediated by immunocompetent donor T lymphocytes moving out of the graft and mounting an immune response against native tissue. It can be considered the opposite process to graft rejection, but again occurs more frequently in patients receiving intestine-containing grafts, affecting around 10% of patients [40–42]. This is due to the large burden of reactive lymphocytes in the mucosa-associated lymphoid tissue and mesenteric lymph nodes.

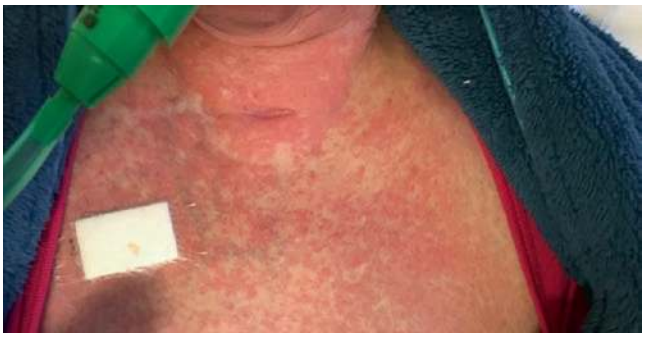

Fig. 9 Typical skin rash of graft versus host disease (plaster depicts biopsy site)

Any native organ is potentially a target for GVHD, though the most common site is the skin. A maculopapular rash usually starts on the trunk (Fig. 9). Biopsy may show interface dermatitis. If there is a sex-mismatch between the donor and recipient, then fluorescence in-situ hybridisation (FISH) can demonstrate the presence of donor lymphocytes within the inflammatory infiltrate.

Other target organs can include lung, eyes, native GI tract or bone marrow. Involvement of the bone marrow leads to cytopenias and unfortunately the prognosis with bone marrow involvement is especially poor. An adjunct method for diagnosis and monitoring of GVHD uses the detection of peripheral T cell chimerism, the detection of reactive donor T cells within the circulating blood. This can be quantified as a percentage of total circulating lymphocytes and used to guide response to treatment.

Management approaches to GVHD differ between units. Some advocate an increase in immunosuppression, initially with pulsed methylprednisolone, to suppress the graft response. If this approach is used, the risk is of increased infectious complications. Others propose that reducing the immunosuppression (cessation of tacrolimus and antimetabolite) may allow the host immune system to counteract that of the graft. Using this latter approach mandates very careful graft monitoring for rejection and reintroduction of immunosuppression at the earliest signs of graft dysfunction.

Post-Transplant Lymphoproliferative Disorder (and Other Cancers)

Post-transplant Lymphoproliferative disorders (PTLD) is the most common *de novo* malignancy occurring after transplantation of the intestine, in both adults and children. It occurs

in around 15% [43, 44] usually within the first 12 months post-transplant. The site (s) affected are often the intestinal graft or mesenteric nodes, but can be extra-intestinal. PTLD is associated with EBV infection in the majority of cases and the development of an EBV viraemia should prompt investigation for possible PTLD.

^{13}FDG-PET CT scanning can be very useful in the work-up of possible PTLD, by identifying sites and giving a guide as to the burden of disease. However, definitive diagnosis requires a biopsy of affected tissue. The histology can vary, from polymorphic lymphoid proliferations, to aggressive monomorphic PTLD or Hodgkin's-like tumours.

Management of PTLD is with a cautious reduction in immunosuppression and Rituximab, a chimeric antibody to CD20, a B cell surface marker. There is some evidence that Ganciclovir has activity against EBV *in vitro*, but not *in vivo*. EBV-specific Cytotoxic T cells are available commercially in some areas and have been used for PTLD following haematopoietic stem cell transplant and PTLD after intestinal transplant. For refractory cases, chemotherapy is necessary. In general, the outlook is good, with reported survival after PTLD at 1 year of 91% and 75% at 5 years [44] of those affected.

All solid-organ recipients are counseled about increased risk of other malignancies, particularly non-melanoma skin cancer. 50–75% of Caucasian transplant recipients will be affected by skin cancer within 20 years of transplant. Risk factors include fair skin, UV exposure, older age and cumulative exposure to immunosuppression. Patients are therefore advised to adhere rigidly to guidance recommending high factor sunblock and protective clothing.

Cytomegalovirus

Cytomegalovirus (CMV) is the most common viral infection after intestinal transplant. Rates are highest in recipients who are naïve to CMV themselves but receive organs from seropositive donors [45]. Intestinal transplant centres may use universal prophylaxis or a pre-emptive strategy to manage risk of CMV infection. Some centres will also list CMV seronegative recipients for matched (also CMV negative) donors.

Manifestations of CMV infection include asymptomatic viraemia, CMV syndrome (fever, malaise and cytopenias) or tissue-invasive disease. Diagnosis is by quantitative PCR-based detection of viral DNA and histological examination of suspected end-organs involved.

Universal prophylaxis is usually with ganciclovir (intravenous) or valganciclovir (oral). Treatment of confirmed disease is also with one of these agents, at higher doses. Dose adjustment is required for renal dysfunction. Ganciclovir resistance is an emerging problem and should be suspected if there is a failure of clinical response within the first 2–3 weeks. Alternatives include foscarnet and cidofovir and newer agents include maribavir and letermovir. Adjunctive therapies are used variably, and include CMV immunoglobulin, lefluonamide and adoptive transfer of CMV-specific T cells.

Neurological Complications

Calcineurin inhibitors (CNI's) such as tacrolimus cause tremor and myoclonic jerks. This is usually dose-related and responds to a lowering of the blood level. CNI's can also cause Posterior Reversible Encephalopathy Syndrome (PRES) which presents in a variable way, with symptoms including headache, visual disturbance, confusion and seizures. Underlying mechanisms are not fully understood, but possibly include cerebral auto-regulation failure. Characteristic imaging features are of vasogenic oedema in the occipital and parietal lobes, best seen on T2-weighted FLAIR MRI head sequences. Patients respond to a change in immunosuppression and the prognosis for recovery is good [46].

In patients who have received an isolated intestinal graft, the donor portal vein that accompanies the graft, is usually anastomosed directly onto the inferior vena cava, effectively forming a porto-systemic shunt. If there is moderate liver fibrosis (perhaps the indication for transplant), then a hepatic-like encephalopathy can occur, with asterixis, confusion and raised ammonia. Management is with laxatives and non-absorbable antibiotics such as Rifaximin. Occasionally this can occur in the context of essentially normal liver function if there is a high burden of small bowel bacterial overgrowth due to stasis. It is of value to exclude reversible causes of stasis such as anastomotic strictures [47].

Haematological Complications

Many of these patients have pro-thrombotic tendencies which have led to their needing an intestinal or multivisceral transplant (mesenteric arterial thrombosis leading to short bowel, venous thrombosis associated with central venous catheters for parenteral nutrition, extensive porto-mesenteric thrombosis associated with cirrhosis). The transplant itself involves the addition of new vascular anastomoses, therefore, for most patients anticoagulation is continued, even in the early post-operative period.

Drug-induced leucopenia or myelosuppression is common [48], as many of the necessary drugs have this side effect. In particular, the antimetabolites such as azathioprine and mycophenolate, and antimicrobial agents ganciclovir and co-trimoxazole are common culprits. Minimising the doses, using alternative agents, or supporting counts with

Granulocyte colony stimulating factor (GCSF), are strategies for overcoming this problem depending on the clinical condition of the patient.

Transplant-Associated Thrombotic Microangiopathy (TA-TMA) is a multisystem disorder characterized by a microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and end-organ damage affecting the kidneys and/or brain. There are no absolute diagnostic criteria but supportive findings include red cell fragments, thrombocytopenia and raised lactate dehydrogenase. In the transplant population, the most common causes are calcineurin inhibitors and sirolimus [49]. Management involves a change in immunosuppression and plasma exchange or eculizumab, a complement-blocking antibody, for refractory cases.

Renal Complications

Intestinal transplant recipients are at particular risk of developing chronic renal failure (CRF) and this must be taken into account during the assessment and listing process. In a large US study of almost 70,000 transplant recipients (but only 228 intestinal grafts), the cumulative incidence of developing CRF (defined as an estimated glomerular filtration rate of ≤29 mL/min/1.73m^2 body surface area), was 14.2% at 3 years and 21.3% at 5 years [50]. A more recent analysis of all adult intestinal transplant recipients in the US included 843 patients and showed alarming 1, 5 and 10-year cumulative incidence of CRF (defined as eGFR <29 mL/min, chronic dialysis or need for renal transplant) was 3.2%, 25.1%, and 54.1% respectively [51]. A smaller case series from the UK showed a median decline in GFR of 40% in the first 3 months after transplant [11]. The mortality rate for those developing CRF after transplant was sixfold higher than those who maintained renal function.

It is critical to preserve renal function pre transplant, as this study also showed that each 10 mL/min/1.73 m^2 increase in GFR pre transplant was associated with a reduced risk of CKD by 7.6%. This is especially important in patients with short bowel who may have high stomal fluid losses. In the UK it is recommended that all patients referred for intestinal transplant assessment are also considered for simultaneous renal transplant [52] if their baseline GFR is <45 mL/min/1.73m^2. Although it increases the time and complexity of the transplant procedure, short term outcomes for those who receive combined grafts are similar to those without [53].

Psychological Considerations

There are no studies evaluating mental health in intestinal transplant recipients. Studies on quality of life have reported disparate results [54], which likely reflects the heterogeneity of the patients. The need for ongoing nutrition support, frequency of hospital admissions and need for interventions strongly influence the self-reported quality of life outcomes for patients. The neuropsychiatric side effects of corticosteroids are well known. Patients who have been dependent on opiates pretransplant may need continued support with this and involvement of a multidisciplinary pain team is extremely helpful. Recent data from the team in Oxford showed lower quality of life metrics in patients being assessed for transplantation compared to patients stable on home parenteral nutrition, but improvement following transplant to levels comparable to this stable HPN cohort [55]. The effect was seen using generic and disease specific measurement tools.

In the UK, two recipients of intestinal transplant set up a support group for all adult and paediatric patients. They provide valuable emotional support to patients and families on every step of their journey, supply care packages to patients who are in hospital and are actively involved in raising awareness and fundraising.

Transition of patients transplanted as children who are now entering adolescence must be carried out in a meticulous, planned way. This time is associated with graft loss and significant morbidity if not conducted properly. The key requirements are a staged handover and multiple joint clinics between the paediatric and adult teams.

Conclusions

Significant advances have been made in the medical and surgical management of patients receiving an intestine-containing transplant. Survival rates are now similar to those on home parenteral nutrition (HPN), thus intestinal transplant should be at least *considered* for all patients with permanent intestinal failure, particularly for those HPN patients in higher risk groups. The development of end-stage IFALD severely disadvantages patients and Intestinal Rehabilitation teams need to develop processes that are more proactive in diagnosing and monitoring IFALD so that timely referral for transplantation can be considered. It is also crucial that patients who are losing vascular access are referred early enough to still be candidates for transplantation.

Aside from Intestinal Failure, the indications for transplant are expanding and with this it is crucial that multidisciplinary decision-making continues and there are robust reporting systems to the appropriate body for the evolving indications (for example, the advisory groups of NHS Blood and Transplant in the UK and the international Intestinal Transplant Registry https://www.odt.nhs.uk/odt-structures-and-standards/clinical-leadership/advisory-groups/; https://tts.org/irta-resources/irta-resources-main).

As patient and graft survival rates improve, surgical techniques are advanced and medical prevention and management of complications continue to improve, the time is approaching when intestinal transplant can be offered as an alternative to HPN. All clinicians caring for patients with intestinal failure should be aware of the possibility of intestinal transplant and be able to discuss this with their patients. Local teams will also need to be involved in the acute management of sick transplant recipients (Box 1). Referring and transplant centres must continue to work cooperatively to optimize outcomes for all patients with intestinal failure. Establishing a dedicated forum for clinicians to present and discuss their patients and learn from each other's experiences in a cooperative and supportive environment is of particular value.

Box 1 Actions to be Taken When an Intestinal Transplant Recipient Is Admitted Unwell to a Non-Transplantation Hospital

1. Contact the appropriate transplant centre without delay for advice and possible transfer
2. Undertake a full infection screen, including culture (and microscopy) of blood, urine, sputum, stoma effluent/stool, EBV/CMV–PCR, chest and/or abdominal imaging as guided by symptoms. Common seasonal viral infections can present as a severe illness in these patients and trigger graft rejection
3. If infection is suspected (usual) commence broad-spectrum antimicrobial therapy without delay, with advice from microbiologists. This usually includes: meropenem, vancomycin, AmBisome®, ganciclovir. If there is evidence of pulmonary infection, consider high-dose co-trimoxazole, which is active against *Pneumocystis jirovecii*. Advice should be sought from the transplant centre (24/7 on call service available). Many of these patients are colonised with multi-resistant micro-organisms, details of which can be obtained from their transplant centre
4. Be aware of the possibility of tacrolimus nephrotoxicity and neutropenia associated with valganciclovir and co-trimoxazole (patients may already be taking these)
5. Fluid balance: patients will be prone to salt and water depletion. They should be aware of their normal body weight, assess sodium and water balance with spot urinary sodium and osmolarity respectively (urine dip stick for specific gravity is a helpful initial guide)
6. Graft rejection is difficult to diagnose so patients should be transferred to an appropriate transplantation centre as soon as possible. Suspect rejection if there is a change in stoma output, abdominal pain, fever and/or vomiting
7. These patients are likely to develop unexpected complications which often present in an unusual manner and transfer back to the transplant centre is usually the best option

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Glossary[1]

Allograft Transplant between two genetically different members of the same species.

Allogeneic Of different genetic make up and therefore capable of inducing rejection.

Antigen A protein molecule that is capable of inducing an immune reaction. In transplantation antigens on the surface of graft cells are the trigger to the immune system of the recipient-inducing rejection.

Carrel patch Full thickness cuff of aorta incorporating the orifices of the coeliac and superior mesenteric arteries to facilitate the arterial anastomosis.

Cell surface markers Antigenic determinants on the surface of cells. In some circumstances these act as binding sites and linkage with a matching determinant is important to allow an immune reaction to proceed. Cell surface antigens have been defined by a number of international workshops that have generated the Cluster of Differentiation (CD) nomenclature.

CD3 The CD3 antigen is composed of five invariable chains and is closely associated with the T-cell antigen receptor. It is expressed on 70–80% of normal peripheral blood lymphocytes and plays a significant role in signal transduction during antigen recognition.

CD4 The CD4 antigen is transmembrane glycoprotein expressed on T helper/inducer cell populations. It is expressed on approximately 45% of peripheral blood lymphocytes and it is involved in the co-recognition of MHC class II antigens in association with the T-cell receptor.

CD8 The CD8 antigen is a two-chain complex expressed on T cytotoxic/suppressor cell populations. It is expressed on 13–48% of peripheral blood lymphocytes and it is involved in the co-recognition of MHC class I antigens in association with the T-cell receptor.

CD25 The CD25 antigen is the low affinity inter-leukin-2 receptor. It associates with the common (CD132) and high affinity (CD122) chains to form the high affinity IL-2 receptor complex. CD25 is expressed on activated T and B lymphocytes and activated macrophages and its expression on lymphocytes is upregulated on activation. Interleukin-2 receptor antagonists are used as induction immunosuppression in certain patients.

CD28 The CD28 antigen is expressed on most mature T-cells and antibody-producing B-cells (plasma cells). It is involved in signal transduction and cell activation events.

[1]This glossary provides definitions of immunological and transplant-related terms, which may be unfamiliar to some readers.

CD44 The CD44 antigen is expressed on leucocytes, erythrocytes and weakly on platelets. The molecule has a functional role in cell migration, leucocyte homing and adhesion during lymphocyte activation.

CD52 The CD52 antigen is present on mature T and B lymphocytes and is the target for Alemtuzumab induction immunosuppression.

Chimerism The presence of donor cells in recipient tissues or bloodstream.

Graft-versus-host disease A reaction in which lymphoid cells in a graft are capable of migrating to recipient tissues and stimulating an inflammatory immune reaction. This is an important feature in bone marrow transplantation but can also occur in intestinal transplantation because the gut contains large numbers of lymphoid cells capable of migrating.

Haplotype A set of genetic determinants located on a single chromosome.

Heterotopic A graft placed in an abnormal anatomical position.

HLA Cell surface proteins encoded by the highly polymorphic major histocompatibility gene in humans. The HLA/MHC proteins are highly involved in antigen presention to T cells.

Natural killer cells Cells capable of reacting against foreign proteins without undergoing prior sensitization. They act as immune scavengers and are important in both cancer (in eliminating abnormal cells) and in transplantation where they may be able to initiate rejection.

Orthotopic A graft placed in its normal anatomical position. In intestinal transplantation the proximal end of the small bowel would therefore be connected to the duodenum and the distal end to the ilio-caecal junction.

Tolerance The specific absence of a destructive immune response to a transplanted tissue in the absence of immunosuppression.

References

1. Grant D, Wall W, Mimeault R, et al. Successful small-bowel/liver transplantation. Lancet. 1990;335(8683):181–4. https://doi.org/10.1016/0140-6736(90)90275-a.
2. Ruemmele FM, Sauvat F, Colomb V, et al. Seventeen years after successful small bowel transplantation: long term graft acceptance without immune tolerance. Gut. 2006;55(6):903–4. https://doi.org/10.1136/gut.2006.093989.
3. Lear PA, Cunningham AJ, Crane PW, Wood RF. Lymphocyte migration patterns in small bowel transplants. Transplant Proc. 1989;21(1 Pt 3):2881–2.
4. Clark CL, Price BA, Crane PW, Lear PA, Wood RF. Persistence of allogeneic cells in graft and host tissues after small bowel transplantation. Br J Surg. 1992;79(5):424–6. https://doi.org/10.1002/bjs.1800790517.
5. Webster GA, Wood RF, Pockley AG. Identification of migratory graft and host cell populations after allogeneic rat small bowel transplantation. Immunol Invest. 1996;25(5–6):435–46. https://doi.org/10.3109/08820139609055733.
6. Clark CL, Price BA, Malcolm P, Lear PA, Wood RF. Graft versus host disease in small bowel transplantation. Br J Surg. 1991;78(9):1077–9. https://doi.org/10.1002/bjs.1800780915.
7. Starzl TE, Demetris AJ, Murase N, Thomson AW, Trucco M, Ricordi C. Donor cell chimerism permitted by immunosuppressive drugs: a new view of organ transplantation. Immunol Today. 1993;14(6):326–32. https://doi.org/10.1016/0167-5699(93)90054-o.
8. Kwon YK, Etesami K, Sharp AL, Matsumoto CS, Fishbein TM, Girlanda R. Hospital readmissions after intestinal and multivisceral transplantation. Transplant Proc. 2016;48(6):2186–91. https://doi.org/10.1016/j.transproceed.2016.03.036.
9. Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. 2008;359(3):242–51. https://doi.org/10.1056/NEJMoa0707894.
10. Cazals-Hatem D, Billiauws L, Rautou P-E, et al. Ultra-short bowel is an independent risk factor for liver fibrosis in adults with home parenteral nutrition. Liver Int. 2018;38(1):174–82. https://doi.org/10.1111/liv.13545.
11. Rutter CS, Russell NK, Sharkey LM, Amin I, Butler AJ. Decline in renal function following intestinal transplant: is the die cast at 3 months? Clin Transpl. 2021;35(5):e14249. https://doi.org/10.1111/ctr.14249.
12. Zerillo J, Kim S, Hill B, et al. Anesthetic management for intestinal transplantation: a decade of experience. Clin Transpl. 2017;31:10. https://doi.org/10.1111/ctr.13085.
13. Sharkey L, Kratzing C, Rutter C, et al. PTH-127 nutritional status after intestinal and multivisceral transplant. Gut. 2014;63(Suppl 1):A267.1–A267. https://doi.org/10.1136/gutjnl-2014-307263.573.
14. Venick RS, Farmer DG, Saikali D, et al. Nutritional outcomes following pediatric intestinal transplantation. Transplant Proc. 2006;38(6):1718–9. https://doi.org/10.1016/j.transproceed.2006.05.051.
15. Venick RS, Wozniak LJ, Colangelo J, et al. Long-term nutrition and predictors of growth and weight gain following pediatric intestinal transplantation. Transplantation. 2011;92(9):1058–62. https://doi.org/10.1097/TP.0b013e31822f2b1b.
16. Foell D, Glasmeyer S, Senninger N, Wolters H, Palmes D, Bahde R. Successful management of passenger lymphocyte syndrome in an ABO-compatible, nonidentical isolated bowel transplant: a case report and review of the literature. Transfusion (Paris). 2017;57(6):1396–400. https://doi.org/10.1111/trf.14086.
17. Sharkey L, Amin I, Russell N, et al. P-74: change in CMV infection rates over time at a UK transplant centre. Transplantation. 2021;105(7S):S87. https://doi.org/10.1097/01.tp.0000758100.45249.07.
18. Starzl TE, Todo S, Tzakis A, et al. The many faces of multivisceral transplantation. Surg Gynecol Obstet. 1991;172(5):335–44.
19. Cruz RJ, Costa G, Bond G, et al. Modified "liver-sparing" multivisceral transplant with preserved native spleen, pancreas, and duodenum: technique and long-term outcome. J Gastrointest Surg. 2010;14(11):1709–21. https://doi.org/10.1007/s11605-010-1317-5.
20. Ceulemans LJ, Jochmans I, Monbaliu D, et al. Preoperative arterial embolization facilitates multivisceral transplantation for portomesenteric thrombosis. Am J Transplant. 2015;15(11):2963–9. https://doi.org/10.1111/ajt.13336.
21. Amin I, Russell N, Shaida N, See TC, Butler A. 320.4: use of arterial embolisation to facilitate exenteration during multi-visceral and intestinal transplantation. Transplantation. 2019;103(7S2):S16. https://doi.org/10.1097/01.tp.0000575500.04445.01.

22. Ewald C, Swanson BJ, Vargas L, et al. Including colon in intestinal transplantation: a focus on post-transplant renal function—a retrospective study. Transpl Int. 2020;33(2):142–8. https://doi.org/10.1111/tri.13523.
23. Kato T, Selvaggi G, Gaynor JJ, et al. Inclusion of donor colon and ileocecal valve in intestinal transplantation. Transplantation. 2008;86(2):293–7. https://doi.org/10.1097/TP.0b013e31817ef01c.
24. Moon JI, Zhang H, Waldron L, Iyer KR. "Stoma or no stoma": first report of intestinal transplantation without stoma. Am J Transplant. 2020;20(12):3550–7. https://doi.org/10.1111/ajt.16065.
25. Levi DM, Tzakis AG, Kato T, et al. Transplantation of the abdominal wall. Lancet. 2003;361(9376):2173–6. https://doi.org/10.1016/S0140-6736(03)13769-5.
26. Selvaggi G, Levi DM, Kato T, et al. Expanded use of transplantation techniques: abdominal wall transplantation and intestinal autotransplantation. Transplant Proc. 2004;36(5):1561–3. https://doi.org/10.1016/j.transproceed.2004.05.037.
27. Gondolesi GE, Aguirre NF. Techniques for abdominal wall reconstruction in intestinal transplantation. Curr Opin Organ Transplant. 2017;22(2):135–41. https://doi.org/10.1097/MOT.0000000000000394.
28. Gondolesi G, Selvaggi G, Tzakis A, et al. Use of the abdominal rectus fascia as a nonvascularized allograft for abdominal wall closure after liver, intestinal, and multivisceral transplantation. Transplantation. 2009;87(12):1884–8. https://doi.org/10.1097/TP.0b013e3181a7697a.
29. Hopfner R, Tran TT, Island ER, McLaughlin GE. Nonsurgical care of intestinal and multivisceral transplant recipients: a review for the intensivist. J Intensive Care Med. 2013;28(4):215–29. https://doi.org/10.1177/0885066611432425.
30. Rees MA, Amesur NB, Cruz RJ, et al. Imaging of intestinal and multivisceral transplantation. Radiographics. 2018;38(2):413–32. https://doi.org/10.1148/rg.2018170086.
31. Smith J, Godfrey E, Bowden D, et al. Imaging of intestinal transplantation. Clin Radiol. 2019;74(8):613–22. https://doi.org/10.1016/j.crad.2018.12.006.
32. Amin I, Russell N, Watson C, et al. P1.45: mycotic aneurysm after liver and small bowel transplantation. Transplantation. 2019;103(7S2):S83. https://doi.org/10.1097/01.tp.0000575896.05819.15.
33. Borle D, Shah J, Barbas A, et al. P1.24: vascular stenting for mycotic aneurysm in multivisceral transplant recipients. Transplantation. 2019;103(7S2):S71. https://doi.org/10.1097/01.tp.0000575816.43044.9e.
34. Pournaras DJ, Hardwick RH, Safranek PM, et al. Endoluminal vacuum therapy (E-Vac): a treatment option in oesophagogastric surgery. World J Surg. 2018;42(8):2507–11. https://doi.org/10.1007/s00268-018-4463-7.
35. Dumronggittigule W, Venick RS, Dubray BJ, et al. Ileostomy after intestinal transplantation: the first in depth report on techniques, complications, and outcomes. Transplantation. 2020;104(3):652–8. https://doi.org/10.1097/TP.0000000000002879.
36. McKenna C, Clarke E, Maddison R, et al. Incidence and management of chylous ascites and chylothorax following intestine and multivisceral transplant. Transplantation. 2017;101(6S2):S82. https://doi.org/10.1097/01.tp.0000521405.37627.d0.
37. Elsabbagh AM, Hawksworth J, Khan KM, et al. Long-term survival in visceral transplant recipients in the new era: a single-center experience. Am J Transplant. 2019;19(7):2077–91. https://doi.org/10.1111/ajt.15269.
38. Ruiz P, Bagni A, Brown R, et al. Histological criteria for the identification of acute cellular rejection in human small bowel allografts: results of the pathology workshop at the VIII international small bowel transplant symposium. Transplant Proc. 2004;36(2):335–7. https://doi.org/10.1016/j.transproceed.2004.01.079.
39. Nagai S, Mangus RS, Anderson E, et al. Intestinal graft failure: should we perform the allograft enterectomy before or with retransplantation? Transplantation. 2017;101(2):411–20. https://doi.org/10.1097/TP.0000000000001102.
40. Sharkey LM, Peacock S, Russell NK, Middleton SJ, Butler AJ. Graft versus host disease after multivisceral transplantation: a UK center experience and update on management. Clin Transpl. 2018;32(5):e13239. https://doi.org/10.1111/ctr.13239.
41. Mazariegos GV, Abu-Elmagd K, Jaffe R, et al. Graft versus host disease in intestinal transplantation. Am J Transplant. 2004;4(9):1459–65. https://doi.org/10.1111/j.1600-6143.2004.00524.x.
42. Wu G, Selvaggi G, Nishida S, et al. Graft-versus-host disease after intestinal and multivisceral transplantation. Transplantation. 2011;91(2):219–24. https://doi.org/10.1097/TP.0b013e3181ff86ec.
43. Devine K, Ranganathan S, Mazariegos G, et al. Induction regimens and post-transplantation lymphoproliferative disorder after pediatric intestinal transplantation: Single-center experience. Pediatr Transplant. 2020;24(5):e13723. https://doi.org/10.1111/petr.13723.
44. Abu-Elmagd KM, Mazariegos G, Costa G, et al. Lymphoproliferative disorders and de novo malignancies in intestinal and multivisceral recipients: improved outcomes with new outlooks. Transplantation. 2009;88(7):926–34. https://doi.org/10.1097/TP.0b013e3181b7509c.
45. Ambrose T, Sharkey LM, Louis-Auguste J, et al. Cytomegalovirus infection and rates of antiviral resistance following intestinal and multivisceral transplantation. Transplant Proc. 2016;48(2):492–6. https://doi.org/10.1016/j.transproceed.2015.09.070.
46. Zivković SA, Eidelman BH, Bond G, Costa G, Abu-Elmagd KM. The clinical spectrum of neurologic disorders after intestinal and multivisceral transplantation. Clin Transpl. 2010;24(2):164–8. https://doi.org/10.1111/j.1399-0012.2009.01065.x.
47. Shah SM, Roberts PJ, Watson CJE, et al. Relapsing encephalopathy following small bowel transplantation. Transplant Proc. 2003;35(4):1565–6. https://doi.org/10.1016/s0041-1345(03)00461-5.
48. Barry M, Chandra S, Hymes KB. Cytopenias in transplant patients. In: Safdar A, editor. Principles and practice of transplant infectious diseases. New York: Springer; 2019. p. 199–207. https://doi.org/10.1007/978-1-4939-9034-4_10.
49. Thomas W, Foukaneli T, Cosgrove J. Transplant associated thrombotic microangiopathy and immune haematological complications following intestine containing organ transplantation: experience from over 100 consecutive cases. Br J Haematol. 2021;193(5):961–70. https://doi.org/10.1111/bjh.17430.
50. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349(10):931–40. https://doi.org/10.1056/NEJMoa021744.
51. Huard G, Iyer K, Moon J, Doucette JT, Nair V, Schiano TD. The high incidence of severe chronic kidney disease after intestinal transplantation and its impact on patient and graft survival. Clin Transpl. 2017;31:5. https://doi.org/10.1111/ctr.12942.
52. NHSBT: Intestinal transplant patient selection policy. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/7757/pol194_4_1-intestinal-patient-selection-policypdf.pdf. Accessed 4 Mar 2021.
53. Amin I, Rutter C, Barlow A, et al. Simultaneous intestinal and kidney transplantation in adults. J Invest Surg. 2019;32(4):283–9. https://doi.org/10.1080/08941939.2017.1409849.
54. Abu-Elmagd KM, Kosmach-Park B, Costa G, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg. 2012;256(3):494–508. https://doi.org/10.1097/SLA.0b013e318265f310.
55. Ambrose T, Holdaway L, Smith A, et al. The impact of intestinal transplantation on quality of life. Clin Nutr. 2020;39(6):1958–67. https://doi.org/10.1016/j.clnu.2019.08.023.

Abdominal Wall Repair in Intestinal Failure

Akash Mehta and Ciaran Walsh

Key Points

1. Even when surgery of the abdominal wall appears simple it may still be very high tariff in an IF patient.
2. Reduce hernia formation in midline wounds by using a small bites closure technique with 2/0 slowly absorbable monofilament suture with self locking knots.
3. Avoid the need for extensive abdominal wall repair surgery by avoiding laparostomies whenever possible. If truly needed then have a plan to close them early with the use of mesh mediated or other graduated fascial traction techniques.
4. Put complex cases through a preoperative planning meeting including a multidisciplinary team with radiology and plastic surgeons present as well as IF and AWR surgeons.
5. Plan carefully with intestinal and abdominal wall mapping. Do not be afraid to perform the abdominal wall surgery in stages. An IF patient's priority is their intestinal integrity and nutritional autonomy. The AWR can follow so align the surgeons and the patient's expectations and priorities.
6. Use a prehabilitation program.
7. Time the surgery correctly and give correct time to the surgery (enterotomies are the devil incarnate).
8. Choose your mesh type carefully on a case by case basis.
9. Consider preoperative botulinum toxin injection to oblique muscles to try and prevent the need for irreversible muscle cutting components separation or to augment it

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Closing the Abdomen

The ideal abdominal closure technique should promote optimal and timely tissue healing, provide adequate protection to the viscera, act as a barrier to infection and have sufficient tensile strength in the short and long term to produce good abdominal wall function. It should be reproducible, efficient, and have a low incidence of complications. It should be as aesthetically pleasing as possible and should not impinge on stoma formation or function. All of this needs to be aligned to the context of the surgery being performed and therapeutic priorities in elective and emergency surgery whether by open or minimally invasive techniques. There is ongoing discussion and debate on the best way to close the abdomen in nearly all circumstances [1].

Primary Wound Closure

The problem with closing the abdomen is that it comes at the end of the operation and may not be regarded as part of the operation. The entire focus, often for many hours, has been doing the intended intraperitoneal surgical procedure. However, abdominal closure decisions and techniques are critical and include how best to close, whether to close permanently or temporarily or not to close at all. These decisions may have lifelong consequences for the patient.

Different techniques are needed for different situations. First time midline incisions in elective open surgery, elective open re-operative surgery with or without a hernia and/or stoma, elective minimally invasive surgery and emergency surgery in an unstable patient may all need to be closed differently. Data from randomised controlled trials in elective surgery may not apply to the patient in front of you who by definition was in an exclusion group for such trials for some reason whether that be having a stoma, an emergency procedure, being morbidly obese or septic.

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Apart from a bowel injury and an enteric fistula, arguably the most important long-term complication of inadequate abdominal wall closure is incisional hernia; the occurrence of which is often used as an arbiter of the quality and appropriateness of a closure technique. Sadly, incisional hernias are common and may significantly impair quality of life or lead to life threatening emergency presentations [2, 3]. Furthermore, they will often recur after they have been repaired and represent a significant burden on the health economy as well as on the individual patient.

Incisional hernias often occur after a surgical site infection (SSI). Every effort has to be made to use a surgical site infection bundle allied to a closure technique that is least likely to result in a wound infection and a subsequent incisional hernia.

For elective surgical closure of elective midline incisions current clinical evidence supports fascial closure with continuous slowly absorbable sutures, using a small bites technique placed 5 mm apart with a 5 mm width using self-locking knots with an overall suture to wound ratio of at least 4:1. This opinion is based on multiple studies from Israelsson's team in Northern Sweden [4–7], and supported further by the Dutch multicentre, randomised controlled STITCH trial [8], as well as a recent meta-analysis [9] and European guidelines [10].

Closure does not only refer to fascial closure. Detailed attention to the lipocutaneous tissues overlying the deep fascia is also important. It is important to prevent dead space and pay careful attention to superficial tissues with careful use of dermal and subcuticular sutures possibly augmented by vacuum dressings [11], whilst avoiding fat stitches and skin staples where possible.

In reoperative and emergency settings, and in different incision types, things are less clear. In re-operative surgery, even in the elective context, using involved wound closure techniques may be less well advised when performing enteric surgery with a higher risk of septic complications. The small bites technique may have benefits in the context of emergency laparotomy as regards acute wound failure, but this needs to be taken in the context of other priorities in many of the severely ill and unstable patients having these operations. In this context incisional hernia prevention may not be the key priority. Alternative techniques such as the Cardiff (Hughes) technique may be preferred for closing abdomens when patients are at high risk of incisional hernias such as after complete abdominal wound dehiscence or after laparostomy [12, 13]. Attention also needs to be paid to subcutaneous and skin closure techniques in these alternative settings and these may need to be different and may include leaving areas of the superficial wound open to heal by secondary intention or to augment the closure with a Vacuum dressing.

Stoma Wound Closure

Optimal fascial closure techniques in isolated stoma closure surgery are uncertain [14]. The incidence of incisional hernias in this cohort is likely between 5–40% depending on study bias, duration of follow up and whether assessed by CT scan or clinical exam alone [15].

Recent prospective randomised data trial data suggest a possible benefit from prophylactic biologic mesh in preventing incisional hernia at the stoma site [16]. Concurrent parastomal hernias are common in this group and how they should be dealt with is uncertain as is the technique of fascial closure when they are absent. It is uncertain whether the fascia of a stoma wound with an associated hernia should be closed differently from one without a hernia. A small bites fascial closure technique with self-locking knots may be an effective and possibly cheaper option than using prophylactic biologic mesh but awaits formal trial. It is certainly the case that the anterior rectus fascia needs to be carefully identified and incorporated in the suture bites. As regards the superficial wound closure at stoma sites there is Level I evidence in favour of purse string closure of the superficial wound rather than primary skin closure in terms of reducing surgical site infection [17]. There is also some small cohort-based data to suggest a role for negative pressure wound therapy applied to these stoma closure wounds [18].

Delayed Primary Closure of the Abdomen

Occasionally it is either not possible or not wise to close the abdomen primarily at the index laparotomy. In such an instance the surgeon may choose to fashion a laparostomy. There is no doubt that laparostomies at the time of emergency surgery have saved lives but equally they are to be avoided whenever possible. In the setting of an emergency laparotomy for an abdominal catastrophe and a damage limitation laparotomy the formation of a laparostomy may well be appropriate. If a laparostomy is performed there must be a definite closure plan to achieve delayed primary fascial approximation. Laparostomies are fistulogenic; moreover, they create a big problem for the future with the formation of an enormous incisional hernia. These hernias are difficult to repair with good outcomes and low morbidity. In essence therefore delayed primary closure of a laparostomy helps prevent a very large incisional hernia and may well prevent intestinal failure (IF) due to an enterocutaneous fistula (ECF) or an entero-atmospheric fistula (EAF).

The key to facilitating delayed primary closure is to prevent the abdominal contents from sticking to the parietal peritoneum at the index laparotomy. This permits the two laterally retracted halves of the midline fascia to be brought together without

shearing and damage to the abdominal contents when the midline fascia is sequentially and progressively approximated and closed at subsequent surgeries. The technique most commonly employed is that of mesh-mediated fascial traction combined with negative pressure wound therapy. In this technique a synthetic mesh (most commonly polypropylene) is sutured around the edges of the fascial defect over a large, fenestrated, non-adhesive plastic sheet (covering the abdominal contents and extending all the way into the flanks). A long slit is made in the middle of the mesh and then the two halves of the mesh are sutured together in the midline and a vacuum system applied on top of the mesh. This makes for an easy to manage wound system in the intensive care unit, prevents well-meaning but potentially damaging wound inspection and manipulation outside of theatre and helps reduce some wound oedema whilst preventing lateralisation of the fascial edges. In the course of sequential planned returns to theatre, the two halves of the mesh are sutured together with a greater degree of tension. Each time the patient is returned to theatre on a planned basis over the coming days this mesh is tightened over the plastic sheeting until gradually the two fascial edges become opposed. Ultimately the plastic sheeting and mesh can be removed completely, and the fascia sutured together to reconstitute the linea alba. In this way the mesh-mediated fascial traction has performed a staged and delayed primary closure of the midline wound, prevented a huge incisional hernia and possible development of IF due to an EAF. It must be stressed that none of this is possible if the non-adhesive plastic sheeting (either home-made or commercially available) is not wrapped around the bowels at the time of the first emergency laparotomy.

For the IF surgeon, quite often one's first encounter with a patient with an open abdomen occurs days or weeks down the line, with or without associated small or large bowel stomas and with or without an enteric fistula. The laparostomy is semi-mature at this point and the bowel loops will have adhered to the parietal peritoneum, the fascial edges retracted laterally and staged primary closure is not possible in this scenario. In this situation the subsequent management will depend on the presence or absence of an ECF/EAF and will be modified according to the presence or absence of stomas, particularly high output jejunostomies. In the absence of a fistula the key abdominal wall management strategy is simply to protect the bowel and avoid a fistula. In the authors' opinion, there is no place for an expensive biologic mesh as a glorified wound dressing. Best care is often with a wound manager system that sits around and over the wound and keeps it in a moist environment permitting wound granulation and shrinkage whilst the abdominal contents are protected. If a suction device is to be used in the gutters of such a system to remove accumulated oedema fluid, then great care must be taken to ensure it does not come in contact with the bowel and cause a fistula.

If the patient has an ECF/EAF at this stage then the management is different and is covered in Chap. 5 on the management of ECF's. Skin care is critical in acute abdominal wall failure and will be covered elsewhere in the book in chapter on ECF's.

Occasionally, a patient may be taken back to theatre at this stage for an attempt at skin/subcutaneous closure, or alternatively placement of a bridging polyglactin (Vicryl) mesh to protect the bowel loops, permit granulation and even subsequent skin grafting. This is aimed at bowel protection rather than any attempt at fascial approximation. It should be emphasised that during such procedures no attempt should be made at adhesiolysis or manipulation of the intestinal cocoon. The benefit of the absorbable polyglactin mesh approach is that when the patient is brought back to theatre many months later for definitive surgery, one finds that instead of paper thin laparostomy skin intimately attached to underlying bowel loops, there is in fact a rind that permits safer entry into the peritoneal cavity and helps reduce the risk of this most tricky part of the laparostomy take down and incisional hernia repair, namely peeling the laparostomy skin off small bowel loops with a scalpel.

Abdominal Wall Repair in IF Patients Without an Incisional Hernia

This situation might simply be someone with a very proximal stoma or ECF without an abdominal wall hernia or it might be a relaparotomy in someone with radiation enteritis or a short bowel syndrome after multiple previous laparotomies, possibly including a prior incisional hernia repair, stoma reversal or both. Even when surgery of the abdominal wall appears relatively straightforward, the effect of previous surgery and radiotherapy in particular on the abdominal wall blood supply requires careful thought. Previous incisions may have damaged the epigastric vessels that supply the mid-abdomen lipocutaneous pedicle (Huger Zone 1) via their perforators and non-healing of the wound may be a problem as a result [19].

The principles of primary wound closure previously described need to be applied but with the additional care to factors that delay or prevent abdominal wound healing. Occasionally an abdominal wall has been operated on so many times that it is failing as a functional unit yet there are no true hernias. There may be areas of poor-quality skin from previous infected wounds or repairs and in these situations, it is strongly advised to involve plastic (i.e. reconstructive) surgeons in the decision making to prevent even further complications if further surgery is proposed. It is often just as important to review old operation notes (often from other hospitals), CT scans and the microbiological history in these

cases as it is in cases with difficult large incisional hernias that require repair.

Abdominal Wall Repair in IF Patients with Incisional Hernias

Incisional hernias are a common complication of abdominal surgery [2], as are further recurrences after their repair. Hernia complexity is related to patient comorbidities, hernia size, dimensions and features of the hernia including loss of domain, previous repair history including previous mesh choice and site as well as clinical context including contamination, tissue characteristics and the nature of the clinical presentation [20–25]. In the context of IF, complexity is likely to be high for many reasons including comorbidities and contamination with or without fistulation or concomitant stomas. Abdominal wall failure accompanying intestinal failure requires an experienced multiprofessional team to get best results for both abdominal wall and IF outcomes.

Fundamentals of Incisional Hernia Repair

Abdominal hernia repair needs to be both durable and dynamic with a functional abdominal wall that provides visceral protection, strength and function with a low complication rate and outcomes that provide an improved quality of life for the patient. There are good quality data showing that suture repair without mesh augmentation is associated with a higher recurrence rate [2, 26].

The most important dimension of an incisional hernia as regards recurrence is its transverse diameter [20, 25]. Historically, and occasionally also today in rare and extreme cases, if the opposing edges of the fascial defect cannot be brought together, despite all adjunctive measures, tips and tricks, the gap between them can be bridged by a piece of mesh. This is suboptimal and midline fascial closure is critical. Bridging is to be avoided if at all possible to prevent hernia recurrence as well as other complications including a lack of abdominal wall function [27]. When a hernia repair technique alone is insufficient or inappropriate then one may need to employ abdominal wall reconstruction techniques. The definitive abdominal wall surgery and the IF surgery may need to be staged. The important thing is that cases are discussed preoperatively by a team of people with different skill sets who can plan the best surgical approach based on history, clinical findings, CT scan information, allied to the patient's priorities, wishes and choices.

It must be borne in mind that hernia recurrence in an IF patient may well not be the main priority. Intestinal continuity and nutritional autonomy are the key priorities to be achieved with a minimum of abdominal wall morbidity.

Fundamentals of Abdominal Wall Reconstruction

The term Abdominal Wall Reconstruction (AWR) refers to techniques used to correct the musculo-aponeurotic integrity of the abdominal wall when a straightforward hernia repair with fascial reunion cannot be achieved. This may involve importing tissue into the defect from elsewhere or manipulating the abdominal wall musculature by releasing incisions with separation of the different components of the myofascial package to permit greater movement of one muscle or fascia on another and ultimately permit fascial apposition and reunion. These approximated fascial edges are then reinforced with mesh. The principles of mesh material choice will be much the same as in incisional hernia repair, but the choice of mesh size and site of placement will depend on the technique used. With smaller defects chemical or pharmacologic release or separation with botulinum toxin may be all that is required as an adjunct to a hernia repair or in addition to surgical muscle or fascial releases. In more severe cases with tissue loss a muscle graft may be required to fill the defect and in the most extreme cases where there is abdominal wall failure an abdominal wall transplant may be performed usually as part of a multivisceral transplant for end stage intestinal failure. Regardless of technique the objectives of abdominal wall reconstruction are restoration of abdominal wall integrity, protection of intra-abdominal viscera and the prevention of herniation [28].

Evolution of Abdominal Wall Reconstruction

The sublay mesh technique, based on retromuscular and preperitoneal repairs of ventral hernias as described by Jean Rives and Rene Stoppa, in 1965 and 1966 respectively, has increasingly become the gold standard approach to bigger or more complex ventral hernias (Fig. 1).

Rives, in performing the retrorectus dissection, may possibly have been setting out to create a suitable plane in an extraperitoneal location for mesh placement excluded from visceral contents; however, in doing so he performed a *myofascial* release of both recti permitting some medialisation and approximation of the two halves of the linea alba. There had been published work on myofascial release in ventral hernia repair since 1916 [29–32], and these papers were arguably the foundations upon which was built the landmark paper by Ramirez describing his components separation technique [33]. He described the division of the external oblique muscle and development of the avascular plane between the external and internal oblique muscles to permit one to slide on the other and that, when combined with the Rives-Stoppa retrorectus dissection, permitted significant medialisation of the recti to repair bigger defects.

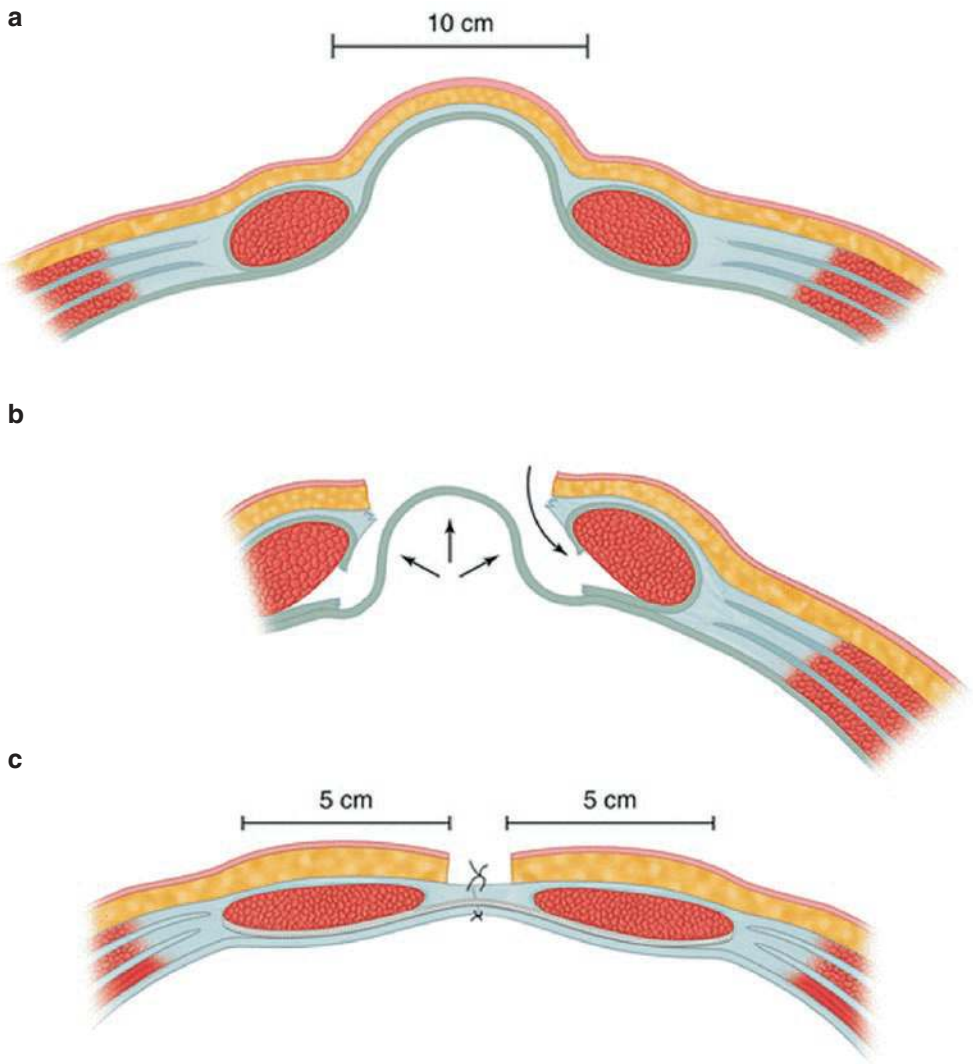

Fig. 1 Rives-stoppa retrorectus mesh repair of midline hernias. (**a**) Midline incisional hernia; note the substantial retraction of the rectus muscles. (**b**) Opening and development of the retrorectus space after incision of the posterior rectus sheath. (**c**) Primary fascial closure with retrorectus mesh reinforcement; note the elongation and medialisation of the rectus muscles

The importance of the concept and popularisation of components separation cannot be overstated. Prior to the publication of Ramirez' paper in 1990 [33], and the development of components separation techniques, ventral defects which could not be closed by en-bloc mobilisation of the abdominal wall were repaired by insertion of a bridging synthetic mesh, exposing patients to potential mesh infections, fistulisation and high hernia recurrence rates. Defects with inadequate soft tissue cover were repaired using autologous tissue transfers (e.g. free or pedicled tensor fascia lata flap), which, although providing coverage, did not actually reconstruct the abdominal wall or its function, leading not only to high hernia recurrence rates, but also significant morbidity related to the donor site. Components separation, in contrast, does not just "close the hole" without the need for a donor site, but restores abdominal wall anatomy and function, by achieving a tension-free re-approximation of the linea alba, restoring the normal anatomical relationship of the abdominal wall muscles and offsetting the lateral pull of the oblique and transverse muscles.

Although truly revolutionary as a concept in the repair of major abdominal wall defects, Ramirez' technique does have some limitations and disadvantages:

- The morbidity associated with the raising of often quite substantial lipocutaneous flaps (seroma formation, skin necrosis, etc)
- The inability to fully close the posterior sheath in large ventral hernias
- The limitations in mesh size being defined by the linea semilunaris bilaterally

To address these limitations, various techniques have been developed and popularised, some of which are modifications of Ramirez' original procedure, whilst others represent completely new avenues and aspects of the core concept of components separation.

Modifications to Ramirez' components separation are all aimed at preserving the integrity of skin/subcutaneous fat/fascia complex to preserve the perforators which form the blood supply to the skin [19].

An endoscopically assisted technique for incision of the external oblique aponeurosis and development of the avascular plane between the external and internal oblique muscles was developed which allowed for direct, minimally invasive access to the external oblique aponeurosis and the inter-oblique plane without the need for development of lipocutaneous flaps [34]. A similar modification, termed the perforator-preserving component separation, also involves direct access to the external oblique aponeurosis just lateral to the semilunar line, reducing the need for raising large lipocutaneous flaps [35].

As stated, Ramirez' component separation involves a "standard" Rives-Stoppa retrorectus dissection. This means that the space available for mesh placement is limited to that of the retrorectus space, between the two semilunar lines. In larger ventral hernias, sufficient mesh overlap of the visceral sac is therefore difficult or even impossible to achieve. A preperitoneal, retrofascial approach was developed which allowed for the creation of a large preperitoneal plane for placement of a widely overlapping synthetic mesh. This method, developed and popularised by Heniford, was first described in 2006 [36, 37]. Following on from work by Carbonell in 2008 [38], Novitsky and Rosen published the novel technique of posterior components separation (PCS) utilising transversus abdominis release (TAR) [39], as opposed to Ramirez' anterior components separation (ACS) utilising external oblique release.

Posterior components separation creates a large retromuscular space allowing for sufficient mesh overlap combined with medialisation of abdominal wall compartments without raising lipocutaneous flaps. This technique again involves an initial standard Rives-Stoppa retrorectus dissection with mandatory identification and preservation of the neurovascular bundles just medial to the semilunar line on each side. Key to the TAR approach is the fact that the transversus abdominis muscle fibers extend medial to the semilunar line in the upper abdomen (Figs. 2 and 3). The key is to go through the posterior rectus sheath medial to the linea semilunaris to identify and go through the transversus abdominis muscle to access the front of the transversalis fascia and develop the plane between the front of the transversalis fascia and the back of the transversus abdominus muscle (Figs. 4 and 5). A key to understanding the versatility of this approach is understanding the origins and insertions of the transversus abdominis muscle; in particular its superior origins are from the costal margin thus by getting behind the transversus abdominis one gets up behind the ribs. The dissection is followed past the xiphoid process to the fascia diaphragmatica (the transversalis fascia covering the diapragm) in the preperitoneal plane and inferiorly into Retzius' and Bogros' space with identification of Cooper's ligaments. These are key points because it means this technique is not limited by the bony costal margin and one can get a mesh

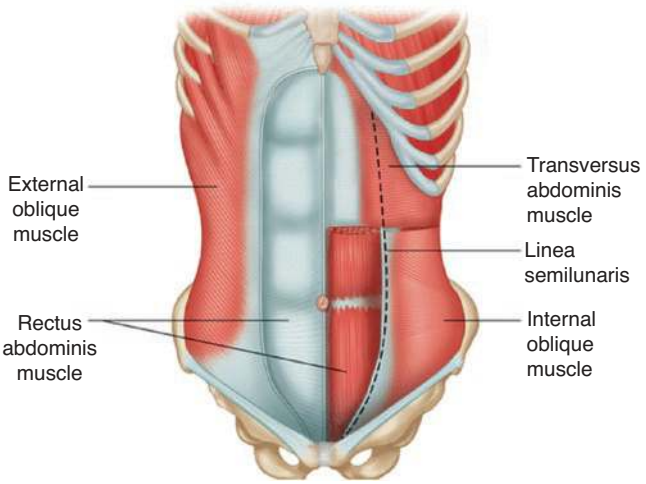

Fig. 2 Sections of the anterior abdominal wall showing the transversus abdominis muscle extending medial to the semilunar line in the upper abdomen

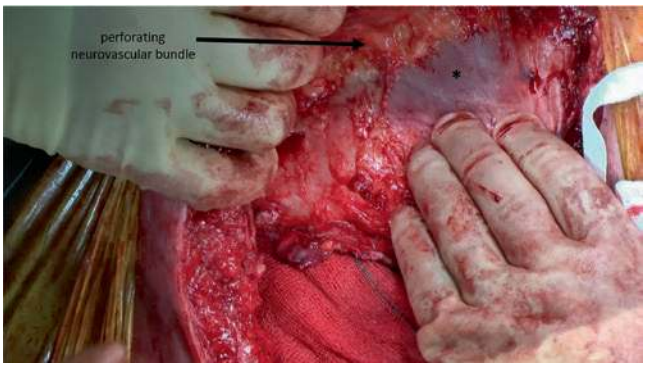

Fig. 3 Intra-operative photograph after completion of full retrorectus dissection upto the semilunar line, clearly showing the muscle fibers of the transversus abdominis (*) extending medial to the semilunar line under the posterior rectus sheath

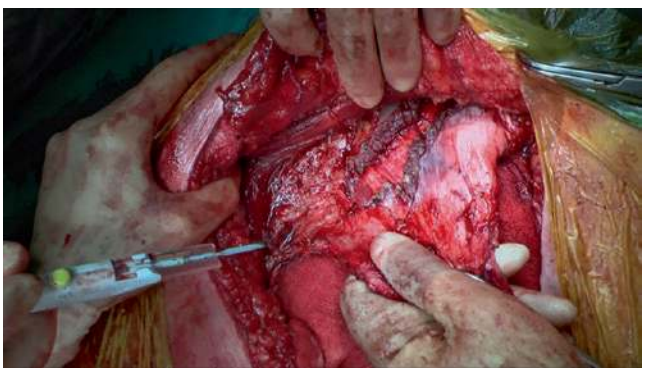

Fig. 4 Division of transversus abdominis muscle fibers exposing the underlying transversalis fascia

under the costal margin right up to the central tendon of the diaphragm, all the way out laterally and posteriorly to the paravertebral muscles and inferiorly into the pelvis. This gives this approach a far wider range of hernia repair possibilities including rooftop incisional hernias, Mercedes incisional hernias, Inverted T incisional hernias, superior and inferior lateral flank incisional hernias, stoma site hernias, complex multi-incision incisional hernias as well as midline ventral hernias.

The traditional top-down TAR may be augmented or replaced by the bottom-up TAR, described, taught and popularised by Miguel Ureña in Madrid where the incision of the posterior rectus sheath is commenced at the arcuate line and then extended upwards [40]. This technique can be particularly useful when there is a concomitant lateral defect or scar that needs to be circumvented and one can approach it from above and below.

A stepwise description of PCS-TAR is provided in the case study at the end of this chapter.

The favourable combination of good long-term outcomes and decreased post-operative morbidity associated with PCS-TAR have led to a rapid broadening of its applicability [41], leading to descriptions of its use in the treatment of giant ventral hernias following laparostomy formation [42], the treatment of parastomal hernias (by performing a modified Sugarbaker procedure, lateralising the stoma limb in the retromuscular space and reinforcing this with a large retromuscular prosthesis) [43], the treatment of lateral hernias [44]; and even as a salvage procedure for recurrent ventral hernias after a failed anterior component separation technique [45].

Although the reconstruction of the abdominal wall (AWR) in patients with intestinal failure (and often concomitant abdominal wall failure) is inherently different from the treatment of ventral hernias, the surgical principles which have evolved since the early twentieth century have been successfully applied to the practice of AWR in IF. In particular, the Rives-Stoppa procedure remains the mainstay of AWR in these patients, frequently augmented by further myofascial release, either via anterior or posterior component separation (Figs. 6 and 7).

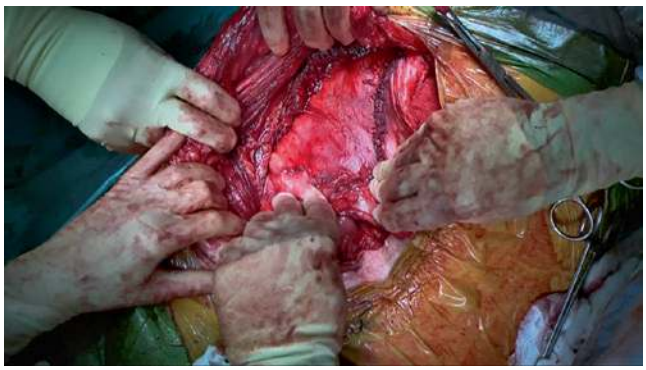

Fig. 5 Significant medialisation of midline after TAR and development of plane behind the transversus abdominis muscle

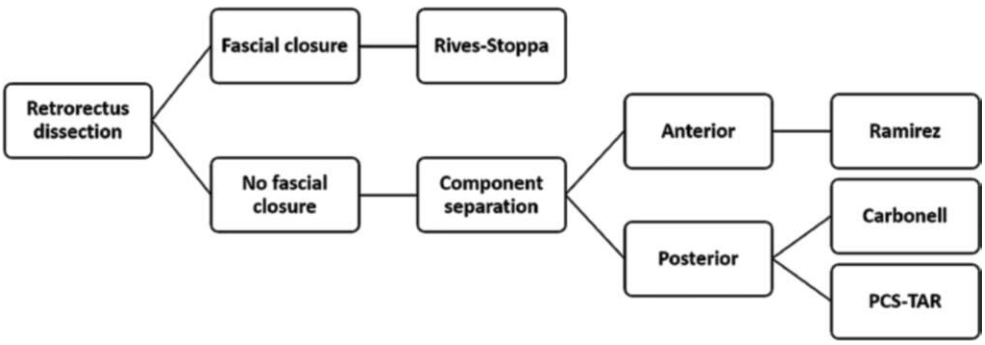

Fig. 6 Options for reconstruction of the abdominal wall

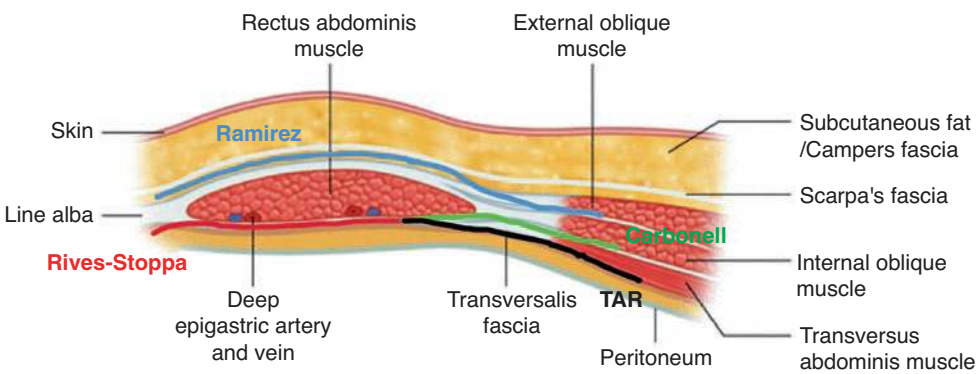

Fig. 7 Planes of dissection for the most widely used AWR techniques

Principles of Mesh Use in Incisional Hernia Repair and AWR

Both hernia repair and AWR techniques involve augmentation with a mesh to reduce recurrence. There are truly endless types of mesh of different materials and configurations. The nature of the mesh used, whether a permanent synthetic mesh, biologic mesh or synthetic absorbable mesh will depend on many factors including hernia grade, site, dimensions and complexity. In the context of intestinal failure, contamination in particular is an important factor and will have a large bearing on mesh choices for abdominal wall repair as will both Crohn's disease and prior radiotherapy. This is an area where using a synthetic absorbable or biologic mesh may need to be considered rather than one's normal first choice of a synthetic macroporous polypropylene mesh. Intestinal failure patients with complex hernias are likely to have travelled a long road with septic episodes and possibly multiple courses of antibiotics prior to their abdominal wall repair. Part of mesh choice is reviewing their microbiological data with regards to resistant organisms as well as detailed previous review of surgical operation notes, review of prior septic sequelae including abscesses and ECF's, up to date CT scans and a clear idea in the surgeon's head of what they are trying to achieve for the patient. The ideal location for the mesh is in the retromuscular plane [46], lying extraperitoneally in front of the transversalis fascia (or peritoneum below the arcuate line) and behind the rectus muscles such that the anterior fascia can be closed primarily above this, thus reconstituting the linea alba in the case of midline incisional hernias. In general, one should avoid using coated synthetic meshes intraperitoneally in the context of IF patients and in Crohn's in particular. One always wants this repair to be the patient's last abdominal operation. In the context of Crohn's disease in particular one may need to temper this ambition and make choices regarding the repair, including mesh choice, with an understanding of the nature of Crohn's disease and the possible need for further surgery. In cases where major IF surgery and major AWR surgery are both required in a staged fashion the mesh choice at the time of the initial IF surgery may depend on the need to bridge the fascial defect at the time of that IF surgery and in this context a biologic mesh may be appropriate. Synthetic absorbable meshes are not usually used for bridging in this context.

Abdominal Wall Transplantation

Severe intestinal failure patients that ultimately require intestinal or multivisceral transplantation will often have extremely damaged abdominal walls and true abdominal wall failure. One of the most important challenges in intestinal and multivisceral transplantation is achieving a successful abdominal wall closure [47]. A tension-free primary closure is the aim but can be very problematic. In most cases a components separation technique is required. If those options are not feasible the patient may benefit from a concurrent abdominal wall transplantation [48]. An abdominal wall composite vascularized allograft transplant utilising direct orthotopic vascularisation can be considered [49]. This is the ultimate abdominal wall reconstruction and is beyond the scope of standard abdominal wall surgeons and is firmly in the realms of transplant surgeons. The abdominal wall graft may be a full-thickness vascularised abdominal wall transplant, a partial-thickness vascularised graft or a partial thickness non-vascularised rectus facia graft. Vascularised and non-vascularised rectus fascia may be effective when there is inadequate healthy muscle/fascia but sufficient skin cover. Temporary 'remote' revascularisation of the allograft has been performed in some cases onto the recipient's forearm vessels when there is a long anticipated cold ischaemia time (>5 h). Preliminary data suggest that in full-thickness grafts, abdominal wall skin rejection might be an early predictor of intestinal rejection.

Loss of Domain

This is a greatly misunderstood concept in relation to abdominal hernias. It means the abdominal contents have prolapsed out into the hernia sack and have lost their place and right of residence or domicile within the abdominal cavity proper. They have lost their original domain and now reside in a second abdominal cavity, outwith the normal confines of the abdomen proper [50]. If they are able to reduce spontaneously when the patient lies flat or can be gently coaxed back in there is therefore room within the abdominal cavity proper for them to reside and there is not a loss of domain (regardless of the size of the hernia sac when the patient stands). If they do not reduce on lying flat, then there is a loss of domain which is to be distinguished from incarceration or irreducibility of a hernia. Loss of domain does not refer to the size of the hernia defect or neck. There may be a small defect with a huge sack or a huge defect with a huge sack. Both will look impressive clinically when the patient stands up. Both will have a loss of domain if the contents do not return into the abdomen when the patient lies down. The degree to which they return determines the degree of loss of domain. Neither will be associated with a loss of domain if their contents return to the abdomen proper when the patient lies flat.

In the presence of significant loss of domain, forcing the abdominal contents back in and pulling the abdominal muscles together at surgery would result in a marked and deleterious increase in intra-abdominal pressure with possible respiratory complications and abdominal compartment syn-

drome possibly with multiorgan failure. In order to try and calculate how much is too much different volumetric assessments such as those described by Sabbagh and Tanaka have been used [51–53]. There are differences between these assessment methods and careful CT assessment and measurement is required but a useful rule of thumb would be that if more than 20% of the abdominal contents are outwith the abdomen proper then there is a significant and clinically relevant loss of domain.

One approach to overcome loss of domain might be to resect colon and/or omentum to make space for the return of the hernia contents but this is less likely to be an attractive option, particularly in IF patients. Another option is to employ adjuncts to prepare the abdominal wall before and during surgery including botulinum toxin injection into the oblique muscles and stretching the abdominal cavity by preoperative air insufflation (progressive preoperative pneumoperitoneum).

Adjuncts in Abdominal Wall Reconstruction

Botulinum Toxin

Botulinum toxin injection into the abdominal wall oblique muscles has a role in the management of the abdominal wall in the context of ventral and incisional hernia repair as well as abdominal wall reconstruction. It may even have a role in the management of the open abdomen and mesh-mediated fascial traction. It was first described by Hurtado in 2009 [54]. The concept has grown in popularity and has been used in different ways by different groups [55–59].

The Botulinum toxin is injected into the three lateral muscles on either side in the preoperative period. This is done by an ultrasound guided technique at a number of points, commonly three, in each muscle with the patient either awake or sedated as a day case or an ambulatory procedure 4–6 weeks before the hernia surgery. The fundamental concept is one of preoperative pharmacologic muscle relaxation and lengthening in order that the midline may be approximated and come together more easily. In midline ventral and incisional hernias, it may be used to augment a Rives-Stoppa repair so that a hernia defect that could not have been repaired in this way due to an inability to achieve medialization and reconstruction of the linea alba can in fact be done. The repair is thus downstaged. By injecting Botox into the oblique muscles in the preoperative period one can both make this repair easier by facilitating medial travel (medialization) of the two sides or one can potentially complete a Rives-Stoppa repair with appropriate tension-free medialization in a case that would otherwise not have been possible and therefore prevent the morbidity of an adjunctive component separation. This concept of downstaging an abdominal wall repair from a bilateral component separation to a Rives-Stoppa repair needs careful consideration on a case by case basis. Whilst the primary goal is undoubtedly the reconstruction of the linea alba by bringing together the two recti it may be necessary in certain hernia configurations to perform a bilateral TAR not just to facilitate medialization but to get a mesh under the costal margins and diaphragm with sufficient “underlap”, especially in patients with lateral defects, stomas and parastomal hernias. These considerations may be modified if the intestinal failure is related to Crohn’s disease as one is reluctant to use synthetic mesh in this context and downstaging a bilateral TAR to a Rives-Stoppa procedure in this context has the additional benefit of being able to use a synthetic absorbable mesh rather than a permanent synthetic mesh in Crohn’s patients.

Another potential role of preoperative Botox is in very big transverse defects of 20 cm or so where one can use Botox to try and help prevent the need for bridging. A further use is in the context of loss of domain, where it will help reduce tension and permit stretching of the abdominal wall in the postoperative period and thus help keep intra-abdominal pressures down.

Progressive Preoperative Pneumoperitoneum

Originally described by Ivan Goñi Moreno from Buenos Aires in 1947 [60], progressive preoperative pneumoperitoneum (PPP) has now gained more popularity but not widespread acceptance as an integral part of an advanced abdominal wall service for hernia patients with a significant loss of domain. In essence and in its simplest form air is gradually instilled into the peritoneal cavity via an intraperitoneal catheter starting approximately 1 week before the hernia repair surgery. Day on day more air is added and gradually stretches the abdominal cavity and makes room for the abdominal contents to return from the second hernia cavity into the abdominal cavity proper at the time of the subsequent hernia repair operation. The aim is to reduce the risk of abdominal compartment syndrome and respiratory complications postoperatively. It is readily apparent how preceeding PPP with botox injection to the oblique muscles would make sense in order to stretch up the abdominal cavity, but some surgeons prefer to use it in isolation. It can be extremely successful in the management of large hernias with significant loss of domain [61, 62], but patients for PPP need to be selected carefully as it is not without its complications including visceral perforation, puncture of solid organs, air embolism, pulmonary embolism, bleeding with haematoma of the abdominal wall, subcutaneous emphysema, mediastinal emphysema and pneumonia [63]. It may well be the case that more severe IF patients who need corrective abdominal wall surgery may in fact be poor candi-

dates for this technique again highlighting the need for truly complex cases to be discussed preoperatively in a multiprofessional forum with IF surgeons, abdominal wall and plastic surgeons.

Obesity

Intestinal failure is not the preserve of the undernourished. The commonest cause of an enterocutaneous fistula is misadventure at the time of surgery and obese patients are not immune. Moreover, obesity is intimately linked to hernia formation [64]. Surgery in acute IF in obese patients brings a lot of unique challenges. Stoma formation can be very difficult due to a dense, fat and shortened mesentery that needs to be delivered through a deep abdominal wall. This often leads to poor quality stomas with skin and subcutaneous erosive and infective complications that cause abdominal wall complications that in turn cause problems for subsequent abdominal wall repair surgery. The catabolism associated with type II IF due to an abdominal catastrophe associated with sepsis, with or without proximal stomas or an ECF/EAF, in an obese patient will likely cause significant weight loss. When they subsequently come to abdominal wall repair, either at the time of their corrective IF surgery or at a later staged operation, it is likely that they will have a significant slack pannus, unhealthy scarred subcutaneous tissues and skin and possibly tissue loss as well as incisional and peristomal hernias. This adds a different dimension to their surgery and often requires the input of a plastic surgeon. Planning and execution of the required excision of unhealthy skin and subcutaneous tissue with or without an associated laparostomy may be even more complicated if prior stoma formation has led to damage to inferior and/or superior epigastric vessels that provide the blood supply to the rectus muscles as well as the overlying skin and subcutaneous tissues via the associated perforator skin blood supply. A wide panniculectomy may be needed to remove redundant unhealthy subcutaneous tissue and skin with a suboptimal blood supply. Vascular mapping preoperatively or intraoperative fluorescence angiography may be required to prevent complications due to an impaired blood supply of the lipocutaneous tissues.

Data on abdominal wall reconstruction in obese patients in the absence of IF suggest that a body mass index greater than or equal to 30 kg/m^2 is associated with significantly higher rates of wound healing complications but not with higher rates of hernia recurrence. It appears that concomitant panniculectomy affects wound morbidity but not hernia recurrence rates in complex AWR not specifically related to IF [65, 66]. Thus, careful surgical planning is critical as is an appreciation of the integrity and quantity of skin and subcutaneous tissues. Superficial remodelling is not an aesthetic bonus in this group but rather a key part of their abdominal wall surgery in order to prevent hernia recurrence and abdominal wall morbidity including wound infection, seroma and abscess formation.

Pre-operative Planning and Intestinal Mapping

The reconstruction of a failed abdominal wall differs significantly from repair of even complex ventral hernias and, in the context of surgery for intestinal failure, requires appropriate consideration and planning. The anterior abdominal wall defect is often large, there is quite often enteric contamination with (low-grade) abdominal wall sepsis, and the abdominal wall can have multiple defects due to fistulae and/or stomas. All these issues should be taken into consideration when planning the abdominal wall reconstruction phase of the surgical procedure. The importance of good quality axial imaging, case planning and multiprofessional discussion supported by high quality radiology cannot be stressed enough. Not just the defect but the relationship of the defect(s) to fistulae and/or stomas should be considered at this stage. Abdominal wall MDT meetings have much to offer in standard AWR practice [67], but in the context of concomitant IF are critical. Ideally, the MDT discussion should involve plastic/reconstructive surgeons as well to assess for and mitigate the degree of tissue loss which is often greater than it appears and to consider the necessity of a panniculectomy as well as the need for a flap transposition rather than components separation.

As described in more detail elsewhere in this book, elective surgery for intestinal failure needs to be considered one of many steps in a multidisciplinary management strategy for what are often extremely complex patients. The management strategy for patients with intestinal and concomitant abdominal wall failure should address the management of sepsis, wound care, nutritional support and optimisation (including the management of high fistula/stoma outputs), intestinal mapping, prehabilitation and surgical planning.

Intestinal Mapping

The anatomy of the digestive tract and abdominal wall is often significantly disrupted in patients with intestinal failure. These changes will often affect decisions regarding nutritional support, the likelihood of spontaneous fistula closure and, ultimately, the proposed strategy for definitive surgical procedures. Crucial information regarding the current anatomy of the digestive tract may often be gained by meticulous perusal of operative records. This will also often yield valuable information on what, if any, attempts were made at abdominal wall closure, whether mesh was used, and, if so,

what type and in which plane and position. This information is often difficult to ascertain by radiological examination alone, and sometimes the radiologic appearances of the abdominal wall may be at variance with the surgery suggested by prior operation notes. Further mapping of the intestinal anatomy is based on imaging; in most centres, the mainstay of this mapping is a CT of the abdomen and pelvis with intravenous and positive oral contrast (supplemented with arterial phase scans for patients with a history of mesenteric ischemia). In addition, contrast-enhanced studies of those sections of the digestive tract which are out of circuit and not amenable to oral contrast enhancement, are often warranted, especially to assess the patency and length of distal bowel when distal limb feeding is being considered and to rule out any distal obstruction which might need to be addressed prior to or during definitive surgical management. In Crohn's disease, full restaging of the disease (both of the small bowel and the colorectum) should be considered. Contrast enhanced CT will also provide an assessment of the maximum dimensions of any abdominal wall defect, the presence of any clinically occult defect (e.g. parastomal hernias), any loss of domain, the degree of tethering of bowel to the anterior abdominal wall, the degree of abdominal wall sepsis, the width, thickness and quality of the rectus muscles as well as the bulk and thickness of the abdominal oblique muscles. Taken together, the information gathered from these various sources forms a comprehensive map of the patient's patho-anatomy which can be used to guide further management and optimisation, as well as to enable adequate planning of the definitive surgical procedure (s). It can be very helpful to amalgamate all the information from different sources and schematically represent these in one single anatomical diagram, which has been useful for other healthcare professionals involved in the care of the patient, in determining the challenges to enteral nutrition and to inform patients about their own anatomy and what further surgery would involve. It has also proved useful in planning surgical procedures and is described in more detail in Chap. 5.

Prehabilitation

Prehabilitation encompasses all of the aforementioned considerations regarding nutrition and wound care, but goes beyond these principles in formulating a pathway (quite often personalised) to enable the team and the patient to work towards their common goal of offering the patient a definitive procedure with the highest possible chance of success with the lowest possible risk of complications (this applies both to the restoration of intestinal continuity and the abdominal repair/reconstruction components of the procedure). Although individualised, basic components of such a prehabilitation "programme" should include the following:

- Exercise and cardiovascular fitness
- Smoking cessation
- Nutritional assessment and optimisation
- Controlled weight loss (ideally to a BMI of less than 30)
- Acceptable diabetic control (measured by HbA1C levels with a cut-off point frequently agreed at 7.3% or 56.3 mmol/mol)
- Anaemia correction
- Psychological well-being and preparation, expectation management, shared decision making on priorities and what the patient considers a good outcome
- Assessment of superficial abdominal lipocutaneous tissues if significant weight loss from when catabolic and what to do with pannus
- Analgesics and opiate review and weaning to provide headroom for perioperative analgesia as not just abdominal pain but also back pain if significant herniation

Surgical Planning

Serious consideration needs to be given to whether or not it is appropriate to perform a formal abdominal wall reconstruction at the time of the definitive restoration of intestinal continuity. It may be more appropriate to bridge the abdominal wall defect with a synthetic absorbable (e.g. Vicryl) or biological mesh without disruption of the retrorectus and retromuscular planes; and perform the definitive abdominal wall reconstruction (possibly with a synthetic mesh) as a staged procedure rather than as part of the restoration of intestinal continuity. This staged approach would allow for "downstaging" of the modified VHWG classification from a grade III to a grade I/II defect [22, 21], and does not "burn any bridges" by avoiding disruption of the retrorectus and retromuscular planes. Moreover, in some patients undergoing restoration of continuity, a temporary stoma may be formed, which will need to be reversed at a later stage, and a case could be made to postpone the abdominal wall reconstruction till that time. Finally, the very nature of these procedures entails a relatively high risk of enteric leak, either from anastomoses or from enterotomies, which could necessitate further surgery, and thereby a re-opening of the reconstructed abdominal wall. Conversely, bridging the abdominal wall defect almost guarantees development of a ventral hernia and, with it, the need for future surgery, which could have been avoided by a single-stage approach. Moreover, the current mindset regarding the use of synthetic mesh in contaminated wounds is different from that of the past: the use of light/medium weight macroporous polypropylene mesh is associated with relatively low rates of mesh infection and mesh excision [68]. However, the majority of the data supporting this stems from series of patient without gross contamination of the abdominal wall, thereby excluding a significant subset of IF patients.

Ultimately, as described eloquently in a 2018 review [69], the decision on whether or not to perform a single-stage or staged approach in IF surgery depends on a number of factors:

- The primary indication for the operation: it must always be borne in mind that the primary goal of IF surgery is hardly ever reconstruction of the abdominal wall; it is restoration of intestinal continuity and nutritional autonomy. If primary fascial closure can be achieved without any formal AWR, this is the preferred approach.
- The likelihood of the patient requiring a re-operation, either unplanned (e.g. bleeding, anastomotic/enteric leak) or planned (e.g. reversal of a temporary stoma).
- The degree to which the operating team is comfortable performing the abdominal wall reconstruction.
- In case of a staged abdominal wall reconstruction, the likelihood that the clinical scenario will be more conducive to successful AWR by delaying (e.g. less contamination, patient optimisation, etc): although a case could be made that there will be less contamination by delaying the AWR, it would be less likely that the patient would be more optimised than they are at the time of restoration of continuity, bearing in mind the aforementioned pre-operative approach to patients with IF. Moreover, it must be borne in mind that the inflammatory response often seen in the postoperative phase following IF surgery could lead to further intra-abdominal adhesions, thereby not necessarily decreasing the risk of contamination from inadvertent enterotomies made during a staged abdominal wall reconstruction.

These factors will be different for every clinical situation and therefore a purely algorithmic, "one size fits all" approach would be inappropriate. In essence, the decision-making will come down to a consideration of the complexity of the intestinal procedure versus the complexity of the abdominal wall reconstruction.

In general, a patient undergoing a low-complexity "simple" restoration of continuity (e.g. reversal of a proximal jejunostomy) and requiring a simple abdominal wall reconstruction (e.g. a Rives-Stoppa repair without the need for additional component separation) would not likely stand to gain much from a staged approach and it would be considered appropriate to perform the AWR at the same time as the restoration of continuity. In contrast, a patient with multiple complex enterocutaneous fistulae in a previously fully dehisced abdominal wall will be undergoing a high-risk intestinal procedure with a complex abdominal wall reconstruction, and simply bridging the abdominal wall defect with a mesh (Vicryl or biologic) and performing a deferred formal AWR with a synthetic mesh would be considered appropriate. However, even this decision is not straightforward and different surgeons would come to different, and equally justified, decisions. In general, it must be borne in mind that a patient with an ECF or more particularly an EAF who ends up with intestinal continuity and nutritional autonomy is a success story regardless of the recurrence/occurrence of an incisional hernia.

Once a decision has been made, taking the aforementioned factors into consideration, due attention must be had for preparing the abdominal wall for reconstruction (whether simultaneous with the restoration of intestinal continuity or as a staged approach) with adjuncts which may facilitate rectus abdominis medialisation and linea alba reconstruction. The two most commonly used adjuncts, intramuscular botulinum toxin injection and progressive pre-operative pneumoperitoneum (PPP), are described elsewhere in this chapter. It is worthwhile pointing out the ability of these adjuncts, especially botulinum toxin injection, to potentially "downscale" a complex abdominal wall reconstruction from a component separation to a "simple" Rives-Stoppa repair, which is yet again another factor to be considered in the aforementioned balancing of the complexity of the planned AWR in deciding on a single-stage versus staged procedure.

Abdominal Wall Reconstruction Leading to Intestinal Failure

Even outside of the context of intestinal failure, abdominal wall reconstruction for a large ventral/lateral hernia can be a complex procedure, with demands placed both on the technical skills of the operating team as well as their dynamic decision-making capabilities.

Inadvertent bowel injury during abdominal wall surgery is not inconsequential. Various reports have found an increased risk of major morbidity after enterotomies and/or unplanned bowel resections, with one report demonstrating a significantly increased risk of ECF formation in patients with an inadvertent bowel injury during AWR compared to patients without bowel injuries (7.3% vs. 0.7%, respectively) [69]. Recently published data from the American Hernia Society Quality Collaborative (AHSGQ) showed that inadvertent full-thickness bowel injuries are recognised in 1.9% of patients undergoing ventral hernia repair, the majority (85%) being small bowel injuries [70]. These tend to occur more frequently in larger hernia defects, recurrent hernias (especially with previous mesh in situ), a history of abdominal wall infection and higher degrees of wound contamination. Unsurprisingly, bowel injury was associated with an increased risk of surgical site infections; specifically, enterocutaneous fistulae were more common amongst patients with an inadvertent bowel injury (4% vs. 1%). Also, there was a higher reoperation rate in the bowel injury group, with an assumed higher rate of hernia repair failure and ultimately hernia recurrence [70].

Case Study

A 57-year-old otherwise fit and healthy male patient was admitted with sigmoid diverticulitis. Initially, he was managed conservatively but developed increasing abdominal sepsis and ultimately underwent an emergency laparotomy. A purulent pelvic collection was washed out but no obvious visceral perforation was seen and no resections were performed. His abdomen was left open due to gross small bowel oedema and a second look laparotomy was planned with a view to delayed closure. At this second look laparotomy, abdominal wall closure was still not possible and a laparostomy was maintained. During his protracted stay in hospital, this patient developed an entero-atmospheric fistula (EAF) in his laparostomy wound. He was ultimately transferred to a tertiary Intestinal Failure unit where his nutritional status and overall condition was optimised, combined with mapping of his intestinal anatomy. His mapping diagram is shown in Fig. 8 and a representative CT image in Fig. 9.

He was established on distal limb feeding using chyme reinfusion and was discharged home, completely avoiding the need for parenteral nutritional support. He was ultimately planned for reconstructive surgery and a multidisciplinary recommendation was made to attempt abdominal wall reconstruction simultaneous with the restoration of intestinal continuity, in view of the relative low complexity of the intestinal procedure as well as the patient's overall fitness and marked conditional and nutritional improvement.

Just prior to commencing laparotomy, the retracted edges of the rectus muscles were palpated and marked (Fig. 10). At laparotomy, a full adhesiolysis was performed and the fistulating small bowel segment resected with a primary small bowel anastomosis. The sigmoid colon, although moderately affected by diverticular disease, was health and therefore a decision was made not to perform a sigmoid colectomy. The abdominal wall reconstruction phase of the procedure was initiated by identifying the medial edge of the rectus muscle

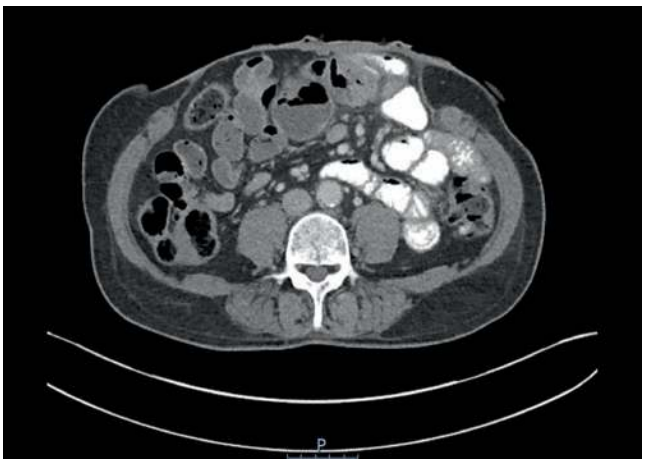

Fig. 9 Axial CT image showing large midline defect with small bowel fistula in laparostomy

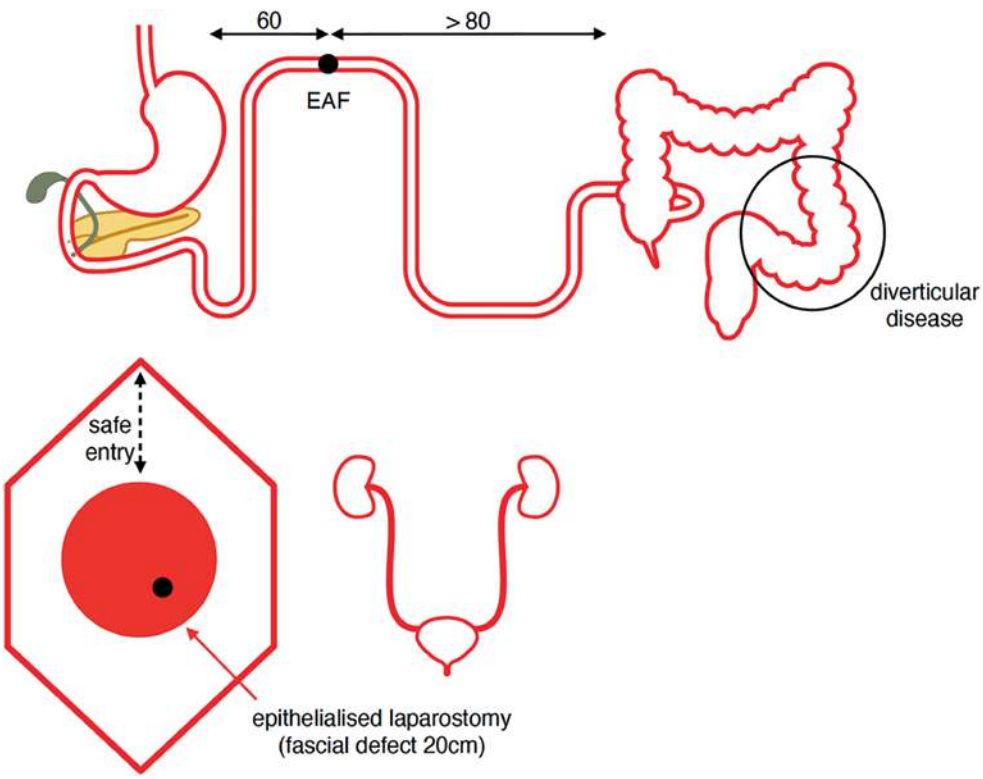

Fig. 8 Initial intestinal + abdominal wall anatomy of patient with an EAF in a laparostomy wound

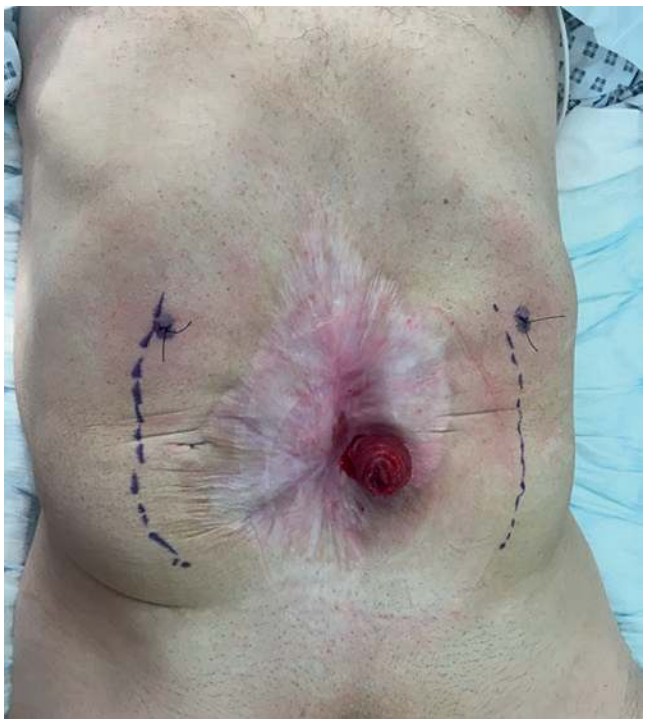

Fig. 10 Pre-operative state of the abdomen with a prolapsing enteric fistula in an epithelialized laparostomy wound; the edges of the retracted rectus muscles have been marked

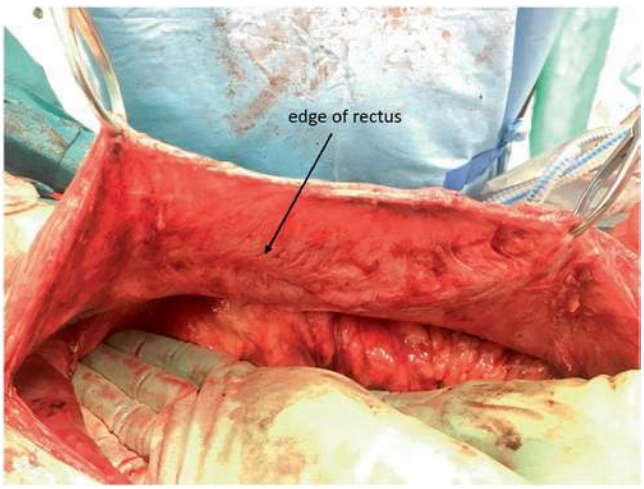

Fig. 11 Intra-operative identification of retracted edge of rectus muscle

(Fig. 11). The retrorectus plane was opened and further developed laterally till the perforating neurovascular bundles at the semilunar line were visualised and preserved (Fig. 12). As in this patient the arcuate line was very clearly visible

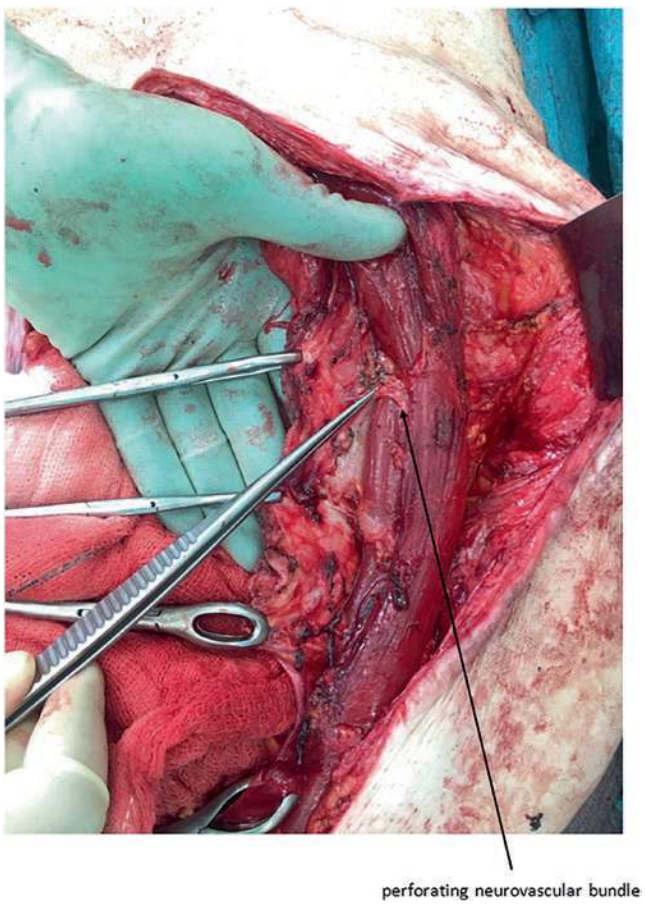

Fig. 12 Retrorectus dissection completed with visualisation of neurovascular bundles. Note the importance of medial traction on the posterior rectus sheath and the importance of visceral protection by placing a large surgical swab over the abdominal viscera

(Fig. 13), a decision was made to perform a bottom-up TAR. The incision of the posterior rectus sheath was therefore commenced at the arcuate line and extended cephalad, always keeping 5-10 mm medial to the neurovascular bundles, thereby exposing the muscle fibers of the transversus abdominis muscle extending medial to the semilunar line (Fig. 14). After division of the transversus abdominis muscle, the underlying transversalis fascia was exposed (Fig. 15) and blunt dissection was initiated in the plane between the transversus abdominis muscle anteriorly and the transversalis fascia posteriorly (Fig. 16). This blunt mobilisation of the visceral sac was extended cephalad beyond the xiphoid process, caudally into Retzius' space and laterally into the flank, exposing the iliopsoas muscle. After completing this same procedure on the contralateral side, significant medialisation had been achieved to allow for easy, tension-free closure of

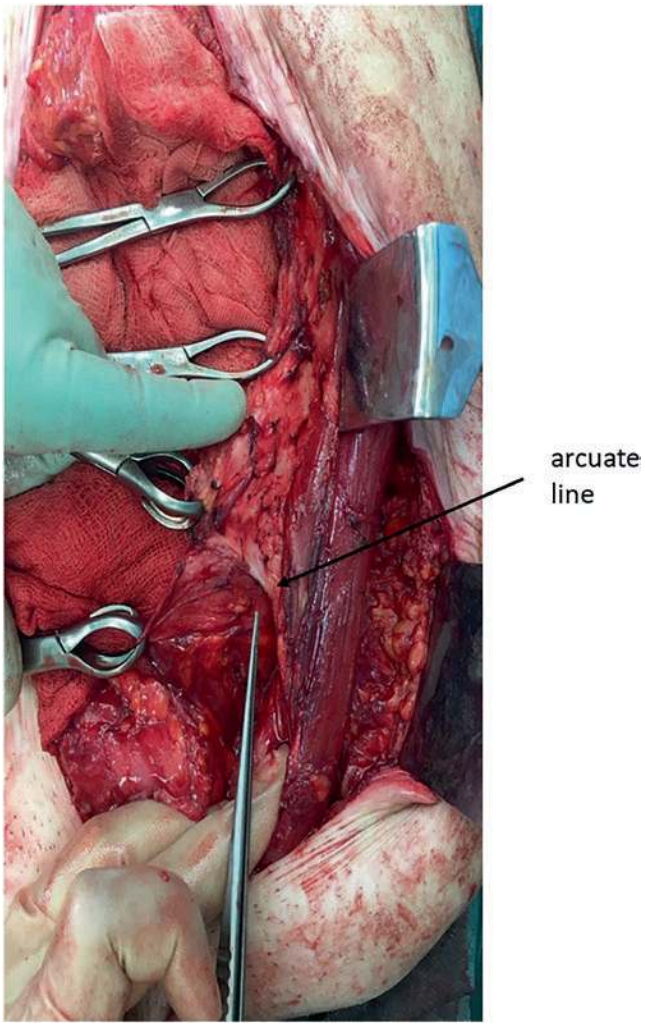

Fig. 13 Arcuate line clearly identified as starting point of bottom-up TAR

the posterior sheath (Fig. 17) and placement of a large synthetic absorbable mesh in the retromuscular space (Fig. 18). Though quite substantial medialisation of the anterior rectus sheath had been achieved as well, midline fascial closure

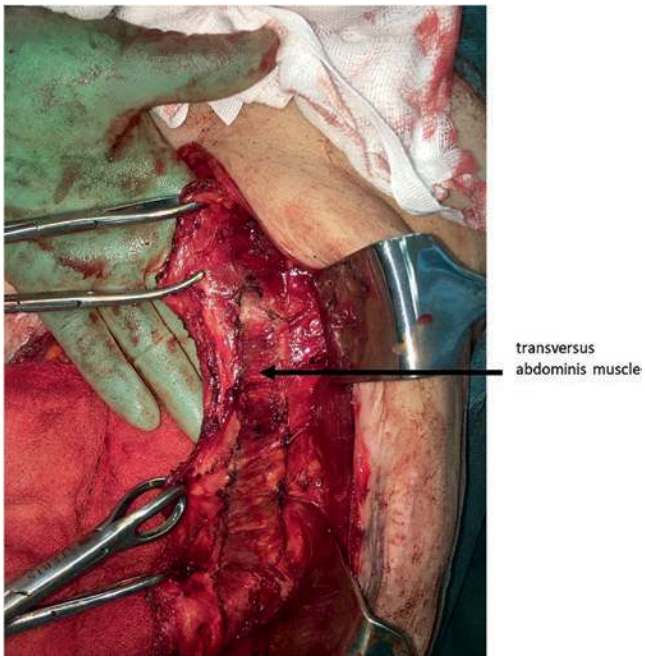

Fig. 14 Transversus abdominis muscle fibers clearly visible after opening the posterior rectus sheath medial to the semilunar line

was not feasible; therefore, the edges of the anterior sheath were medialised as far as possible and secured to the underlying mesh, thereby reconstructing the linea alba and closing the abdominal wall "cylinder" (Fig. 19).

Postoperatively, this patient made an excellent recovery with only a superficial wound infection. He was discharged home on the 18th postoperative day and at review at 6 months, was nutritionally autonomous with a well-healed laparotomy wound without any clinical signs of a hernia. His postoperative anatomy is shown in Fig. 20.

This case highlights the importance of a multidisciplinary approach to complex abdominal defect in intestinal failure. It also illustrates the fistulogenic natures of laparostomies and how every effort should be made to avoid leaving a patient with an open abdomen.

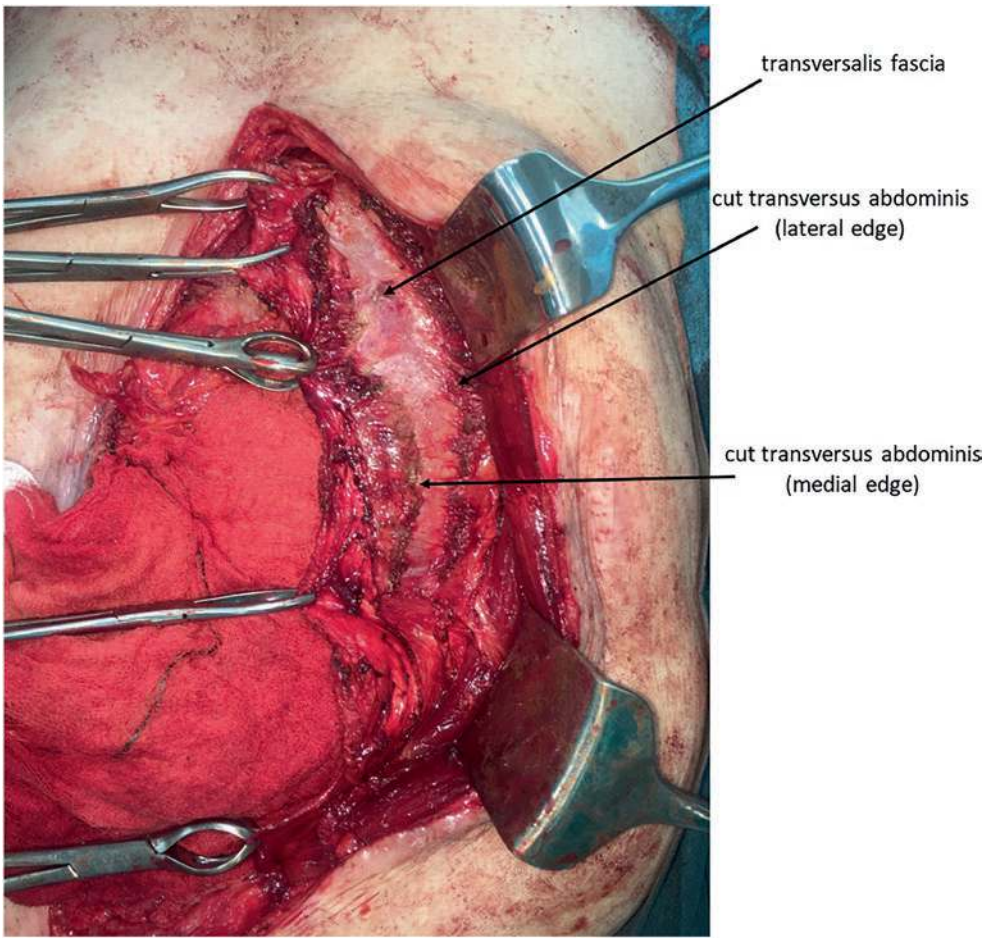

Fig. 15 Exposure of the transversalis fascia after division of the transversus abdominis muscle. Note again the importance of medial traction in exposing the transversalis fascia

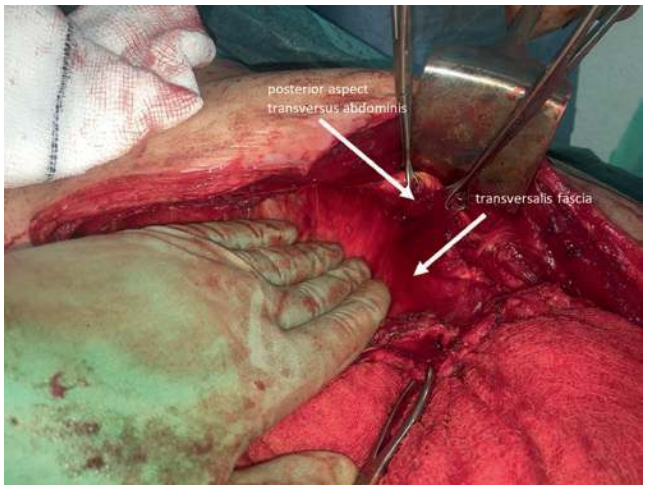

Fig. 16 Development of plane between posterior aspect of transversus abdominis muscle and transversalis fascia after division of the transversus abdominis muscle medial to the semilunar line. Note the importance of close dissection to the posterior aspect of the transversus abdominis muscle and exposing its bare fibers to develop the extratransversalis rather than the extraperitoneal plane

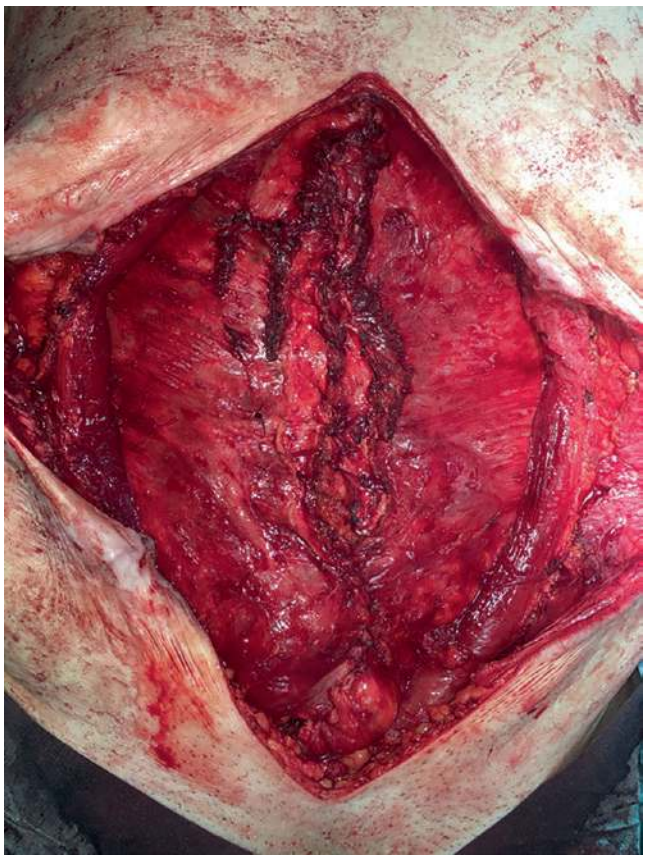

Fig. 17 Tension-free closure of posterior rectus sheath after bilateral TAR

Fig. 18 Large synthetic absorbable mesh placed in retromuscular space

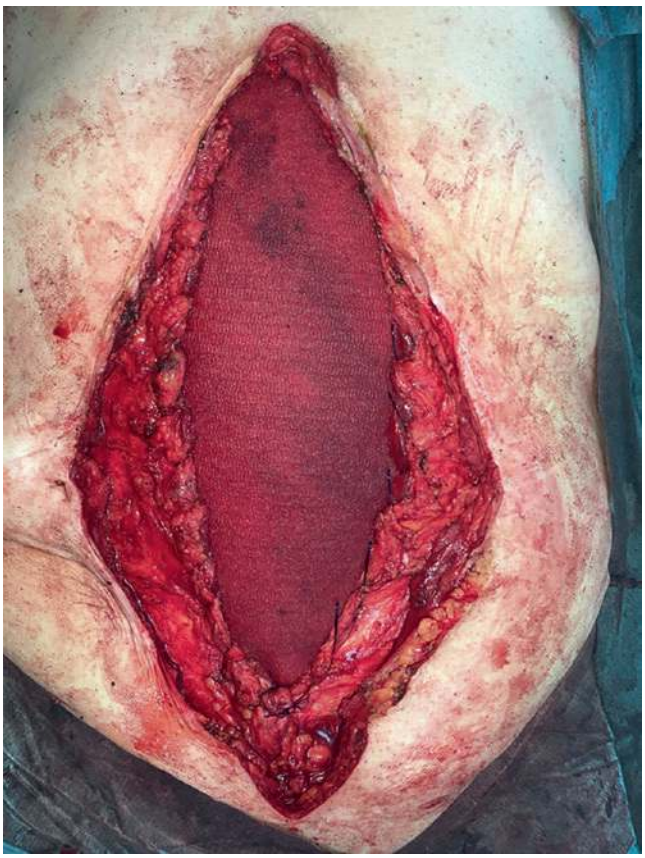

Fig. 19 Medial edges of anterior rectus sheath secured to underlying synthetic absorbable mesh to reconstruct the abdominal wall cylinder

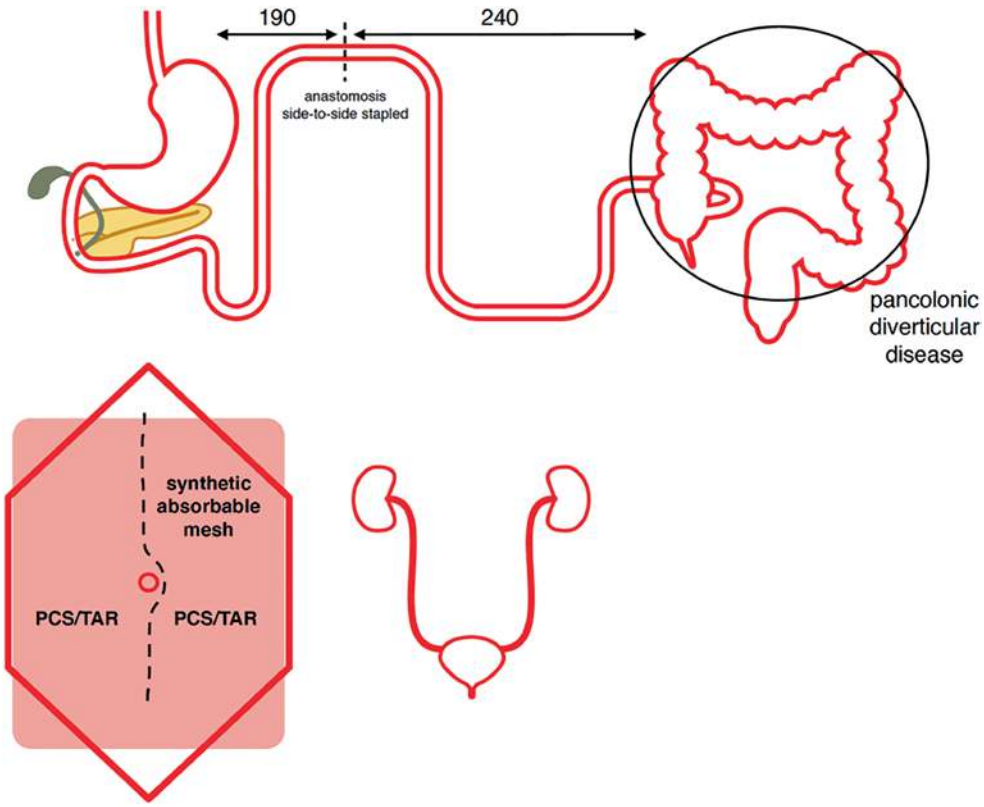

Fig. 20 Postoperative anatomy after repair of EAF and abdominal wall reconstruction using bilateral PCS-TAR reinforced by a large retromuscular synthetic absorbable mesh

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References

1. van Rooijen MMJ, Lange JF. Preventing incisional hernia: closing the midline laparotomy. Tech Coloproctol. 2018;22:623–5.
2. Burger JW, Luijendijk RW, Hop WC, et al. Long-term follow-up of a randomized controlled trial of suture versus mesh repair of incisional hernia. Ann Surg. 2004;240:578–83; discussion 583-575.
3. Pereira JA, Pera M, Grande L. Incidence of incisional hernia after open and laparoscopic colorectal cancer resection. Cir Esp. 2013;91:44–9.
4. Israelsson LA, Jonsson T. Suture length to wound length ratio and healing of midline laparotomy incisions. Br J Surg. 1993;80:1284–6.
5. Israelsson LA, Jonsson T. Closure of midline laparotomy incisions with polydioxanone and nylon: the importance of suture technique. Br J Surg. 1994;81:1606–8.
6. Israelsson LA, Jonsson T. Physical properties of self locking and conventional surgical knots. Eur J Surg. 1994;160:323–7.
7. Millbourn D, Cengiz Y, Israelsson LA. Effect of stitch length on wound complications after closure of midline incisions: a randomized controlled trial. Arch Surg. 2009;144:1056–9.
8. Deerenberg EB, Harlaar JJ, Steyerberg EW, et al. Small bites versus large bites for closure of abdominal midline incisions (STITCH): a double-blind, multicentre, randomised controlled trial. Lancet. 2015;386:1254–60.
9. Henriksen NA, Deerenberg EB, Venclauskas L, et al. Meta-analysis on materials and techniques for laparotomy closure: the MATCH review. World J Surg. 2018;42:1666–78.
10. Muysoms FE, Antoniou SA, Bury K, et al. European hernia society guidelines on the closure of abdominal wall incisions. Hernia. 2015;19:1–24.
11. Sahebally SM, McKevitt K, Stephens I, et al. Negative pressure wound therapy for closed laparotomy incisions in general and colorectal surgery: a systematic review and meta-analysis. JAMA Surg. 2018;153:e183467.
12. Shukla VK, Gupta A, Singh H, Pandey M, Gautam A. Cardiff repair of incisional hernia: a university hospital experience. Eur J Surg. 1998;164:271–4.
13. Malik RA, Scott NA. Double near and far prolene suture closure: a technique for abdominal wall closure after laparostomy. Br J Surg. 2001;88:146–7.
14. Harries RL, Torkington J. Stomal closure: strategies to prevent incisional hernia. Front Surg. 2018;5:28.
15. Bhangu A, Nepogodiev D, Futaba K, West Midlands Research Collaborative. Systematic review and meta-analysis of the incidence of incisional hernia at the site of stoma closure. World J Surg. 2012;36:973–83.
16. Reinforcement of Closure of Stoma Site Collaborative, West Midlands Research Collaborative. Prophylactic biological mesh reinforcement versus standard closure of stoma site (ROCSS): a multicentre, randomised controlled trial. Lancet. 2020;395:417–26.
17. Lee JT, Marquez TT, Clerc D, et al. Pursestring closure of the stoma site leads to fewer wound infections: results from a multicenter randomized controlled trial. Dis Colon Rectum. 2014;57:1282–9.
18. Obeid N, Sharma E, Dunstan M, et al. Negative pressure therapy for stoma closure sites-a nonrandomised case control study. Int J Colorectal Dis. 2020;36(1):161–7. https://doi.org/10.1007/s00384-020-03749-x.
19. Huger WE Jr. The anatomic rationale for abdominal lipectomy. Am Surg. 1979;45:612–7.
20. Korenkov M, Paul A, Sauerland S, et al. Classification and surgical treatment of incisional hernia. Results of an experts' meeting. Langenbecks Arch Surg. 2001;386:65–73.

21. Ventral Hernia Working Group, Breuing K, Butler CE, et al. Incisional ventral hernias: review of the literature and recommendations regarding the grading and technique of repair. Surgery. 2010;148:544–58.
22. Kanters AE, Krpata DM, Blatnik JA, Novitsky YM, Rosen MJ. Modified hernia grading scale to stratify surgical site occurrence after open ventral hernia repairs. J Am Coll Surg. 2012;215:787–93.
23. Slater NJ, Montgomery A, Berrevoet F, et al. Criteria for definition of a complex abdominal wall hernia. Hernia. 2014;18:7–17.
24. Petro CC, O'Rourke CP, Posielski NM, et al. Designing a ventral hernia staging system. Hernia. 2016;20:111–7.
25. Muysoms FE, Miserez M, Berrevoet F, et al. Classification of primary and incisional abdominal wall hernias. Hernia. 2009;13:407–14.
26. Luijendijk RW, Hop WC, van den Tol MP, et al. A comparison of suture repair with mesh repair for incisional hernia. N Engl J Med. 2000;343:392–8.
27. Itani KM, Rosen M, Vargo D, et al. Prospective study of single-stage repair of contaminated hernias using a biologic porcine tissue matrix: the RICH Study. Surgery. 2012;152:498–505.
28. Sacks JM, Broyles JM, Baumann DP. Considerations in abdominal wall reconstruction. Semin Plast Surg. 2012;26:5–7.
29. Gibson CL. Post-operative intestinal obstruction. Ann Surg. 1916;63:442–51.
30. Gibson CL. Operation for cure of large ventral hernia. Ann Surg. 1920;72:214–7.
31. Young D. Repair of epigastric incisional hernia. Br J Surg. 1961;48:514–6.
32. Maguire J, Young D. Repair of epigastric incisional hernia. Br J Surg. 1976;63:125–7.
33. Ramirez OM, Ruas E, Dellon AL. "Components separation" method for closure of abdominal-wall defects: an anatomic and clinical study. Plast Reconstr Surg. 1990;86:519–26.
34. Lowe JB, Garza JR, Bowman JL, Rohrich RJ, Strodel WE. Endoscopically assisted "components separation" for closure of abdominal wall defects. Plast Reconstr Surg. 2000;105:720–9; quiz 730.
35. Saulis AS, Dumanian GA. Periumbilical rectus abdominis perforator preservation significantly reduces superficial wound complications in "separation of parts" hernia repairs. Plast Reconstr Surg. 2002;109:2275–80; discussion 2281-2272.
36. Novitsky YW, Porter JR, Rucho ZC, et al. Open preperitoneal retrofascial mesh repair for multiply recurrent ventral incisional hernias. J Am Coll Surg. 2006;203:283–9.
37. Heniford BT, Ross SW, Wormer BA, et al. Preperitoneal ventral hernia repair: a decade long prospective observational study with analysis of 1023 patient outcomes. Ann Surg. 2020;271:364–74.
38. Carbonell AM, Cobb WS, Chen SM. Posterior components separation during retromuscular hernia repair. Hernia. 2008;12:359–62.
39. Novitsky YW, Elliott HL, Orenstein SB, Rosen MJ. Transversus abdominis muscle release: a novel approach to posterior component separation during complex abdominal wall reconstruction. Am J Surg. 2012;204:709–16.
40. Robin-Lersundi A, Blazquez Hernando L, Lopez-Monclus J, et al. How we do it: down to up posterior components separation. Langenbecks Arch Surg. 2018;403:539–46.
41. Wegdam JA, Thoolen JMM, Nienhuijs SW, de Bouvy N, de Vries Reilingh TS. Systematic review of transversus abdominis release in complex abdominal wall reconstruction. Hernia. 2019;23:5–15.
42. Petro CC, Como JJ, Yee S, et al. Posterior component separation and transversus abdominis muscle release for complex incisional hernia repair in patients with a history of an open abdomen. J Trauma Acute Care Surg. 2015;78:422–9.
43. Pauli EM, Juza RM, Winder JS. How I do it: novel parastomal herniorrhaphy utilizing transversus abdominis release. Hernia. 2016;20:547–52.
44. Munoz-Rodriguez JM, Lopez-Monclus J, San Miguel Mendez C, et al. Outcomes of abdominal wall reconstruction in patients with the combination of complex midline and lateral incisional hernias. Surgery. 2020;168:532–42.
45. Pauli EM, Wang J, Petro CC, et al. Posterior component separation with transversus abdominis release successfully addresses recurrent ventral hernias following anterior component separation. Hernia. 2015;19:285–91.
46. Parker SG, Halligan S, Liang MK, et al. International classification of abdominal wall planes (ICAP) to describe mesh insertion for ventral hernia repair. Br J Surg. 2020;107:209–17.
47. Carlsen BT, Farmer DG, Busuttil RW, Miller TA, Rudkin GH. Incidence and management of abdominal wall defects after intestinal and multivisceral transplantation. Plast Reconstr Surg. 2007;119:1247–55; discussion 1256-1248.
48. Giele H, Vaidya A, Reddy S, Vrakas G, Friend P. Current state of abdominal wall transplantation. Curr Opin Organ Transplant. 2016;21:159–64.
49. Gondolesi GE, Aguirre NF. Techniques for abdominal wall reconstruction in intestinal transplantation. Curr Opin Organ Transplant. 2017;22:135–41.
50. Parker SG, Halligan S, Blackburn S, et al. What exactly is meant by "loss of domain" for ventral hernia? Systematic review of definitions. World J Surg. 2019;43:396–404.
51. Martre P, Sarsam M, Tuech JJ, et al. New, simple and reliable volumetric calculation technique in incisional hernias with loss of domain. Hernia. 2020;24:403–9.
52. Sabbagh C, Dumont F, Robert B, et al. Peritoneal volume is predictive of tension-free fascia closure of large incisional hernias with loss of domain: a prospective study. Hernia. 2011;15:559–65.
53. Tanaka EY, Yoo JH, Rodrigues AJ Jr, et al. A computerized tomography scan method for calculating the hernia sac and abdominal cavity volume in complex large incisional hernia with loss of domain. Hernia. 2010;14:63–9.
54. Ibarra-Hurtado TR, Nuno-Guzman CM, Echeagaray-Herrera JE, Robles-Velez E, de Jesus G-JJ. Use of botulinum toxin type a before abdominal wall hernia reconstruction. World J Surg. 2009;33:2553–6.
55. Farooque F, Jacombs AS, Roussos E, et al. Preoperative abdominal muscle elongation with botulinum toxin A for complex incisional ventral hernia repair. ANZ J Surg. 2016;86:79–83.
56. Deerenberg EB, Elhage SA, Raible RJ, et al. Image-guided botulinum toxin injection in the lateral abdominal wall prior to abdominal wall reconstruction surgery: review of techniques and results. Skeletal Radiol. 2020;50(1):1–7. https://doi.org/10.1007/s00256-020-03533-6.
57. Zielinski MD, Goussous N, Schiller HJ, Jenkins D. Chemical components separation with botulinum toxin A: a novel technique to improve primary fascial closure rates of the open abdomen. Hernia. 2013;17:101–7.
58. Elstner KE, Read JW, Saunders J, et al. Selective muscle botulinum toxin A component paralysis in complex ventral hernia repair. Hernia. 2020;24:287–93.
59. Yurtkap Y, van Rooijen MMJ, Roels S, et al. Implementing preoperative Botulinum toxin A and progressive pneumoperitoneum through the use of an algorithm in giant ventral hernia repair. Hernia. 2020;25(2):389–98. https://doi.org/10.1007/s10029-020-02226-2.
60. Moreno IG. Chronic eventrations and large hernias; preoperative treatment by progressive pneumoperitomeum; original procedure. Surgery. 1947;22:945–53.
61. Bueno-Lledo J, Carreno-Saenz O, Torregrosa-Gallud A, Pous-Serrano S. Preoperative botulinum toxin and progressive pneumoperitoneum in loss of domain hernias-our first 100 cases. Front Surg. 2020;7:3.

62. Renard Y, Lardiere-Deguelte S, de Mestier L, et al. Management of large incisional hernias with loss of domain: a prospective series of patients prepared by progressive preoperative pneumoperitoneum. Surgery. 2016;160:426–35.
63. Martinez-Hoed J, Bonafe-Diana S, Bueno-Lledo J. A systematic review of the use of progressive preoperative pneumoperitoneum since its inception. Hernia. 2020;25(6):1443–58. https://doi.org/10.1007/s10029-020-02247-x.
64. Sugerman HJ, Kellum JM Jr, Reines HD, et al. Greater risk of incisional hernia with morbidly obese than steroid-dependent patients and low recurrence with prefascial polypropylene mesh. Am J Surg. 1996;171:80–4.
65. Giordano S, Garvey PB, Baumann DP, Liu J, Butler CE. Concomitant panniculectomy affects wound morbidity but not hernia recurrence rates in abdominal wall reconstruction: a propensity score analysis. Plast Reconstr Surg. 2017;140:1263–73.
66. Elhage SA, Marturano MN, Deerenberg EB, et al. Impact of panniculectomy in complex abdominal wall reconstruction: a propensity matched analysis in 624 patients. Surg Endosc. 2020;35(9):5287–94. https://doi.org/10.1007/s00464-020-08011-7.
67. Muirhead LJ, Shaw AV, Kontovounisios C, Warren OJ. Establishing a robust multidisciplinary team process in complex abdominal wall reconstruction within a colorectal surgical unit. Tech Coloproctol. 2019;23:379–83.
68. Birolini C, de Miranda JS, Tanaka EY, et al. The use of synthetic mesh in contaminated and infected abdominal wall repairs: challenging the dogma—a long-term prospective clinical trial. Hernia. 2020;24:307–23.
69. Petro CC, Rosen MJ. Fight or flight: the role of staged approaches to complex abdominal wall reconstruction. Plast Reconstr Surg. 2018;142:38S–44S.
70. Krpata DM, Prabhu AS, Tastaldi L, et al. Impact of inadvertent enterotomy on short-term outcomes after ventral hernia repair: an AHSQC analysis. Surgery. 2018;164:327–32.

Part IX

Pancreatitis

Intestinal Dysfunction and Failure in Acute Pancreatitis

John A. Windsor and Stephen A. McClave

Key Points

1. Acute pancreatitis is commonly is secondary to alcohol excess, gallstones or occasionally hyperlipidaemia.
2. A third of patients have a severe illness and may deteriorate over several days/weeks.
3. Severe acute pancreatitis is associated with a breakdown of the intestinal barrier, an increase in gut permeability, dysregulated immune responses, and dysbiosis and there develops an adversarial relationship between pathogenic bacteria and the host.
4. Intestinal dysfunction occurs early and is a key driver of disease severity. Infected pancreatic necrosis, organ failure and non occlusive mesenteric ischaemia are the main determinants for a poor outcome.
5. Citrulline and intestinal fatty acid binding protein (iFABP) are promising serum markers of intestinal injury.
6. Most patients can be given nutrition orally or via a nasogastric tube. However some need jejunal feeding but if insufficient or not tolerated then parenteral nutrition should be given.
7. Early aggressive enteral feeding should be avoided in patients who have persisting splanchnic vasoconstriction (e.g. ongoing volume and/or vasopressor requirements) as it can worsen the ischaemia leading to bowel perforation.
8. Although jejunal feeding has been traditionally advocated to rest the pancreas, nasogastric feeding has been shown to be safe and effective in the majority of patients.

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Acute Pancreatitis and Determinants of Severity

Acute pancreatitis is one of the most common gastrointestinal diseases requiring hospital admission. While the majority of patients have a mild, self-limiting course with no sequelae, up to a third of patients develop significant complications. These patients usually have a prolonged hospital admission, often require admission to intensive care units and a third may die [1].

While there are many aetiological factors, including gallstones, alcohol and hyperlipidaemia, the clinical, biochemical and radiological presentation of acute pancreatitis is remarkably similar. This suggests a common disease mechanisms. Studies of intra-acinar events show that premature activation of pancreatic proteases, calcium influx and activation of the NF-kB pathway are important early events [1]. Local inflammation ensues and the attraction and activation of macrophages and neutrophils stoke the flames of inflammation further.

Patients usually present with abdominal pain associated with an elevated blood amylase or lipase levels. The pancreas on contrast enhanced CT scanning during the first week will either demonstrate an oedematous pancreas or areas of hypoperfusion, which is termed pancreatic necrosis. Necrosis can also occur alongside the pancreas and is termed peripancreatic necrosis.

Acute pancreatitis is complicated by a wide range of local and systemic complications. The local complications of acute pancreatitis have been defined on the basis of morphological features and duration by CT scanning [2]. A collection within 4 weeks of the onset of acute pancreatitis that is not associated with any pancreatic necrosis is called an 'acute fluid collection' If associated with pancreatic necrosis it is an 'acute necrotic collection' (ANC). When these persist beyond 4 weeks these are characterised by a reactive fibroinflammatory wall and are called pseudocyst and walled-off-necrosis (WON), respectively. All of these collections can

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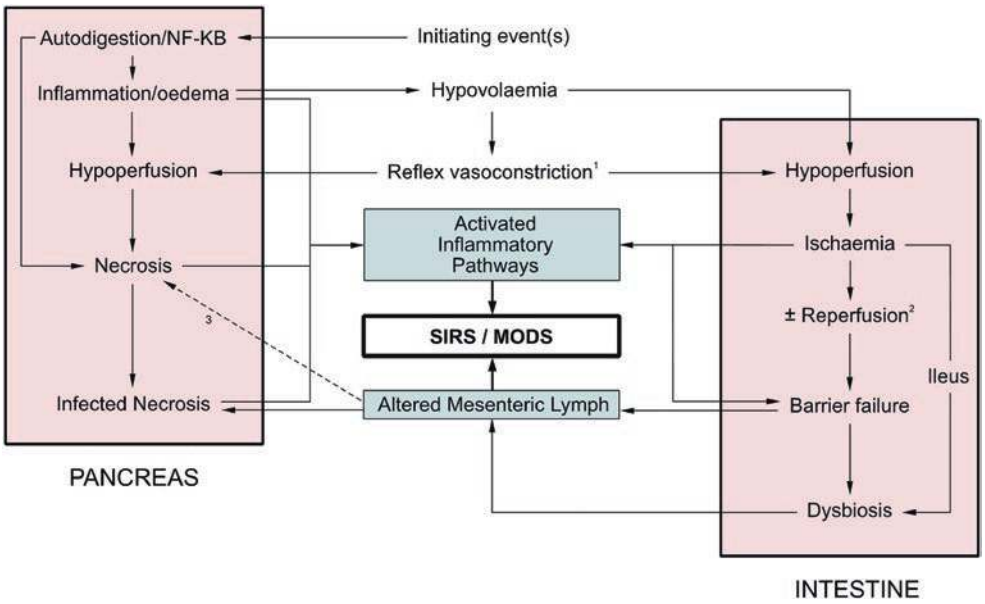

Fig. 1 The locoregional events in the pancreas and the intestine contribute to the development of systemic inflammation and organ dysfunction. (Adapted from [7])

become infected, often from an intestinal source, and this often heralds a downward clinical course.

The systemic complications of acute pancreatitis are analogous to that seen with severe sepsis, major trauma, hemorrhagic shock and other acute diseases. There is a systemic inflammatory response (with a compensatory anti-inflammatory response) driven by complex cytokine cascades. There is also end-organ dysfunction, which can lead to organ failure [2]. When organ dysfunction or failure is present for more than 48 h this is defined as 'persistent' organ failure, rather than 'transient'.

The two most important determinants of acute pancreatitis severity are infected pancreatic necrosis (as ANC or WON) and persistent organ failure [3], and the intestine has an important role in the development of both. These determinants are the basis for a validated classification of severity [4], which is useful for prospective trials and retrospective audits. The Determinants Based Classification (DBC) defines 4 categories of severity based on these two determinants: mild AP (no local or systemic complications), moderate AP (sterile local complication and/or transient organ dysfunction), severe AP (infected pancreatic necrosis or persistent organ failure) and critical AP (both infected pancreatic necrosis and persistent organ failure). The recent modified DBC has highlighted that severe AP with infected pancreatic necrosis has a very different morbidity and mortality profile than severe AP with persistent organ failure [5]. The former has high morbidity and a lower mortality because of improvements in the treatment of infected pancreatic necrosis. The latter is the opposite and reflects the ongoing challenges of treating multiple organ failure, where no specific treatment exists and management amounts to no more than organ support, while the disease takes its course.

A better understanding the fundamental pathophysiology of acute pancreatitis is required to reduce the morbidity and mortality of severe and critical acute pancreatitis. It is the pathophysiological events that are driving the diseases once the patient is admitted to hospital, usually 24–36 h following the onset of pain, that provide potential targets for effective treatment. The locoregional events that occur within the pancreas and the intestine are closely linked and serve to highlight the role of intestinal dysfunction in the outcome of acute pancreatitis (Fig. 1).

Intestinal dysfunction and failure is common, occurring up to 60% of patients in the intensive care unit [6] and this contributes to disease severity. This chapter will focus on the cause, effect, prevention and treatment of intestinal dysfunction and failure in acute pancreatitis. Important new insights and implications for management will be highlighted.

Causes of Intestinal Dysfunction and Failure in Acute Pancreatitis

The intestine is not an innocent bystander in severe AP, but is both a victim and a culprit. Intestinal dysfunction in AP has an important role in the development of the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) [7].

Acute pancreatitis is characterised by retroperitoneal edema, 'third space' fluid loss, and hypovolaemia [8]. The physiological response to this is the prioritisation blood flow

to vital organs at the expense of splanchnic blood flow. The increased sympathetic outflow that accompanies circulatory shock causes vasoconstriction of the mesenteric post-capillary veins and venules via alpha-adrenergic receptors. This causes 'auto-transfusion' of up to 30% of the total circulating blood volume, so improving the cardiac output and perfusion of other vital organs [9]. Vasoconstriction of the mesenteric afferent arterioles also occurs but this effect is mediated by the renin-angiotensin axis rather than the sympathetic nervous system [10]. The resulting increase in systemic vascular resistance helps to sustain the systemic blood pressure but results in low perfusion through the splanchnic bed.

The intestine, and other splanchnic organs, can adapt to low perfusion states by extracting up to 90% of the oxygen from the blood. This protective effect is has limits because prolonged extraction rates over 70% lead to regional ischaemia [11]. Resuscitation does not provide immediate relief, as the splanchnic region is the last to be reperfused [12]. Indeed, patients who appear to be adequately resuscitated, without clinical evidence of hypovolaemia, may continue to have intestinal ischaemia [13].

The importance of maintaining the barrier between luminal content and the systemic circulation has long been emphasized. It has been found that intestinal barrier dysfunction was present in almost 60% of patients with acute pancreatitis, and that increases in gut permeability correlate with markers of severity and the risk of organ failure and death [14, 15]. The intestinal barrier has several functional and structural components, which include the intestinal microflora, intestinal motility, digestive enzymes, unstirred water and mucous layer, glycocalyx [16], epithelial and endothelial layers, mucosal associated lymphoid tissue and the gut-liver axis. The most important element of the barrier is the epithelial layer which is a single layer of columnar cells arranged into villi and crypts. Microvilli line the apex of the cell and help provide a barrier to microbes. Tight junctions encircle the apical pole which help prevent the passage of molecules, including lipopolysaccharide and other bacterial proinflammatory mediators.

The intestine is particularly susceptible to ischemia because of the anatomy of the villus microcirculation. The countercurrent arrangement of veins around a central arteriole allows for arteriovenous shunting of oxygen and causes anoxia of the villus tip [17]. Ischemia causes hypoxanthine to accumulate and ATP is depleted through inadequate oxidative phosphorylation. In addition, xanthine dehydrogenase is converted to xanthine oxidase. When blood flow is restored xanthine oxidase converts hypoxanthine to xanthine with the liberation of the superoxide ion. The superoxide ion leads to the formation of further oxygen free radicals that injure intestinal cell membranes by lipid peroxidation [18]. Oxygen free radicals are also chemoattractant for neutrophils, and along with other mediators initiate migration of activated neutrophils into the re-perfused tissue. Thus, intestinal reperfusion causes further damage through oxidative stress and inflammatory mediators [19, 20]. Jejunal mitochondrial dysfunction occurs early in experimental acute pancreatitis [21] and could be a treatment target.

There are a number of other important mediators of intestinal injury. Phospholipase A_2, found in high concentration in the intestinal mucosa, plays an important role in mucosal injury and translocation [22]. It is excessively activated in intestinal ischaemia and is released under the partial control of TNF-a [23]. It generates proinflammatory lipid mediators such as platelet activating factor that stimulates endothelial cells and neutrophils, enhancing neutrophil-mediated tissue injury. It also generates arachidonic acid to liberate eicosanoids that cause direct tissue injury. Nitric oxide (NO) has both protective and injurious effects on the intestinal barrier [24]. Under normal conditions it is an antioxidant and signalling molecule that helps to maintain intestinal perfusion. But during ischaemia and reperfusion, NO is converted to cytotoxic nitrites by superoxide radicals. One such nitrite, peroxynitrite, activates poly(ADP-ribose) synthetase by breaking single strands of DNA. This nuclear enzyme then depletes enterocyte NADH and ATP and increases intestinal permeability [25]. The large concentrations of NO liberated from the intestine during ischaemia and reperfusion are probably due to an upregulation of inducible NO synthase (iNOS). Blockade of iNOS prevents the increased intestinal permeability [26] and mesenteric vascular hyporeactivity [27] caused by endotoxin. It also limits bacterial translocation during intestinal ischaemia and reperfusion [28].

In summary, intestinal ischaemia and reperfusion results in oxidative stress which damages cell membranes, with the direct insult to the intestine being triggered through activation of NFk-B and release of lysosomes (containing several proteases which degrade elastin, collagen, and fibrinogen) [14]. This injury to the intestine leads to increased permeability, the extent of which correlates with disease severity and is predictive of mortality [14]. Slowing of gut motility early after intestinal ischemia/reperfusion injury results in small intestinal bacterial overgrowth (SIBO), alteration in the microbiota [29], and bacterial translocation. The translocating bacteria can lead to infection of necrotic pancreatic tissue, an important determinant of mortality [3]. The early phase of inflammation is driven by molecular sensing of tissue damage, as the initial injury is characteristically sterile. But the increase in intestinal permeability and bacterial overgrowth can lead to secondary infection and endotoxemia [29], most often noted in severe AP after the first week.

Effects of Intestinal Dysfunction and Failure on the Severity and Prognosis of Acute Pancreatitis

Local pancreatic inflammation and the development of necrosis and infected necrosis are, in themselves, potent drivers of SIRS [20]. To this the development of intestinal ischaemia, injury and dysfunction adds significant further impetus towards the development of SIRS and MODS. Several models have been suggested to explain the role of the intestine in the development SIRS/MODS [30] covering the spectrum of acute and critical illness, and they are not mutually exclusive.

'Gut Starter' Model

This model focuses on the role of the neutrophil, which is primed as it passes through the mesenteric circulation during ischaemia and reperfusion of the intestine. These continue to circulate around the body in this primed yet inactive state until they are provoked by a second insult such as exposure to endotoxin [31]. Priming of the neutrophil is initiated by mesenteric lymph rather than portal blood and it is the lipid fraction generated by phospholipase A_2 that appears to be most important in priming neutrophils [32]. Neutrophils primed in this way exhibit an increased oxidative burst, augmented release of proteases and cytokines [33], and reduced apoptosis [34]. Neutrophils mediate damage by enhancing the ischaemic effect, releasing of oxygen free radicals and proteases, and amplifying the inflammatory response. Thus, neutrophils becoming potent mediators of SIRS/MODS when activated.

'Gut Motor' Model

In contrast this model focuses on the role of the intestinal barrier in the development of SIRS and MODS [30, 35]. In health, with an intact intestinal barrier, there is a dynamic symbiotic relationship between the intestinal microbiome and the host [30, 36]. There is ongoing crosstalk signalling between the commensal bacteria in the gut and pattern recognition receptors (PRRs) on the surface of the intestinal epithelium [37, 38]. The PRRs are Toll-like receptors (TLRs) and Nucleotide-binding Oligomerization Domain (NOD)-like receptors (NLRs) on the surface epithelium and within the cytoplasm of the epithelial cell. Commensal bacteria do not have the machinery to adhere to the intestinal epithelium, so parts of the commensal organisms (flagella, polysaccharides in the cell wall, or LPS endotoxin) serve as Microbial-Associated Molecular Patterns (MAMPs) which bind to the family of PRRs [37]. The depletion of IgG anti-endotoxin antibodies is a feature of severe acute pancreatitis [39]. This ongoing binding and crosstalk signalling maintains important aspects of barrier function. The crosstalk signalling between PRRs and the MAMPs cause Paneth cells to release anti-microbial peptides (Defensins and Trefoil proteins), goblet cells to produce mucus, intestinal epithelial cells to produce tight-junction proteins, and the dendritic cells to influence immune signalling in the submucosa [38]. In the presence of the commensal bacteria, appropriate immune responses result, as naïve T-lymphocytes are stimulated to mature into T-regulatory cells and Th2 cells of the humoral immune system. Butyrate production as a result of commensal organisms fermenting soluble fiber to short-chain fatty acids has an independent effect on this process, stimulating and enhancing barrier function, competitively excluding pathogens, inhibiting NFk-B production, and supporting appropriate immune responses [37].

Many of these processes are altered with acute pancreatitis. There is a breakdown of the intestinal barrier, an increase in gut permeability, dysregulated immune responses, and dysbiosis and there develops an adversarial relationship between pathogenic bacteria and the host [30, 36, 37]. Tight junctions are breached, enterocytes undergo increased apoptosis, endothelial repair mechanisms are compromised, and microbes penetrate the intestinal wall [37]. Cross-talk signalling between PRRs and MAMPs are replaced by signalling with products of stressed cells and necrosis called Danger-Associated Molecular Patterns (DAMPs) [35]. Virulent pathogenic bacteria, which emerge through quorum sensing, have the capability to bind to the intestinal epithelium directly. As a result of this binding, the pathogens themselves serve as Pathogen-Associated Molecular Patterns (PAMPs). The shift in binding from MAMPs to DAMPs/PAMPs induces differentiation of naïve T-cells to Th1 and Th17 lymphocytes (instead of Th2 and T-Regulatory cells), which has a proinflammatory effect [35]. Binding of the DAMPs and PAMPs to the PRRs leads to dysregulated immune responses, which are considered to be the basis for 'gut-origin sepsis' [30, 35]. With breakdown of the intestinal barrier there is thinning of the mucus layer which allows activated pancreatic enzymes to autodigest gut epithelium [40]. This facilitates further passage of luminal content into the portal venous and mesenteric lymphatic systems, including the pancreatic proteases [41] and lipoprotein lipases [42]. This translocation activates immune cells down-stream from the intestinal mucosa (i.e. Peyer's patches), macrophages in the lamina propria of the gut, mesenteric lymph nodes and Kupffer cells in the liver. These activated immune cells release inflammatory mediators that drive the onset of SIRS and MODS even without a focus of infection [38].

Emergence of a virulent pathobiome results in disappearance of over 90% of commensal bacteria, loss of biodiversity, antibiotic resistance, and an increase in systemic infectious complications [37]. Evidence of a shift in the gut microbiota is seen in severe AP, with an increase in pathogenic bacteria of the Enterobacteriaciae and Firmicutes family, and a decrease in the beneficial Bacteroidetes and Lactobacillus organisms [43]. Pathogenic Enterococcus of the Firmicutes phyla is increased, while the Acinetobacter of the Bifidoacterium phyla is decreased [43]. The extent of these gut microbiota modifications predict the severity of pancreatitis and the occurrence of systemic complications [40]. Coupled with the changes in the microbiota are an overexpression of proinflammatory cytokines and chemokines and a parallel decrease in Paneth cell-related antimicrobial peptides (Defensins and Trefoil peptides) [29, 43].

'Gut Lymph' Model

The role of mesenteric or gut lymph in the promotion of SIRS and MODS has received recent attention [42, 44–46]. This route from the intestine to the systemic circulation has been largely overlooked. Lymph draining from the injured intestine in acute and critical illness undergoes profound compositional changes and drains directly into the systemic circulation (i.e. bypassing the liver) and immediately upstream of the organs that fail most often, the heart, lungs and kidneys [47]. Toxic lymph activates TLRs and neutrophils at these distant sites promoting SIRS/MODS. Confirmation of the 'gut lymph'model in patients has been impeded by the difficulty in accessing mesenteric lymph for investigation, but there are a number of compelling animal studies which support this as an important disease mechanism. For instance, when animals with mild acute pancreatitis were subjected to mild intestinal ischaemia there was a marked decrease in pancreatic perfusion, an increase in the histological severity of acute pancreatitis and this effect was mediated by mesenteric lymph [48]. In another animal model of moderately severe acute pancreatitis ligation of the thoracic lymph duct prevented cardiac failure, independent of hypotension [49].

Clinical and Radiological Evidence of Intestinal Dysfunction and Failure in Acute Pancreatitis

The most common clinical evidence of intestinal dysfunction in patients with acute pancreatitis is seen with *feeding intolerance* [50]. Most guidelines indicate the need for early nutritional support, and have usually advocated naso-jejunal feeding [51], even for those with mild to moderate severity [52]. Although controversial, the latest evidence suggests that ward patients can be allowed *ad libitum* oral access to fluid and food for up to 96 h after admission [53]. If they are unable to tolerate sufficient intake to meet their calculated requirements then enteral nutrition is provided, initially via a nasogastric [54], but this tube can be advanced to the duodenum/jejunum, if required. If enteral nutrition fails to meet requirements, because of feeding intolerance, then supplemental parenteral nutrition may be required. Feeding intolerance is usually reported by patients as abdominal pain and bloating, nausea and/or vomiting. It can be reasonably predicted using a nomogram based on the Gastrointestinal Cardinal Symptom Index on day 2 and the aetiology of acute pancreatitis [55]. Patients requiring mechanical ventilation will not be able to report symptoms, making the diagnosis of intestinal dysfunction more difficult. But clinical signs will be apparent with a reduction or absence of bowel sounds, increased abdominal girth and a tympanic percussion note.

The clinical diagnosis of an ileus is strengthened by the presence of radiological features indicative of intestinal dysfunction, but this depends on the stage of the disease. The early features of small bowel distension with increased gas may be due to aerophagia when a patient is in severe pain. The classical features of an *adynamic ileus* may develop over several days, with distension of multiple loops of small and large bowel with air-fluid levels on an erect film. Classical descriptions of acute pancreatitis, before the advent of cross sectional imaging, included two radiological signs, usually in the left hypochondrium: 'sentinel loop' and 'colon cut-off'. These were taken as diagnostic features of acute pancreatitis itself, and are examples of a localised ileus in proximity to the inflammatory pancreatic phlegmon. Much more commonly, these features are seen on cross-sectional imaging, with contrast enhanced CT scanning which provides additional information about wall thickness, adequacy of mucosal perfusion, and presence of free peritoneal fluid. The presence of an ileus is a predictor of local infection in patients with acute necrotizing pancreatitis [56].

With severe and critical AP intestinal dysfunction can progress to non-occlusive mesenteric ischaemia (NOMI) and this occurs most often in patients within the ICU environment [57]. Initially the clinical symptoms and signs are that of ileus. Radiologically the development of NOMI is seen as *pneumatosis intestinalis*, or the presence of gas within the wall of the intestine, reflecting a loss of the intestinal barrier. This can be extensive and reversible, but further progression to transmural necrosis can result in intestinal perforation, peritonitis and death. Biomarkers for the early detection of reversible NOMI are urgently required [45, 58].

Clinical Assessment and Measurement of Intestinal Dysfunction and Failure in Acute Pancreatitis

The clinical assessment of intestinal dysfunction is limited to clinical and radiological methods because there is no reliable biomarker [6]. All the symptoms and signs are non-specific in relation to acute pancreatitis. A scoring system would be helpful for both clinical management and interventional studies, but of the14 scoring systems published to date, few have been adequately validated and none have been widely recommended or adopted.

The 'modified gastrointestinal failure' (mGIF) score is an excellent example of a clinical scoring system designed to assess intestinal dysfunction and failure in patients with severe acute pancreatitis [59]. Table 1 indicates the components of the scoring system, which includes clinical symptoms (feeding intolerance, intrabdominal hypertension and abdominal compartment syndrome) to which is added endotoxin concentration and CT findings. When measured within the first 3 days, this score strongly predicts the risk of infected pancreatic necrosis, MOF and mortality. Independent prospective validation of mGIF is warranted. When the mGIF score is combined with the SOFA or APACHE II scores the prediction of prognosis was even more accurate than with either score alone [59]. There is an argument for incorporating a measure of intestinal dysfunction and failure into scoring systems for MODS/MOF [60].

Another approach to the assessment of intestinal dysfunction in acute pancreatitis is the use of nasogastric tonometry, which combines CO_2 from the gastric lumen with bicarbonate from peripheral arterial blood to calculate a pHi. This has face validity because it is known that severe acute pancreatitis is associated with ischaemia of intestinal mucosa. The first pilot study showed that gastric intramucosal pH of <7.25 in the first 48 h was highly predictive of mortality [61]. Subsequent studies have shown that prolonged intestinal mucosal acidosis is associated with MOF after 24 h [62, 63]. Gastric tonometry has been used as an endpoint to monitor the response to resuscitation in critically ill patients. An early study found that the patients in whom resuscitation failed to correct a low pHi over the first 12 h had a higher mortality rate [64].

Several serum biomarkers of intestinal dysfunction have also been investigated. A recent meta-analysis on intestinal barrier dysfunction in patients with acute pancreatitis a number of tests of intestinal barrier function, including those that assess epithelial integrity, barrier function and bacterial translocation [65]. These are summarized in Table 2. A systematic review of potential biomarkers of intestinal ischaemia, irrespective of aetiology, revealed that the best diagnostic accuracy (by diagnostic odds ratios and area under the curve) were D-lactate (10.75, 0.86), glutathione S-transferase (8.82, 0.87) and intestinal fatty-acid binding protein (7.62 and 0.78) [66]. While promising, the performance of these biomarkers is suboptimal for routine clinical

Table 1 The modified gastrointestinal failure score (mGIF) to assess intestinal dysfunction in patients with severe acute pancreatitis (adapted from [59])

Modified gastrointestinal failure score			
Item	*Points*		
	0	*1*	*2*
gastrointestinal failure score	0	1–2	≥3
Intra-abdominal pressure (mmHg)	<12	12–20	>20 or ACS
Endotoxin concentration (pg/mL)	<10	10–50	>50
CT scan findings of bowel wall	None	Thickening or dilation	Thickening and dilation

	Gastrointestinal failure score
Points	*Clinical symptomatology*
0	Normal gastrointestinal function
1	Enteral feeding <50% of calculated requirements
2	Food intolerance or intra-abdominal hypertension
3	Food intolerance and intra-abdominal hypertension
4	Abdominal compartment syndrome

This comprises 4 items, one of which is the gastrointestinal failure score. ACS is abdominal compartment syndrome [106]. CT scan findings including thickening of the small bowel wall (oedema) and/or dilation (diameter > 2.5 cm). Food intolerance is when enteral feeding is not applicable because of high gastric aspirate volume, vomiting, bowel distension or severe diarrhoea

Table 2 Tests used to assess gut barrier function [adapted from [65]]

Classification	Subclassification	Test
Assessment of intestinal epithelial barrier integrity	Enterocyte injury	Intestinal fatty acid binding protein
		Citrulline
		Reduced glutathione
	Loss of paracellular barrier integrity	F-actin
Functional assessment of intestinal barrier	Active measurements	Lactose/mannitol ratio
		Lactose/rhamnose ratio
		Polyethylene glycols
		D-xylose
		Serum diamine oxidase
	Passive measurements	Endotoxins
Assessment of bacterial translocation		Endogenous anti-endotoxin antibodies
		DNA/RNA
		D-lactate
		Nitric oxide
		Rectal luminal lactate

use in individual patients, but may well have an important role when combined with other assessment methods.

Both citrulline (a byproduct of glutamine metabolism and synthesized in small bowel enterocyte) and intestinal fatty acid binding protein (iFABP, synthesized in mature enterocytes at the tip of small bowel villi, the region most susceptible to ischaemia) have been investigated as markers of intestinal injury in patients with acute pancreatitis, and they identified patients at high risk of complications [67]. In a large (n = 402) prospective multicenter cohort study higher admission serum iFABP levels were associated with pancreatic necrosis, systemic complications, invasive treatment, intensive care admission and mortality, and prediction was improved when iFABP was combined with venous lactate (AUC 0.8) [68]. This is consistent with the importance of early intestinal dysfunction in acute pancreatitis and it was suggested that this combination might be useful in guiding early fluid resuscitation [68] and predicting abdominal pressure related complications [69]. It has been found that iFABP is released almost too readily with mucosal ischaemia [70], and that a marker of ischaemia in the muscle layer of the intestine might have greater utility. For this serum alpha smooth muscle actin has been proposed as a 'troponin T of the gut' [71], but requires investigation in patients with acute pancreatitis.

Prevention and Treatment of Intestinal Dysfunction and Failure in Acute Pancreatitis

Historically the management of acute pancreatitis, as with other acute and critically diseases, has not given due regard to the role of the intestine. This relative 'intestinal neglect' suggests that some of the intestinal dysfunction associated with AP may be iatrogenic, particularly in the Intensive Care Unit (ICU). Aggressive volume replacement can lead to gut-wall (and generalised) edema [72], which with abdominal third spacing of fluids, ileus, and pancreatic fluid collections can contribute to abdominal compartment syndrome, causing further impairment of intestinal perfusion. Effective, goal-directed fluid resuscitation is required to reduce the risk of intestinal injury and dysfunction. The type of resuscitation fluid matters [73], but level 1 evidence is lacking [74]. The use of narcotics should be minimized, as both endogenous and exogenous opioid narcotics stimulate virulent expression of potential pathogens [43, 75]. Opioid narcotics may be avoided by providing alternative therapy [37] with sedatives, hypnotics, propofol or epidural. The inappropriate use of antibiotics may predispose to loss of intestinal commensal bacteria, reduced biodiversity (dysbiosis), and facilitate emergence of virulent antibiotic-resistent pathogens [37]. The judicious use of antibiotics, such as shortening the duration of therapy or employing de-escalation strategies will help promote refaunation of the gut with commensal organisms [75]. The need for vasopressor therapy, especially when non-selective agents are used, increases splanchnic vasoconstriction with the enhanced risk of intestinal ischaemia and pancreatic necrosis. And reliance on the parenteral route for nutrition therapy may exacerbate inflammation within the intestinal mucosa and retard efforts to restore intestinal barrier defences [37].

Oral and enteral nutritional support helps maintain the intestinal barrier and provide the nutritional requirements in a disease that can be highly catabolic. There is no place for not drinking or eating in order to 'rest the pancreas'. This is an outdated concept and might be replaced by the concept of 'gut rousing' which emphasizes the positive benefits of enteral nutrition in patients with acute pancreatitis [76]. Patients with mild to moderate acute pancreatitis can safely commence a soft normal diet on a voluntary basis, do not need to have a period of prior clear oral fluids, and do need to wait for the absence of pain and the normalization of serum pancreatic enzymes [77, 78]. This approach reduces the length of hospital stay. Processed foods containing emulsifying agents (e.g. carboxymethylcellulose or polysorbate 80) should be avoided as they decrease the mucus layer of the intestinal tract, reduce butyrate production, and promote a low-grade virulence of the microbiota [75].

Enteral nutrition becomes more important with more severe acute pancreatitis, and it is the preferred route for nutritional support because of safety, cost, efficacy, and benefits from this route of feeding [79]. It is important to avoid early aggressive enteral feeding in patients who have persisting splanchnic vasoconstriction (e.g. ongoing volume and/or vasopressor requirements) [80]. A slower advancement to goal over 3–4 days is important to decrease risk of mucosal ischemia in such an under-resuscitated patient, reduce the risk of refeeding syndrome, avoid the potential for overfeeding (where exogenous calories are added to the endogenous glucose produced by the liver), and allow time to guage tolerance to enteral feeding. In moderate acute pancreatitis with mild SIRS an on-demand oral diet is tolerated in 69% of patients and has the same outcome as similar patients placed on early enteral tube feeding within 24–36 h of onset of symptoms. However, in patients with severe acute pancreatitis, where SIRS/MODS requires admission to the ICU (especially if placed on mechanical ventilation), achieving enteral access and early initiation of enteral nutrition is required. While supplemental parenteral nutrition is required in 30–40% of patients with severe and critical acute pancreatitis, it is more expensive (~20×), associated with increased mucosal inflammation, increased proinflammatory cytokine release, loss of intestinal barrier function, upregulation of TLRs [37], and a shift in the microbiome from Firmicutes to the potentially pathogenic Proteobacter [81].

Enteral formulations have been evaluated in the context of acute pancreatitis. In an animal model, provision of a commercial blenderized whole food formula was shown to reduce systemic inflammation (measured by serum Il-6 levels), decrease growth of pathogens, and lead to greater colonic bacterial diversity than a chemically refined formula (unpublished). Elemental formulations and immunonutrition have not been shown to have any benefits over polymeric formulations [82]. Immune-modulating formulas (e.g. containing fish oil with or without arginine) have been tested in three small randomized controlled trials but the meta-analysis failed to show any significant impact on outcome [82]. This strategy probably warrants study in larger trials, as arginine acts as a vasodilator and might counter the splanchnic vasoconstriction with severe AP [20]. Glutamine supplementation appears of confer an advantage with parenteral nutrition but not with enteral nutrition [83]. Also polyamines derived from arginine and ornithine have been shown to be essential for epithelial cell migration, resolving intestinal wounds, and helping regulate epithelial permeability (by increasing expression of E-Cadherin tight junction proteins) [14].

Reducing the severity of intestinal mucosal injury is another potential strategy and there have been a number of promising approaches. In experimental models of severe acute pancreatitis the severity of intestinal mucosal barrier injury/dysfunction can be reduced with treatment by apocynin (NADPH oxidase inhibitor) [84], berberine from plants [85], anthraquinones isolated from rhubarb [86, 87], and continuous blood purification [88].

There are other approaches that target the intestinal lumen and microbiome to reduce intestinal dysfunction but these all require further investigation, These include soluable prebiotic fibre, which has been shown to decrease neutrophil infiltration and mucosal injury due to butyrate [14, 43]. The use of probiotics to promote refaunation with commensal organisms remains controversial. The probiotic arm of the PROPATRIA trial had a worse outcome due to non-occlusive mesenteric ischaemia [89]. Subsequent trials of probiotics have shown a reduced infection and hospital length of stay [90, 91]. Faecal transplantation to restore normal microbiome also has potential [29]. It has been shown that commensal bacterial populations in the context of AP are associated with a reduced level of inflammatory cytokines, systemic infectious complications and disease severity [43]. Other approaches requiring investigation in the context of AP include bovine serum derived immunoglobulin that can bind pathogens in the lumen and improve mucosal health [75]; fish oil derived Specialized Proresolving Molecules to reduce intestinal inflammation [92]; interference with bile salt metabolism by Farnesoid-X receptor antagonists to decrease the Firmicutes:Bacteroidetes ratio and improve insulin sensitivity [93]; the release of phosphate (bound to PEG and released in cecum) to reduce virulence expression by promoting reversion towards commensal pattern [36].

Experimental treatment strategies that improve intestinal motility include melatonin (induced by enteral feeding) [14], rhubarb [94, 95] and other traditional chinese medicines which are anti-inflammatory and prokinetic (producing diarrhoea and gut decontamination) [96]. Systemic experimental anti-inflammatory treatments that might reduce intestinal and systemic inflammation, include anti-TNF-alpha [14], PPAR-alpha agonists [29], and Lactated Ringer's solution for fluid resuscitation [29, 97].

Treatment strategies are being developed to target the effects of toxic mesenteric lymph in acute pancreatitis [47]. Enteral lipophilic supplements that target toxic moieties in mesenteric lymph may reduce SIRS/MODS [98] and prove more effective than external drainage of thoracic duct lymph [99, 100].

Role of Surgery in Treating Intestinal Failure in Acute Pancreatitis

The 'step-up approach' to the treatment of infected local complications of acute pancreatitis has meant that open surgical treatment is now rarely required [101, 102]. This approach entails drainage (endoscopic or percutaneous) which is successful in up to half of the patients for whom open pancreatic necrosectomy would have previously been required. Minimally invasive necrosectomy (MIN, endoscopic or percutaneous debridement) is indicated when this drainage fails, and only if MIN fails would a patient be considered for open pancreatic necrosectomy. The open surgical treatment of infected pancreatic necrosis is associated with an increased risk of enterocutaneous fistulae [102, 103]. Surgery may also be required for the management of enterocutaneous fistulae (see Acute Surgical Intestinal Failure. Sepsis and Enterocutaneous Fistula(s)). These rarely occur spontaneously, and are most often seen following open surgery where there has been inadvertent bowel injury. It also happens as a result of drain erosion into bowel.

Surgery is no longer first-line treatment for the haemorrhagic complications of acute pancreatitis, as selective angiography and embolization are usually successful [104]. Open surgery is now only required for a number of specific indications, and these have some relevance to intestinal dysfunction. The development of abdominal compartment syndrome, which contributes to intestinal and renal dysfunction, might be treatment by temporary laparostomy for decompression [105]. This problem is now less frequent with a less aggressive approach to fluid resuscitation [106, 107]. Urgent abdominal surgery is sometimes required for NOMI, and the extent of intestinal resection will be dictated by the extent of infarction. Early detection of NOMI by CT might circum-

vent surgery by stopping enteral feeding, non-selective vasopressors and close observation [57].

Conclusion

Intestinal dysfunction and failure are important features of acute pancreatitis, that have not been given due regard. For decades, the focus of management in severe AP has centered on reducing inflammation within the gland, forbidding oral intake and 'putting the pancreas to rest'. Current management of acute pancreatitis can result in an iatrogenic intestinal dysfunction and failure. This can occur with aggressive fluid resuscitation, narcotic analgesia, antibiotic treatment and vasopressor support. Intestinal dysfunction occurs early and is a key driver of disease severity, amplifying the systemic inflammation and organ dysfunction, increasing disease severity, increasing the need for intervention and the risk of local and systemic complications, including mortality. There are new developments in the clinical and radiological assessment of intestinal dysfunction, which should allow earlier detection and intervention. The causes and effects of intestinal dysfunction are being elucidated and these give impetus to new treatment approaches that will specifically target aspects of intestinal dysfunction, including intestinal permeability, dysregulated immune responses, dysbiosis, and gut-derived sepsis. Successful treatments will be evidenced by refaunation of commensal bacteria, intact barrier defenses and intestinal homeostasis. And enteral nutrition will continue to have a vital role in the prevention and treatment of intestinal dysfunction, and further advances will include supplements to improve barrier and immune dysfunction. These should in turn reduce the systemic inflammatory response, the risk of end-organ dysfunction and the severity of acute pancreatitis.

References

1. Forsmark CE, Campion EW, Swaroop Vege S, Wilcox CM. Acute pancreatitis. N Engl J Med. 2016;375(20):1972–81.
2. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102–11.
3. Petrov MS, Shanbhag S, Chakraborty M, Phillips ARJ, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology. 2010;139(3):813–20.
4. Dellinger EP, Forsmark CE, Layer P, Levy P, Maravi-Poma E, Petrov MS, et al. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. Ann Surg. 2012;256(6):875–80.
5. Zubia-Olaskoaga F, Maravi-Poma E, Urreta-Barallobre I, Ramirez-Puerta MR, Mourelo-Farina M, Marcos-Neira MP, et al. Comparison between revised Atlanta classification and determinant-based classification for acute pancreatitis in intensive care medicine. Why do not use a modified determinant-based classification? Crit Care Med. 2016;44(5):910–7.
6. Reintam Blaser A, Jakob SM, Starkopf J. Gastrointestinal failure in the ICU. Curr Opin Crit Care. 2016;22(2):128–41.
7. Flint RS, Windsor JA. The role of the intestine in the pathophysiology and management of severe acute pancreatitis. HPB (Oxford). 2003;5(2):69–85.
8. Thandassery RB, Yadav TD, Dutta U, Appasani S, Singh K, Kochhar R. Hypotension in the first week of acute pancreatitis and APACHE II score predict development of infected pancreatic necrosis. Dig Dis Sci. 2015;60(2):537–42.
9. Flint R, Windsor J, Bonham M. Trends in the management of severe acute pancreatitis: interventions and outcome. ANZ J Surg. 2004;74(5):335–42.
10. Aneman A, Svensson M, Broome M, Biber B, Petterson A, Fandriks L. Specific angiotensin II receptor blockage improves intestinal perfusion during graded hypovolemia in pigs. Crit Care Med. 2000;28(3):818–23.
11. Rowell LB, Blackmon JR, Kenny MA, Escourrou P. Splanchnic vasomotor and metabolic adjustments to hypoxia and exercise in humans. Am J Physiol. 1984;247(2 Pt 2):H251–8.
12. Biffl WL, Moore EE. Splanchnic ischaemia/reperfusion and multiple organ failure. Br J Anaesth. 1996;77(1):59–70.
13. Ruokonen E, Uusaro A, Alhava E, Takala J. The effect of dobutamine infusion on splanchnic blood flow and oxygen transport in patients with acute pancreatitis. Intensive Care Med. 1997;23(7):732–7.
14. Guo ZZ, Wang P, Yi ZH, Huang ZY, Tang CW. The crosstalk between gut inflammation and gastrointestinal disorders during acute pancreatitis. Curr Pharm Des. 2014;20(7):1051–62.
15. Ammori BJ, Fitzgerald P, Hawkey P, McMahon MJ. The early increase in intestinal permeability and systemic endotoxin exposure in patients with severe acute pancreatitis is not associated with systemic bacterial translocation: molecular investigation of microbial DNA in the blood. Pancreas. 2003;26(1):18–22.
16. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med. 2013;369(13):1243–51.
17. Takala J. Determinants of splanchnic blood flow. Br J Anaesth. 1996;77(1):50–8.
18. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med. 1985;312(3):159–63.
19. Tian R, Tan JT, Wang RL, Xie H, Qian YB, Yu KL. The role of intestinal mucosa oxidative stress in gut barrier dysfunction of severe acute pancreatitis. Eur Rev Med Pharmacol Sci. 2013;17(3):349–55.
20. McClave SA. Drivers of oxidative stress in acute pancreatitis: the role of nutrition therapy. JPEN J Parenter Enteral Nutr. 2012;36(1):24–35.
21. Mittal A, Hickey AJ, Chai CC, Loveday BP, Thompson N, Dare A, et al. Early organ-specific mitochondrial dysfunction of jejunum and lung found in rats with experimental acute pancreatitis. HPB (Oxford). 2011;13(5):332–41.
22. Xu D, Lu Q, Deitch EA. Calcium and phospholipase A2 appear to be involved in the pathogenesis of hemorrhagic shock-induced mucosal injury and bacterial translocation. Crit Care Med. 1995;23(1):125–31.
23. Redl H, Schlag G, Schiesser A, Davies J. Tumor necrosis factor is a mediator of phospholipase release during bacteremia in baboons. Am J Physiol. 1993;264(6 Pt 2):H2119–23.
24. Salzman AL, Menconi MJ, Unno N, Ezzell RM, Casey DM, Gonzalez PK, et al. Nitric oxide dilates tight junctions and depletes ATP in cultured Caco-2BBe intestinal epithelial monolayers. Am J Physiol. 1995;268(2 Pt 1):G361–73.
25. Kennedy M, Denenberg AG, Szabo C, Salzman AL. Poly(ADP-ribose) synthetase activation mediates increased permeability

induced by peroxynitrite in Caco-2BBe cells. Gastroenterology. 1998;114(3):510–8.
26. Mishima S, Xu D, Deitch EA. Increase in endotoxin-induced mucosal permeability is related to increased nitric oxide synthase activity using the ussing chamber. Crit Care Med. 1999;27(5):880–6.
27. Kavuklu B, Iskit AB, Guc MO, Ilhan M, Sayek I. Aminoguanidine attenuates endotoxin-induced mesenteric vascular hyporeactivity. Br J Surg. 2000;87(4):448–53.
28. Suzuki Y, Deitch EA, Mishima S, Lu Q, Xu D. Inducible nitric oxide synthase gene knockout mice have increased resistance to gut injury and bacterial translocation after an intestinal ischemia-reperfusion injury. Crit Care Med. 2000;28(11):3692–6.
29. Leal-Lopes C, Velloso FJ, Campopiano JC, Sogayar MC, Correa RG. Roles of commensal microbiota in pancreas homeostasis and pancreatic pathologies. J Diabetes Res. 2015;2015:284680.
30. Mittal R, Coopersmith CM. Redefining the gut as the motor of critical illness. Trends Mol Med. 2014;20(4):214–23.
31. Moore EE, Moore FA, Franciose RJ, Kim FJ, Biffl WL, Banerjee A. The postischemic gut serves as a priming bed for circulating neutrophils that provoke multiple organ failure. J Trauma. 1994;37(6):881–7.
32. Gonzalez RJ, Moore EE, Ciesla DJ, Biffl WL, Offner PJ, Silliman CC. Phospholipase A(2)—derived neutral lipids from posthemorrhagic shock mesenteric lymph prime the neutrophil oxidative burst. Surgery. 2001;130(2):198–203.
33. Zallen G, Moore EE, Johnson JL, Tamura DY, Aiboshi J, Biffl WL, et al. Circulating postinjury neutrophils are primed for the release of proinflammatory cytokines. J Trauma. 1999;46(1):42–8.
34. Biffl WL, Moore EE, Zallen G, Johnson JL, Gabriel J, Offner PJ, et al. Neutrophils are primed for cytotoxicity and resist apoptosis in injured patients at risk for multiple organ failure. Surgery. 1999;126(2):198–202.
35. Klingensmith NJ, Coopersmith CM. The Gut as the motor of multiple organ dysfunction in critical illness. Crit Care Clin. 2016;32(2):203–12.
36. Krezalek MA, DeFazio J, Zaborina O, Zaborin A, Alverdy JC. The Shift of an intestinal "Microbiome" to a "Pathobiome" governs the course and outcome of sepsis following surgical injury. Shock. 2016;45(5):475–82.
37. McClave SA, Lowen CC, Martindale RG. The 2016 ESPEN Arvid wretlind lecture: The gut in stress. Clin Nutr. 2018;37(1):19–36.
38. Lebeer S, Vanderleyden J, De Keersmaecker SC. Host interactions of probiotic bacterial surface molecules: comparison with commensals and pathogens. Nat Rev Microbiol. 2010;8(3):171–84.
39. Windsor JA, Fearon KC, Ross JA, Barclay GR, Smyth E, Poxton I, et al. Role of serum endotoxin and antiendotoxin core antibody levels in predicting the development of multiple organ failure in acute pancreatitis. Br J Surg. 1993;80(8):1042–6.
40. Schmid-Schonbein GW, Chang M. The autodigestion hypothesis for shock and multi-organ failure. Ann Biomed Eng. 2014;42(2):405–14.
41. Mittal A, Middleditch M, Ruggiero K, Buchanan CM, Jullig M, Loveday B, et al. The proteome of rodent mesenteric lymph. Am J Physiol Gastrointest Liver Physiol. 2008;295(5):G895–903.
42. Deitch EA. Gut-origin sepsis: evolution of a concept. Surgeon. 2012;10(6):350–6.
43. Pagliari D, Saviano A, Newton EE, Serricchio ML, Dal Lago AA, Gasbarrini A, et al. Gut microbiota-immune system crosstalk and pancreatic disorders. Mediators Inflamm. 2018;2018:7946431.
44. Fanous MY, Phillips AJ, Windsor JA. Mesenteric lymph: the bridge to future management of critical illness. JOP. 2007;8(4):374–99.
45. Assimakopoulos SF, Triantos C, Thomopoulos K, Fligou F, Maroulis I, Marangos M, et al. Gut-origin sepsis in the critically ill patient: pathophysiology and treatment. Infection. 2018;46(6):751–60.
46. Windsor JA, Trevaskis N, Phillips AJ. Gut lymph model gives new treatment strategies for organ failure. JAMA Surgery. 2022;157(6):540–1. https://doi.org/10.1001/jamasurg.2022.0654.
47. Windsor JA, Escott A, Brown L, Phillips AR. Novel strategies for the treatment of acute pancreatitis based on the determinants of severity. J Gastroenterol Hepatol. 2017;32(11):1796–803.
48. Flint RS, Phillips AR, Power SE, Dunbar PR, Brown C, Delahunt B, et al. Acute pancreatitis severity is exacerbated by intestinal ischemia-reperfusion conditioned mesenteric lymph. Surgery. 2008;143(3):404–13.
49. Shanbhag ST, Choong B, Petrov M, Delahunt B, Windsor JA, Phillips ARJ. Acute pancreatitis conditioned mesenteric lymph causes cardiac dysfunction in rats independent of hypotension. Surgery. 2018;163(5):1097–105.
50. Bevan MG, Asrani VM, Bharmal S, Wu LM, Windsor JA, Petrov MS. Incidence and predictors of oral feeding intolerance in acute pancreatitis: a systematic review, meta-analysis, and meta-regression. Clin Nutr. 2017;36(3):722–9.
51. Working Group IAPAPAAPG. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013;13(4 Suppl 2):e1–15.
52. Petrov MS, McIlroy K, Grayson L, Phillips AR, Windsor JA. Early nasogastric tube feeding versus nil per os in mild to moderate acute pancreatitis: a randomized controlled trial. Clin Nutr. 2013;32(5):697–703.
53. Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Boermeester MA, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. N Engl J Med. 2014;371(21):1983–93.
54. Eatock FC, Chong P, Menezes N, Murray L, McKay CJ, Carter CR, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. Am J Gastroenterol. 2005;100(2):432–9.
55. Bevan MG, Asrani VM, Pendharkar SA, Goodger RL, Windsor JA, Petrov MS. Nomogram for predicting oral feeding intolerance in patients with acute pancreatitis. Nutrition. 2017;36:41–5.
56. Moran RA, Jalaly NY, Kamal A, Rao S, Klapheke R, James TW, et al. Ileus is a predictor of local infection in patients with acute necrotizing pancreatitis. Pancreatology. 2016;16(6):966–72.
57. Al-Diery H, Phillips A, Evennett N, Pandanaboyana S, Gilham M, Windsor JA. The Pathogenesis of nonocclusive mesenteric ischemia: implications for research and clinical practice: review article. J Intensive Care Med. 2018;34(10):771–81. https://doi.org/10.1177/0885066618788827.
58. Hong J, Gilder E, Blenkiron C, Jiang Y, Evennett NJ, Petrov MS, et al. Nonocclusive mesenteric infarction after cardiac surgery: potential biomarkers. J Surg Res. 2017;211:21–9.
59. Sun JK, Li WQ, Ni HB, Ke L, Tong ZH, Li N, et al. Modified gastrointestinal failure score for patients with severe acute pancreatitis. Surg Today. 2013;43(5):506–13.
60. Khadaroo RG, Marshall JC. Gastrointestinal dysfunction in the critically ill: can we measure it? Crit Care. 2008;12(5):180.
61. Bonham MJ, Abu-Zidan FM, Simovic MO, Windsor JA. Gastric intramucosal pH predicts death in severe acute pancreatitis. Br J Surg. 1997;84(12):1670–4.
62. Juvonen PO, Alhava EM, Takala JA. Gastric tonometry in assessing splanchnic tissue perfusion in acute pancreatitis. Scand J Gastroenterol. 2000;35(3):318–21.
63. Kovacs GC, Telek G, Hamar J, Furesz J, Regoly-Merei J. Prolonged intestinal mucosal acidosis is associated with multiple organ failure in human acute pancreatitis: gastric tonometry revisited. World J Gastroenterol. 2006;12(30):4892–6.
64. Doglio GR, et al. Gastric mucosal pH as a prognostic index of mortality in critically ill patients. Crit Care Med. 1991;9(8):1037–40.

65. Wu LM, Sankaran SJ, Plank LD, Windsor JA, Petrov MS. Meta-analysis of gut barrier dysfunction in patients with acute pancreatitis. Br J Surg. 2014;101(13):1644–56.
66. Evennett NJ, Petrov MS, Mittal A, Windsor JA. Systematic review and pooled estimates for the diagnostic accuracy of serological markers for intestinal ischemia. World J Surg. 2009;33(7):1374–83.
67. Goswami P, Sonika U, Moka P, Sreenivas V, Saraya A. Intestinal fatty acid binding protein and citrulline as markers of gut injury and prognosis in patients with acute pancreatitis. Pancreas. 2017;46(10):1275–80.
68. Kupcinskas J, Gedgaudas R, Hartman H, Sippola T, Lindstrom O, Johnson CD, et al. Intestinal fatty acid binding protein as a marker of necrosis and severity in acute pancreatitis. Pancreas. 2018;47(6):715–20.
69. Strang SG, Van Waes OJ, Van der Hoven B, Ali S, Verhofstad MH, Pickkers P, et al. Intestinal fatty acid binding protein as a marker for intra-abdominal pressure-related complications in patients admitted to the intensive care unit; study protocol for a prospective cohort study (I-Fabulous study). Scand J Trauma Resusc Emerg Med. 2015;23:6.
70. Jin T, Jiang K, Deng L, Guo J, Wu Y, Wang Z, et al. Response and outcome from fluid resuscitation in acute pancreatitis: a prospective cohort study. HPB (Oxford). 2018;20(11):1082–91.
71. Evennett N, Cerigioni E, Hall NJ, Pierro A, Eaton S. Smooth muscle actin as a novel serologic marker of severe intestinal damage in rat intestinal ischemia-reperfusion and human necrotising enterocolitis. J Surg Res. 2014;191(2):323–30.
72. Wu LM, Pendharkar SA, Asrani VM, Windsor JA, Petrov MS. Effect of intravenous fluids and analgesia on dysmotility in patients with acute pancreatitis. Pancreas. 2017;46(7):858–66.
73. Zhao G, Zhang JG, Wu HS, Tao J, Qin Q, Deng SC, et al. Effects of different resuscitation fluid on severe acute pancreatitis. World J Gastroenterol. 2013;19(13):2044–52.
74. Haydock MD, Mittal A, Wilms HR, Phillips A, Petrov MS, Windsor JA. Fluid therapy in acute pancreatitis. Ann Surg. 2013;257(2):182–8.
75. McClave SA, Martindale RG. Why do current strategies for optimal nutritional therapy neglect the microbiome? Nutrition. 2019;60:100–5.
76. Petrov MS, Windsor JA. Nutritional management of acute pancreatitis: the concept of 'gut rousing'. Curr Opin Clin Nutr Metab Care. 2013;16(5):557–63.
77. Teich N, Aghdassi A, Fischer J, Walz B, Caca K, Wallochny T, et al. Optimal timing of oral refeeding in mild acute pancreatitis: results of an open randomized multicenter trial. Pancreas. 2010;39(7):1088–92.
78. Sathiaraj E, Murthy S, Mansard MJ, Rao GV, Mahukar S, Reddy DN. Clinical trial: oral feeding with a soft diet compared with clear liquid diet as initial meal in mild acute pancreatitis. Aliment Pharmacol Ther. 2008;28(6):777–81.
79. Olah A, Romics L Jr. Enteral nutrition in acute pancreatitis: a review of the current evidence. World J Gastroenterol. 2014;20(43):16123–31.
80. Arabi YM, McClave SA. Enteral nutrition should not be given to patients on vasopressor agents. Crit Care Med. 2020;48(1):119–21.
81. Ralls MW, Miyasaka E, Teitelbaum DH. Intestinal microbial diversity and perioperative complications. JPEN J Parenter Enteral Nutr. 2014;38(3):392–9.
82. Petrov MS, Loveday BP, Pylypchuk RD, McIlroy K, Phillips AR, Windsor JA. Systematic review and meta-analysis of enteral nutrition formulations in acute pancreatitis. Br J Surg. 2009;96(11):1243–52.
83. Asrani V, Chang WK, Dong Z, Hardy G, Windsor JA, Petrov MS. Glutamine supplementation in acute pancreatitis: a meta-analysis of randomized controlled trials. Pancreatology. 2013;13(5):468–74.
84. Deng W, Abliz A, Xu S, Sun R, Guo W, Shi Q, et al. Severity of pancreatitisassociated intestinal mucosal barrier injury is reduced following treatment with the NADPH oxidase inhibitor apocynin. Mol Med Rep. 2016;14(4):3525–34.
85. Liang HY, Chen T, Yan HT, Huang Z, Tang LJ. Berberine ameliorates severe acute pancreatitisinduced intestinal barrier dysfunction via a myosin light chain phosphorylationdependent pathway. Mol Med Rep. 2014;9(5):1827–33.
86. Ning JW, Zhang Y, Yu MS, Gu ML, Xu J, Usman A, et al. Emodin alleviates intestinal mucosal injury in rats with severe acute pancreatitis via the caspase-1 inhibition. Hepatobiliary Pancreat Dis Int. 2017;16(4):431–6.
87. Xiong Y, Chen L, Fan L, Wang L, Zhou Y, Qin D, et al. Free total rhubarb anthraquinones protect intestinal injury via regulation of the intestinal immune response in a rat model of severe acute pancreatitis. Front Pharmacol. 2018;9:75.
88. Shen Q, Li Z, Huang S, Li L, Gan H, Du XG. Intestinal mucosal barrier dysfunction in SAP patients with MODS ameliorated by continuous blood purification. Int J Artif Organs. 2017;0 https://doi.org/10.5301/ijao.5000644.
89. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2008;371(9613):651–9.
90. Gou S, Yang Z, Liu T, Wu H, Wang C. Use of probiotics in the treatment of severe acute pancreatitis: a systematic review and meta-analysis of randomized controlled trials. Crit Care. 2014;18(2):R57.
91. Qin HL, Zheng JJ, Tong DN, Chen WX, Fan XB, Hang XM, et al. Effect of lactobacillus plantarum enteral feeding on the gut permeability and septic complications in the patients with acute pancreatitis. Eur J Clin Nutr. 2008;62(7):923–30.
92. Martindale RG, Warren MM, McClave SA. Does the use of specialized proresolving molecules in critical care offer a more focused approach to controlling inflammation than that of fish oils? Curr Opin Clin Nutr Metab Care. 2016;19(2):151–4.
93. Zhang L, Xie C, Nichols RG, Chan SH, Jiang C, Hao R, et al. Farnesoid X receptor signaling shapes the gut microbiota and controls hepatic lipid metabolism. mSystems. 2016;1(5):e00070–16.
94. Zhao YQ, Liu XH, Ito T, Qian JM. Protective effects of rhubarb on experimental severe acute pancreatitis. World J Gastroenterol. 2004;10(7):1005–9.
95. Wan B, Fu H, Yin J, Xu F. Efficacy of rhubarb combined with early enteral nutrition for the treatment of severe acute pancreatitis: a randomized controlled trial. Scand J Gastroenterol. 2014;49(11):1375–84.
96. Zhang CL, Lin ZQ, Luo RJ, Zhang XX, Guo J, Wu W, et al. Chai-Qin-Cheng-Qi decoction and carbachol improve intestinal motility by regulating protein kinase C-mediated Ca(2+) release in colonic smooth muscle cells in rats with acute necrotising pancreatitis. Evid Based Complement Alternat Med. 2017;2017:5864945.
97. Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol. 2011;9(8):710–7.e1.
98. Trevaskis NL, Kaminskas LM, Porter CJ. From sewer to saviour—targeting the lymphatic system to promote drug exposure and activity. Nat Rev Drug Discov. 2015;14(11):781–803.
99. Wang HW, Escott AB, Phang KL, Petrov MS, Phillips AR, Windsor JA. Indications, techniques, and clinical outcomes of thoracic duct interventions in patients: a forgotten literature? J Surg Res. 2016;204(1):213–27.
100. Ratnayake CBB, Escott ABJ, Phillips ARJ, Windsor JA. The anatomy and physiology of the terminal thoracic duct and ostial valve

in health and disease: potential implications for intervention. J Anat. 2018;233(1):1–14.
101. Gooszen HG, Besselink MG, van Santvoort HC, Bollen TL. Surgical treatment of acute pancreatitis. Langenbecks Arch Surg. 2013;398(6):799–806.
102. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010;362(16):1491–502.
103. Babu BI, Sheen AJ, Lee SH, O'Shea S, Eddleston JM, Siriwardena AK. Open pancreatic necrosectomy in the multidisciplinary management of postinflammatory necrosis. Ann Surg. 2010;251(5):783–6.
104. Fitzpatrick J, Bhat R, Young JA. Angiographic embolization is an effective treatment of severe hemorrhage in pancreatitis. Pancreas. 2014;43(3):436–9.
105. Marcos-Neira P, Zubia-Olaskoaga F, Lopez-Cuenca S, Bordeje-Laguna L, Epidemiology of Acute Pancreatitis in Intensive Care Medicine Study Group. Relationship between intra-abdominal hypertension, outcome and the revised Atlanta and determinant-based classifications in acute pancreatitis. BJS Open. 2017;1(6):175–81.
106. Radenkovic DV, Johnson CD, Milic N, Gregoric P, Ivancevic N, Bezmarevic M, et al. Interventional treatment of abdominal compartment syndrome during severe acute pancreatitis: current status and historical perspective. Gastroenterol Res Pract. 2016;2016:5251806.
107. Malbrain ML, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I Definitions. Intensive Care Med. 2006;32(11):1722–32.

Medical, Nutritional and Surgical Management of Chronic Pancreatitis

John S. Leeds

Key Points

1. Alcohol is often overestimated as an aetiological factor. 10% of people who have high alcohol consumption develop exocrine pancreatic disease. Tobacoo smoking has a synergistic effect with alcohol.
2. Other important aetiological factors for chronic pancreatitis include: hypercalcaemia, hypertriglyceridaemia, chronic kidney disease and immunoglobulin G4 related disease (this responds to steroids).
3. Faecal elastase may aid early detection of chronic pancreatitis; however about 85% of the pancreatic parenchyma needs to be lost before steatorrhoea occurs.
4. Measurement of weight, fat soluble vitamins, glycosylated haemoglobin and an assessment of bone mineral density should all be undertaken as a baseline assessment and at follow up assessments (except bone density which may be repeated every 3 years).
5. At diagnosis around 30% of patients with chronic pancreatitis have diabetes mellitus and this prevalence increases with duration of the disease.
6. Symptoms include abdominal pain, weight loss, diarrhoea and any combination of these. Asymptomatic presentations, as an incidental finding, also occurs.
7. The starting dose for pancreatic enzyme replacement therapy (PERT) should be a minimum of 50,000 units of lipase with meals and 25,000 units with snacks. Not more than 150,000 units at a time should be necessary.
8. Complications include pseudocyst formation (with compression of the upper gastrointestinal system), pancreatic strictures and stones, thromboses (splenic and portal veins), reduced bone mineral density, fat soluble vitamin deficiencies, undernutrition and pancreatic cancer.
9. Most treatments are to prevent further parenchymal damage and management of complications. These include pain management, diabetes control, nutritional input, assessment of bone health and vigilance for cancer. Endoscopic and/or surgical treatments may be used to decompress the pancreatic duct in managing pain.

Chronic Pancreatitis

Definition and Epidemiology

Chronic pancreatitis is a progressive, fibro-inflammatory disorder which occurs in individuals with genetic, environmental and/or other risk factors and leads to irreversible damage to pancreatic tissue [1]. In most cases, this is occurs over many years and begins with a subclinical phase that is very difficult to identify. Current understanding is that most cases of chronic pancreatitis develop following serial episodes of acute insults to the pancreas. Older post-mortem studies have shown that the prevalence of chronic pancreatitis between 6–12% [2, 3]. Whilst this seems high compared to clinical practice, a more recent study using digital autopsy techniques appears to confirm these findings showing that 13.5% had pancreatic calcifications and 16% had pancreatic atrophy [4]. The true incidence and prevalence of chronic pancreatitis is not fully known due to subclinical disease but current estimates of global incidence are around 9.6 per 100,000 person years [5]. Prevalence of clinically apparent chronic pancreatitis varies depending upon which population is examined but ranges between 11–50 per 100,000 people [6, 7]. Prevalence is also higher in males and with increasing age [6].

Causes

Unfortunately, chronic pancreatitis has been closely associated with alcohol however most recent surveys have shown that this is over-represented as a cause [8, 9]. Multiple causes have been identified for chronic pancreatitis and, interest-

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Table 1 The TIGARO classification of causes of chronic pancreatitis

Group	Aetiological factor	Estimated prevalence in people with chronic pancreatitis
Toxins/metabolic	Alcohol Smoking Hypercalcaemia Hyperlipidaemia Chronic kidney disease	40–70% 60% Unknown 3–13% 2–5%
Idiopathic	True idiopathic Tropical pancreatitis	Approximately 10% Unknown
Genetic	PRSS1 cationic trypsinogen CFTR mutations SPINK1 mutations Other mutations	3–10% Up to 7% 10% 3–5%
Autoimmune	IgG4 disease Other autoimmune disease e.g. Sjorgrens syndrome	1–2%Unknown
Recurrent and severe acute pancreatitis	Any cause of recurrent acute pancreatitis Sentinel attack of severe necrotising pancreatitis	Unknown Unknown
Obstructive	Duct obstruction due to tumours Pancreas divisum	Overall all account for between 2–9%

TIGAR-O: Abbreviation for the aetiology of chronic pancreatitis. Toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive

ingly, most lead to the same pathological features on imaging. This suggests that whatever the cause, there is a common pathophysiological mechanism leading to pancreatic inflammation and fibrogenesis [10]. The current classification system for the aetiology of chronic pancreatitis is called TIGAR-O (Table 1) [11].

As above, alcohol excess is associated with development of chronic pancreatitis but the exact mechanism and risks are not entirely elucidated. Alcohol is most likely a cofactor in susceptible patients and has certainly been shown to be synergistic with tobacco smoking [12, 13]. Similar to development of alcohol related liver disease, only around 10% of people who have high alcohol consumption develop exocrine pancreatic disease [14]. There is no threshold of alcohol intake that is associated with development of chronic pancreatitis and the correlation with the level of alcohol consumption is weak [15].

Tobacco smoking has been shown to be an independent factor for the development of chronic pancreatitis [12]. Smokers have a significantly higher risk of developing chronic pancreatitis compared to non-smokers [16]. The mechanism is not entirely understood but older studies have shown that smoking reduces pancreatic output particularly of bicarbonate [17].

Other toxic and metabolic causes include hypercalcaemia, hypertriglyceridaemia and chronic kidney disease. Hypercalcaemia has long been known to cause acute pancreatitis, however, conditions such as hyperparathyroidism have been shown to be associated with development of chronic pancreatitis [18]. Development of chronic pancreatitis due to derangement of lipid metabolism has been controversial. The likely mechanism is via episodes of recurrent acute pancreatitis leading eventually to a chronically scarred gland [19]. The finding of pancreatic abnormalities in patients with chronic kidney disease has been previously demonstrated but the underlying mechanisms are again uncertain [20].

The contribution of genetics to the development of chronic pancreatitis is an area of great interest. Several gene polymorphisms have been associated and have also helped to uncover some of the mechanisms for development of chronic pancreatitis. Mutations in the cationic trypsinogen gene (PRSS1) lead to a "gain of function" mutation causing premature activation of trypsin within the pancreas leading to recurrent episodes of pancreatitis [21]. The most common mutations are R122H, R122C or N29I. Other genetic mutations in proteases have also been found.

Mutations in the SPINK1 gene, which encodes for the pancreatic secretory trypsin inhibitor, are also associated with an increased risk of chronic pancreatitis. This gene product helps to "mop up" any excess trypsin and therefore is the natural defence protein against trypsin in the pancreas. The most common mutation is N34S. Other well-known genes include mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This gene encodes for a protein that enables secretion of fluid and bicarbonate into the pancreatic duct and loss of this function causes pancreatitis. Most patients are heterozygous for these genes and therefore the interplay between them and other environmental factors may be important [22].

Autoimmune pancreatitis is now known to be a manifestation of the systemic disorder Immunoglobulin G4 related disease (IgG4 RD). This disease may involve multiple organs throughout the body, has characteristic imaging and histological findings. These include an abundance of IgG4-positive plasma cell infiltrate in the involved organs and a predictable response to steroid therapy [23, 24]. There have been several diagnostic criteria culminating in the International Consensus Diagnostic Criteria (ICDC) [25]. These criteria use a combination of radiological, histological and serological findings along with evidence of extra-pancreatic involvement and a rapid (<2 week) response to corticosteroid treatment. This disease can present in several forms, including a mass forming type, often mimicking pancreatic cancer. Biopsy of the "mass" is usually performed by endoscopic ultrasound and confirms a lack of cancer tissue

and an abundance of IgG4 positive chronic inflammatory cells with associated fibrosis and vascular inflammation [26]. This is a particularly important type of chronic pancreatitis to identify as treatment with steroids can salvage both endocrine and exocrine function [27].

As above, recurrent acute pancreatitis from any cause can lead to enough of the gland to be damaged giving changes of chronic pancreatitis. If a cause can be identified then treatment directed at aborting or reducing number and severity of attacks may prevent progression to chronicity. A severe, sentinel attack of necrotising pancreatitis may destroy enough of the pancreas to lead to exocrine and/or endocrine dysfunction [28]. Duct obstruction, mainly seen in pancreatic tumours, can lead to obstructive pancreatopathy with subsequent exocrine and endocrine insufficiency.

In all of these underlying mechanisms, as the disease progresses and more of the pancreatic tissue is destroyed, both the endocrine and exocrine functions of the pancreas begin to become deranged. This leads onto the different clinical presentations of chronic pancreatitis.

Clinical Presentations

There several ways in which patients with chronic pancreatitis present to medical services. These symptoms can present individually or in combination and require assessment and specific treatments.

Pain

The most common symptom described by patients with chronic pancreatitis is abdominal pain. This is usually in the epigastric region and commonly radiates through to the back and left side of the abdomen. The pain is often worse after food and helped by leaning forward, avoiding food and applying heat pads (can result in erythema ab igne). It may last for a week. The pain can be episodic with acute presentations sometimes due to acute flares mainly due to acute pancreatitis superimposed upon a background of chronic pancreatitis. Most patients describe a background of chronic pain. This pain can be severe and patients often require strong analgesia including opiates for relief. There does also appear to be a neurogenic component to the pain and therefore use of neuromodulators such as amitryptylline, gabapentin or pregabalin is also common. The cause of the pain can be multifactorial and includes increased pressure in the pancreatic duct, pancreatic duct strictures, pancreatic duct stones, scarring of the pancreas, pseudocyst formation, and other associated diseases such as coeliac disease, Crohns' disease and gallstones [29].

Exocrine Insufficiency

The pancreas is almost entirely responsible for digestion of fat and when enough of the exocrine component is destroyed fat malabsorption will occur. Previous studies have suggested that loss of more than 85% of the pancreatic parenchyma is needed before steatorrhoea occurs and lipase production is also less than 10% of normal [30, 31]. However, steatorrhoea is a late symptom and many patients describe diarrhoea. Waiting for frank steatorrhea to occur promotes a late diagnosis and complications such as a lack of fat soluble vitamins may not be recognised. Use of tests to identify exocrine insufficiency earlier, such as faecal elastase-1, can allow prompt treatment of this important manifestation and reduce or prevent the clinical sequelae [32]. No test is 100% sensitive in identifying exocrine insufficiency and it is not clear exactly when this occurs in patients with chronic pancreatitis. The prevalence of exocrine insufficiency increases with duration of chronic pancreatitis and therefore, even if not clinically apparent at presentation, should be monitored for during clinical follow up. In patients with overt steatorrhoea and clear evidence of chronic pancreatitis there is little need to perform a test of exocrine function and treatment with pancreatic enzymes replacement therapy (PERT) should be commenced. In the absence of symptoms of exocrine insufficiency, including weight loss, testing exocrine function at presentation should be performed and repeat assessment conducted during follow up. Measurement of weight, fat soluble vitamins and assessment of bone mineral density should all be undertaken at baseline assessment [33, 34].

Dietetic involvement can help patients to titrate PERT dosage, give guidance on diet and has been shown to stop weight loss [35].

Some patients present via colorectal cancer pathways with change in bowel habit due to exocrine insufficiency and weight loss. There is often little pain and the diagnosis is usually made following CT scanning which picks up the abnormal pancreas. The exact proportion of patients with chronic pancreatitis that present this way is unknown.

Diabetes

Diabetes secondary to diseases of the exocrine pancreas have been classified as Type 3c diabetes in the American Diabetes Association classification [36]. Table 2 shows the causes of Type 3c diabetes. The risk of developing diabetes appears to increase with duration of chronic pancreatitis [35]. Some patients present initially as endocrine failure to diabetes services and often have minimal gastrointestinal symptoms that

Table 2 Causes of type 3c diabetes mellitus

Pancreatitis (acute and chronic)
Pancreatic resection
Pancreatic cancer with or without resection
Haemochromatosis
Cystic fibrosis
Pancreatic trauma

may alert the clinicians to the diagnosis of chronic pancreatitis. Gastrointestinal symptoms are quite common in patients with diabetes [37] and previous studies have examined cohorts of patients with diabetes showing that approximately 10% could be re-classified as type 3c [38].

It has long been known that patients with both type 1 and type 2 diabetes have a high prevalence of abnormal levels of faecal elastase-1 [39]. This high prevalence of abnormal elastase does not seem to translate into large numbers of patients with diabetes being treated with PERT. In fact, only one study exists which showed no change in diabetes markers (namely Hb_{A1c}) or symptoms but did show improvement in number of episodes of hypoglycaemia and that PERT does not destabilise diabetes control [40].

Incidental

There are a group of patients that are identified as "incidentalomas". These patients have usually undergone cross sectional abdominal imaging for other reasons, e.g. renal scanning, and this has identified pancreatic changes consistent with chronic pancreatitis. These patients often have minimal symptoms of either pain or exocrine insufficiency but should be assessed clinically and exocrine and endocrine testing performed along with measurement of fat soluble vitamins and bone mineral density.

Diagnosis

Diagnosis of chronic pancreatitis is sometimes challenging. Obvious cases of late stage disease with clear symptoms, exocrine insufficiency, diabetes and gross changes on imaging are straight forward. However, as mentioned above, the changes in the pancreas usually develop over time and many cases are subclinical. In earlier stages the diagnosis is usually made by using a combination of factors. These include symptoms, exocrine function testing, endocrine function testing, nutritional markers and cross sectional imaging. In cases of IgG4 RD there are specific criteria which also include histological changes [25]. Symptoms have been described above.

Table 3 Testing of exocrine pancreatic function

Direct tests	Indirect tests
USS	Faecal fat
Pancreatic EUS	PABA
CT scanning	MTBT
MRCP	Triolein breath test
Lundh test meal	Pancreolauryl test
SCT/SPT	Faecal chymotrypsin
ERCP	Faecal elastase
Histology	

SCT secretin cerulean test, *SPT* secretin pancreozymin test, *PABA* para-aminobenzoate test, *MTBT* mixed triglyceride breath test

Exocrine Function Testing

There have been many tests of exocrine pancreatic function over the years which are shown in Table 3. Many of these test are now not available routinely in European centres. The gold standard for exocrine testing was the secretin cerulean test (SCT) which involved laying on the right side for 4 h with a naso-duodenal tube in situ. Secretin was then given intravenously and aspirates were taken every 15 min for measurement of enzyme levels and bicarbonate. This was difficult to perform and not favoured by patients. This led onto the 'indirect' tests which used a substrate that was ingested orally and digested by pancreatic enzymes. The products of this digestion were then measured in blood, breath or urine and the amount of product correlated to exocrine function. Many of these tests had limitations or involved several hours with repeated measurements. Assessment of pancreas specific proteins in the stool led to the faecal chymotrypsin test and subsequently this was modified to the faecal elastase test. This is almost exclusively the only test remaining in many centres. Faecal elastase measurement is very good for moderate and severe exocrine insufficiency but has limited sensitivity for early disease. It should also be noted that this is a test for exocrine insufficiency and not chronic pancreatitis and has been used to other disease areas. The test has some limitations including dilution in watery stool but has the advantage of being cheap, outpatient and can be performed in large numbers. Faecal elastase has been compared the previous gold standard tests and appears to have good sensitivity and specificity for severe and moderate disease (both approaching 100%) [41, 42] but is less accurate in mild disease [43, 44]. Additionally, faecal elastase cannot be used to monitor progress or response to therapy.

More recently a new type of mixed triglyceride breath test has been proposed by the group in Santiago De Compostela which appears to have a good sensitivity and specificity [45]. This test has been compared to faecal fat estimation and correlates well with the coefficient of fat absorption. This test can also be used to determine whether a patient is receiving sufficient doses of PERT but has the disadvantage that it

takes around 6 h to complete and requires a special spectrometer to measure carbon-14 [46].

The ideal test for measuring exocrine pancreatic function is still being searched for and would need to be cheap, outpatient based, reproducible in large numbers, highly accurate, acceptable to patients and changes dynamically with enzyme replacement.

Endocrine Function

The main easily measureable endocrine function is glycaemic control. At diagnosis around 30% of patients with chronic pancreatitis have diabetes mellitus and this prevalence increases with duration of the disease [33, 35]. At diagnosis of chronic pancreatitis all patients should have an assessment of glycaemic control and the NICE guidelines recommend measuring HbA1c at least every 6 months. If there is uncertainty around glycaemic control then either glucose tolerance testing or assessment by diabetes services can be performed. It is important to note that patients with type 3c diabetes also have reduced alpha cell mass meaning that their ability to produce glucagon is impaired, meaning that they are at higher risk of developing severe hypoglycaemia and generally they need lower doses of insulin than other types of diabetic. It is important to note that not every patient with chronic pancreatitis that has diabetes has type 3c diabetes. Patients with type 3c diabetes have similar cardiovascular and neuropathic risks to patients with other types of diabetes and should be monitored by diabetes services appropriately. Both type 1 and type 2 diabetes can have occurred prior to the diagnosis of chronic pancreatitis.

Nutritional Markers

Patients with chronic pancreatitis can have a number of nutritional deficiencies mainly as a consequence of fat malabsorption but others occur as alongside fat malabsorption [47]. The most commonly identified micronutrient deficiency in patients with chronic pancreatitis is vitamin D and occurs in 50–60% of patients [48, 49]. Deficiency in vitamins A, E and K have also been reported but only rarely have clinical manifestations [48–51]. Iron deficiency is also seen in patients with chronic pancreatitis and may be due to reduced intake, duodenitis due to lack of bicarbonate production or part of the general malabsorptive condition. Zinc deficiency has been noted [52]. Epidemiological studies have also identified deficiency in magnesium as a marker for underlying exocrine insufficiency although the exact mechanisms are not clear [47].

Current UK guidelines recommend measurement of iron, B_{12}, folic acid, fat-soluble vitamins (although not specified), selenium, zinc, magnesium, copper and clotting status [34]. It should be noted that none of the micronutrient deficiencies are specific enough to chronic pancreatitis or exocrine insufficiency and cannot be used as a screening tool.

Imaging

Structural information about the pancreas is essential in aiding diagnosis. Many studies have been conducted that report the specific characteristics and accuracy of different imaging modalities in making a definitive diagnosis of chronic pancreatitis. Historically, transabdominal ultrasound scanning and ERCP were used to confirm or refute the diagnosis of chronic pancreatitis. With increasing access to and resolution of cross sectional imaging with multi-detector CT scanners and higher Tesla MRI scanners, these modalities are now often the first line investigations for patients with abdominal and suspected pancreatic diseases. Furthermore, endoscopic ultrasound has also progressed from mechanical radial images to high quality, high resolution images and is not affected by bowel gas in the same way that transabdominal ultrasound is (Fig. 1). The main issue with endoscopic ultrasound is the "endoscopy" part requiring an invasive procedure which has a long learning curve and similar issues with operator variability as transabdominal ultrasound. One of the benefits of CT and MRI imaging is the ability for this to be stored, transferred and reviewed in fora such as a multidisciplinary team meeting. A recent meta-analysis of imaging modalities for aiding diagnosis in patients with suspected

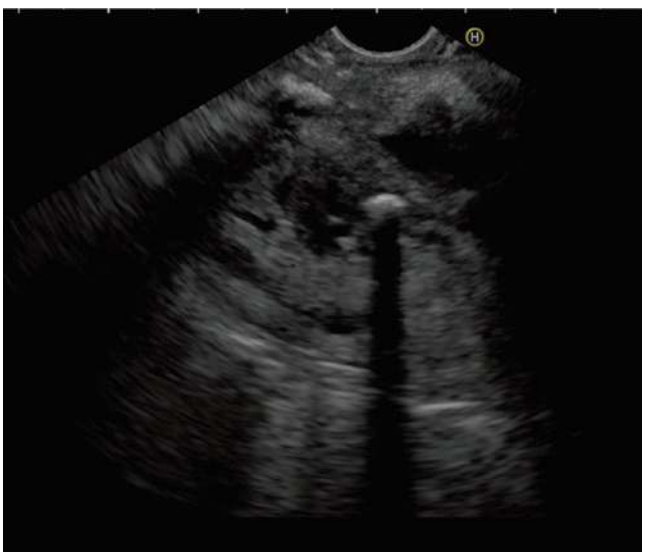

Fig. 1 Endoscopic ultrasound image showing calcific chronic pancreatitis (hyperechoic stone in duct with acoustic shadowing)

Table 4 Sensitivity and specificity of different imaging modalities for suspected chronic pancreatitis

Imaging modality	Sensitivity	Specificity
Transabdominal ultrasound	67% (53–78%)	98% (89–100%)
CT	75% (66–83%)	91% (81–96%)
MRI	78% (69–85%)	96% (90–98%)
ERCP	82% (76–87%)	94% (87–98%)
Endoscopic ultrasound	81% (70–89%)	90% (82–95%)

chronic pancreatitis reported the highest sensitivity with endoscopic ultrasound and ERCP and the lowest was transabdominal ultrasound [53]. Table 4 shows the reported sensitivity and specificity of each of these imaging modalities as reported by Issa and colleagues [53]. Despite these findings, it is recommended that non-invasive testing is conducted first and that the need for endoscopic ultrasound is mainly when there is uncertainty from cross sectional imaging. ERCP should not be used as a diagnostic tool at all due to the high risk of causing acute pancreatitis. Often both CT and MRI are utilised as they provide complimentary information with CT being better for soft tissue findings and MRI giving more detail on ductal anatomy. The addition of secretin during MRI scanning can also give dynamic imaging changes which can increase the diagnostic yield [54]. Similarly, adjunctive technologies at endoscopic ultrasound may also help to increase the yield including elastography which determines tissue "stiffness". This adjunct is easy to perform during the examination but validation is required [55].

Most guidelines recommend the initial imaging modality to be CT scanning or MRI depending upon local availability and expertise.

Complications of Chronic Pancreatitis

Given the progressive and irreversible nature of chronic pancreatitis some patients develop secondary complications which require surveillance and management. Recurrent episodes of acute pancreatitis can lead to local pancreatic complications such as pseudocyst formation which may cause more pain and occasionally lead to compression of the upper intestinal tract. Stricture formation in the pancreatic duct, and often associated stones, can also lead to episodes of pain from obstruction and flares of acute pancreatitis. Vascular complications such as splenic vein thrombosis, portal vein thrombosis and pseudoaneurysm formation are also described and can present with bleeding or ascites. Formation of an inflammatory mass in the pancreas (particularly the head of the gland) can cause gastric outlet obstruction and/or biliary obstruction. Duodenal strictures can also be encountered either from compression from the head of pancreas or potentially recurrent duodenal ulceration due to a lack of bicarbonate production.

Endocrine and exocrine insufficiencies are described above. Abnormalities of bone mineral density are common in patients with chronic pancreatitis and occur in around 40% of patients [56]. There is also an increased risk of developing pancreatic cancer which can be very difficult to identify on cross sectional imaging as well as endoscopic ultrasound particularly in very calcified, diseased glands. The overall risk of developing pancreatic cancer for most types of chronic pancreatitis is increased but this risk is confounded by other variables such as smoking [57]. For patients with genetic causes and those with PRSS1 mutations in particular, the risk is very significantly elevated [58]. Screening for pancreatic cancer is not currently performed for most forms of chronic pancreatitis and familial/hereditary aetiologies are encouraged to enrol in well conducted research registries such as EUROPAC. Otherwise, urgent CT scanning should be performed in patients with chronic pancreatitis and worrisome symptoms such as unexplained weight loss and jaundice.

Management of Chronic Pancreatitis

The majority of management options for patients with chronic pancreatitis are medical. However, some patients may benefit from other interventions including endoscopic and surgical treatments. The mainstay of management is to relieve symptoms, manage complications and prevent/slow the progression of the disease.

Pain

Management of pain can be difficult in chronic pancreatitis and has been discussed previously. Use of the analgesic ladder is recommended with use of adjunctive treatments such as neuromodulatory medications. If pain is due to ductal stones and/or structuring then endoscopic or surgical intervention may be required and this will be discussed later.

Coeliac plexus block has been investigated for this group of patients and has been found wanting. Pain relief is temporary and lasts for up to 3 months only with around 50% of patients describing a response [59].

Pancreatic Enzyme Replacement Therapy

One of the main treatments is pancreatic enzyme replacement therapy (PERT) which is required in the majority of patients with chronic pancreatitis. Historically, PERT has been under prescribed and patients under treated with resultant subtherapeutic outcomes. In patients with clear symptoms of exocrine insufficiency and other supportive evidence of chronic pancreatitis on imaging, testing exocrine function prior to commencing treatment is not required. (UK guidelines) Treatment

with PERT has been shown to ameliorate symptoms of exocrine insufficiency, improve nutritional status, improve survival and has a positive effect on quality of life in patients with chronic pancreatitis [60–62]. One study examined 2 cohorts of patients with chronic pancreatitis who were referred to a specialist centre in Germany. One cohort were patients with a new diagnosis of chronic pancreatitis and the other cohort were patients with an existing diagnosis of chronic pancreatitis who were already on PERT. Assessment of gastrointestinal symptoms and quality of life (measured using the Gastrointestinal Quality of Life Index) was conducted at baseline, 6 months and 1 year. Unsurprisingly, the cohort with a new diagnosis showed significant improvement in all parameters during follow up. Perhaps most interesting was the improvement seen in those patients whom had already been started on PERT at another centre and then referred on [63]. The reasons for this group improving are not easily elucidated from the study but most patients had their PERT titrated up and had other adjunctive input including dietetics. This study reinforces the historical issue of under dosing of PERT and the need for follow up by clinicians with the relevant knowledge for managing exocrine insufficiency.

With this in mind, the starting dose for PERT should be a minimum of 50,000 units of lipase with meals and 25,000 units with snacks [60, 64]. The expectation should be that this is very much the starting dose and that this is likely to increase dependent upon clinical response [34]. PERT is most effective when taken throughout the course of the meal and this has been confirmed in randomised studies [65]. If patient cannot swallow the capsules then either one of the powdered preparations can be used or capsules can be opened and the contents sprinkled over the food. Many formulations are enteric coated, however, inpatients who have undergone previous gastric surgery, non-enteric coated formulations should be used or the capsules opened and sprinkled onto the food.

There is no maximum dose of enzymes that can be provided. Historically, there were reports of a rare complication called fibrosing colonopathy in patients on high dose PERT [66]. This was only seen in paediatric patients with cystic fibrosis and with an enzyme formulation that is no longer available. It is thought that this may have been related to materials in the capsule rather than the enzyme preparation [67]. However, if total lipase dose per meal is higher than 150,000 units without sufficient improvement in symptoms then investigation of other causes should be undertaken.

Lack of response to PERT should lead to a systematic reassessment of the causes for this. The most common reason for lack of response is related to total lipase intake, timing of PERT throughout the meal or denaturing of the enzymes by inappropriate storage [68]. Involvement of a dietitian to provide education around these issues can be of great benefit to the patient [35]. If there is still a lack of response despite addressing these issues and increasing the dose of PERT, adding in a proton pump inhibitor to reduce acidic destruction of enzymes should be considered [69]. If this does not improve symptoms then further investigations should be undertaken to exclude secondary causes [68]. Commonly associated conditions include small bowel bacterial overgrowth, bile acid malabsorption, coeliac disease and inflammatory bowel disease [70–72].

Other considerations for PERT are that all current commercially available products are porcine in nature and patients should be made aware of this prior to prescription. A non-porcine formulation is in development but is yet to be deemed non-inferior to currently available products. As there is no current alternative, most religious groups will accept current products [73, 74].

Special Circumstances

Patients with chronic pancreatitis may require enteral feeding via tubes such as nasojejunal tubes or a gastrostomy (insertion techniques are discussed elsewhere). Provision of PERT in a patient on infusion feeding regimens can be an additional challenge and little data is available to guide practice. Addition of enzymes to the feed or flushing of powdered preparations through the feeding tube every 2 h are suggested [75]. This appears to work most optimally when a peptide feed is used.

Endoscopic Treatment

Interventional endoscopic techniques have rapidly expanded over the last decade and perhaps this is best demonstrated in the area of therapeutic endoscopic ultrasound. Endoscopic interventions for patients with chronic pancreatitis need to be considered carefully and is best done in a multidisciplinary team meeting involving endoscopists, surgeons and radiologists. Most endoscopic interventions are for management of complications of chronic pancreatitis mainly in the form of drainage procedures. Conventionally, interventions in chronic pancreatitis were in the form of surgery but some patients are not suitable for surgical intervention and some procedures are best performed endoscopically.

Pseudocysts are common in patients with chronic pancreatitis and can occur in up to 20% of patients. Intervention is only required in those patients in whom the cyst is causing symptoms which are mainly pain or compression of the gut or biliary tree. If occurring after an acute flare episode many of these will spontaneously resolve and some can be managed expectantly. Those with severe and/or persistent symp-

toms may benefit from cyst drainage which is most commonly performed using endoscopic ultrasound. Endoscopic ultrasound allows for assessment of the cyst, identification of local vascular structures and drainage under real time ultrasound. This can be done in the endoscopy department rather than theatre using conscious sedation, is faster and less costly than surgery and has a high technical and clinical success rate [76]. Pure pseudocysts can be drained using plastic stents rather than lumen apposing metal stents (LAMS) which are cheaper. Cyst with evidence of necrotic material are best drained using LAMS which allows for endoscopic necrosectomy [77].

Pancreatic duct stones and strictures can also be managed using endoscopy ususally in the form of ERCP. Pancreatic duct stones are conceptually different to bile duct stones. Bile duct stones *are* the disease whereas pancreatic duct stones are a *consequence* of the disease and therefore removal does not necessarily improve symptoms for the patient. Pancreatic duct stones should therefore only be treated if they are causing symptoms particularly acute episodes of pain or pancreatitis [78]. Location of the stones is very important as is the presence of stricturing of the duct proximal to the stone. Smaller stones, located in the head in a dilated duct have a higher chance of endoscopic extraction than larger stones found in the body or tail especially if associated with a stricture [79].

Strictures causing symptoms in the absence of stones can also be managed endoscopically using stents. Figure 2 shows the ERCP findings in a 60 year old female patient with a symptomatic stricture in the head of pancreas causing dilatation of the main pancreatic duct with subsequent plastic stent insertion leading to resolution of pain. Newer fully covered metal stents are now available for use in the pancreatic duct for remodelling of strictures in selected cases.

One of the most common indications for ERCP in patients with chronic pancreatitis is for management of biliary strictures. These occur due to fibro-inflammatory tissue encroaching on the distal bile duct causing obstruction and up until the last 10 years were managed surgically. In patients who were not suitable for surgery, insertion of multiple plastic stents to slowly dilate the stricture was employed but this has now been largely superseded by the use of fully covered metal stents [80, 81]. Use of fully covered stents allows for high volume, reliable biliary drainage with dilatation and remodelling of the stricture. The majority of patients have resolution of the stricture with one stent but some do recur mainly due to factors leading to relapse of chronic pancreatitis such as smoking.

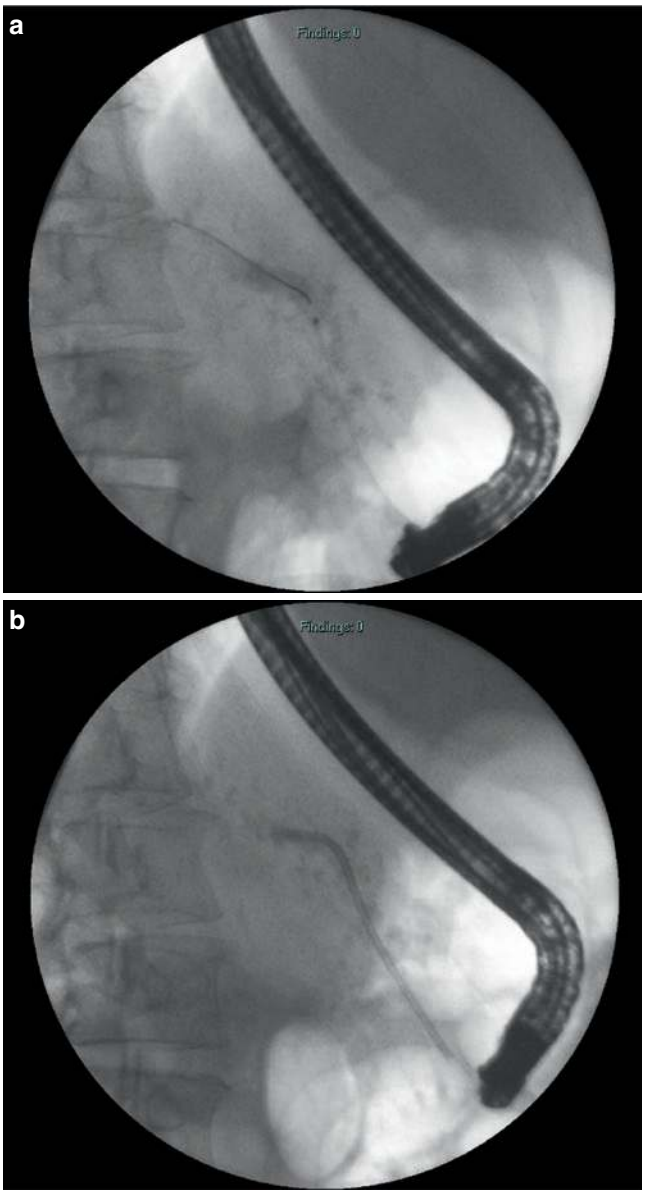

Fig. 2 ERCP findings in patient with chronic pancreatitis and recurring pain. (**a**) Visible calcifications on plain film. Stricturing of the duct in the head. (**b**) Subsequent plastic stent insertion

Surgical Treatment

Surgical treatment of chronic pancreatitis follows the same principles as endoscopic treatment and ideally used for symptom control. Surgery used to be the main treatment modality for management of pseudocysts, pancreatic duct stones, pancreatic duct strictures and biliary strictures but

has largely been replaced with endoscopic intervention as above. There are some areas where surgery should be considered primarily. In patients with pain and a dilated pancreatic duct, one randomised control trial showed superiority of open surgical duct drainage using the Puestow procedure (lateral pancreatico-jejunostomy) compared to endoscopic therapy using ERCP [82]. The primary outcome measure was relief of pain and this was significantly better at all time points in the surgical arm. Long term follow up of this cohort showed that these effects were long lasting [83]. One of the difficulties with this trial were the large number of exclusions meaning that surgical intervention was not an option for some patients. Therefore, whilst surgical intervention has moved to the fore in this group of patients, for those in whom surgery is not suitable or not palatable, endoscopic intervention still carries some value.

Surgical intervention is also beneficial in patients with an inflammatory mass in the head of pancreas. Surgery (usually in the form of a Whipple's procedure) removes the inflammatory tissue and also improves luminal symptoms of delayed gastric emptying. Some surgeons use partial head resection techniques such as the Frey-Beger procedure if there is duct dilatation but no enlargement of the pancreatic head [84, 85].

In very selected cases, total pancreatectomy may be required. For young patients and those with hereditary pancreatitis, the addition of islet cell transplantation to maintain some degree of glycaemic control can be considered [86, 87]. In the UK, there are currently only 3 pancreatic centres that offer this intervention.

Radiological Treatment

In some patients with chronic pancreatitis, endoscopic and/or surgical intervention is not suitable or desirable and therefore radiological approaches can be considered. These are usually via the percutaneous route and are reserved for collections or cysts not reachable by endoscopic means or where previous surgery (such as gastric bypass) prevents an endoscopic treatment [88]. Some centres use radiological interventions more readily due to local availablility and expertise in this area compared to endoscopic or surgical skill mixes. High volume operators have been shown to have improved outcomes for procedure such as percutaneous transhepatic cholangiography [89].

References

1. Whitcomb DC. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. Pancreatology. 2016;16:218–24.
2. Olsen TS. The incidence and clinical relevance of chronic inflammation in the pancreas in autopsy material. Acta Pathol Microbiol Scand. 1978;86:361–4.
3. Doerr W. Pathogenesis of acute and chronic pancreatitis [German]. Verh Dtsch Ges Inn Med. 1964;70:718–58.
4. Campbell JA, Hampton JNS, Löhr M, Howard C, Sanders DS, Hopper AD. The prevalence of pancreatic morphological abnormalities detected by digital autopsy. Pancreatology. 2018;18(7):717–20.
5. Xiao AY, Tan ML, Wu LM, Asrani VM, Windsor JA, Yadav D, Petrov MS. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol. 2016;1(1):45–55.
6. Joergensen M, Brusgaard K, Crüger DG, Gerdes AM, de Muckadell OB. Incidence, prevalence, etiology, and prognosis of first-time chronic pancreatitis in young patients: a nationwide cohort study. Dig Dis Sci. 2010;55(10):2988–98.
7. Kleeff J, Whitcomb DC, Shimosegawa T, Esposito I, Lerch MM, Gress T, Mayerle J, Drewes AM, Rebours V, Akisik F, Muñoz JED, Neoptolemos JP. Chronic pancreatitis. Nat Rev Dis Primers. 2017;3:17060.
8. Lin Y, Tamakoshi A, Hayakawa T, Ogawa M, Ohno Y. Associations of alcohol drinking and nutrient intake with chronic pancreatitis: findings from a case-control study in Japan. Am J Gastroenterol. 2001;96:2622–7.
9. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144:1252–61.
10. Beyer G, Habtezion A, Werner J, Lerch MM, Mayerle J. Chronic pancreatitis. Lancet. 2020;396(10249):499–512.
11. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120(3):682–707.
12. Luaces-Regueira M, Iglesias-García J, Lindkvist B, Castiñeira-Alvariño M, Nieto-García L, Lariño-Noia J, Domínguez-Muñoz JE. Smoking as a risk factor for complications in chronic pancreatitis. Pancreas. 2014;43(2):275–80.
13. Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Brink MA, Schaapherder AF, Dejong CH, Spanier BW, Heisterkamp J, van der Harst E, van Eijck CH, Besselink MG, Gooszen HG, van Santvoort HC, Boermeester MA, Dutch Pancreatitis Study Group. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol. 2016;14(5):738–46.
14. Gumaste VV. Alcoholic pancreatitis: unraveling the mystery. Gastroenterology. 1995;108:297–9.
15. Corrao G, Bagnardi V, Zambon A, Arico S. Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol-related conditions: a meta-analysis. Addiction. 1999;94:1551–73.
16. Lin Y, Tamakoshi A, Hayakawa T, Ogawa M, Ohno Y. Cigarette smoking as a risk factor for chronic pancreatitis: a case-control study in Japan. Research committee on intractable pancreatic diseases. Pancreas. 2000;21:109–14.
17. Bynum TE, Solomon TE, Johnson LR, Jacobson ED. Inhibition of pancreatic secretion in man by cigarette smoking. Gut. 1972;13:361–5.
18. Bess MA, Edis AJ, van Heerden JA. Hyperparathyroidism and pancreatitis. Chance or a causal association? JAMA. 1980;243:246–7.
19. Fortson MR, Freedman SN, Webster PD III. Clinical assessment of hyperlipidemic pancreatitis. Am J Gastroenterol. 1995;90:2134–9.
20. Herzig KH, Purhonen AK, Räsänen KM, Idziak J, Juvonen P, Phillps R, Walkowiak J. Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes mellitus. BMC Geriatr. 2011;11:4.
21. Mayerle J, Sendler M, Hegyi E, Beyer G, Lerch MM, Sahin-Toth M. Genetics, cell biology, and pathophysiology of pancreatitis. Gastroenterology. 2019;156:1951–68.e1.

22. Maléth J, Balázs A, Pallagi P, Balla Z, Kui B, Katona M, Judák L, Németh I, Kemény LV, Rakonczay Z Jr, Venglovecz V, Földesi I, Pető Z, Somorácz Á, Borka K, Perdomo D, Lukacs GL, Gray MA, Monterisi S, Zaccolo M, Sendler M, Mayerle J, Kühn JP, Lerch MM, Sahin-Tóth M, Hegyi P. Alcohol disrupts levels and function of the cystic fibrosis transmembrane conductance regulator to promote development of pancreatitis. Gastroenterology. 2015;148(2):427–39.e16.
23. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol. 2003;38(10):982–4.
24. Culver EL, Sadler R, Simpson D, Cargill T, Makuch M, Bateman AC, Ellis AJ, Collier J, Chapman RW, Klenerman P, Barnes E, Ferry B. Elevated serum IgG4 levels in diagnosis, treatment response, organ involvement, and relapse in a prospective IgG4-related disease UK cohort. Am J Gastroenterol. 2016;111(5):733–43.
25. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011;40(3):352–8.
26. Oppong KW, Maheshwari P, Nayar MK, Darne A, Parkinson D, Leeds JS, Haugk B. Utility of endoscopic ultrasound-guided fine-needle biopsy in the diagnosis of type 1 autoimmune pancreatitis. Endosc Int Open. 2020;8(12):E1855–61.
27. Webster GJ. Autoimmune pancreatitis—a riddle wrapped in an enigma. Dig Dis. 2016;34(5):532–9.
28. Majumder S, Chari ST. Chronic pancreatitis. Lancet. 2016;387:1957–66.
29. Hobbs PM, Johnson WG, Graham DY. Management of pain in chronic pancreatitis with emphasis on exogenous pancreatic enzymes. World J Gastrointest Pharmacol Ther. 2016;7(3):370–86.
30. Pongprasobchai S. Maldigestion from pancreatic exocrine insufficiency. J Gastroenterol Hepatol. 2013;28(Suppl 4):99–102.
31. Duggan SN. Negotiating the complexities of exocrine and endocrine dysfunction in chronic pancreatitis. Proc Nutr Soc. 2017;76(4):484–94.
32. Anaizi A, Hart PA, Conwell DL. Diagnosing chronic pancreatitis. Dig Dis Sci. 2017;62(7):1713–20.
33. National Guideline Centre, hosted by the Royal College of Physicians. NICE guideline NG104 Pancreatitis Published: 5 Sept 2018. https://www.nice.org.uk/guidance/ng104/evidence/full-guideline-pdf-6535536157. Accessed 16 Dec 2020.
34. Phillips ME, Hopper AD, Leeds JS, Roberts KJ, McGeeney L, Duggan SN, Kumar R. Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines. BMJ Open Gastroenterol. 2021;8(1):e000643.
35. Bourne DM, White H, French JJ, Leeds JS. A retrospective cohort study of nutritional status, nutritional interventions and hospital admissions in patients with chronic pancreatitis managed at a tertiary referral centre. Clin Nutr ESPEN. 2021;43:290–5.
36. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S14–31.
37. Leeds JS, Hadjivassiliou M, Tesfaye S, Sanders DS. Lower gastrointestinal symptoms are associated with worse glycemic control and quality of life in type 1 diabetes mellitus. BMJ Open Diabetes Res Care. 2018;6(1):e000514.
38. Ewald N, Kaufmann C, Raspe A, Kloer HU, Bretzel RG, Hardt PD. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). Diabetes Metab Res Rev. 2012;28(4):338–42.
39. Hardt PD, Hauenschild A, Nalop J, Marzeion AM, Jaeger C, Teichmann J, Bretzel RG, Hollenhorst M, Kloer HU, S2453112/S2453113 Study Group. High prevalence of exocrine pancreatic insufficiency in diabetes mellitus. A multicenter study screening fecal elastase 1 concentrations in 1,021 diabetic patients. Pancreatology. 2003;3(5):395–402.
40. Ewald N, Bretzel RG, Fantus IG, Hollenhorst M, Kloer HU, Hardt PD, S-2453110 Study Group. Pancreatin therapy in patients with insulin-treated diabetes mellitus and exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations. Results of a prospective multi-centre trial. Diabetes Metab Res Rev. 2007;23(5):386–91.
41. Löser C, Möllgaard A, Fölsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. Gut. 1996;39(4):580–6.
42. Gullo L, Ventrucci M, Tomassetti P, Migliori M, Pezzilli R. Fecal elastase 1 determination in chronic pancreatitis. Dig Dis Sci. 1999;44(1):210–3.
43. Glasbrenner B, et al. Clinical evaluation of the faecal elastase test in the diagnosis and staging of chronic pancreatitis. Eur J Gastroenterol Hepatol. 1996;8:1117–20.
44. Lankisch PG, Schmidt I, König H, Lehnick D, Knollmann R, Löhr M, Liebe S. Faecal elastase 1: not helpful in diagnosing chronic pancreatitis associated with mild to moderate exocrine pancreatic insufficiency. Gut. 1998;42(4):551–4.
45. Domínguez-Muñoz JE, Iglesias-García J, Vilariño-Insua M, Iglesias-Rey M. 13C-mixed triglyceride breath test to assess oral enzyme substitution therapy in patients with chronic pancreatitis. Clin Gastroenterol Hepatol. 2007;5(4):484–8.
46. Domínguez-Muñoz JE, Nieto L, Vilariño M, Lourido MV, Iglesias-García J. Development and diagnostic accuracy of a breath test for pancreatic exocrine insufficiency in chronic pancreatitis. Pancreas. 2016;45(2):241–7.
47. Lindkvist B, Domínguez-Muñoz JE, Luaces-Regueira M, et al. Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. Pancreatology. 2012;12:305–10.
48. Sikkens ECM, Cahen DL, Koch AD, et al. The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. Pancreatology. 2013;13:238–42.
49. Martínez-Moneo E, Stigliano S, Hedström A, et al. Deficiency of fat-soluble vitamins in chronic pancreatitis: a systematic review and meta-analysis. Pancreatology. 2016;16:988–94.
50. Dutta SK, Bustin MP, Russell RM. Deficiency of fat-soluble vitamins in treated patients with pancreatic insufficiency. Ann Intern Med. 1982;97:549–52.
51. Livingstone C, Davis J, Marvin V, et al. Vitamin A deficiency presenting as night blindness during pregnancy. Ann Clin Biochem. 2003;40:292–4.
52. Vujasinovic M, Hedström A, Maisonneuve P, Valente R, von Horn H, Löhr JM, Haas SL. Zinc deficiency in patients with chronic pancreatitis. World J Gastroenterol. 2019;25(5):600–7.
53. Issa Y, Kempeneers MA, van Santvoort HC, Bollen TL, Bipat S, Boermeester MA. Diagnostic performance of imaging modalities in chronic pancreatitis: a systematic review and meta-analysis. Eur Radiol. 2017;27:3820–44.
54. Dronamraju S, Scott J, Oppong K, Nayar M. Diagnostic yield of secretin-enhanced magnetic resonance cholangiopancreatography in the investigation of patients with acalculous biliary pain. Ann Gastroenterol. 2016;29(3):367–72.
55. Iglesias-Garcia J, Domínguez-Muñoz JE, Castiñeira-Alvariño M, Luaces-Regueira M, Lariño-Noia J. Quantitative elastography associated with endoscopic ultrasound for the diagnosis of chronic pancreatitis. Endoscopy. 2013;45:781–8.
56. Duggan SN, Smyth ND, Murphy A, Macnaughton D, O'Keefe SJ, Conlon KC. High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12(2):219–28.

57. Hao L, Zeng XP, Xin L, et al. Incidence of and risk factors for pancreatic cancer in chronic pancreatitis: a cohort of 1656 patients. Dig Liver Dis. 2017;49:1249–56.
58. Goggins M, Overbeek KA, Brand R, Syngal S, Del Chiaro M, Bartsch DK, Bassi C, Carrato A, Farrell J, Fishman EK, Fockens P, Gress TM, van Hooft JE, Hruban RH, Kastrinos F, Klein A, Lennon AM, Lucas A, Park W, Rustgi A, Simeone D, Stoffel E, Vasen HFA, Cahen DL, Canto MI, Bruno M, International Cancer of the Pancreas Screening (CAPS) consortium. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International cancer of the pancreas screening (CAPS) consortium. Gut. 2020;69(1):7–17.
59. Leung JW, Bowen-Wright M, Aveling W, Shorvon PJ, Cotton PB. Coeliac plexus block for pain in pancreatic cancer and chronic pancreatitis. Br J Surg. 1983;70(12):730–2. 53.
60. Ramesh H, Reddy N, Bhatia S, et al. A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated minimicrospheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. Pancreatology. 2013;13:133–9.
61. Winny M, Paroglou V, Bektas H, Kaltenborn A, Reichert B, Zachau L, Kleine M, Klempnauer J, Schrem H. Insulin dependence and pancreatic enzyme replacement therapy are independent prognostic factors for long-term survival after operation for chronic pancreatitis. Surgery. 2014;155(2):271–9.
62. de la Iglesia-Garcia D, Vallejo-Senra N, Iglesias-Garcia J, et al. Increased risk of mortality associated with pancreatic exocrine insufficiency in patients with chronic pancreatitis. J Clin Gastroenterol. 2018;52:e63–72.
63. D'Haese JG, Ceyhan GO, Demir IE, Layer P, Uhl W, Löhr M, Rychlik R, Pirilis K, Zöllner Y, Gradl B, Foerster D, Möbius J, Henniges F, Friess H. Pancreatic enzyme replacement therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis: a 1-year disease management study on symptom control and quality of life. Pancreas. 2014;43(6):834–41.
64. Seiler CM, Izbicki J, Varga-Szabó L, Czakó L, Fiók J, Sperti C, Lerch MM, Pezzilli R, Vasileva G, Pap A, Varga M, Friess H. Randomised clinical trial: a 1-week, double-blind, placebo-controlled study of pancreatin 25 000 Ph. Eur. minimicrospheres (Creon 25000 MMS) for pancreatic exocrine insufficiency after pancreatic surgery, with a 1-year open-label extension. Aliment Pharmacol Ther. 2013;37(7):691–702.
65. Domínguez-Muñoz JE, Iglesias-García J, Iglesias-Rey M, Figueiras A, Vilariño-Insua M. Effect of the administration schedule on the therapeutic efficacy of oral pancreatic enzyme supplements in patients with exocrine pancreatic insufficiency: a randomized, three-way crossover study. Aliment Pharmacol Ther. 2005;21(8):993–1000.
66. FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ, Hammerstrom T, Durie PR, Lloyd-Still JD, Lowenfels AB. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med. 1997;336(18):1283–9.
67. Taylor CJ. Fibrosing colonopathy unrelated to pancreatic enzyme supplementation. J Pediatr Gastroenterol Nutr. 2002;35:268–9.
68. Löhr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, Haas S, Akisik F, Kartalis N, Iglesias-Garcia J, Keller J, Boermeester M, Werner J, Dumonceau JM, Fockens P, Drewes A, Ceyhan G, Lindkvist B, Drenth J, Ewald N, Hardt P, de Madaria E, Witt H, Schneider A, Manfredi R, Brøndum FJ, Rudolf S, Bollen T, Bruno M, HaPanEU/UEG Working Group. United European gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United European Gastroenterol J. 2017;5(2):153–99.
69. Vecht J, Symersky T, Lamers CB, Masclee AA. Efficacy of lower than standard doses of pancreatic enzyme supplementation therapy during acid inhibition in patients with pancreatic exocrine insufficiency. J Clin Gastroenterol. 2006;40(8):721–5.
70. Capurso G, Signoretti M, Archibugi L, Stigliano S, Delle FG. Systematic review and meta-analysis: small intestinal bacterial overgrowth in chronic pancreatitis. United European Gastroenterol J. 2016;4(5):697–705.
71. Ruiz-Campos L, Gisbert JP, Ysamat M, Arau B, Loras C, Esteve M, Fernández-Bañares F. Systematic review with meta-analysis: the prevalence of bile acid malabsorption and response to colestyramine in patients with chronic watery diarrhoea and previous cholecystectomy. Aliment Pharmacol Ther. 2019;49(3):242–50.
72. Leeds JS, Hopper AD, Hurlstone DP, Edwards SJ, McAlindon ME, Lobo AJ, Donnelly MT, Morley S, Sanders DS. Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? Aliment Pharmacol Ther. 2007;25(3):265–71.
73. Konstan MW, Wagener JS, Wilschanski M, Laki I, Boas SR, Sands D, Gangal M, Martin RS, Shanahan W, Pennington J. A comparison of liprotamase, a non-porcine pancreatic enzyme replacement therapy, to porcine extracted pancrelipase in a noninferiority randomized clinical trial in patients with cystic fibrosis. Clin Investig. 2018;08:147–54.
74. Pancreatic Cancer Action. Pancreatic cancer: nutrition, 2021. https://pancreaticcanceraction.org/healthcareprofessionals/patients-journey/nutrition-for-your-patient/.
75. Phillips ME, Berry A, Gettle LS. Pancreatic exocrine insufficiency and enteral feeding: a practical guide with case studies. Pract Gastroenterol. 2018;XLII:181.
76. Varadarajulu S, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. Gastroenterology. 2013;145(3):583–90.e1.
77. Nayar M, Leeds JS, Oppong K, UK & Ireland LAMS Colloborative. Lumen-apposing metal stents for drainage of pancreatic fluid collections: does timing of removal matter? Gut. 2022;71(5):850–3.
78. Hoffmeister A, Mayerle J, Beglinger C, Büchler MW, Bufler P, Dathe K, Fölsch UR, Friess H, Izbicki J, Kahl S, Klar E, Keller J, Knoefel WT, Layer P, Loehr M, Meier R, Riemann JF, Rünzi M, Schmid RM, Schreyer A, Tribl B, Werner J, Witt H, Mössner J, Lerch MM, Members of the Guideline Committee. English language version of the S3-consensus guidelines on chronic pancreatitis: definition, aetiology, diagnostic examinations, medical, endoscopic and surgical management of chronic pancreatitis. Z Gastroenterol. 2015;53(12):1447–95.
79. Drewes AM, Kempeneers MA, Andersen DK, Arendt-Nielsen L, Besselink MG, Boermeester MA, Bouwense S, Bruno M, Freeman M, Gress TM, van Hooft JE, Morlion B, Olesen SS, van Santvoort H, Singh V, Windsor J. Controversies on the endoscopic and surgical management of pain in patients with chronic pancreatitis: pros and cons! Gut. 2019;68(8):1343–51.
80. Khan MA, Baron TH, Kamal F, Ali B, Nollan R, Ismail MK, Tombazzi C, Artifon ELA, Repici A, Khashab MA. Efficacy of self-expandable metal stents in management of benign biliary strictures and comparison with multiple plastic stents: a meta-analysis. Endoscopy. 2017;49(7):682–94.
81. Haapamäki C, Kylänpää L, Udd M, Lindström O, Grönroos J, Saarela A, Mustonen H, Halttunen J. Randomized multicenter study of multiple plastic stents vs. covered self-expandable metallic stent in the treatment of biliary stricture in chronic pancreatitis. Endoscopy. 2015;47(7):605–10.
82. Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, Stoker J, Laméris JS, Dijkgraaf MG, Huibregtse K, Bruno MJ. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med. 2007;356(7):676–84.
83. Cahen DL, Gouma DJ, Laramée P, Nio Y, Rauws EA, Boermeester MA, Busch OR, Fockens P, Kuipers EJ, Pereira SP, Wonderling D,

Dijkgraaf MG, Bruno MJ. Long-term outcomes of endoscopic vs. surgical drainage of the pancreatic duct in patients with chronic pancreatitis. Gastroenterology. 2011;141(5):1690–5.
84. Beger HG, Schlosser W, Friess HM, Büchler MW. Duodenumpreserving head resection in chronic pancreatitis changes the natural course of the disease: a single-center 26-year experience. Ann Surg. 1999;230:512–9; discussion 519–23.
85. Klaiber U, Alldinger I, Probst P, et al. Duodenum-preserving pancreatic head resection: 10-year follow-up of a randomized controlled trial comparing the beger procedure with the berne modification. Surgery. 2016;160:127–35.
86. Bellin MD, Prokhoda P, Hodges JS, Schwarzenberg SJ, Freeman ML, Dunn TB, Wilhelm JJ, Pruett TL, Kirchner VA, Beilman GJ, Chinnakotla S. Age and disease duration impact outcomes of total pancreatectomy and islet autotransplant for PRSS1 hereditary pancreatitis. Pancreas. 2018;47(4):466–70.
87. Wilson GC, Sutton JM, Abbott DE, Smith MT, Lowy AM, Matthews JB, Rilo HL, Schmulewitz N, Salehi M, Choe K, Brunner J, Hanseman DJ, Sussman JJ, Edwards MJ, Ahmad SA. Long-term outcomes after total pancreatectomy and islet cell autotransplantation: is it a durable operation? Ann Surg. 2014;260(4):659–65; discussion 665–7.
88. Bezmarević M, van Dijk SM, Voermans RP, van Santvoort HC, Besselink MG. Management of (Peri)pancreatic collections in acute pancreatitis. Visc Med. 2019;35(2):91–6.
89. Rees J, Mytton J, Evison F, Mangat KS, Patel P, Trudgill N. The outcomes of biliary drainage by percutaneous transhepatic cholangiography for the palliation of malignant biliary obstruction in England between 2001 and 2014: a retrospective cohort study. BMJ Open. 2020;10(1):e033576.

Appendix: Useful Websites

Academy of Nutrition and Dietetics
www.eatright.org/
American Society for Parenteral and Enteral Nutrition – ASPEN
www.clinnutr.org
Association for Nutrition. Medical student curriculum
www.associationfornutrition.org/wp-content/uploads/2021/10/2021-UK-Undergraduate-Curriculum-in-Nutrition-for-Medical-Doctors-FINAL.pdf
Australian Society for Parenteral and Enteral Nutrition – AuSPEN
www.auspen.org.au
Biopharmaceutical Classification System (BCS)
www.ddfint.org
www.ncbi.nlm.nih.gov/pmc/articles/PMC4476996/
British Association for Parenteral and Enteral Nutriton – BAPEN (includes BANS and MAG)
www.bapen.org.uk
British Intestinal Failure Alliance (BIFA)
https://www.bapen.org.uk/about-bapen/bapen-special-interest-groups/bifa
British Dietetic Association
www.bda.uk.com/
British Medical Journal
www.bmj.com
British Pharmaceutical Nutrition Group
www.bpng.co.uk/
British Society of Gastroenterology
www.bsg.org.uk/
British Society of Paediatric Gastroenterology, Hepatology and Nutrition
https://bspghan.org.uk/
Canadian Nutrition Society
www.cns-scn.ca/
Canadian Patient Parenteral and Enteral Nutrition Alliance (CPPENA)
https://cns-scn.ca/education-resources/cppena
Cochrane Collaboration
www.cochrane.org/
Dietitians of Canada
www.dietitians.ca/
European Society of Coloproctology. Consensus on the surgical management of intestinal failure in adults
https://pericles.pericles-prod.literatumonline.com/doi/10.1111/codi.13321
European Society of Parenteral and Enteral Nutriton – ESPEN
www.espen.org
Italian Society for artificial nutrition and metabolism
www.sinpe.org
Motor Neurone Disease Association
www.mndassociation.org
National Audit of Small Bowel Obstruction (NASBO)
www.acpgbi.org.uk/_userfiles/import/2017/12/NASBO-REPORT-2017.pdf
National Library of Medicine
www.nlm.nih.gov/
The National Nurses Nutrition Group (NNNG)
https://nnng.org.uk/
The Oley Foundation (home PEN organisation)
www.oley.org
Parenteral and Enteral Nutrition Society of Asia – PENSA
www.pensa-online.org
Parenteral and Enteral Nutrition Group of the British Dietetic Association
www.peng.org.uk
Patients on Intravenous and Naso-gastric Nutrition Therapy – PINNT
www.pinnt.com
PubMed. National Library of Medicine (Citations from MEDLINE, life science journals, and online books)
https://pubmed.ncbi.nlm.nih.gov and www.ncbi.nlm.nih.gov/pmc
Scottish Intercollegiate Guidelines Network (SIGN)
www.sign.ac.uk
South African Society for Parenteral and Enteral Nutrition – SASPEN
www.saspen.com
UK Government
www.gov.uk
Web addresses for most PEN societies
https://www.espen.org/espen-national-societies

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