THE INDISPENSABLE GUIDE TO CRITICAL CARE

OXFORD HANDBOOK OF CRITICAL CARE

Alice Carter | Mervyn Singer | Andrew Webb

Clinically orientated and patient focused - the first port of call when caring for critically ill patients

Comprehensively revised, with new chapters including sepsis, peri-operative care, and scoring systems

Provides updated guidance on the latest drugs, therapies, and devices in critical care

OXFORD MEDICAL PUBLICATIONS

Oxford Handbook of Critical Care

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FOURTH EDITION

Alice Carter

Consultant in Anaesthesia and Critical Care
University College London Hospitals London, UK
Associate Dean and Director
London Foundation School
NHS England, London, UK

Mervyn Singer

Professor of Intensive Care Medicine
Director, Bloomsbury Institute of Intensive Care Medicine
NIHR Emeritus Senior Investigator
University College London
London, UK

Andrew Webb

Retired Critical Care Physician and Medical Director
University College London Hospitals
London, UK
Retired Senior Healthcare Executive
Surrey, BC, Canada and Sault Ste Marie, ON, Canada

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Foreword

It's a real privilege to write this foreword. The *Oxford Handbook of Critical Care* has been a popular, staple reference book for more than 25 years now, and is a familiar volume on the desks or in the pockets of all involved in the management of critically ill patients, myself included!

This edition has been extensively updated since the last version, containing all the latest, relevant developments in clinical practice in this field. Although slightly larger than previous editions, it maintains its handbook format and appeal. With skilled writing and editing, the authors have managed to include an enormous amount of information in the one volume, providing important essentials for the less experienced and a useful refresher for the more expert practitioner. The layout, with ample illustrations and tables, short subtitled sections, and bulleted lists, makes it easy for the reader to scan and locate the required information on any topic rapidly. Not intended to be read cover to cover, but to provide rapid access to key information, this new edition lives up to its reputation as an indispensable reference book in this highly complex area of medicine.

Jean-Louis Vincent
Professor of Intensive Care Medicine (Université Libre de Bruxelles)
Consultant, Dept of Intensive Care, Erasme University Hospital

Preface

Critical care medicine is complex and exacting, yet exciting and fulfilling. It is truly holistic, covering every organ system, addressing the emotional as well as physical needs of the patient. It requires a broad knowledge base covering disease conditions, physiology and pathophysiology, biochemistry, pharmacology, and technology, including principles of engineering and physics. It also demands practical aptitude, excellent communication skills with colleagues, patients, and relatives, and the ability to work closely with and, if needs be, to lead a multidisciplinary team. Responses often have to be delivered in a time-critical manner in view of the many varied and stressful emergency situations that can arise, and these responses must be calm, considered, targeted, and—hopefully—successful. Regular legal, ethical, and life-and-death dilemmas must also be managed tactfully and appropriately.

We are thus delighted to offer the fourth edition of this handbook. It has been considerably revised and updated since the last iteration. Many new sections have been added covering the wide gamut of therapeutic techniques and monitoring, drugs and fluids, specific organ system disorders and complications, and general management strategies. Non-clinical sections have also been enhanced. Ongoing controversies are highlighted and discussed. We fully acknowledge that many grey areas still remain in critical care practice where the evidence base is weak, conflicting, or non-existent. We offer our approach, fully acknowledging there are alternatives that may be as effective, or perhaps even more so. Many aspects of critical care management are changing; the multiple revisions in this new edition reflect this rapid evolutionary process.

We have endeavoured to retain a succinct, concise, readable style that will continue to serve as a handy pocket/web-based reference for both experienced and novice clinical staff from all disciplines. We trust that the framework provided herein represents sound clinical practice. We would, however, emphasize that patients are individuals and do not necessarily respond in an identical manner. It is thus crucial to recognize promptly how the illness is unfolding and to react accordingly, retaining flexibility of thought and action based on sound rationale and good practice.

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Alice Carter
Mervyn Singer
Andrew Webb
2024

Symbols and abbreviations

➲	cross-reference
~	approximately
>	greater than
≥	greater than or equal to
<	less than
≤	less than or equal to
±	with/without
A–aDO_2	alveolar–arterial oxygen difference
ABC	airway, breathing, and circulation
ABE	arterial base excess
AC	alternating current
ACCP	advanced critical care practitioner
ACE	angiotensin-converting enzyme
ACMV	assist control mechanical ventilation
ACT	activated clotting time
ACTH	adrenocorticotropic hormone
ADEM	acute disseminated encephalomyelitis
ADH	antidiuretic hormone
ADRT	advance decision to refuse treatment
AG	anion gap
AGP	aerosol-generating procedure
AHP	allied health professional
AI	artificial intelligence
AIS	Abbreviated Injury Scale
AKI	acute kidney injury
ALI	acute lung injury
ALS	Advanced Life Support
ALT	alanine aminotransferase
AMI	acute myocardial infarction
ANCA	antinuclear cytoplasmic antibodies
APACHE	Acute Physiology and Chronic Health Evaluation
APRV	airway pressure release ventilation
APTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
ASD	atrioseptal defect
AST	aspartate aminotransferase
ATLS	Advanced Trauma Life Support
AV	atrioventricular
BAL	bronchoalveolar lavage
bd	*bis die* (twice daily)
BDG	(1,3)-β-d-glucan
BiPAP	bi-level positive airway pressure
BNP	B-type natriuretic peptide
BOOP	bronchiolitis obliterans with organizing pneumonia
BP	blood pressure
bpm	beats per minute
BSA	burn surface area
CAA	cerebral amyloid angiopathy
CABG	coronary artery bypass grafting
$CaCl_2$	calcium chloride
CAL	chronic airflow limitation
cAMP	cyclic adenosine monophosphate
cANCA	core antineutrophil cytoplasmic antibodies
CAP	community-acquired pneumonia
cART	combination antiretroviral chemotherapy
CAR-T	chimeric antigen receptor T cell
CASPR-2	contactin-associated protein-like 2
CBF	cerebral blood flow
CBV	cerebral blood volume
CFM	cerebral function monitor
cGMP	cyclic guanosine monophosphate
CIRCI	critical illness-related corticosteroid insufficiency
CJD	Creutzfeldt–Jakob disease
CK	creatine kinase
CKD	chronic kidney disease
CK-MB	creatine kinase myocardial band
cmH_2O	centimetres of water

$CMRO_2$	cerebral metabolic rate for oxygen
CMV	cytomegalovirus
CNS	central nervous system
CO	carbon monoxide *or* cardiac output
CO_2	carbon dioxide
COHb	carboxyhaemoglobin
COP	cryptogenic organizing pneumonia
CPAP	continuous positive airways pressure
CPK	creatine phosphokinase
CPM	central pontine myelinolysis
CPP	cerebral perfusion pressure
CPR	cardiopulmonary resuscitation
CRO	carbapenem-resistant organism
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CVA	cerebrovascular accident
CVP	central venous pressure
CVVH	continuous veno-venous haemofiltration
CVVHD	continuous veno-venous haemodiafiltration
CXR	chest X-ray
Da	dalton
DA	dopamine
DAMP	damage-associated molecular pattern
DAPT	dual antiplatelet therapy
DC	direct current
DDAVP	1-deamino-8-D-arginine vasopressin
DEAFF	detection of early antigen fluorescent foci
DES	drug-eluting stent
DIC	disseminated intravascular coagulation
DISE	direct ion-selective electrode
DNACPR	do not attempt cardiopulmonary resuscitation
D/NOAC	direct/novel oral anticoagulant
DO_2	oxygen delivery
DoLS	Deprivation of liberty safeguards
DPG	diphosphoglycerate
DVT	deep vein thrombosis
EBV	Epstein–Barr virus
$ECCO_2R$	extracorporeal carbon dioxide removal
ECF	extracellular fluid
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ECTR	extracorporeal therapy removal
EEG	electroencephalogram
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EIT	electrical impedance tomography
ELAD	extracorporeal liver assist device
ELISA	enzyme-linked immunosorbent assay
ELSO	Extracorporeal Life Support Organisation
EMG	electromyography
EN	enteral nutrition
EPAP	expiratory positive airway pressure
ERCP	endoscopic retrograde pancreatography
ET	endotracheal
EVLW	extravascular lung water
FDP	fibrin degradation product
FEV_1	forced expired volume in 1 second
FFP	fresh frozen plasma
FiO_2	fraction of inspired oxygen
FPSA	fractionated plasma separation and adsorption
Fr	French gauge
FRC	functional residual capacity
FTc	flow time corrected for heart rate
fullPIERS	full pre-eclampsia integrated estimate of risk
FVC	forced vital capacity
g	gram
G	gauge
GAS	group A *Streptococcus*
GBM	glomerular basement membrane
GBS	group B *Streptococcus*
GCS	Glasgow Coma Scale

G-CSF	granulocyte colony-stimulating factor
GEDV	global end-diastolic volume
GFR	glomerular filtration rate
γGT	gamma-glutamyl transferase
GHB	gamma-hydroxybutyric acid
GI	gastrointestinal
GIK	glucose–insulin–potassium
GlyR	glycine receptor
GM	galactomannan
GMP	guanosine monophosphate
GPA	granulomatosis with polyangiitis
GPI	glycoprotein IIb/IIIa inhibitor
GTN	glyceryl trinitrate
GVHD	graft-versus-host disease
h	hour
HAP	hospital-acquired pneumonia
HASU	hyperacute stroke unit
Hb	haemoglobin
HBOT	hyperbaric oxygen therapy
HCl	hydrochloric acid
HCST	haematopoietic stem cell transplantation
HD	haemodialysis
HELLP	haemolysis, elevated liver enzymes, and low platelets
HFNC	high-flow nasal cannula
HFNO	high-flow nasal oxygen
HFJV	high-frequency jet ventilation
HFOV	high-frequency oscillation ventilation
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HLH	haemophagocytic lymphohistiocytosis
HME	heat and moisture exchange
HMGB1	high motility group box 1
HOCM	hypertrophic obstructive cardiomyopathy
HR	heart rate
hrly	hourly
HSP	heat shock protein
hs-Trop T	high-sensitivity troponin T
HUS	haemolytic uraemic syndrome
IABP	intra-aortic balloon pump
IBW	ideal body weight
ICANS	immune effector cell-associated neurotoxicity syndrome
ICP	intracranial pressure
ICU	intensive care unit
I:E	inspiratory:expiratory
IGFBP-7	insulin growth factor binding protein 7
IgG	immunoglobulin G
IISE	indirect ion-selective electrode
IM	intramuscular
IMCA	Independent Mental Capacity Advocate
IMV	intermittent mandatory ventilation
iNO	inhaled nitric oxide
INR	international normalized ratio
IO	intraosseous
IPAP	inspiratory positive airway pressure
IPPV	intermittent positive pressure ventilation
IRIS	immune reconstitution inflammatory syndrome
ISS	Injury Severity Score
ITBV	intrathoracic blood volume
ITP	idiopathic thrombocytopenic purpura
IU	international unit
IV	intravenous
IVIg	intravenous immunoglobulin
JAK	Janus kinase
KCl	potassium chloride
kDa	kilodalton
kg	kilogram
kHz	kilohertz
kJ	kilojoule
kPa	kilopascal
L	litre
LAMP	loop-mediated isothermal amplification
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LGI-1	leucine-rich glioma-inactivated 1
LMA	laryngeal mask airway
LMWH	low-molecular-weight heparin
LOLA	L-ornithine-L-aspartate
LP	lumbar puncture
LUS	Lung Ultrasound Score

LV	left ventricle/ventricular
LVEDP	left ventricular end diastolic pressure
LVF	left ventricular failure
LVOT	left ventricular outflow tract
LVSW	left ventricular stroke work
mA	milliamp
MALDI-TOF	matrix-assisted laser desorption ionization–time of flight
MAHA	microangiopathic haemolytic anaemia
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MARS	Molecular Adsorbent Recirculation System
MCA	middle cerebral artery
mcg	microgram
MCV	mean cellular volume
MDAC	multi-dose activated charcoal
MDMA	3,4 methylenedioxy-methamphetamine
MDT	multidisciplinary team
MERS	Middle East Respiratory Syndrome
metHb	methaemoglobin
mg	milligram
MH	malignant hyperthermia
MI	myocardial infarction
min	minute
mmHg	millimetre of mercury
µmol	micromole
mmol	millimole
MODS	multiple organ dysfunction syndrome
MOF	multiple organ failure
mOsm	milliosmole
MPAP	mean pulmonary artery pressure
MRSA	meticillin (methicillin)-resistant *Staphylococcus aureus*
ms	millisecond
MuSK	muscle specific kinase
NAC	*N*-acetylcysteine
NAG	*N*-acetyl-D-glucosaminidase
NBM	nil by mouth
NET	neutrophil extracellular trap
NEWS	National Early Warning Score
NEX	distance from nose to ear lobe to xiphisternum
NG	nasogastric
NGAL	neutrophil gelatinase-associated lipocalin
NIRS	near-infrared spectroscopy *or* non-invasive respiratory support
NIV	non-invasive ventilation
NJ	nasojejunal
nm	nanometre
NMDA	*N*-methyl-D-aspartate
NMS	neuroleptic malignant syndrome
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug
NSE	neurone-specific enolase
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
O_2	oxygen
O_2ER	oxygen extraction ratio
od	*omni die* (once daily)
ODS	osmotic demyelination syndrome
OPS	orthogonal polarization spectroscopy
ORC	oxidized regenerated cellulose
oxyHb	oxyhaemoglobin
PA	pulmonary artery
$PaCO_2$	arterial partial pressure of carbon dioxide
PAF	platelet activating factor
PAMP	pathogen-associated molecular pattern
PAN	polyarteritis nodosa
PaO_2	arterial partial pressure of oxygen
PAO_2	alveolar partial pressure of oxygen
PAWP	pulmonary artery wedge pressure
PCA	patient-controlled analgesia
PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
PCO_2	partial pressure of carbon dioxide
PCR	polymerase chain reaction
PD	peritoneal dialysis
PDE	phosphodiesterase

PE	pulmonary embolism
PEEP	positive end-expiratory pressure
PEEPi	intrinsic positive end-expiratory pressure (auto-PEEP)
PEG	percutaneous endoscopic gastrostomy
PEJ	percutaneous endoscopic jejunostomy
PERM	progressive encephalomyelitis, rigidity, and myoclonus
P:F ratio	PaO_2:FiO_2 ratio
PGE1	prostaglandin E1 (alprostadil)
PGI2α	prostaglandin I2 alpha (epoprostenol)
pHi	intramucosal pH
PI	pulsatility index
PICC	percutaneous intravenous central catheter
PiCCO	pulse contour cardiac output
PImax	maximum inspiratory pressure
PN	parenteral nutrition
PO	*per os* (by mouth)
PO_2	partial pressure of oxygen
POCT	point-of-care testing
POCUS	point-of-care ultrasound
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin abnormalities
PP	pulse pressure
PPE	personal protective equipment
PPH	postpartum haemorrhage
ppm	parts per million
PRES	posterior reversible encephalopathy syndrome
prn	*pro re nata* (as required)
PRR	pattern recognition receptor
pSILI	patient self-induced lung injury
PSV	pressure support ventilation
PT	prothrombin time
PTCA	percutaneous transluminal coronary angioplasty
PVR	pulmonary vascular resistance
qds	*quater die sumendum* (take four times daily)
Qs/Qt	shunt fraction
RASS	Richmond Agitation Sedation Scale
RBBB	right bundle branch block
RBC	red blood cell
RCT	randomized controlled trial
RDS	respiratory distress syndrome
RER	respiratory exchange ratio
RESP	Respiratory ECMO Survival Prediction
RIFLE	risk, injury, failure, loss, and end-stage renal disease
ROSC	return of spontaneous circulation
ROTEM	rotational thromboelastometry
RQ	respiratory quotient
RRT	renal replacement therapy
RSV	respiratory syncytial virus
rtPA	recombinant tissue plasminogen activator
RTS	Revised Trauma Score
RV	right ventricle/ventricular
RVSW	right ventricular stroke work
s	second
SAH	subarachnoid haemorrhage
SaO_2	arterial oxygen saturation
SAPS	Simplified Acute Physiology Score
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2 (COVID-19)
SB	Sengstaken–Blakemore (tube)
SC	subcutaneously
SCUF	slow continuous ultrafiltration
$ScvO_2$	central venous saturation
SDD	selective digestive decontamination
SDF	sidestream dark field
S:F ratio	SpO_2:FiO_2 ratio
SGLT2	sodium–glucose cotransporter 2
SIADH	syndrome of inappropriate ADH secretion
SID	strong ion difference
SILI	self-induced lung injury
SIMV	synchronized intermittent mandatory ventilation
SIPP	Severity Index of Paraquat Poisoning
SIRS	systemic inflammatory response syndrome
SjO_2	jugular bulb oxygen saturation

SL	sublingual
SLE	systemic lupus erythematosus
SLED	sustained low-efficiency dialysis
SMR	standardized mortality ratio
SOFA	Sequential Organ Failure Assessment
SPAD	single-pass albumin dialysis
SpO_2	pulse oximetry oxygen saturation
spp.	species
SPV	systolic pressure variation
SSC	Surviving Sepsis Campaign
stat	*statim* (immediately)
StO_2	tissue oxyhaemoglobin saturation
SV	stroke volume
SvO_2	mixed venous saturation
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
T_3	triiodothyronine
T_4	thyroxine
TAPSE	tricuspid annular plane systolic excursion
TB	tuberculosis
TBI	traumatic brain injury
TCD	transcranial Doppler
tds	*ter die sumendum* (take three times daily)
TED	thromboembolic deterrent
TEG	thromboelastography
TEN	toxic epidermal necrolysis
TIMP-2	tissue inhibitor of metalloproteinase-2
TIPSS	transjugular intrahepatic portosystemic stented shunt
TISS	Therapeutic Intervention Scoring System
TLC	total lung capacity
TLS	tumour lysis syndrome
TOE	transoesophageal echocardiography
TPN	total parenteral nutrition
TPO-RA	thrombopoietin receptor agonist
Trop T	troponin T
TRISS	Combined Revised Trauma and Injury Severity Scores
TSS	toxic shock syndrome
TT	thrombin time
TTE	transthoracic echocardiography
TTM	targeted temperature management
TTP	thrombotic thrombocytopenic purpura
TURP	transurethral resection of prostate
VAC	vacuum-assisted closure
VAD	ventricular assist device
VAP	ventilator-associated pneumonia
VC	vital capacity
VCO_2	carbon dioxide production
V_D	dead space
VDRL	Venereal Diseases Reference Laboratory
V_D/V_T	dead space:tidal volume ratio
VF	ventricular fibrillation
VILI	ventilator-induced lung injury
VO_2	oxygen consumption
VRE	vancomycin-resistant enterococci
VSD	ventricular septal defect
V_T	tidal volume
VT	ventricular tachycardia
WBC	white blood cell

Chapter 1

Organization & management

Critical care unit layout

The critical care unit should be readily accessible by departments from which patients are admitted. In a new hospital, critical care facilities should ideally be proximal to operating theatres, emergency department, imaging suites and laboratories, or have rapid access (e.g. pneumatic tube transport of samples).

Critically ill patients should ideally be separated from those in the recovery phase where a quiet, less stressful environment is needed to facilitate rest and sleep. Providing intensive care and high dependency care within the same unit allows flexibility of staffing, although the differing requirements of these patients may limit such flexibility.

Size of unit

This depends on the overall activity of the hospital. Additional beds would be needed for regional specialties such as cardiothoracic or neurosurgery. Small (<6 beds) or large (>14 beds) units may be difficult to manage. Larger units can be divided operationally to allow better concentration of resources.

Patient areas

- There should be unobstructed passage around the bed.
- Floors and ceilings must be constructed to support heavy equipment (some equipment may weigh >1000 kg).
- Doors must allow for passage of bulky equipment and wide beds.
- A wash hand basin with elbow-operated or proximity-operated mixer taps, soap and antiseptic dispensers should be close to every bed space.
- Services must include an adequate electricity supply and sockets per bed, with an uninterruptable power supply for essential equipment. Oxygen (four), medical air (two), and high- (two) and low-pressure (two) suction outlets must be available at every bedspace.
- At least 50% of beds should be isolation rooms. Positive and negative air pressure control in these rooms should ensure effective patient isolation.
- Single rooms are better for infection control and privacy aspects but harder to supervise. In bays, bed centres should be at least 4.6 m apart with curtains/screens for privacy. Curtain materials should be selected to reduce noise and aid privacy.
- Bed areas should have natural daylight. Patients and staff should ideally have an outside view.
- Light levels should be locally adjustable for day–night rhythm.
- Communications systems should include an adequate number of telephones, intercom systems to allow bed-to-bed communication, and a system to control entry to the department.
- Computers should be available at each bedspace and in administrative work areas. The computer network should enable quick communication with other hospital staff, laboratory and radiology systems, and the internet.

Other areas required

Other areas include adequate storage space, separate clean-treatment and dirty utility/sluice areas, office space, medical physics roo m, cleaners' room, kitchen space, staff rest area, seminar room, staff change and locker room, separate staff and patient toilet and shower facilities, and a communal area for relatives. There should also be a quiet room for confidential discussions with family and friends, and for privacy for those who are distressed.

Further reading

'Critical care units: planning and design (HBN 04-02)'. Department of Health. Accessed June 2023. https://www.england.nhs.uk/publication/critical-care-units-planning-and-design-hbn-04-02/

See Infection control—general principles, p580.

Medical staffing

Critical care has evolved significantly from its early success in mechanically ventilating polio victims. Patients who have, or are at risk of developing, dysfunction of one or more organ systems can now receive multiple mechanical and pharmacological organ supports and sophisticated monitoring. The unit should have dedicated specialist consultant sessions allocated for direct patient care, with additional sessions for management, teaching, and audit. These critical care-trained specialists should be supported by resident doctors providing continuous cover on a rota that provides adequate rest. The UK Intensive Care Society recommends ratios of one consultant for every 8–15 patients, and one resident doctor for up to eight patients. There must be 24/7 availability of a practitioner with advanced airway skills. This may require local arrangements with anaesthesia departments.

Required skills of critical care medical staff

Management

Senior medical staff, assisted by senior nursing and other allied health professionals and hospital managers, have responsibility for structural and financial management of the unit.

Decision-making

Many decisions are made by consensus though ultimate responsibility lies with the on-call intensivist. Case conferences involving multiple consultants and other relevant staff are particularly useful for challenging situations. Clinical decisions fall under three categories:

- Those relating to common issues for which unit guidelines exist.
- Decisions relating to uncommon problems requiring discussion with unit colleagues ± non-intensive care unit (ICU) specialist teams.
- Decisions of an urgent nature taken by critical care staff without delay.

Practical skills

For management of complex equipment, monitoring, and performance of invasive procedures.

Clinical experience

For recognition, prevention, and management of critical illness, infection control, sedation, analgesia, organ support, and advanced resuscitation skills.

Technical knowledge

The critical care specialist has an important role in the choice of equipment. Advice should be sought from other clinical and non-medical colleagues, e.g. medical physicists.

Pharmacological knowledge

Critically ill patients receive multiple drugs and are highly susceptible to drug interactions. Pharmacokinetics are often severely altered, e.g. by the effects of major organ system dysfunction (especially the liver and kidneys), decreased protein levels, and/or altered volumes of distribution. Adverse reactions are common.

Teaching and training

The critical care specialist has acquired skills and knowledge that cannot be gained outside the critical care unit. This expertise must be imparted to clinicians in training.

Non-critical care specialist advice

Such input is integral to patient management and the smooth running of the unit for specialist input. In particular, microbiology should offer daily ward rounds and 24/7 telephone availability for advice. Other teams that are frequently consulted for advice/support include surgical teams, radiology, infection control teams, pain control specialists, and palliative care teams.

Further reading

'Core Standards for Intensive Care Units'. Intensive Care Society. Accessed June 2023. https://ics.ac.uk/resource/core-standards-for-icus.html

➔ See Non-medical staffing, p6.

Non-medical staffing

Nursing staff

ICU patients require close nursing supervision 24/7, often at high intensity. Extra staff are needed to manage day-to-day running, to assist in lifting and handling, to facilitate breaks, and to collect drugs and equipment. These additional nurses (or nurse assistants) can be termed the 'fixed nursing establishment'. This usually includes higher-grade nurses. The bedside nurses are a 'variable establishment'; their numbers depend on patient numbers and demands. Most units fix part of their variable establishment by assuming an average activity.

Fixed establishment

Providing one nurse per patient per shift requires a rota of 5.5 nurses. In addition, staff handover, annual leave, study leave, and sickness are usually calculated at 22% such that one additional nurse is required. Thus, provision of one nurse in charge of each shift and one nurse to support the bedside nurses requires 11 nurses in those two roles alone. In larger units (>10 beds) there will be a need for additional nurses supporting the nurse in charge. Nurse educators are also a fundamental requirement to coordinate education, training, and continuing professional development framework needs.

Variable establishment

To provide a 1:1 bedside nurse:patient ratio also requires 5.5 nurses per bed, or 2.75 nurses to provide 1:2 nursing. The total number required depends on total ICU occupancy and the ratio needed for each individual patient bed. Difficulty in staffing relates to variable dependency and occupancy. An average dependency-weighted occupancy (average occupancy × average nurse:patient ratio) should be used to set the establishment of bedside nurses, with additional agency/bank nurses drafted in to cover peak demands.

Skill mix

Nursing skill mix is a balance between economy and providing quality care. As stated above, the fixed nursing body will usually be of higher grade since their role incorporates administration and supervision. A minimum of 50% of bedside registered nursing staff should be in possession of a post-registration award in critical care nursing.

Allied healthcare professionals (AHPs)

Care of the critically ill patient requires many healthcare professionals as part of an integrated interprofessional team. In addition to ICU physicians, nurses, and nurse assistants, other healthcare professionals e.g. pharmacists, physiotherapists, dietitians, and psychologists who specialize in the care of the critically ill, will provide daily support.

Other AHPs are often needed on an ad hoc basis to provide specialist support, e.g. speech and language therapy. 24/7 technical support is necessary for equipment breakdowns, maintenance, and to ensure correct functioning.

Advanced critical care practitioners (ACCPs)

In the UK, nurses, physiotherapists, paramedics, and pharmacists can, if desired, undertake a 2–3-year training period to gain a postgraduate qualification and become an ACCP. This enables them to prescribe independently (under consultant supervision), and provides them with an expanded diagnostic and clinical management role in caring for patients. A qualified ACCP should work under the supervision of the on-call consultant.

Other staff

Administration support is needed for infrastructure management, staffing the reception area and external telephones, audit, stock control, human resources, and finance.

Further reading

'Core Standards for Intensive Care Units'. Intensive Care Society. Accessed June 2023. https://ics.ac.uk/resource/core-standards-for-icus.html

See Medical staffing, p4.

Outreach/medical emergency team

Critical care outreach supports the effectiveness of critical care units by utilizing their expertise outside the ICU. Outreach teams typically support patients outside the critical care unit who may require admission or recently been discharged from ICU. The outreach team will aim to expedite timely admission to a critical care unit for those that need it. Outreach teams work in collaboration with general ward staff and should be called following identification of a deterioration in the patient's condition to provide advice, support, education, and a link to the critical care facility. Outreach teams in the UK are usually developed around critical care nurses but can also call upon ICU medical staff and other members of the multidisciplinary team. In other countries, such as Australia, the model of a medical emergency team, staffed by intensivists or resident doctors, is more commonplace.

The outreach team should support and facilitate the ability of ward or emergency department staff to:

- Identify patients at risk of developing life-threatening acute illness. Patients suffering cardiorespiratory arrest in hospital usually show gradual deterioration (especially in conscious level and respiratory rate) rather than an abrupt collapse.
- Initiate immediate resuscitation.
- Make appropriate referral, documentation, and communication.
- Provide psychological support and physiological surveillance to patients after discharge from the critical care unit.
- Educate and train general ward staff in the identification of deteriorating vital signs, the use of appropriate early warning scoring systems, and the institution of appropriate management.
- Though no study has specifically shown mortality reduction through the use of outreach or medical emergency teams, ward staff and patients greatly value their support. The outreach teams can prompt decisions regarding resuscitation status and this has led to a reduction in inappropriate cardiac arrest calls.

Outreach team calling criteria

Hospitals should have agreed calling criteria based on an Early Warning Score. In the UK, a single score has been introduced nationwide across nursing homes, paramedics, emergency departments, and hospital wards as a common language. The original National Early Warning Score (NEWS) was updated in 2017 to NEWS-2 (Table 1.1). Weighted points are scored for abnormalities in each of seven physiological variables that are readily collectable at the patient's bedside.

Early warning systems

Table 1.1a UK National Early Warning Score (NEWS-2)

	3	2	1	0	1	2	3
Resp rate	≤8		9–11	12–20		21–24	≥25
SpO_2–1* (%)	≤91	92–93	94–95	≥96			
SpO_2–2* (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on O_2	95–96 on O_2	≥97 on O_2
O_2 suppl		Yes		No			
Temp	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	
Syst BP	≤90	91–100	101–110	111–219			≥220
HR	≤40		41–50	51–90	91–110	111–130	≥131
CNS				A			CVPU

CNS = central nervous system; HR = heart rate; Resp = respiratory; SpO_2 = pulse oximetry oxygen saturation; suppl = supplementary; Syst = systolic; Temp = temperature.

ACVPU scale: A = alert; C= confused; V = responds to voice; P = responds to pain; U = unconscious.

* SpO_2–2 for patients with chronic type II respiratory disease who rely on their hypoxaemic drive. SpO_2–1 for all others.

Adapted from Royal College of Physicians. 2017. *National Early Warning Score (NEWS) 2*.

Table 1.1b NEWS-2 thresholds and triggers

NEWS-2 score	Clinical risk	Response
Aggregate score 0–4	Low	Ward-based response
Score of 3 in any individual parameter	Low–medium	Urgent ward-based response*
Aggregate score 5–6	Medium	Key threshold for urgent response*
Aggregate score ≥7	High	Urgent or emergency response**

* Response by a clinician or team with competence in assessment and treatment of acutely ill patients and in recognizing when escalation of care to a critical care team is appropriate.

** The response team must include staff with critical care skills, including airway management.

Further reading

Chen J, Bellomo R, Flabouris A, et al for the MERIT Study Investigators for the Simpson Centre and the ANZICS Clinical Trials Group. 2009. 'The relationship between early emergency team calls and serious adverse events'. *Crit Care Med* 37: pp148–53. doi: 10.1097/CCM.0b013e3181928ce3

'National Early Warning Score (NEWS) 2'. Royal College of Physicians. 2017. Accessed June 2023. https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2

See Critical care unit admission criteria, p10.

Critical care unit admission criteria

The critical care unit is the hub of critical care provision for the hospital. In the UK, critical illness is defined according to patient dependency levels (Table 1.2), ranging from those suitable for ward care through to intensive care requirement. Admission to critical care is not necessary for all those with more severe illness, particularly where a well-functioning outreach team can support care on the general ward, or where ICU admission is not considered beneficial. While dependency levels do not necessarily define the need for admission to a critical care unit, it is generally those patients requiring level 2 or 3 care who are considered for admission (Table 1.2).

Admission criteria may be set on a priority basis related to patient dependency levels, their specific diagnosis, physiological or biochemical abnormalities, or investigational findings. Local policies for critical care admission should:

- Identify who has responsibility to make admission decisions.
- Include a mechanism for reviewing difficult cases and difficult ethical decisions.
- Identify those who are too well or too sick to benefit from critical care admission (in the context of other facilities available locally).
- Identify priorities for admission during times of high utilization of beds, e.g. level 3 patients are admitted as a higher priority over level 2.
- Identify when, who, and how to transfer patients to other units.
- Identify categories of patients who should or should not be admitted to critical care units, including conditions where admission is mandatory.
- Identify any age criteria below which admission is precluded.
- Clarify links with local incident management policies, contingency plans, and triggers for the implementation of these plans.

A critical care consultant should consider the nature and severity of the patient's illness, the potential reversibility of their condition, the long- and short-term probability of survival, and the wishes of the patient or appropriate advocate when deciding on ICU admission.

Although patients with 'do not attempt cardiopulmonary resuscitation orders' (DNACPRs) or terminal illness for palliative care may fit the criteria for level 2 or 3 care, a clear assessment needs to be made as to how they would benefit from ICU admission. Admission may be justified if there is benefit to the patient in terms of avoiding cardiac arrest or better provision of palliation. However, many such patients will clearly not benefit from ICU admission or from continuation of life-prolonging treatment once admitted. Management of such patients can be difficult. Decisions should be reviewed regularly. Mechanisms to share decision-making between several senior members of the team (sometimes with senior staff uninvolved with the patient's care) should be in place given the potential of legal challenge.

Table 1.2 Critical care levels of dependency.

Level Ward care	Patient needs can be met through normal ward care in an acute hospital. Additional advice and support can be provided by the critical care outreach team. Observations would usually be required less frequently than every 4 h
Level 1: Enhanced care	Patients whose care cannot be met on a normal ward. Examples include (i) need for more detailed observation and monitoring after stepping down from higher levels of care (ii) requirement for ongoing interventions (that may require the outreach team) to prevent deterioration or to support escalation of care and (iii) those who would benefit from enhanced perioperative care. Observations would be required at least every 4 h
Level 2: Critical care	Patients requiring observations or interventions beyond Level 1. Examples include patients (i) needing basic monitoring and support for ≥2 organ systems; (ii) advanced support for 1 organ system; (iii) stepping down from higher levels of care; (iv) requiring further intervention to prevent deterioration; (v) requiring enhanced nursing care for safety reasons; (vi) needing extended postoperative care; (vii) with major uncorrected physiological abnormalities whose care needs cannot be met elsewhere
Level 3: Critical care	Patients requiring (i) advanced respiratory monitoring and/or support; (ii) monitoring and support at an advanced level for ≥2 organ systems (or one organ system with chronic impairment of at least one other); (iii) management of significant delirium and agitation in addition to Level 2 care

Modified from Intensive Care Society (2021) Levels of care. 2nd Edition. https://ics.ac.uk/resource/levels-of-care.html

Surviving critical illness

Many survivors of critical illness have long-term physical, behavioural, and/or neurocognitive dysfunction. The role of inflammation, dysglycaemia, mitochondrial dysfunction, and hypoxia coupled with psychological stress, delirium, and drugs (including sedatives and catecholamines) are increasingly understood. Recovery from critical illness continues for a prolonged period after discharge from hospital, particularly after a severe critical illness involving a long stay. Mortality after hospital discharge is up to three times higher than that of the general population for 2–3 years after hospital discharge. Patients often experience physical and psychological symptoms after prolonged critical illness (Box 1.1). If not recognized as sequelae, this can lead to unnecessary treatment and investigation, contributing further to patient morbidity. Protocol-driven rehabilitation programmes offer benefit in terms of improving neurocognitive and physical function.

Many hospitals now run critical care follow-up clinics to provide multidisciplinary support to patients after discharge. These clinics allow patients to gain an understanding of their illness. Patients often have gaps in the recollection of events. They may suffer hallucinations, delusions, or misinterpret events. This can lead to frustration and anger. Explanations to complete their knowledge aid patients to come to terms with what happened to them and this is usually reassuring. Provision of information helps the patient and family develop a realistic time frame for recovery and overcomes any unrealistic expectations they may harbour. This may also be an opportunity to review a patient diary kept during their hospital stay, if one was kept.

The whole family dynamic often changes as a result of critical illness. Those close to the patient may also experience anxiety and depression. This may evolve into a state of overprotection after the illness, which can be frustrating for the patient.

A follow-up clinic also provides an opportunity for patients and relatives to provide feedback on areas of care that could be improved for the benefit of future patients.

Further reading

'Rehabilitation after critical illness in adults'. National Institute for Health and Care Excellence. March 2009. Accessed June 2023. https://www.nice.org.uk/guidance/CG83

Iwashyna T, Ely E, Smith D, et al. 2010. 'Long-term cognitive impairment and functional disability among survivors of severe sepsis'. *JAMA* 304: pp1787–94. doi: 10.1001/jama.2010.1553

Prescott H, Angus D. 2018. 'Enhancing recovery from sepsis: a review'. *JAMA* 319: pp62–75. doi: 10.1001/jama.2017.17687

Box 1.1 Typical problems post critical care discharge

- Weakness
- Weight loss
- Fatigue
- Poor appetite and taste changes
- Voice changes
- Insomnia
- Skin and nail changes
- Itching
- Hair loss
- Painful joints
- Peripheral neuropathy
- Stress
- Irritability
- Depression
- Anxiety
- Amenorrhoea
- Lack of confidence
- Guilt
- Poor concentration
- Poor memory
- Social isolation
- Sexual problems (impotence/libido).

Patient safety

The nature of critical illness makes patients particularly vulnerable. They often cannot communicate or react normally to protect themselves. Normal defence mechanisms are breached by drains, tubes, and catheters, increasing the risk of infection. Complex drug treatment regimens increase the risk of adverse reactions. Immobility increases the risk of muscle wasting or thromboembolism. It is often unclear whether deterioration results from the disease or treatment.

Protection in a complex environment

The critical care team must deal with an increasing array of data on multiple organ systems, support devices, monitors, treatments, and evidence on which to make decisions. Without some decision support aids, it is easy to overlook issues, with patient harm as a possible consequence. Decision support in its simplest form includes aide-memoires to remind the team of attention to detail that may help prevent harm. The Fast Hug mnemonic (Table 1.3) is one such tool to ensure some of the basics of critical care are not forgotten. Other aids include communication sheets and structured record systems.

Table 1.3 The Fast Hug mnemonic

Feeding	Nil by mouth/enteral or parenteral route
Analgesia	Minimum amount to manage pain—epidural/patient-controlled analgesia/enteral/none
Sedation	Minimum amount to achieve a calm patient—continuous/as required intravenously, enteral, none
Thromboprophylaxis	Low-molecular-weight heparin, if not contraindicated
Head of bed elevated	30° head up, if not contraindicated
Ulcer prophylaxis	Such as proton pump inhibitor in patients in whom evidence of benefit exists
Glucose control	Glycaemic control protocol

Learning from mistakes

A common cause of treatment error relates to drug prescription and administration. Electronic prescribing from templates will reduce errors associated with poor handwriting but is not foolproof.

Learning from mistakes is fundamental to improving patient safety. Incident reporting systems are now widespread to:

- Ensure action is taken to prevent similar incidents in the future.
- Fulfil legal duties to report certain kinds of accident, violent incidents, dangerous occurrences, and occupational ill health.

- Ensure accurate information is collected in a contemporaneous manner to identify trends and take steps to prevent similar incidents from reoccurring.
- Provide evidence relating to litigation claims.
- Record incidents of particular interest for quality assurance, including the ability to demonstrate accident reductions, as part of a risk management strategy.

Patient confidentiality must be maintained. Disciplinary action should be avoided except where acts or omissions are malicious, criminal, or constitute gross or repeated misconduct.

Deliberate harm

As critically ill patients are vulnerable, the possibility of deliberate harm exists. Staff must undergo pre-employment checks of their health and criminal records. Staff must be vigilant to ensure visitors are given no opportunity to harm patients. There must be clear record keeping and review by all members of the multidisciplinary critical care team to ensure unexpected changes in condition are recognized. Because deliberate harm is uncommon, recognition requires a high index of suspicion.

Further reading

Vincent J. 2005. 'Give your patient a fast hug (at least) once a day'. *Crit Care Med* 33: pp1225–30. doi: 10.1097/01.ccm.0000165962.16682.46

➔ See Fire safety, p16; Clinical governance & audit, p22; Infection control—general principles, p580.

Fire safety

Fires affecting the critical care unit are rare but are particularly challenging in that patients are not easily evacuated. Yet their lives depend on services that fire may disrupt. Smoke, while dangerous to staff and the less sick patient who may be breathing spontaneously, is less of a problem to those receiving mechanical ventilation since their fresh gas supply is from outside the affected environment. In the event of fire, the priority is to ensure safety and means of escape for the staff.

Control of smoke

Smoke and toxic gases commonly occur with fire. Toxic gases may be flammable, particularly in association with high concentrations of oxygen. Smoke may be controlled by containment (e.g. fire-resisting walls, doors, and seals) and/or dispersal (e.g. positive pressure air flow within the bay).

Escape from fire

- Escape routes should be well marked and unobstructed.
- Evacuation of patients and staff should be only commenced after instruction from the hospital fire officer or fire brigade.
- Patients should be evacuated in the order of the least sick first.
- Not all critically ill patients can be evacuated.
- If patients are to be evacuated, they should be moved to a place of safety on the same floor as the critical care unit (horizontal). Patients should not be moved to another floor including use of lifts (vertical) unless approved by a fire officer.
- For most fires, containment will reduce/remove the need for full evacuation.

Preventing fire

- All staff should undertake yearly retraining in local fire safety policies.
- Automatic smoke or heat alarms should be provided in all areas.
- Cooking areas and laboratory areas must be separated from patient areas by fire doors.
- Fire doors are provided to protect staff and patients and should not be wedged open.
- If a closed door would compromise the care given to patients but is essential to separate fire compartments, an electromechanical device should hold the door open and be disabled by the fire alarm.
- Fire extinguishers and blankets of the appropriate types should be readily available and staff should be properly trained in their use.
- Any electrical equipment should be approved and regularly rechecked by medical physics technicians.

Communication

Good communication is essential to ensure smooth running of the unit. This includes communication between staff, and with visiting professionals, patient, family, and friends.

Patient communication

The healthcare practitioner should always introduce themselves to the patient. They should address the patient's ideas, concerns, and expectations. Bad news may be distressing but should be conveyed to the patient with tact and compassion. With the patient's agreement, it may be appropriate to have their next of kin/advocate and member(s) of their primary medical team, present.

Patients may still be able to hear bedside conversations despite sedation or apparent unconsciousness. Provide a commentary to the patient in simple terms, both before and during procedures, even if they appear to be unconscious. The patient who is not competent to consent to treatment may still appreciate verbal discussion and explanation.

Multidisciplinary team (MDT) communication

Medical, nursing, and AHPs should be involved in discussions regarding patient management. Ward rounds or a specific MDT meeting are good fora for such interdisciplinary communication. The intensivist should ensure all present are involved and understand the management plan. Subsequent deviations from the plan should be fully documented and rationale provided.

Communication with visiting teams

The critical care team is responsible for the day-to-day care of critically ill patients and should coordinate with various external professionals. The parent team should be involved in major strategy decisions. The management plan and rationale should be clearly documented in the patient's records.

Communication with family and/or named patient advocates

The critical care environment can be overwhelming to those unfamiliar with it. Lay people may misinterpret or forget information given and may require frequent reinforcement. Most communication should ideally be face to face. Where several people are imparting information, differences in emphasis or content may confuse.

- All communication should be fully documented.
- Communication on medical progress and prognosis should only be held with the next of kin if the patient has not previously raised an objection.
- A nurse should ideally be present since there are often questions and concerns that they can best address, especially as they may have developed a strong rapport with the patient and relatives/friends.
- Where parent teams need to communicate with relatives about a specific aspect of the illness, a critical care nurse and doctor should ideally be present.
- Difficult discussions should be held away from the bedside. It is advisable to have two clinicians present to provide subsequent corroboration of the discussion, if required.

- While not always practical or appropriate, staff should use discretion as to which family members and friends should be present at discussions. Patient confidentiality should be respected.

Further reading

Pronovost P, Berenholtz S, Dorman T, et al. 2003. 'Improving communication in the ICU using daily goals'. *J Crit Care* 18: pp71–5. doi: 10.1053/jcrc.2003.50008

Medicolegal aspects

Medicolegal issues are common in critical care. Patients may be admitted following trauma, violence, or poisoning, all of which may involve a legal process. Admission may follow complications of treatment or medical mishap elsewhere in the hospital. Complications of critical illness are common and litigation may follow.

Consent and agreement

Many procedures in critical care are invasive or involve significant risk. The patient often lacks capacity to consent for such treatment. In some countries surrogate consent or assent cannot be legally given by the next of kin. It is good practice to explain risks and benefits of any major procedure and to document this discussion. For major decisions, particularly those involving withdrawal or withholding of life-prolonging treatments, the patient should be involved in discussions where possible. If not feasible, relatives/friends should be asked to give their view of what the patient would want in this situation.

Emergency treatment

In the UK, 'treatment first' is lawful for life-saving treatment in a patient lacking capacity unless an advance decision to refuse treatment (ADRT) is in place. Otherwise, the patient's capacity to consent to or decline treatment should be assessed (as per the Mental Capacity Act). Even life-saving treatment is deemed unlawful if given to a patient with capacity to consent who has refused it.

Non-emergency treatment

In the UK, if a patient lacks capacity and no ADRT is in place, establish if there is a lasting power of attorney (LPA) for health and welfare or a guardian. Decision-making should be collaborative, taking account of the patient's best interests, wishes, beliefs, and values. There should be consultation with those closely engaged with the patient, e.g. next of kin or friend. If nobody is available, an Independent Mental Capacity Advocate (IMCA) or (in some countries) hospital ethicist can be consulted. In the UK a Deprivation of Liberty Safeguards (DoLS) application to the local authority may be needed in certain circumstances for patients lacking capacity to consent to treatment to keep them safe from harm.

There are separate guidelines for participation in research studies for patients lacking capacity.

Documentation

It is impossible to document everything that happens in critical care. The 24 h observation chart provides the most detailed record of events, but summary notes are essential. All entries must be dated, timed, and signed. Records of ward rounds must include the name of the intensivist leading the ward round. These notes should be well kept as they may be used in subsequent investigations or legal proceedings.

Use of restraints

Laws regarding physical and pharmacological restraints vary between countries. In the UK the law does not distinguish between physical and pharmacological restraint by sedation. Where restraint is used, it:

- Must be in the patient's best interests.

- Must be necessary to prevent harm.
- Should be proportionate to the likelihood and seriousness of harm.

Errors and mishaps

In the event of an error or mishap the episode should be clearly documented after witnessed explanation to the patient and/or relatives. Open and transparent explanation is appreciated and a requirement in the UK under statutory duty of candour regulations. An apology is not an admission of liability. Hospitals will have their own policies and protocols to deal with errors. Minor errors should be reported and reviewed. Those causing moderate-to-severe harm may require a 72 h review while still fresh in the minds of those involved. This may progress to a formal serious incident investigation, the report of which should be made available to the patient or next of kin.

Interacting with the police

Most police enquiries relate to patients admitted after suspicious circumstances or under arrest. There is a duty to maintain patient confidentiality unless it is in the consenting patient's interests to impart information about them. Written statements or verbal information given should be strictly factual, avoiding opinion.

Interacting with the coroner

Requirements to notify the coroner vary between countries. Box 1.2 shows UK criteria as an example.

Box 1.2 Deaths that must be notified to HM Coroner in the UK

- The cause of death is unknown.
- Death was violent or unnatural.
- Death was sudden and unexplained.
- Person who died was not visited by a medical practitioner during their final illness.
- Medical certificate is not available.
- Person who died was not seen by the doctor who signed the medical certificate within 14 days before death or after death
- Death occurred during an operation or before the person came out of anaesthetic.
- Medical certificate suggests the death may have been caused by an industrial disease or industrial poisoning

Further reading

'Physical restraints in critical care'. Intensive Care Society. March 2021. Accessed June 2023. https://ics.ac.uk/resource/physical-restraints-guidance.html

'UK Regulation 20: duty of candour'. Care Quality Commission. June 2022. Accessed June 2023. https://www.cqc.org.uk/guidance-providers/regulations-enforcement/regulation-20-duty-candour

'When death is reported to a coroner'. UK Government. Accessed June 2023. https://www.gov.uk/after-a-death/when-a-death-is-reported-to-a-coroner

See Communication, p18; Care of the dying patient in ICU, p706.

Clinical governance & audit

Clinical governance is a framework through which healthcare organizations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence will flourish. For critical care, clinical governance requires the culture, systems, and support mechanisms to achieve good clinical performance and ensure quality improvement are embedded into daily routine. This includes ensuring risks are managed; adverse effects are rapidly detected, openly investigated, and lessons learned; good practice is rapidly disseminated; and systems are in place to ensure continuous improvement. There must be systems to ensure all clinicians have the right training, skills, and competencies to deliver good care. Systems should also be in place to identify and improve upon substandard practice.

As the critical care unit interfaces with most of the rest of the hospital, its clinical governance arrangements must contribute to patient care throughout the hospital. Some aspects of critical illness are managed outside the unit yet the critical care team retain some responsibility for ensuring quality and safety of care.

Essential components of clinical governance

Clear management arrangements

Everyone must know who they are accountable to, the limits of their decision-making, and who must be informed during decision-making.

Quality improvement

Through the process of clinical audit, the standard of practice is monitored and changes effected to improve quality.

Clinical effectiveness

Best practice is an amalgam of evidence-based medicine plus clinical expertise. Management must be individualized as patients do not always fit population norms. Deviation from standard practice is acceptable, but the rationale should be clearly documented.

Risk assessment and management

A register of clinical risks should be kept, to which new risks can be appended. An action plan should be developed for managing each risk and its implementation monitored.

Staff and organizational development

This includes continuing professional education, clinical supervision, and professional regulation.

Patient input

Complaint monitoring should be used to learn lessons and improve practice. Patient and relative suggestions and surveys can be used to adapt quality initiatives to patient/family needs.

Audit

Audit is essential to improve quality of care and should involve all members of the multidisciplinary team. Changing practice in one discipline will often have a knock-on effect on others. Audit may involve a review of activity, performance against predetermined indicators, or cost-effectiveness. Audit

may focus on specific topics or may encompass the performance of several critical care units. Successful audit requires commitment from senior staff to ensure practice is defined, data are collected, and change is effected where necessary, with further review to ensure that change has successfully occurred.

A commonly used tool in quality improvement is the Plan–Do–Study–Act (PDSA) cycle (Table 1.4).

Table 1.4 The four stages of the PDSA cycle

Plan	Define objectives, study questions, and data collection
Do	Implement and test the change
Study	Based on the measures agreed, collect data before and after the change and identify what was learned
Act	Plan the next change cycle or full implementation

Data collection

A basic dataset should be common to all critical care units nationally to enable meaningful comparisons. The dataset should be detailed enough to answer questions posed, but not so detailed that collection becomes unsustainable. Resources must be provided to collect and analyse data. The data collector should be familiar with the fundamentals of critical care and to maintain quality control. Typographical mistakes destroy the value of collected data so error trapping and data validation are necessary. Data collection outside the basic dataset requires clear question setting and care in choosing appropriate data items.

Audit meetings

Regular audit meetings should follow a predefined timetable to encourage maximum staff attendance and set target dates for data collection and analysis. Audit meetings should be chaired and have defined aims. Discussion should lead to recommended changes in practice that should be followed through subsequently. All staff cannot attend all meetings so dissemination and feedback are important before implementing proposed changes.

Further reading

'Online library of quality service improvement and redesign tools: plan, do, study, act cycles and the model for improvement'. NHS England. Accessed June 2023. https://www.england.nhs.uk/wp-content/uploads/2022/01/qsir-pdsa-cycles-model-for-improvement.pdf

See Critical care information systems, p24; Critical care scoring systems, p28.

Critical care information systems

Information systems provide real-time data on patients, planning data for regional management of ICUs, data for later analysis for performance improvement, coding, reimbursement, and service planning. Handwritten records contain transcription errors and ambiguous abbreviations; physician hand-writing is famed for its illegibility. Pan-hospital electronic healthcare record systems are increasingly commonplace and overcome many of these risks to patient safety. Artificial intelligence (AI) is increasingly used within information systems to assist in making decisions, monitoring patients, detecting complications, and predicting outcomes.

Roles of information systems

Automation

- Order sets provide a method of easily and accurately prescribing a commonly occurring set of treatments and processes. Order sets reduce errors by ensuring elements of complex processes are not missed, correct drugs and dosages are used, and best practice protocols and guidelines are followed. An order set also minimizes the time required for documentation.
- Multiple electronic devices are used to monitor and support patients. Data can be sent directly to the electronic record avoiding transcription errors and further minimizing documentation time. AI can interpret changes in physiological parameters, such as heart rate, blood pressure, oxygen saturation or respiratory rate, and recognize patterns of behaviour, such as agitation, delirium, or pain.
- Laboratory, radiology, and pharmacy data can be integrated to ensure timely and accurate documentation at the bedside, rapid diagnostic and therapeutic orders, and medication reconciliation. Integration with other departments ensures timely exchange of information with staff in operating theatres, emergency department, and general wards.

Decision support

- Clinical decision support includes alerting to 'out-of-range events', reminding clinicians to perform key processes, and alerting to unsafe orders (e.g. dose modification for renal failure, drug interactions).
- AI can suggest optimal ventilator settings, fluid management, sedation levels, or antibiotic therapy.

Outcome prediction

- AI-guided algorithms have been used to predict mortality, length of stay, and complications.

Telemedicine

Specialist critical care support is not always available in smaller hospitals, especially out of hours. Telemedicine allows remote monitoring, including video images of the patient and surroundings. Specialist intervention may include consultation, remote intervention via control of electronic devices, and remote orders.

Quality improvement

Evidence-based medicine has allowed rapid evolution of evidence synthesis and knowledge transfer in the form of best practice guidelines and protocols. Information systems allow compliance with guidelines and protocols to be tracked.

Implementation of information systems and AI

- Implementation of information technology systems requires careful focus on workflow redesign, education, change communication, and supported change management.
- Workflow redesign can create new errors through unfamiliarity, poor process mapping, and loss of clarity of responsibility or roles.
- Early adopters within the team must be selected as champions, based on their organizational, analytical, and communication capabilities. Failure to do so risks ineffective utilization of the technology. In the worst case, patient outcomes can be compromised.
- Information technology must not impede clinical care. Focus is needed on mobile solutions, a balance between ease of access and personal data security, and limiting data display to the most relevant.
- Ethical and legal issues are complex and evolving. They include privacy, consent, accountability, transparency, fairness, and trust. There should be clear guidelines and regulations for the use and oversight of AI in the ICU.
- Human factors involved in the integration of AI include usability, reliability, explainability, feedback, and communication. There must be collaboration and co-design between clinicians, patients, researchers, developers, and policymakers to ensure AI meets the needs and expectations of the end-users. Training and education for clinicians and patients on how to understand and use AI are required.

Big data

Data from multiple sources have grown to a size that cannot be analysed by traditional applications. The size of datasets, the immediacy of their availability, and the variety of sources and formats of data have created a new science and new technologies (data mining) to analyse and overcome boundaries that traditionally existed in handling disconnected datasets.

Decision-making in critical care has to be timely but information is often incomplete. The science of big data analysis provides tools to overcome such ambiguity and to contribute to clinical decision support. Machine learning, a form of AI, can be used in the analysis to extract valuable insights and optimize decision-making.

Traditional data analysis assumes the connections between the data are known while big data searches the patterns between unconnected data and does not assume linearity between cause and effect.

Further reading

Wong A, Otles E, Donnelly J, et al. 2021. 'External validation of a widely implemented proprietary sepsis prediction model in hospitalized patients'. *JAMA Intern Med* 181: pp1065–70. doi: 10.1001/jamainternmed.2021.2626

Yoon J, Pinsky M, Clermont G. 2022. 'Artificial intelligence in critical care medicine'. *Crit Care* 26:75. doi: 10.1186/s13054-022-03915-3

Kulkarni P, Singh H. 2023. 'Artificial intelligence in clinical diagnosis. Opportunities, challenges, and hype'. *JAMA* 330: pp317–8. doi: 10.1001/jama.2023.11440

See Clinical governance & audit, p22; Critical care scoring systems, p28.

Chapter 2

Scoring systems

Critical care scoring systems

Various critical care scoring systems have evolved to allow:

- Comparison of disease severity.
- Auditing performance—either in the same unit or between units.
- Research, e.g. evaluating new products or treatment regimens.
- Patient management objectives, e.g. sedation, pressure area care.
- Performance management, e.g. unit, staff, or hospital quality improvement.

The Glasgow Coma Scale (GCS) apart, no scoring system is practised universally. Systems based on the Acute Physiology and Chronic Health Evaluation (APACHE) severity score are predominantly used in North America and the UK, while the Simplified Acute Physiology Score (SAPS) is more popular in mainland Europe. Inter-user interpretation of the same scoring system can be variable.

Prognostic scoring

Prognostic scores predict mortality in populations rather than individual patients. They allow performance between or within intensive care units (ICUs) to be audited. Predicted mortality is usually compared to an expected mortality derived from initial validation data to derive a standardized mortality ratio (SMR). Experience with SAPS III has demonstrated variation in validation data between geographical regions, indicating the need for care in judging performance of an ICU whose population is not truly represented by the validation data. As healthcare advances, predicted outcomes should be regularly updated.

Clinical decision support

As these models are not attuned to prognostication at an individual level, some patients at high risk of dying will still survive and vice versa. Mortality risk may still be useful to guide communication with families but should not be used as an absolute guide to clinical decision-making.

Research

Prognostic scoring systems may be used for risk stratification and/or enrichment of patients entering clinical trials. Changes in SMR derived from prognostic scoring may also be used as an outcome measure in research applied to the ICU or to evaluate changes in ICU processes and protocols.

Disease severity scoring

While disease severity is a contributor to prognostic scoring models, critical illness affects multiple organ systems to varying degrees and this fluctuates over time. Scores such as the Sequential Organ Failure Assessment (SOFA) score and the Multiple Organ Dysfunction Score are often used to document temporal changes in disease severity.

Further reading

See APACHE scoring, p30; SAPS scoring, p32; Organ failure scoring, p34; Trauma score, p36.

APACHE scoring

The Acute Physiology and Chronic Health Evaluation (APACHE) scoring system utilizes a point score derived from the degree of abnormality of readily obtainable physiological and laboratory variables in the first 24 h of ICU admission, plus extra points for age and chronic ill health.

- The summated score provides a measure of severity while the percentage risk of subsequent death can be computed from specific coefficients applied to a wide range of admission disorders (excluding burns and cardiac surgery).
- APACHE I, first described in 1981, utilized 34 physiological and biochemical variables.
- A simplified version (APACHE II, Table 2.1) utilizing just 12 variables was published in 1985 and extensively validated in different countries.

Further refinements, published in 1990 (APACHE III) and 2006 (APACHE IV), improve upon the statistical predictive power by adding five new physiological variables (albumin, bilirubin, glucose, urea, urine output), changing thresholds and weighting of existing variables, comparing both admission and 24 h scores, incorporating the admission source (e.g. ward, operating theatre), and reassessing effects of age, chronic health, and specific disease category. APACHE IV also uses new diagnostic categories. The risk stratification system for APACHE III and IV is proprietary and must be purchased. APACHE IV is complex, requiring 142 variables. Its validation is based on data from US ICUs only.

Table 2.1 APACHE II score

Acute physiology points								
+4	+3	+2	+1	0	+1	+2	+3	+4
Core temperature (°C)								
≥41	39–40.9		38.2–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9
Mean BP (mmHg)								
≥160	130–159	110–129		70–109		50–69		≤49
Heart rate (/min)								
≥180	140–179	110–139		70–109		55–69	40–54	≤39
Respiratory rate (/min)								
≥50	35–49		25–34	12–24	10–11	6–9		≤5
If FiO_2 ≥0.5: A–aDO_2 (kPa)								
≥66.7	46.7–66.6	26.7–46.6		<26.7				
If FiO_2 <0.5: PO_2 (kPa)								
				>9.3	8.1–9.2		7.3–8.0	<7.3
Arterial pH								
≥7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	≤7.15

Table 2.1 (*Contd.*)

Serum Na^+ (mmol/L)								
≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110
Serum K^+ (mmol/L)								
≥7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5
Serum creatinine (μmol/L); NB: double points score if acute kidney injury								
≥300	171–299	121–170		50–120		<50		
Haematocrit (%)								
≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
Leukocytes (×10^9/L)								
≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1
Neurological points = 15 − GCS points								

Acute physiology points (conversion factor 1 kPa = 7.5 mmHg). A–aDO_2 = alveolar–arterial oxygen difference; BP = blood pressure; FiO_2 = fraction of inspired oxygen; PO_2 = partial pressure of oxygen.

Age Points					
Years	≤44	45–54	55–64	65–74	≥75
Points	0	2	3	5	6

Chronic health points

2 points for elective postoperative admission or 5 points if emergency operation or non-operative admission, if patient has either:

- Biopsy-proven cirrhosis, portal hypertension, or previous hepatic failure
- Chronic heart failure (NYHA class 4)
- Chronic hypoxia, hypercapnia, severe exercise limitation, 2° polycythaemia or pulmonary hypertension
- Dialysis-dependent renal disease
- Immunosuppression by disease or drugs

NYHA= New York Heart Association.

Further reading

Knaus W, Draper E, Wagner D, et al. 1985. 'APACHE II: a severity of disease classification system'. *Crit Care Med* 13: pp818–29.

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Zimmerman J, Kramer A, McNair D, et al. 'Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients'. *Crit Care Med* 34: pp1297–310.

SAPS scoring

- Has a similar role to APACHE, but more widely utilized in Europe.
- The Simplified Acute Physiology Score (SAPS) was devised in 1984 (SAPS I), modified in 1993 (SAPS II), and again in 2005 (SAPS III).
- SAPS III is based on variables available within the first hour of ICU admission (Table 2.2). It comprises physiology variables, age, type of admission (medical, scheduled or unscheduled surgical), and three underlying disease variables.
- The advantage of this system over APACHE is that it estimates the risk of death without having to specify a primary diagnosis.
- Outcome prediction is possible before ICU intervention and based on the summed scores for pre-admission patient characteristics, circumstances of admission, and admission physiological variables.

Table 2.2 SAPS III score

Pre-admission patient characteristics	
Age (years)	<40 (0); 40–59 (5); 60–69 (9); 70–74 (13); 75–79 (15); ≥80 (18)
Comorbidities	Cancer therapy (3); NYHA IV chronic heart failure (6); haematological cancer (6); cirrhosis (8); AIDS (8); metastatic cancer (11)
Hospital stay pre-ICU (days)	<14 (0); 14–27 (6); >27 (7)
Pre-ICU hospital location	Emergency room (5); other ICU (7); other (8)
Therapy pre-ICU	Vasoactive drugs (3)

Point score in brackets.

Circumstances of ICU admission	
ICU admission	Planned (16); unplanned (19)
Reason for ICU admission	Rhythm disturbance (−5*); seizures (−4*); hypovolaemic shock (30); acute abdomen (3); altered consciousness, confusion, delirium (4); septic, anaphylactic, or other shock (5); liver failure (6); focal neurological deficit (7); severe pancreatitis (9); intracranial mass effect (10)
Surgical status pre-ICU admission	Scheduled surgery (0); no surgery (5); emergency surgery (6)
Anatomical site of surgery	Transplantation (−11); trauma (−8); CABG (−6); neurosurgery for CVA (5)
Acute infection at ICU admission	Nosocomial (4); respiratory (5)

Point score in brackets.

CABG = coronary artery bypass grafting; CVA = cerebrovascular accident.

* Only score for seizure if both seizures and rhythm disturbance present.

Physiological status	
Lowest estimated GCS	<5 (15); 5 (10); 6 (7); 7–12 (2); >12(0)
Highest bilirubin (μmol/L)	<34.2 (0); 34.2–102.5 (4); >102.5 (5)
Highest body temperature (°C)	<35 (7); ≥35 (0)
Highest creatinine (μmol/L)	<106.1 (0); 106.1–176.7 (2); 176.8–309.3 (7); ≥309.4 (8)
Highest heart rate (/min)	<120 (0); 120–159 (5); >159 (7)
Highest white cell count ($\times 10^9$/L)	<15 (0); >14.9 (2)
Lowest pH	<7.26 (3); >7.25 (0)
Lowest platelet count ($\times 10^9$/L)	<20 (13); 20–49.9 (8); 50–99.9 (5); >99.9 (0)
Lowest systolic BP (mmHg)	<40 (11); 40–69 (8); 70–119 (3); >119 (0)
PaO_2 (kPa) if no mechanical ventilation	<8 (5); ≥8 (0)
PaO_2:FiO_2 (kPa) ratio if on mechanical ventilation	<13.3 (11); ≥13.3 (7)

Point score in brackets.

Arterial partial pressure of oxygen (PaO_2) conversion factor: 1 kPa = 7.5 mmHg.

Further reading

Le Gall J, Lemeshow S, Saulnier F. 1993. 'A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study'. *JAMA* 270: pp2957–63.

Metnitz P, Moreno R, Almeida E, et al. 2005. 'SAPS3—from evaluation of the patient to evaluation of the intensive care unit. Part 1: objectives, methods and cohort description'. *Intensive Care Med* 31: pp1336–44. doi: 10.1007/s00134-005-2762-6

Moreno R, Metnitz P, Almeida E, et al. 2005, 'SAPS3—from evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission'. *Intensive Care Med* 31: pp1345–55. doi: 10.1007/s00134-005-2763-5

Organ failure scoring

Glasgow Coma Scale

First described in 1974, it utilizes eye opening, best motor response, and best verbal response to categorize neurological status (Table 2.3). It is the only system used universally in critical care units though limitations exist in mechanically ventilated, sedated patients. It can be used for prognostication and for therapeutic decision-making, e.g. elective ventilation in patients presenting with a GCS <8.

Table 2.3 The Glasgow Coma Scale

Points	Eyes open	Best motor response	Best verbal response
6	–	Obeys commands	–
5	–	Localizes pain	Orientated
4	Spontaneously	Flexion withdrawal	Confused
3	To speech	Decerebrate flexion	Inappropriate words
2	To pain	Decerebrate extension	Incomprehensible sounds
1	Never	No response	Silent

Sequential Organ Failure Assessment (SOFA) score

A limitation of APACHE and SAPS scores is that they were designed and validated on the most extreme data obtained during the first 24 h of ICU admission. Other systems for immediate or daily scoring enable quicker assessment and/or trends in the patient's condition. The most widely used is the SOFA score (Table 2.4).

SOFA was initially designed to improve patient characterization for multicentre drug trials in sepsis but was subsequently applied to ICU patients in general with 'Sequential' being substituted for 'Sepsis-related'.

A point score denoting severity of dysfunction in one organ system does not translate directly to an equivalent severity in another organ. However, the SOFA score has been used successfully to prognosticate and to follow changes in patient status throughout their ICU stay. A change in SOFA score ≥2 from baseline in a patient with infection is the operationalization of organ dysfunction used in the Sepsis-3 definitions. A SOFA-2 score is due to be published in 2024.

Table 2.4 The SOFA score

	0	1	2	3	4
Respiratory PaO_2:FiO_2 ratio (kPa)*	>53.3	≤53.3	≤40	≤26.7**	<13.3**
Renal Creatinine (μmol/L) or urine output (mL/day)	<106	106–168	169–304	305–436 or <500 mL/day	>437 or <200 mL/day
Hepatic Bilirubin (μmol/L)	<20	20–32	33–101	102–204	>204
Cardiovascular Mean arterial pressure (MAP; mmHg)	No hypotension	MAP <70	Dop ≤5 or Dob >0†	Dop >5 or NE/E ≤0.1†	Dop >15 or NE/E >0.1†
Haematological Platelet count ($\times 10^9$/L)	>150	≤150	≤100	≤50	≤20
Neurological GCS	15	13–14	10–12	6–9	<6

* PaO_2:FiO_2 ratio conversion factor: 1 kPa = 7.5 mmHg.

** With ventilatory support.

† Dob = dobutamine; Dop = dopamine; E = epinephrine; NE = norepinephrine. Doses in μg/kg/min administered for at least 1 h.

Further reading

Teasdale G, Jennet B. 1974. 'Assessment of coma and impaired consciousness: a practical scale'. *Lancet* ii: pp81–4.

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Raith E, Udy A, Bailey M, et al. 2017. 'Prognostic accuracy of the SOFA Score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit'. *JAMA* 317: pp290–300. doi: 10.1001/jama.2016.20328

Trauma score

Scoring systems are used in trauma for:

- Rapid field triage to direct the patient to appropriate levels of care.
- Quality assurance.
- Developing and improving trauma care systems by categorizing patients and identifying problems within the systems.
- Making comparisons between groups from different hospitals, in the same hospital over time, and/or undergoing different treatments.

The Injury Severity Score (ISS) is a severity scoring system based on the anatomical injuries sustained by the patient. The Revised Trauma Score (RTS) utilizes measures of physiological abnormality to predict survival. A combination of ISS and RTS—TRISS—was developed to overcome the shortcomings of anatomical or physiological scoring alone. The TRISS methodology uses ISS, RTS, patient age, and whether the injury was blunt or penetrating to provide a measure of survival probability.

For trauma patients admitted to ICU, physiological-based models better predict outcome than anatomical-based models.

Abbreviated Injury Severity Scale

This anatomical-based coding system classifies injury severity and associated threat to life. The injury is coded on a scale of 1 (minor) to 6 (maximal and currently untreatable). It is a measurement tool for single injuries rather than a comprehensive assessment. The first version was published in 1969 and the last update in 2015.

Injury Severity Score

Uses the Abbreviated Injury Scale 2005 (AIS05) dictionary to identify injuries. The score for each injury ranges from 1 (minor) to 6 (non-survivable) (see Table 2.5 for an example).

Identify highest score for body region. Add together the squares of the three highest body region scores to give a score between 1 and 75 (75 is scored if one region scores 6). In the example in Table 2.5:

$$\text{ISS} = 5^2 + 4^2 + 3^2 = 50$$

A modification of the ISS (new ISS) sums the squares of the scores for the most severe injuries regardless of the region affected (rather than scoring the single most severe injury per region). In the example in Table 2.5:

$$\text{New ISS} = 52 + 42 + 42 = 57$$

Revised Trauma Score

Data are collected on first assessment of the patient, weighted, and summed to give a score between 0 and 0.78408 (Table 2.6). In addition to mortality prediction, the RTS can be used to facilitate pre-hospital triage and determine location for treatment. To simplify pre-hospital use, the coded values can be summed; a total <11 may be used to indicate transport to a designated trauma centre.

Table 2.5 Example scores for injuries within body regions

Body region	Injury(example)	Score(example)
Head & neck	Cerebral contusion	3
Abdomen & pelvic contents	Splenic ruptureLacerated liver	54
Bony pelvis & limbs	Fractured femurFractured radius	32
Face	Fractured mandible	2
Chest	Fractured ribs with flail segment	4
Body surface	Skin abrasions	1

Table 2.6 The Revised Trauma Score

	Measure	Coded value	× weighting	= score
Respiratory rate (breaths/min)	10–29	4	0.2908	
	>29	3		
	6–9	2		
	1–5	1		
	0	0		
Systolic BP (mmHg)	>89	4	0.7326	
	76–89	3		
	50–75	2		
	1–49	1		
	0	0		
Glasgow Coma Scale	13–15	4	0.9368	
	9–12	3		
	6–8	2		
	4–5	1		
	3	0		

Total score = revised trauma score.

Further reading

Champion H, Sacco W, Copes W, et al. 1989. 'A revision of the Trauma Score'. *J Trauma* 29: pp623–9.
Osler T, Baker S, Long W. 1997. 'A modification of the injury severity score that both improves accuracy and simplifies scoring'. *J Trauma* 43: pp922–5. doi: 10.1097/00005373-199712000-0000
'Abbreviated Injury Scale: 2015', 6th ed. Association for the Advancement of Automotive Medicine (AAAM). https://www.aaam.org/abbreviated-injury-scale-ais/
Magee F, Wilson A, Bailey M, et al. 2021. 'Comparison of intensive care and trauma-specific scoring systems in critically ill patients'. *Injury* 52: pp2543–50.
See Multiple trauma—initial management, p628; Multiple trauma—ongoing management, p630.

Chapter 3

Respiratory therapy

Oxygen therapy

Most critically ill patients receive additional inspired oxygen (O_2). Increasing evidence indicates conservative targets avoiding hyperoxaemia, outside emergency situations or specific circumstances, reduces the risk of O_2 toxicity.

Principles

- High-flow, high-concentration O_2 should be given in the first instance to any acutely dyspnoeic or hypoxaemic patient. Down-titration can then be performed using pulse oximetry or arterial blood gas analysis.
- In general, maintain arterial oxygen saturation (SaO_2) at 92–98%. This target may be revised in patients with chronic hypoxaemic respiratory failure, or during prolonged severe acute respiratory distress syndrome (ARDS) when lower values may suffice provided tissue O_2 delivery remains adequate.
- Apart from patients being treated for carbon monoxide poisoning or hyperbaric oxygen therapy (HBOT), e.g. for diving accidents, supranormal levels of PaO_2 should be avoided.

Type II respiratory failure

Patients in chronic type II (hypoxaemic, hypercapnic) respiratory failure may develop apnoea if their central hypoxic drive is removed by supplemental O_2. This is seldom (if ever) abrupt; a period of deterioration and increasing drowsiness will prompt consideration of either:

- FiO_2 reduction if overall condition allows.
- Non-invasive or invasive mechanical ventilation if fatiguing.
- Use of respiratory stimulants such as doxapram.

Close supervision and monitoring are necessary.

Oxygen toxicity

This is well described in animal models and, increasingly, in clinical studies. Normal volunteers become symptomatic (chest pain, dyspnoea) after several hours of breathing pure O_2. Washout of nitrogen can cause microatelectasis. O_2 may induce direct oxidant damage to proteins, lipids, and DNA and is a potent vasoconstrictor; high levels of PaO_2 may paradoxically compromise regional O_2 delivery. The relative importance of O_2 toxicity to the lung compared to other forms of ventilator trauma in critically ill patients remains unclear. Efforts should be made to minimize FiO_2 whenever possible.

Monitoring

- Normal pulse oximetry readings may obscure deteriorating gas exchange with progressive hypercapnia.
- An O_2 analyser in the inspiratory limb of the ventilator or continuous positive airway pressure (CPAP)/bi-level positive airway pressure (BiPAP) circuit confirms the patient is receiving a known fraction of inspired oxygen (FiO_2).
- Monitor changes in arterial O_2 saturation by pulse oximetry (NB: may over-read in dark-skin toned patients and in carbon monoxide poisoning) ± formal blood gas analysis.

Oxygen masks

- Hudson-type masks or nasal cannulae deliver an imprecise FiO_2 and should only be used when hypoxaemia is not a major concern. Hudson-type masks do allow delivery of humidified gas (e.g. via an 'Aquapak'). Valves fitted to the Aquapak system do not deliver an accurate FiO_2 unless gas flow is at the recommended level.
- Masks fitted with a Venturi valve deliver reasonably accurate FiO_2 (0.21 at 2 L/min, 0.28 at 4 L/min, 0.35 at 8 L/min, 0.40 at 10 L/min, 0.60 at 15 L/min) except in patients with very high inspiratory flow rates. A jet of oxygen is delivered with air drawn in at the valve to dilute the O_2 to the desired concentration. These masks do not allow delivery of humidified gas but are preferable in the short term for dyspnoeic patients as they enable more precise monitoring of P:F (arterial partial pressure of oxygen (PaO_2):FiO_2) or S:F (pulse oximetry oxygen saturation (SpO_2):FiO_2) ratio.
- A tight-fitting anaesthetic face mask and reservoir bag allows 100% O_2 to be delivered in emergency situations or pre-induction of anaesthesia.
- Tight-fitting masks (partial or full-face) or helmets are used for delivery of non-invasive ventilation (CPAP/BiPAP).

Airway maintenance

The airway may become occluded by secretions, vomitus, blood, or a foreign body. Reduced muscle tone in the obtunded patient may result in occlusion by the tongue and surrounding upper airway structures.

Opening the airway

- Clear secretions, vomitus, debris or blood with a rigid Yankauer sucker. If failing, Magill's forceps can be used to remove solid matter under direct vision.
- In the absence of neck injury, and with the patient supine, tilt the head back with one hand on the forehead and lift the chin with the fingers of the other hand (Figure 3.1).
- If there is a suspected neck injury, perform a jaw thrust without extending the neck (Figure 3.2). With the patient supine, place the fingers behind the angle of the mandible on both sides and lift the mandible forward and upward until the lower teeth (or gum) are in front of the upper teeth (or gum).

Maintaining the airway

If the patient can be turned and is breathing adequately it may suffice to adopt a lateral recovery position. If manual ventilation is required, or the patient must remain supine, an oro- or nasopharyngeal airway may be used.

Oropharyngeal (Guedel) airway

- This hard plastic tube shaped to keep the tongue forward should only be used in obtunded patients.
- The correct size should be selected by comparing the airway to the distance between the teeth and the angle of the jaw.
- Open the patient's mouth and remove any obstruction by suction.
- Insert the airway into the mouth with the curve pointing toward the skull top.
- Rotate the airway through 180° once the soft palate is reached.
- The curve of the airway will retain its position in the oropharynx once fully inserted.

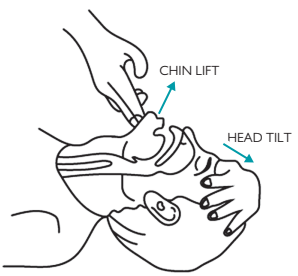

Fig. 3.1 Opening the airway with head tilt and chin lift.

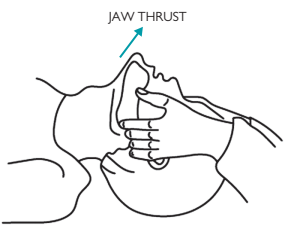

Fig. 3.2 Opening the airway with a jaw thrust.

Nasopharyngeal airway

- This soft, shaped plastic tube fits the passage from nares to pharynx.
- It is better tolerated in the semi-conscious patient but should be avoided where basal skull fracture is known/suspected.
- Assess the correct size by approximating the diameter of the airway to the nasal aperture.
- Some nasopharyngeal airways require insertion of a safety pin through the flange of the airway to prevent accidental inhalation after insertion.
- Gently pass a lubricated airway into the patent nostril with a slight twisting motion.
- If excessive resistance is felt, do not force. If so, try the other nostril which may be bigger, or try a smaller size nasopharyngeal airway.

Further reading

➔ See Endotracheal intubation—indications & equipment, p44; Basic resuscitation, p358; Airway obstruction, p368.

Endotracheal intubation—indications & equipment

Indications

An artificial airway is usually required in the following circumstances:

- Airway protection—Glasgow Coma Scale score <8, trauma, aspiration risk, poisoning.
- Airway obstruction, e.g. trauma, laryngeal oedema, tumour, burns.
- Apnoea for mechanical ventilation, e.g. unconsciousness, severe respiratory muscle weakness, self-poisoning.
- Severe respiratory failure requiring mechanical ventilation.
- Haemodynamic instability to facilitate mechanical ventilation.
- Uncontrolled agitation or seizures carrying risk of harm.
- Figure 3.3 shows a checklist for preparation for intubation.

Equipment required

- Suction (Yankauer and catheters to pass down endotracheal (ET) tube).
- O_2 supply, rebreathing bag and mask.
- Laryngoscope (two curved blades), preferably a videolaryngoscope with screen visible to all.
- Stylet/bougie.
- ETs (preferred size and smaller).
- Water-based gel to lubricate tube.
- Magill forceps.
- Drugs (induction agent, muscle relaxant, sedative).
- Syringe for cuff inflation.
- Capnograph.
- Ties, tube fixation device.
- Stethoscope.
- Cardiopulmonary resuscitation equipment.

Further reading

'Intubation guidelines'. Difficult Airway Society. 2017. Accessed June 2023. https://das.uk.com/guidelines/icu_guidelines2017

See Airway maintenance, p42; Endotracheal intubation—procedure & complications, p46; Ventilatory support—indications, p48; Airway obstruction, p368; Respiratory failure, p370; Coma, p466; Acute weakness, p468; Poisoning—general principles, p554.

Intubation Checklist : critically ill adults – to be done with whole team present.

Prepare the patient

- ❑ **Reliable IV/IO access**
- ❑ **Optimise position**
  - ❑ Sit-up?
  - ❑ Mattress hard
- ❑ **Airway assessment**
  - ❑ Identify cricothyroid membrane
  - ❑ Awake intubation option?
- ❑ **Optimal preoxygenation**
  - ❑ 3 mins or ETO_2>85%
  - ❑ Consider CPAP/NIV
  - ❑ Nasal O_2
- ❑ **Optimise patient state**
  - ❑ Fluid/pressor/inotrope
  - ❑ Aspirate NG tube
  - ❑ Delayed sequence induction
- ❑ **Allergies?**
  - ❑ ↑ Potassium risk?
    - avoid suxamethonium

Prepare the equipment

- ❑ **Apply monitors**
  - ❑ SpO_2/waveform $ETCO_2$/ ECG/BP
- ❑ **Check equipment**
  - ❑ Tracheal tubes × 2
    - cuffs checked
  - ❑ Direct laryngoscopes × 2
  - ❑ Videolaryngoscope
  - ❑ Bougie/stylet
  - ❑ Working suction
  - ❑ Supraglottic airways
  - ❑ Guedel/nasal airways
  - ❑ Flexible scope/Aintree
  - ❑ FONA set
- ❑ **Check drugs**
  - ❑ Consider ketamine
  - ❑ Relaxant
  - ❑ Pressor/inotrope
  - ❑ Maintenance sedation

Prepare the team

- ❑ **Allocate roles**

One person may have more than one role.

- ❑ Team Leader
- ❑ 1st Intubator
- ❑ 2nd Intubator
- ❑ Cricoid force
- ❑ Intubator's assistant
- ❑ Drugs
- ❑ Monitoring patient
- ❑ Runner
- ❑ MILS (if indicated)
- ❑ Who will perform FONA?

- ❑ **Who do we call for help?**
- ❑ **Who is noting the time?**

Prepare for difficulty

- ❑ **Can we wake the patient if intubation fails?**
- ❑ **Verbalise** "Airway Plan is:"
  - ❑ **Plan A:** Drugs & laryngoscopy
  - ❑ **Plan B/C:** Supraglottic airway Face-mask Fibreoptic intubation via supraglottic airway
  - ❑ **Plan D:** FONA Scalpel-bougie-tube
- ❑ **Does anyone have questions or concerns?**

Fig. 3.3 Difficult Airway Society intensive care unit intubation checklist.

Reproduced with permission of the Difficult Airway Society.

Endotracheal intubation—procedure & complications

Route of intubation

Orotracheal intubation is generally preferred. The nasotracheal route provides increased patient comfort and easier blind placement; however, the smaller diameter tube carries a greater risk of obstruction and difficulty in suctioning. There is also a risk of sinusitis and otitis media. It is generally contraindicated with coagulopathy, CSF leak and suspected nasal/base-of-skull fractures.

The incidence of difficult airways is higher in intensive care unit (ICU) compared with elective theatre settings. In addition, ICU patients often have reduced oxygen reserve and are therefore likely to desaturate more quickly if difficulties are encountered.

Difficult intubation

The Difficult Airway Society has produced comprehensive guidelines to standardize airway management and equipment, and addresses some of the human factors involved (Figure 3.4 shows a laminated sheet to be kept on the airway trolley).

The airway may be known to be difficult to intubate. Difficulty may be predicted in patients with a small mouth, high-arched palate, large upper incisors, small chin, large tongue, anterior larynx, short neck, immobile temporomandibular joints, immobile cervical joints (e.g. rheumatoid arthritis), or morbid obesity. Other factors to consider are recent intubation (check case notes for grade), oedema, burn or inhalation injury, radiotherapy, and previous head and neck surgery.

Preparation and good communication are key. A clear plan should be agreed with consideration of the 4 Ps: Prepare patient, Prepare equipment, Prepare drugs, and Prepare team. This should be facilitated by an intubation checklist. Ideally, two experienced intubators should be present. Intubation should not be attempted by an inexperienced, unaccompanied operator except in acute life-threatening situations. To avoid task fixation and prompt identification of failure, guidelines highlight early reversion to bag–mask ventilation to ensure adequate oxygenation. In case of 'can't intubate, can't oxygenate' (a life-threatening emergency), front of neck access (FONA) with scalpel/bougie/tube may be necessary.

Complications of intubation

Early complications

- Trauma, e.g. haemorrhage, mediastinal perforation.
- Haemodynamic collapse, e.g. positive pressure ventilation, vasodilatation, arrhythmias, or rapid correction of hypercapnia.
- Tube malposition, e.g. failed or endobronchial intubation.

Later complications

- Infection including maxillary sinusitis if nasally intubated.
- Cuff trauma (avoid by maintaining cuff pressure <25 cmH_2O).
- Mouth/lip or pharyngeal trauma.

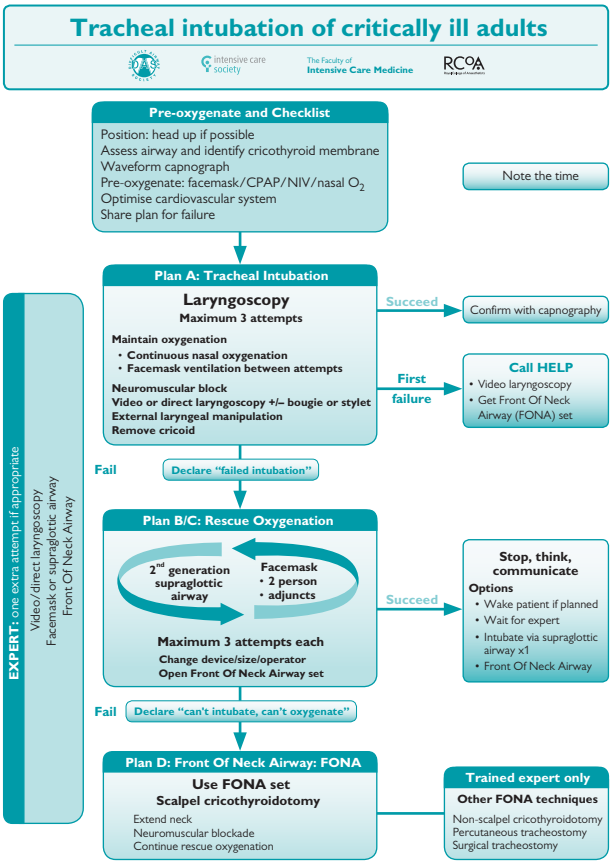

Fig. 3.4 Difficult Airway Society ICU intubation algorithm.
Reproduced with permission of the Difficult Airway Society.

Further reading

'NAP4: Major Complications of Airway Management in the United Kingdom'. National Audit Projects. March 2011. Accessed June 2023. https://www.nationalauditprojects.org.uk/NAP4_Report#pt

Frerk C, Mitchell V, McNarry A, et al. for the Difficult Airway Society Intubation Guidelines Working Group. 2015. 'Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults'. *Br J Anaesth* 115: pp827–48. doi: 10.1093/bja/aev371

'Intubation guidelines'. Difficult Airway Society. 2017. Accessed June 2023. https://das.uk.com/guidelines/icu_guidelines2017

➲ See Airway maintenance, p42; Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Airway obstruction, p368; Respiratory failure, p370; Coma, p466; Acute weakness, p468; Poisoning—general principles, p554.

Ventilatory support—indications

Oxygenation failure (type I respiratory failure)

Hypoxaemia may be due to:

- Ventilation/perfusion mismatch (reduced ventilation in, or preferential perfusion of, some lung areas), e.g. pneumonia, pulmonary oedema, pulmonary vascular disease, high cardiac output.
- Shunt (normal perfusion but absent ventilation in some lung zones), e.g. pneumonia, lung collapse.
- Diffusion limitation due to reduced alveolar surface area with normal ventilation, e.g. emphysema, or reduced inspired O_2 tension, e.g. altitude, suffocation.
- Acute ventilatory insufficiency (as above).

Acute ventilatory insufficiency (type II respiratory failure)

Defined by an acute rise in arterial partial pressure of carbon dioxide ($PaCO_2$) and significant respiratory acidosis. $PaCO_2$ is directly proportional to the body's CO_2 production and inversely proportional to alveolar ventilation (minute ventilation minus dead space ventilation). Causes include:

- Respiratory centre depression, e.g. drugs, intracranial pathology.
- Peripheral neuromuscular disease, e.g. Guillain–Barré syndrome, myasthenia gravis, spinal cord pathology.
- Therapeutic muscle paralysis.
- Loss of chest wall integrity, e.g. chest trauma, diaphragm rupture.
- High CO_2 production, e.g. burns, severe agitation.
- Reduced alveolar ventilation, e.g. airway obstruction (asthma, acute bronchitis, foreign body), atelectasis, pneumonia, pulmonary oedema (ARDS, cardiac failure), pleural pathology, fibrotic lung disease, obesity.
- Pulmonary vascular disease (e.g. pulmonary embolus, ARDS).

Reduction of intracranial pressure (ICP)

Reduction of $PaCO_2$ <4–4.5 kPa causes cerebral vasoconstriction and will transiently reduce ICP after brain injury. However, studies suggest this short-lasting effect may possibly impair an already critical cerebral blood flow.

Reduction of work of breathing

Assisted ventilation, sedation, ± muscle relaxation reduce respiratory muscle activity and the work of breathing. In cardiac failure, the resulting reduction in myocardial O_2 demand is more easily matched to the supply of O_2.

Indications for ventilatory support

Consider ventilatory support (invasive or non-invasive) if:

- Respiratory rate >25/min.
- PaO_2 <11 kPa on FiO_2 ≥0.4.
- $PaCO_2$ high with significant respiratory acidosis (e.g. pH <7.2).
- Vital capacity <10–15 mL/kg (Guillain–Barré syndrome).
- Patient self-induced lung injury (pSILI): large tidal volume (V_T) spontaneous breaths may be injurious over a prolonged period.
- Obviously tiring or exhaustion.

- Extreme agitation or delirium not manageable by calming manoeuvres and sedative drugs.
- Severe shock.
- Severe heart failure.
- Raised ICP.

Further reading

See Respiratory failure, p370; Acute weakness, p468.

Invasive ventilation—ventilators

Classification of mechanical ventilators

Modern ventilators deliver a gas flow with a cycling mechanism that cuts flow during expiration. They may be classified by the method of cycling from inspiration to expiration:

- When a pre-set time has elapsed (time-cycled).
- When a pre-set pressure is reached (pressure-cycled).
- When a pre-set volume is delivered (volume-cycled).

The ventilator breath may be:

- Volume controlled—predetermined V_T is delivered.
- Pressure controlled—gas flow is at a predetermined pressure.
- Volume controlled with a limited pressure—a pre-set V_T is delivered within a pressure limit unless the lungs are non-compliant or airway resistance is high. This may be useful to avoid high airway pressures.

Various 'mixed' modes are available. In volume-cycled mode with a time limit, the inspiratory flow is reduced; the ventilator delivers the pre-set V_T unless impossible at the set respiratory rate (limiting airway pressure). In time-cycled mode with pressure control, pre-set pressure is delivered throughout inspiration with cycling determined by time. V_T is dependent on respiratory compliance and airway resistance.

Setting up the mechanical ventilator

Tidal volume

Values of 6–7 mL/kg ideal body weight (IBW) are related to better outcomes in severe acute respiratory failure, by reducing ventilator-associated trauma and distant inflammatory effects. IBW is based on height and sex using the Devine formula:

$$\text{Male IBW (kg)} = 50 + \left(0.9 \times \left[\text{height (cm)}\right]\right) - 152$$

$$\text{Male IBW (lb)} = 110 + \left(5.1 \times \left[\text{height (inch)}\right]\right) - 60$$

$$\text{Female IBW (kg)} = 45.5 + \left(0.9 \times \left[\text{height (cm)}\right]\right) - 152$$

$$\text{Female IBW (lb)} = 100 + \left(5.1 \times \left[\text{height (inch)}\right]\right) - 60$$

Respiratory rate

Usually start at 12–16 breaths/min. In time-cycled or time-limited modes the rate determines timing of the ventilator cycles.

Inspiratory flow

Usually set between 40 and 80 L/min. Higher flow rates are more comfortable for alert patients. This allows for longer expiration in patients with severe airflow limitation but may result in higher peak airway pressures. The flow pattern can be adjusted on most modern ventilators. A square waveform is often used but decelerating flow may reduce peak airway pressure.

I:E ratio

A function of rate, V_T, inspiratory flow, and time. Prolonged expiration is useful in severe airflow limitation while a prolonged inspiratory time is used in ARDS to allow slow-reacting alveoli time to fill. Alert patients are more comfortable with shorter inspiratory times.

FiO_2

Set according to arterial blood gases and pulse oximetry. Adjust FiO_2 to target PaO_2/SpO_2.

Airway pressure

In pressure-controlled or limited modes a peak airway pressure can be set to generate adequate but not excessive V_T (usually 6–7 mL/kg IBW) or pressures (≤30 cmH_2O).

Positive end-expiratory pressure (PEEP)

This is the airway pressure at end expiration and can be increased to prevent atelectasis by alveolar recruitment thus improving oxygenation. The usual extrinsic PEEP value set on the ventilator is 5–10 cmH_2O but may occasionally be increased in hypoxaemic patients. However, excess PEEP may compromise ventricular filling, especially in a hypovolaemic patient. An insufficient expiratory time may result in an increase in intrinsic PEEP which may have similar effects. In some patients, extrinsic and intrinsic PEEP may be additive.

Initial ventilator set-up

Check for leaks and calibrate ventilator sensors. Table 3.1 shows initial settings. Choose method of humidification, e.g. heat and moisture exchange (HME) filter, water bath humidifier.

Table 3.1 Initial ventilator settings

FiO_2	0.4–1—titrate to target SpO_2
V_T	6–7 mL/kg ideal body weight
Rate	12–16/min
I:E ratio	1:2
Peak pressure	≤30 cmH_2O
PEEP	5 cmH_2O (consider higher if very hypoxaemic)

Further reading

Acute Respiratory Distress Syndrome Network. 2000. 'Ventilation with lower tidal volumes compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome'. *N Engl J Med* 342: pp1301–8. doi: 10.1056/NEJM200005043421801

See Invasive ventilation—modes, p52; High frequency ventilation, p68; Non-invasive respiratory support, p74; Continuous positive airway pressure (CPAP), p76.

Invasive ventilation—modes

Pressure control ventilation (PCV)

A pre-set number of breaths are delivered to supply all the patient's ventilatory requirements. Breaths are set to an inspiratory pressure and the pressure level is then adjusted to deliver the desired V_T.

Volume control ventilation (VCV)

A pre-set number of breaths are delivered to supply all the patient's ventilatory requirements. Breaths are set to a desired V_T. However, this may generate high peak pressures if respiratory compliance is poor. On some ventilators an alarm setting may cut off the breath if a preset pressure is exceeded; the desired V_T is thus not delivered.

Assist-control mechanical ventilation (ACMV)

Patients can breathe, triggering the ventilator to determine the respiratory rate. A pre-set number of breaths are delivered if the spontaneous respiratory rate falls below the pre-set level.

Intermittent mandatory ventilation (IMV)

Patients may initiate breaths spontaneously. The ventilator provides mandatory breaths that synchronize with the patient's own efforts (synchronized IMV) at a preset rate. Pressure support may be added to spontaneous breaths to reduce the work of breathing. Useful in patients with an inadequate respiratory rate.

Pressure support ventilation (PSV)

Pre-set positive pressure is added to the ventilator circuit during inspiration in spontaneously breathing patients. Pre-set pressures should be adjusted to an adequate but not excessive V_T.

Volume support ventilation (VSV)

A target volume is set and the ventilator then automatically adjusts the pressure support to maintain this target V_T.

Pressure-regulated volume control (PRVC)

Regulates pressure to changing lung compliance to adjust inspiratory flow and pressure to maintain a set V_T. Breaths are delivered at a preset rate and may be patient triggered.

Airway pressure release ventilation (APRV) or BiVent

CPAP is delivered at set intervals (P_{high}) with intermittent cycling (release) to zero (P_{low}). This type of pressure control utilizes a reverse I:E ratio usually starting at 10:1. T_{high} is the time in seconds at P_{high} (inhalation), while T_{low} is the release time (exhalation). Unrestricted spontaneous breathing can occur at any time during the breath cycle. This mode is used for lung protective ventilation and enhancing alveolar recruitment in patients with severe respiratory failure.

Choosing the appropriate mode

No single mode has been shown to be superior in terms of outcomes and prevention of lung injury. The choice of mode is largely determined by clinician preference and familiarity. Controlled modes are needed if the patient is paralysed or not initiating any breaths (e.g. brainstem death, opiate toxicity).

Allowing the patient to make spontaneous respiratory efforts with suitable pressure or volume support generally allows reduction in sedation requirements, retraining respiratory muscles and reducing mean airway pressure. As the patient gets stronger, the degree of support can be progressively reduced (weaning).

Further reading

See Invasive ventilation—ventilators, p50.

Invasive ventilation—adjustments

Adjustments are made in response to blood gases, pulse oximetry or capnography, patient discomfort, and during weaning. Migration of the ET tube, either distally to the carina or beyond, or proximally such that the cuff is at vocal cord level, may result in agitation, excess coughing and/or worsening blood gases. Before changing ventilator settings or sedative dosing, consider tube position, pneumothorax, secretion load or mucus plugging, cuff deflation or a water-logged HME filter. Pulmonary oedema and low cardiac output/shunt may also contribute to poor gas exchange.

The choice of ventilator mode depends upon conscious level, the number of spontaneous breaths being taken, and blood gas values. Many spontaneously breathing patients can cope adequately with pressure support ventilation alone. However, intermittent mandatory breaths (synchronized intermittent mandatory ventilation) may be needed to assist gas exchange or slow an excessive spontaneous rate. The paralysed/heavily sedated patient will require either volume- or pressure-controlled mandatory breaths.

The order of change will be dictated by the severity of respiratory failure and individual operator preference. Earlier use of increased PEEP is advocated to recruit collapsed alveoli and thus improve oxygenation in severe respiratory failure.

Low PaO_2 considerations

- Increase FiO_2.
- Increase pressure support or pressure control if V_T <6 mL/kg.
- Increase I:E ratio (may increase intrinsic PEEP and $PaCO_2$).
- Increase PEEP (may raise peak airway pressure or lower cardiac output).
- Consider tolerating low PaO_2 ('permissive hypoxaemia').
- Consider other modes of ventilation.
- Consider muscle relaxants if chest wall compliance low.
- Other options: prone ventilation, inhaled nitric oxide, extracorporeal membrane oxygenation (ECMO).

High PaO_2 considerations

- Decrease FiO_2.
- Decrease PEEP.
- Decrease level of pressure control/support if V_T adequate.
- Normalize I:E ratio.

High $PaCO_2$ considerations

- Increase V_T if low and peak airway pressure allows, but maintain ≤8 mL/kg.
- Increase respiratory rate if minute ventilation too low.
- Adjust respiratory rate or I:E ratio (to reduce intrinsic PEEP).
- Reduce dead space.
- Consider reducing basal metabolic rate (e.g. reducing pyrexia).
- Consider tolerating high levels ('permissive hypercapnia').
- Change mode of ventilation and/or sedation if ventilator asynchrony.
- Consider muscle relaxants if chest wall compliance low.

Low $PaCO_2$ considerations

- Decrease respiratory rate.
- Decrease V_T.

Further reading

See Invasive ventilation—modes, p52; Invasive ventilation—failure to tolerate ventilation, p56; Invasive ventilation—failure to deliver ventilation, p58; Invasive ventilation—lung recruitment, p60; Invasive ventilation—complications, p62; Invasive ventilation—principles of weaning, p64; Invasive ventilation—assessment of weaning, p66.

Invasive ventilation—failure to tolerate ventilation

Agitation or 'fighting the ventilator' may occur at any time from multiple causes including tube intolerance or migration, ventilator dyssynchrony, pain, delirium, hypoxaemia, hypercapnia, or hypoperfusion. The priority is to assess the patient and identify the problem utilizing an airway, breathing, and circulation (ABC) approach.

Clinical assessment is necessary to judge how serious the problem is and whether immediate resuscitative steps are required. If the problem is serious, consider manual ventilation with 100% O_2 and a non-rebreathe bag while checking for ventilator malfunction. Manual bagging enables assessment of how difficult it is to inflate the lungs, how long exhalation takes, and whether the problem with ventilation relates to patient (problem persists) or ventilator (problem resolved) factors. Note that manual ventilation delivers unknown V_T at unknown peak pressures and levels of PEEP, and may be injurious to the lungs.

Poor initial tolerance

- Increase FiO_2 up to 1.0 (depending on degree of hypoxaemia).
- Consider manual bagging.
- Consider bolus of rapid-acting sedative.
- Check ET tube is correctly positioned and both lungs are being inflated. Consider tube replacement, intratracheal obstruction, pneumothorax, or bronchospasm.
- Check ventilator circuit is intact, patent, not water-logged, and the ventilator is functioning correctly. Check ventilator settings including FiO_2, PEEP, I:E ratio, set V_T, respiratory rate, and/or pressure control. Check 'pressure limit' alarm settings as these may be set too low causing the ventilator to cycle prematurely to expiration.

Poor tolerance after previous good tolerance

New-onset poor tolerance may relate to the patient directly (e.g. delirium) or to a problem in the ventilator or circuit. Increasing sedation ± muscle relaxation alone may be unnecessary and/or potentially dangerous.

- Check patency of the ET tube (e.g. with a suction catheter) and the ventilator circuit.
- Assess ET tube malposition (e.g. cuff at vocal cords, tip at carina, tube in main bronchus).
- Assess the patient, e.g. for hypoxaemia, bronchospasm, tension pneumothorax, sputum plug, pain, raised intra-abdominal pressure, and pulmonary oedema. Aim to resolve the problem.
- Where patients are making spontaneous respiratory efforts, consider increasing pressure support or adding mandatory breaths.
- If stacking spontaneous and mandatory breaths, increasing pressure support and reducing mandatory rate may help.

Further reading

See Invasive ventilation—modes, p52; Invasive ventilation—lung recruitment, p60; Positive end-expiratory pressure—principles, p70; Positive end-expiratory pressure—management, p72; Continuous positive airway pressure (CPAP), p76; Chest physiotherapy, p98; Atelectasis & pulmonary collapse, p372.

Invasive ventilation—failure to deliver ventilation

Failure to ventilate despite apparently appropriate ventilator settings and exclusion of patient factors requires assessment of which ventilator settings are not being delivered.

Poor gas exchange

- Increase FiO_2 to 1.0 and start manual ventilation.
- Exclude patient factors.
- Check ET tube is correctly positioned, patent, and both lungs are being inflated. Consider tube replacement.
- Check ventilator circuit is both intact and patent, and ventilator is functioning correctly. Check ventilator settings including FiO_2, PEEP, I:E ratio, set V_T, respiratory rate, and/or pressure control.

Low V_T or low-pressure alarm

Expired V_T will be lower than inspired V_T with a bronchopleural fistula. Otherwise, when expired V_T is suddenly much lower than inspired V_T, or maintenance of circuit pressure is not possible, consider a leak in the ventilator circuit. The patient should be manually ventilated while the leak is identified and corrected. If the leak persists with manual ventilation, repositioning or replacement of the ET tube is required.

High-pressure alarm

A sudden increase in airway pressure indicates a change in resistance to gas flow. After patient factors have been excluded:

- Check patency of the ET tube (e.g. with a suction catheter); re-intubate if tube cannot be unblocked.
- Check patency of ventilator circuit and catheter mount. Look for excessive trapped water or inline suction catheter partially occluding the catheter mount.
- Check for sputum or excess water obstructing the HME.
- Consider bronchoscopy, ultrasound, or chest X-ray (CXR) to identify problems such as ET tube malposition (e.g. cuff above vocal cords, tip at carina, tube in main bronchus) or other issue (e.g. bronchial obstruction, pneumothorax).

Further reading

➔ See Invasive ventilation—modes, p52; Invasive ventilation—lung recruitment, p60; Positive end-expiratory pressure—principles, p70; Positive end-expiratory pressure—management, p72; Continuous positive airway pressure (CPAP), p76; Chest physiotherapy, p98; Atelectasis & pulmonary collapse, p372.

Invasive ventilation—lung recruitment

Reopening of collapsed alveoli often results in improved gas exchange, with resulting reductions in airway pressures and FiO_2. Collapsed alveoli are more likely to be recruitable in the early stages of respiratory failure and soon after intubation. A systematic review of recruitment manoeuvres showed improved oxygenation but no impact on mortality and an increased risk of haemodynamic deterioration.

Benefit is more likely for extrapulmonary causes of ARDS rather than direct pulmonary pathology such as pneumonia. Animal studies suggest that recruitment procedures may be potentially injurious in the latter situation due to overdistension of compliant alveoli.

Consider recruitment soon after intubation of patients with severe respiratory failure or procedures causing de-recruitment, e.g. ET suction, airway disconnection.

Recruitment manoeuvres

- Several techniques are used to recruit collapsed alveoli, e.g. applying 40 cm H_2O PEEP for 40 s with no ventilator breaths; delivering a few large-volume, ventilator-delivered breaths; or by using a combination of varying levels of PEEP and increasing pressure-delivered breaths to obtain optimal gas exchange.
- Although oxygenation is often improved, sometimes dramatically so, no outcome studies have been performed nor comparisons made between different recruitment techniques.

Further reading

Brower R, Morris A, MacIntyre N, et al. for the ARDS Clinical Trials Network. 2003. 'Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure'. *Crit Care Med* 31: pp2592–7.

Pensier J, de Jong A, Hajjej Z, et al. 2019. 'Effect of lung recruitment maneuver on oxygenation, physiological parameters and mortality in acute respiratory distress syndrome patients: a systematic review and meta-analysis'. *Intensive Care Med* 45: pp1691–702. doi: 10.1007/s00134-019-05821-9

See Invasive ventilation—modes, p52; Invasive ventilation—failure to tolerate ventilation, p56; Positive end-expiratory pressure—principles, p70; Positive end-expiratory pressure—management, p72; Continuous positive airway pressure (CPAP), p76; Chest physiotherapy, p98; Atelectasis & pulmonary collapse, p372.

Invasive ventilation—complications

Haemodynamic complications

Venous return depends on passive flow from central veins to right atrium. An increase in intrathoracic pressure is transmitted across compliant lungs to increase right atrial pressure and reduce venous return. This is less problematic with stiff lungs (e.g. ARDS) but can be exacerbated by inverse I:E ratio, high PEEP, or excess V_T. As lung volume is increased by intermittent positive pressure ventilation (IPPV), the pulmonary vasculature is constricted. Pulmonary vascular resistance and right ventricular diastolic volume rise and, by septal shift, left ventricular filling is impeded. These effects can result in a reduced stroke volume. This can be minimized by optimizing ventilator settings and maintaining adequate volaemia. A high venous pressure may exert back pressure on organs (e.g. kidneys), potentially impairing perfusion.

Ventilator-induced lung injury (VILI)

High inflation pressures, high distending volumes, and high shear stresses contribute to VILI. This may not be apparent clinically, but can manifest acutely as a pneumothorax. A tension pneumothorax is life-threatening and should be considered in any ventilated patient who becomes agitated, tachycardic, hypotensive, or exhibits sudden deterioration in blood gases. Prevention of VILI relies upon avoiding high V_T and airway pressures. A common strategy is to maintain the driving pressure (= plateau airway pressure − PEEP) <13–15 cmH_2O. No prospective studies have confirmed this approach.

Nosocomial infection (ventilator-associated pneumonia)

ET intubation bypasses normal defence mechanisms. Ciliary activity and cellular morphology in the tracheobronchial tree are altered and normal coughing is impaired. Usual HME mechanisms are bypassed. Failure to provide adequate humidification increases the risk of sputum retention and infection. Micro-aspiration around the ET tube cuff may introduce pathogens from the nasopharynx and upper gastrointestinal tract. Maintaining patients at 30° head-up tilt may reduce the incidence of ventilator-associated pneumonia.

Acid–base disturbance

Over-ventilating patients with chronic type II respiratory failure may cause a respiratory alkalosis by rapidly correcting the hypercapnia. Respiratory acidosis due to hypercapnia may be due to inappropriate ventilator settings or may be tolerated to avoid ventilator trauma (permissive hypercapnia).

Water retention

Plasma vasopressin and angiotensin levels are increased due to reduced intrathoracic blood volume. High airway pressure and/or high PEEP may also reduce lymphatic flow and venous return with consequent peripheral oedema, especially affecting the upper body.

Respiratory muscle wasting

Prolonged ventilation may lead to disuse atrophy of respiratory muscles.

Further reading

Slutsky A, Ranieri V. 2013. 'Ventilator-induced lung injury'. *N Engl J Med* 369: pp2126–36. doi: 10.1016/j.ccm.2016.07.004

Alviar C, Miller P, McAreavey D, et al. and the ACC Critical Care Cardiology Working Group. 2018. 'Positive pressure ventilation in the cardiac intensive care unit'. *J Am Coll Cardiol* 72: pp1532–53. doi: 10.1016/j.jacc.2018.06.074

➔ See Invasive ventilation—modes, p52; Invasive ventilation—adjustments, p54; Invasive ventilation—failure to tolerate ventilation, p56; Invasive ventilation—principles of weaning, p64; Invasive ventilation—assessment of weaning, p66; Positive end-expiratory pressure—principles, p70; Positive end-expiratory pressure—management, p72; Fibreoptic bronchoscopy, p96; Chest physiotherapy, p98; Bronchodilators, p278.

Invasive ventilation—principles of weaning

Weaning may follow several patterns, mainly dependent on the period of time the patient has been ventilated and the degree of underlying lung, heart, and/or muscle disease. For patients receiving longer-term ventilation it is unlikely that mechanical support can be withdrawn rapidly; several methods are commonly used to wean these patients from mechanical ventilation. There is no strong evidence that any technique is superior in terms of weaning success. Different strategies may suit individual patients. Patients should be assessed daily for weaning suitability and progress. A trial of extubation may be needed, accepting a proportion will fail and require reintubation.

Prior to weaning, it is important that the cause of respiratory failure and any complications arising have been corrected.

Weaning the patient

- Explanation should be given to the awake, aware patient.
- Remove factors that increase O_2 demand.
- Patient positioning (sitting up in bed or in a chair) will enhance diaphragmatic breathing and adequate V_T.
- Ensure adequate analgesia to enable deep breathing and self-clearing of secretions.
- Sedatives, antipsychotics, and/or anxiolytics may still be needed in specific situations for residual agitation.
- The weaning rate depends on the duration of mechanical ventilation and underlying comorbidities. This may be a lengthy process, sometimes taking months. Occasionally, patients cannot be weaned and consideration of long-term ventilation either in hospital, a care home, or the patient's home may be needed.
- Set realistic daily targets. A multidisciplinary teamwork approach including doctors, nurses, and physiotherapists ensures a consistent and cohesive management plan.
- Regularly reassess the weaning plan. The patient may wean faster or slower than anticipated.
- Different strategies may suit different patients. Some prefer gradual weaning of pressure support while others prefer increasing periods of spontaneous breathing interspersed by rest periods.
- Use patient appearance and signs of tachypnoea, increased respiratory efforts, or fatigue rather than specific blood gas values to judge the duration of spontaneous breathing.
- Early mobilization is usually advantageous. However, do not tire by prolonged spontaneous breathing, over-rapid reduction of pressure support, or excessive exercise.
- Ensure a good night's sleep. Increased ventilatory support overnight may assist sleep and avoid fatigue the following day.
- Provide plentiful encouragement and psychological support.
- Early tracheostomy may benefit if difficult weaning is expected.
- PEEP or CPAP may prevent early airway closure reducing the work of breathing.

- Consider heart failure as a cause of difficulty in weaning.
- Ensure appropriate nutrition, fluid, and electrolyte balance.
- If patient is weak and debilitated, consider non-weaning periods (1–7 days) with rehabilitation exercises to improve strength.

Intermittent mandatory ventilation (IMV)

The set mandatory rate is gradually reduced as the spontaneous rate increases. Spontaneous breaths are usually pressure supported to overcome circuit and ventilator valve resistance. The patient's required minute ventilation is provided by a combination of ventilator-delivered and spontaneous breaths without an excessive spontaneous rate. Any reduction in mandatory rate should not compromise minute ventilation. The patient should be able to synchronize respiratory efforts with mandatory breaths; when the spontaneous rate is high, there may be 'stacking' with mandatory breaths causing hyperinflation.

Pressure support ventilation

All respiratory efforts are spontaneous but positive pressure is added to each breath, the level being chosen to maintain an appropriate V_T. Weaning is performed by a gradual reduction of pressure support while the respiratory rate should generally remain <30 breaths/min.

Too rapid a wean may be manifest by increased work of breathing, nasal flaring, use of accessory muscles, tachypnoea, tiring, and/or agitation. It can be assessed on the ventilator by seeing if $P_{0.1}$ (the pressure generated at the airways during the first 0.1 s of the spontaneous inspiratory effort) is raised. Values >4 cmH_2O are associated with increased effort.

Pressure support is gradually reduced according to patient comfort and blood gases until the level is ~5 cmH_2O. Extubation can then be considered provided other criteria are also met, e.g. ability to clear secretions.

CPAP and intermittent 'T'-piece breathing

Spontaneous CPAP breathing is used for increasing periods with intermittent rest periods on mechanical ventilation. In the early stages of weaning, mechanical ventilation is often continued at night to encourage sleep. Avoid fatigue and rest respiratory muscles.

In some circumstances, a 'T-piece' trial can be attempted just prior to anticipated extubation. The patient breathes spontaneously without CPAP for 20–30 min to gauge their comfort, respiratory rate, and gas exchange. This may be particularly helpful in patients with known or covert heart failure as CPAP offers useful cardiac support.

Further reading

Burns K, Rizvi L, Cook D, et al. and the Canadian Critical Care Trials Group. 2021. 'Ventilator weaning and discontinuation practices for critically ill patients'. *JAMA* 325: pp1173–84. doi: 10.1001/jama.2021.2384

See Invasive ventilation—assessment of weaning, p66; Pulse oximetry, p162; CO_2 monitoring, p164; Pulmonary function tests, p166; Blood gas analysis, p174.

Invasive ventilation—assessment of weaning

Weaning with the intention of removing mechanical support is less successful while FiO_2 >0.4.

Factors predicting weaning success

- PaO_2 >11 kPa on FiO_2 0.4 (PaO_2/FiO_2 ratio >27.5 kPa).
- Minute volume <12 L/min.
- Vital capacity >10 mL/kg.
- Maximum inspiratory force (PImax) >20 cmH_2O.
- Respiratory rate/V_T <100.
- Qs/Qt <15%.
- Dead space/V_T <60%.
- Haemodynamic stability.

The ratio of respiratory rate to tidal volume (f/V_T, shallow breathing index) ≤105 has a 78% positive predictive value for successful weaning.

Factors associated with weaning failure

Failure to wean is associated with:

- Increased O_2 cost of breathing.
- Parenchymal lung disease.
- High secretion load.
- Muscle fatigue (malnutrition, peripheral neuropathy or myopathy, and electrolyte abnormalities (e.g. low Mg^{2+}, K^+)).
- Inadequate respiratory drive (alkalosis, opiates, sedatives, malnutrition, cerebrovascular accident, coma).
- Inadequate cardiac reserve and heart failure. Monitor cardiac function during spontaneous breathing periods. Any deterioration should be treated aggressively (e.g. vasodilators, inotropes, optimize fluid therapy). Early muscle fatigue due to prolonged disuse requires regular and controlled exercise with correction of nutritional deficit. Hold weaning during periods of rehabilitation. Patients who are building up muscle bulk and strength with physiotherapy may also benefit from night rest periods with graded increases in ventilator free time.

Indications for re-ventilation

- Increased work of breathing or discomfort.
- Patient is exhausted, agitated, or clammy.
- Tachypnoea (>30/min), tachycardia (>110/min), respiratory acidosis with rising $PaCO_2$, hypoxaemia.

Further reading

Yang K, Tobin M. 1991. 'A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation'. *N Engl J Med* 324: pp1445–50. doi: 10.1056/NEJM199105233242101

Ouellette D, Patel S, Girard T, et al. 2017. 'Liberation from mechanical ventilation in critically ill adults'. *Chest* 151: pp166–80. doi: 10.1016/j.chest.2016.10.036

➔ See Invasive ventilation—principles of weaning, p64; Pulse oximetry, p162; CO_2 monitoring, p164; Pulmonary function tests, p166; Blood gas analysis, p174.

High-frequency ventilation

These techniques are included for completeness, but have largely fallen out of use in adult intensive care practice.

High-frequency jet ventilation (HFJV)

- A high-pressure jet of gas entrains further fresh gas that is directed by the jet towards the lungs. Respiratory rates of 100–300/min ensure minute ventilation of about 20 L/min, even though V_T may be lower than dead space. CO_2 elimination is usually more efficient than conventional IPPV.
- The method of gas exchange is not fully elucidated but includes turbulent gas mixing and convection.
- Oxygenation is dependent on mean airway pressure. Peak airway pressures are lower than with conventional mechanical ventilation but auto-PEEP and mean airway pressures are maintained.
- SaO_2 may fall when starting HFJV, but usually improves with time.
- The high gas flow rates employed require additional humidification (30–100 mL/h); this is usually nebulized with the jet.
- HFJV has been used successfully for management of bronchopleural fistula.

High-frequency oscillation ventilation (HFOV)

HFOV is an extreme form of standard ventilation with sub-dead space V_T (1–2 mL/kg) delivered at very high rate (3–15 breaths/s). This generates higher levels of PEEP (equal to the continuous distending pressure or mean airway pressure). It may thus be viewed as a CPAP device that allows generation of pressure oscillations around a continuous distending pressure, eliminating CO_2 by accelerating molecular diffusion processes. Precise mechanisms of action on gas exchange are uncertain.

Two large randomized controlled trials found no outcome benefit for HFOV over conventional protective lung strategies in patients with ARDS.

Further reading

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Young D, Lamb S, Shah S, et al. for the OSCAR Study Group. 2013. 'High-frequency oscillation for acute respiratory distress syndrome'. *N Engl J Med* 386: pp806–13. doi: 10.1056/NEJMoa1215716

➔ See Invasive ventilation—ventilators, p50; Invasive ventilation—modes, p52; Positive end-expiratory pressure—principles, p70; Positive end-expiratory pressure—management, p72; Acute respiratory distress syndrome—diagnosis, p384; Acute respiratory distress syndrome—management, p386; Pneumothorax, p398.

Positive end-expiratory pressure—principles

Positive end-expiratory pressure (PEEP) is used in positive pressure ventilation to prevent alveoli returning to atmospheric pressure at end expiration. This compensates for loss of laryngeal PEEP when a patient is intubated. It is routinely set at 5 cmH_2O, however in severe respiratory failure it may need to exceed 10 cmH_2O to be above the lower inflexion point of the pressure–volume curve. It rarely needs to exceed 20 cmH_2O to avoid cardiorespiratory complications and alveolar overdistension. In theory, the PEEP level should be high enough to maintain patency of most lung units at risk of injury (atelectrauma) from repetitive opening and closing of recruitable units. However, it should not be too high to cause overdistension of compliant lung.

Respiratory effects

PEEP improves oxygenation by recruiting collapsed alveoli, redistributing lung water, decreasing A–V mismatch, and increasing functional residual capacity (FRC).

Haemodynamics

PEEP usually lowers both left and right ventricular preload and increases right ventricular afterload. Though PEEP may increase cardiac output in left heart failure and fluid overload states by preload reduction, in most other cases cardiac output falls with increasing PEEP. PEEP may also compromise a poorly functioning right ventricle. Improved PaO_2 resulting from decreased venous admixture may sometimes arise solely from reductions in cardiac output.

Physiological/laryngeal PEEP

A small degree of PEEP (2–3 cmH_2O) is usually provided physiologically by a closed larynx. It is lost when the patient is intubated or tracheostomized and breathing spontaneously on a T-piece with no CPAP valve (see CPAP section).

Intrinsic PEEP (auto-PEEP, air-trapping, $PEEP_i$)

PEEP may increase when there is insufficient time for expiration. This rise in $PEEP_i$ may lead to 'air trapping', CO_2 retention, increased airway pressure, and increased FRC. It can be seen in pathological conditions of increased airflow resistance (e.g. asthma, emphysema) and when insufficient expiratory time is set on the ventilator. $PEEP_i$ is generated by inverse ratio ventilation to increase oxygenation and decrease peak airway pressures. The above complications should be considered. $PEEP_i$ can be measured in a ventilated, non-spontaneously breathing patient by temporarily occluding the ventilator expiratory outlet at end expiration for a few seconds to allow equilibration of pressure between upper and lower airway and then reading the ventilator pressures.

Further reading

The ART investigators. 2017. 'Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome'. *JAMA* 318: pp1335–45. doi: 10.1001/jama.2017.14171

Beitler J, Sarge T, Banner-Goodspeed V, et al. 2019. 'Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-FiO_2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome'. *JAMA* 321: pp846–57. doi: 10.1001/jama.2019.0555

➲ See Invasive ventilation—ventilators, p50; Invasive ventilation—modes, p52; Invasive ventilation—adjustments, p54; Invasive ventilation—lung recruitment, p60; Invasive ventilation—complications, p62; Positive end-expiratory pressure—management, p72; Continuous positive airway pressure (CPAP), p76; Atelectasis & pulmonary collapse, p372.

Positive end-expiratory pressure—management

Indications

- Hypoxaemia requiring high FiO_2.
- Optimizing the pressure–volume curve in severe respiratory failure.
- Hypoxaemia secondary to left heart failure.
- Improvement of cardiac output in left heart failure.
- Reduced work of breathing while weaning patients with high $PEEP_i$.
- Neurogenic pulmonary oedema (i.e. non-cardiogenic pulmonary oedema following relief of upper airway obstruction).

Adjusting PEEP

1. Measure blood gases and monitored haemodynamic variables.
2. If indicated, alter level of PEEP by 3–5 cmH_2O increments.
3. Re-measure gases and haemodynamics after 15–20 min.
4. Consider further changes as necessary (e.g. additional changes in PEEP, fluid challenge, or vasoactive drugs).

Several clinical trials have arbitrarily adjusted PEEP levels according to FiO_2 need (Table 3.2). Current practice uses lower levels at higher FiO_2 values.

Table 3.2 PEEP adjustment according to FiO_2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP (cmH_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	≥18

'Best' PEEP

Initially described as the level of PEEP producing the lowest shunt value. It is now generally considered to be the lowest level of PEEP that achieves SaO_2 ≥90% allowing lowering of FiO_2 though not at the expense of high airway pressures or significant reductions in DO_2. The ART multicentre trial in patients with moderate-to-severe ARDS showed higher mortality in patients managed with a strategy of lung recruitment and PEEP titration to optimal compliance compared to a low PEEP strategy. Another study titrating PEEP to a target intrathoracic pressure (using an oesophageal balloon) failed to show any outcome differences compared to empirically set values of high PEEP.

Complications

- Reduced cardiac output. May need additional fluid loading or even inotropes. This should generally be avoided unless higher PEEP is needed to maintain adequate arterial oxygenation.
- Increased airway pressure (and potential risk of ventilator trauma).
- Overinflation leading to air-trapping and raised $PaCO_2$. May be beneficial but use with caution in patients with chronic airflow limitation

or asthma. In pressure-controlled ventilation, overdistension is suggested when an increase in PEEP produces a significant fall in V_T.
- High PEEP levels will decrease venous return, raise ICP, and increase hepatic congestion.
- PEEP may change the area of lung in which a pulmonary artery catheter tip is positioned from West zone III to non-zone III. This is suggested by a rise in wedge pressure of at least half the increase in PEEP and requires re-siting of the catheter tip.

Further reading

The ART investigators. 2017. 'Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial'. *JAMA* 318: pp1335–45. doi: 10.1001/jama.2017.14171

Beitler J, Sarge T, Banner-Goodspeed V, et al. 2019. 'Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-FiO_2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome'. *JAMA* 321: pp846–57. doi: 10.1001/jama.2019.0555

➲ See Invasive ventilation—ventilators, p50; Invasive ventilation—modes, p52; Invasive ventilation—adjustments, p54; Invasive ventilation—lung recruitment, p60; Invasive ventilation—complications, p62; Positive end-expiratory pressure—principles, p70; Continuous positive airway pressure (CPAP), p76; Volume–pressure relationship, p168; Electrical impedance tomography, p170; Atelectasis & pulmonary collapse, p372.

Non-invasive respiratory support

Devices of varying sophistication are available to augment spontaneous breathing in the compliant patient.

Continuous positive airway pressure (CPAP) can be achieved by an air–oxygen mix (usually at high flow) being introduced to the patient under continuous positive pressure to stent the airways open. The positive pressure is maintained by the patient wearing a tight-fitting partial or full-face mask, or helmet. Alternatively, low-level CPAP can be delivered by high-flow nasal oxygenation (HFNO).

Addition of inspiratory positive pressure support to CPAP is known as bi-level positive airway pressure (BiPAP).

Negative pressure inspiratory devices such as cuirasses and iron lungs are not currently in routine use outside of a few specialized respiratory weaning units.

Selection of support modality

CPAP and HFNO are generally indicated to improve oxygenation whereas inspiratory support is added for patients who have an increased work of breathing, a rising CO_2, or are tiring.

Indications

- Hypoxaemia requiring high respiratory rate, effort, and FiO_2.
- Hypercapnia in a fatiguing patient.
- Weaning modality.
- To avoid ET intubation where desirable (e.g. severe chronic airflow limitation, immunosuppressed patients).
- Reduces work of breathing in patients with high $PEEP_i$ (e.g. asthma, chronic airflow limitation). Use with caution and monitor closely.
- Heart failure—improves haemodynamics and oxygenation.
- Physiotherapy technique for improving FRC.
- Sleep apnoea.

Inspiratory support

A pre-set inspiratory pressure is given when triggered by the patient's breath. The trigger can be adjusted according to the degree of patient effort. Some devices deliver breaths automatically at adjustable rates. The I:E ratio may also be adjustable. The V_T delivered for a given level of inspiratory support varies according to the patient's lung compliance. An example of an inspiratory support device is the Bird ventilator used by physiotherapists to improve FRC and expand lung bases.

Further reading

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Ferreyro B, Angriman F, Munshi L, et al. 2020. 'Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis'. *JAMA* 324: pp57–67. doi: 10.1001/jama.2020.9524

See Ventilatory support—indications, p48; Invasive ventilation—principles of weaning, p64; Invasive ventilation—assessment of weaning, p66; Continuous positive airway pressure (CPAP), p76; Bi-level positive airway pressure (BiPAP), p78; High flow nasal oxygenation (HFNO), p80.

Continuous positive airway pressure (CPAP)

CPAP is the addition of positive continuous pressure in a spontaneously breathing patient who may/may not be intubated. A PEEP valve in the expiratory limb of the breathing circuit, or altering the PEEP/CPAP setting on a ventilator prevents alveolar collapse and helps recruit collapsed alveoli. CPAP is usually started at 5 cmH_2O. Depending on patient comfort, work of breathing, respiratory rate, and gases, it may be increased in 2.5–5 cmH_2O increments though rarely needs to exceed 10 cmH_2O. CPAP is applied either via a tight-fitting partial or full-face mask or a whole-head helmet connected to either a ventilator or CPAP machine. If the patient is intubated, CPAP can be delivered via the ventilator, or by a PEEP valve placed at the end of the expiratory limb of a T-piece circuit. A high-flow (i.e. above peak inspiratory flow) inspired air–O_2 mix, or a large reservoir bag in the inspiratory circuit is necessary to keep the valve open in non-ventilator devices. CPAP improves oxygenation and the work of breathing by reducing the alveolar-to-mouth pressure.

Devices

- All modern ICU ventilators offer CPAP (setting inspiratory pressure support to zero).
- Stand-alone high-flow devices plug directly into the pressurized wall oxygen supply and entrain air adjusted to the desired FiO_2.
- Low-flow devices are often used with nasal masks for sleep apnoea management in the community. These run off room air though supplementary oxygen can be added. In some devices FiO_2 values cannot exceed 0.35–0.4.

Indications

- Hypoxaemia requiring high respiratory rate, effort, and FiO_2.
- Left heart failure to improve hypoxaemia and cardiac output.
- Weaning modality.
- Reduces work of breathing in patients with high $PEEP_i$ (e.g. asthma, chronic airflow limitation)—NB: use with caution, monitor closely.

Complications

- Aspiration risk increases as gastric dilatation may occur from swallowed air, especially if ileus is present. Insert a nasogastric tube, especially if consciousness is impaired or gastric motility is reduced.
- Reduced cardiac output due to reduced venous return (raised intrathoracic pressure). May need additional fluid or inotropes.
- Overinflation leading to air-trapping and high $PaCO_2$. Caution is recommended in patients with chronic airflow limitation or asthma.
- Reduced venous return may increase ICP.
- Poor patient compliance with mask or hood due to claustrophobia. The mask edges and/or straps may cause discomfort, skin abrasions, or even ulceration. Patients benefit from regular breaks (e.g. using HFNO) or alternating between different masks and hoods. Low level sedation may be useful to calm the patient and improve tolerance.

- Thickened secretions due to high-flow, dry gas delivered by stand-alone devices. Use humidified air/oxygen and/or nebulizers during break periods.

Further reading

➔ See Invasive ventilation—lung recruitment, p60; Positive end-expiratory pressure—principles, p70; Bi-level positive airway pressure (BiPAP), p78; High flow nasal oxygenation (HFNO), p80; Dyspnoea, p366; Airway obstruction, p368; Respiratory failure, p370; Atelectasis & pulmonary collapse, p372.

Bi-level positive airway pressure (BiPAP)

BiPAP delivers adjustable levels of pressure support and PEEP. Breaths can be either patient triggered and/or mandatory. BiPAP can be delivered through a conventional ICU ventilator or a stand-alone device. Some low-level BiPAP devices (usually for community use) are driven by air; supplemental O_2 can be given to increase the FiO_2 via a circuit connection or through a portal in the face mask.

Management

Select type and delivery mode of ventilatory support.

1. Connect patient as per device instructions.
2. Use an appropriate-sized mask or helmet that is comfortable and leak-free.
3. Start with a delivered inspiratory positive airway pressure (IPAP) of 5–10 cmH_2O and expiratory positive airway pressure support (EPAP) of 5–10 cmH_2O.
4. Adjust according to patient response (respiratory rate, degree of fatigue, comfort) and blood gases.
5. Patients in respiratory distress may have initial difficulty in coping. Encourage while different levels of support, I:E ratios etc. are tested. Cautious administration of low-dose opiate (e.g. morphine 2.5 mg subcutaneously) may help to calm the patient without depressing respiratory drive.
6. The tight-fitting mask or helmet may become increasingly claustrophobic after a few days' use. Allow the patient regular breaks and use humidified oxygen and nebulizers as most stand-alone BiPAP devices use dry air.
7. Protect pressure areas such as the bridge of the nose.

Further reading

See Invasive ventilation—lung recruitment, p60; Positive end-expiratory pressure—principles, p70; Continuous positive airway pressure (CPAP), p76; High flow nasal oxygenation (HFNO), p80; Dyspnoea, p366; Airway obstruction, p368; Respiratory failure, p370; Atelectasis & pulmonary collapse, p372.

High-flow nasal oxygenation (HFNO)

This system enables high-flow oxygen to be delivered via soft nasal cannulae. The warmed, humidified oxygen is generally tolerated well and is less irritating to nasal mucosa. Advantages include improved oxygenation, better tolerance and humidification compared to other NIV support techniques, and ability to talk, eat, and drink more freely.

Mechanism

The high flow (30–60 L/min) facilitates a constant inspiratory oxygen delivery despite intense respiratory efforts, reduces the nasopharyngeal dead space, increases oxygen reserve, and reduces CO_2 rebreathing. There is a low-level CPAP effect which aids alveolar recruitment, improves compliance, and reduces work of breathing. The CPAP is not measurable and may fall if the patient's mouth remains open.

Indications

- Acute severe respiratory failure.
- Need for high oxygen delivery such as pre-oxygenation, apnoeic oxygenation, and during procedures (e.g. bronchoalveolar lavage (BAL)).
- After difficult extubation.
- Rest periods from non-invasive ventilation.

Contraindications

- Epistaxis, base-of-skull fracture, blocked nasal passage.

Management

- Select appropriate sized nasal cannulae (should not totally occlude nostrils) and circuit.
- Requires water for humidification. Allow humidifier to warm up before use; set water temperature to 37°C.
- Set oxygen flow rate (up to 60 L/min).
- Set FiO_2 from 0.21 to 1.0.
- Titrate flow rate and FiO_2 as required.

Complications

- Local trauma.
- Epistaxis.
- Gastric distension.
- Blocked cannulae with secretions.

Further reading

Frat J, Thille A, Mercat A, et al. 2015. 'High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure'. *N Engl J Med* 372: pp2185–96. doi: 10.1056/NEJMoa1503326

Monro-Somerville T, Sim M, Ruddy J, et al. 2017. 'The effect of high-flow nasal cannula oxygen therapy on mortality and intubation rate in acute respiratory failure: a systematic review and meta-analysis'. *Crit Care Med* 45: ppe449–56.

Rochwerg B, Einav S, Chaudhuri D, et al. 2020. 'The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline'. *Intensive Care Med* 46: pp2226–37. doi: 10.1007/s00134-020-06312-y

➔ See Invasive ventilation—lung recruitment, p60; Positive end-expiratory pressure—principles, p70; Continuous positive airway pressure (CPAP), p76; Dyspnoea, p366.

Prone positioning

Prone positioning is used to improve gas exchange. Studies have suggested mortality benefit in the severe ARDS group if used early and for at least 16 h/day. Various theories have been proposed to explain improvement, including reduction in compression atelectasis of dependent lung regions (temporary), reduction in chest wall compliance increasing intrathoracic pressure and alveolar recruitment, better regional diaphragmatic movement, better ventilation:perfusion matching, improved secretion clearance, and less alveolar distension leading to better oxygenation.

Indications

Prone positioning should be considered when PaO_2:FiO_2 ratio <20 kPa (<150 mmHg), despite optimization of ventilator settings.

Technique

Positioning the patient takes time and preparation. At least four members of staff are required to turn a patient and one person to secure the head and ET tube. The turn itself is a two-stage procedure via the lateral position. The arm on which the patient is to be rolled is tucked under the hip with the other arm laid across the chest. Pillows are placed under the abdomen and chest prior to rotation to the lateral position. If stable, the turn may be completed to prone. Pillows are placed under shoulders and pelvis. The head of the bed may be raised. One arm is extended at the patient's side while the other is flexed with head facing the opposite way (swimmer's position). Patients who are tracheostomized may require adjustments to position to ensure the airway remains patent and accessible, e.g. for suction.

While patients are often paralysed, this is not an absolute requirement. However, patients must be adequately sedated to avoid self-extubation, ventilator dyssynchrony, etc.

Frequency of turns

The response to prone ventilation is difficult to predict. Some patients may show no improvement in gas exchange, others may have a dramatic sustained effect, whereas others only show temporary benefit. The head and arms should ideally be repositioned 2-hrly to reduce the risk of pressure sores.

Complications

Problems associated with prone positioning include facial oedema, incorrect positioning of limbs leading to nerve palsy, shoulder dislocation, accidental displacement of the airway, removal of drains and catheters, pressure necrosis of parts of the face including eyes, corneal abrasions, and, rarely, myositis ossificans. These problems are often preventable with good care.

Gas exchange and/or haemodynamics may deteriorate significantly during prone positioning, even to the point of cardiac arrest. This may necessitate abandoning the procedure; however, cardiorespiratory status usually stabilizes over several minutes.

Cautions and contraindications

- Severe haemodynamic instability.
- Recent abdominal injury or surgery.
- Second or third trimester pregnancy.
- Severe head or spinal injury.
- Spinal instability (special beds are available for turning).
- Frequent seizures.
- Polytrauma.

Further reading

Gattinoni L, Carlesso E, Taccone P, et al. 2010. 'Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis'. *Minerva Anestesiol* 76: pp448–54.

Guérin C, Reigner J, Richard J-C, et al. for the PROSEVA Study Group. 2013. 'Prone positioning in severe acute respiratory distress syndrome'. *N Engl J Med* 368: pp2159–68. doi: 10.1056/NEJMoa1214103

Parhar K, Zuege D, Shariff K, et al. 2021. 'Prone positioning for ARDS patients-tips for preparation and use during the COVID-19 pandemic'. *Can J Anaesth* 68: pp541–5. doi: 10.1007/s12630-020-01885-0

➔ See Acute respiratory distress syndrome—diagnosis, p384; Acute respiratory distress syndrome—management, p386.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is used to deliver cardiac and/or respiratory support to those unresponsive to conventional therapies. ECMO should only be delivered in specialist centres with appropriate expertise and resources, typically co-located with cardiac surgery. ECMO centres usually operate a local retrieval team. Patient selection is paramount with strict criteria due to cost and complications. Consult local ECMO team for further advice. Inclusion criteria include:

- Potentially reversible cause of severe respiratory failure.
- Lung injury (Murray) score ≥3.
- Clinical Frailty Scale ≤3.
- Respiratory ECMO Survival Prediction (RESP) Score ≤3.

Equipment

Large bore (15–28 Fr) wire-reinforced catheters with varying length are used. Dual-lumen options exist. The circuit is usually coated with heparin but systemic anticoagulation is usually also administered. Circuits can be run without if needed. Hollow-fibre membranes have a large surface area for oxygenation and a heat exchanger to regulate temperature.

Centrifugal magnetic pumps are both preload and afterload dependent, determining blood flow through the circuit. In veno-arterial (VA)-ECMO, the centrifugal pump rate also determines cardiac output and mean arterial pressure, in combination with exogenous vasoconstrictors.

Veno-venous ECMO (VV-ECMO)

Utilized in acute, severe respiratory failure refractory to conventional mechanical ventilation strategies. Blood is removed via large venous cannula, passed through a membrane oxygenator, and returned to the venous system near to the right atrium. The patient must have preserved cardiac function. Patients remain on mechanical ventilation with ultra-low settings aimed at reducing further lung injury (V_T <4 mL/kg; P_{plat} <25 cmH_2O; PEEP 10–15 cmH_2O; respiratory rate 4–6/min). Indications include:

- Severe hypoxaemia (P:F ratio < 80 mmHg (10.7 kPa)).
- Severe hypercapnic acidaemia (pH <7.2).
- Inability to achieve lung protective ventilation.
- Failure to improve despite prone position, high PEEP.

Veno-arterial ECMO (VA-ECMO)

Utilized to support cardiac failure. Consider if refractory cardiogenic shock, cardiac arrest, massive PE, acute decompensated cardiomyopathy, sepsis, anaphylactic shock, failure to separate from cardiopulmonary bypass following cardiac surgery or drug overdose. Blood is removed via a large venous cannula in the femoral or internal jugular vein, passed through a membrane oxygenator and returned to the aorta via a second large bore cannula in a femoral artery (peripheral) or ascending aorta (central).

Veno-venous extracorporeal CO_2 removal ($ECCO_2R$)

Relatively low-flow removal of CO_2 with little to no impact on oxygenation—less commonly used in modern practice.

Contraindications

- Significant comorbidities (e.g. liver, renal failure).
- Progressive non-reversible disease.
- Chronic severe pulmonary hypertension.
- Advanced malignancy.
- Contraindications to anticoagulation (relative).
- Prolonged mechanical ventilation and profound shock associated with increased mortality.
- Significant vasoplegia.

Weaning and decannulation

For VV-ECMO, as lung compliance improves and initial injury recovers, fresh gas flow may be gradually reduced. When fresh gas flow = 0, patient is considered off ECMO. A decision is then made when to remove the cannulae.

Once weaned off ECMO, patients may be repatriated to a hospital closer to home and require continued monitoring for complications.

For VA-ECMO, gradual recovery of native cardiac function is usually accompanied by a reduction in ECMO support or need for vasoactive therapies—where patients do not wean, transition to durable devices, transplant or withdrawal of therapy are potential options.

Complications

Often related to the presence of large cannulae or use of anticoagulant.

- Bleeding, e.g. intracranial haemorrhage.
- Lower limb ischaemia, compartment syndrome.
- Cerebral ischaemia, e.g. embolic stroke.
- Venous thromboembolism.
- Haemolysis.
- Infection.

Outcomes

While individual patients may survive because of ECMO, randomized prospective controlled trials do not demonstrate significant outcome differences for VV-ECMO, VA-ECMO, or $ECCO_2R$. against standard care.

Further reading

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See Anticoagulants—parenteral, p334; Acute respiratory distress syndrome—diagnosis, p384; Acute respiratory distress syndrome—management, p386.

Tracheotomy—indications & technique

The technique of creating a hole (the tracheostomy) in the trachea to provide an artificial airway in place of oro- or nasotracheal intubation.

Indications

Indications include greater patient comfort, avoiding vocal cord, mouth, or nasal damage, or, in an emergency, to bypass acute upper airway obstruction. Reduced sedation, potential to eat, drink, and speak and facilitation of mouth care are all advantages. The TracMan trial showed no difference in outcome for early versus late tracheotomy.

Technique of percutaneous tracheotomy

Percutaneous tracheotomy can be performed at the bedside. Coagulopathy should be excluded or corrected. In general, the platelet count should be $>50 \times 10^9$/L and international normalized ratio <1.4. There are different techniques and operator styles. Some advocate ultrasound to exclude overlying blood vessels and guide needle placement whereas others prefer blunt dissection of the overlying subcutaneous tissues down to the anterior tracheal wall. Similarly, some use bronchoscopy as an aid to placement. End-tidal CO_2 monitoring should be used to confirm adequate ventilation during the procedure and correct placement of the tracheotomy. A skilled airway operator must be present throughout to maintain adequate ventilation and deal with any airway emergencies.

Before insertion through a 1–1.5 cm midline skin crease incision in the neck, infiltrate overlying tissues with 1% lidocaine and epinephrine (adrenaline) to provide local anaesthesia and reduce local bleeding. The ET tube tip is withdrawn to the level of the vocal cords. The trachea is then punctured in the midline with a 14 G needle between the second and third tracheal cartilages (or lower), allowing guidewire insertion. The stoma is created by dilatation to 32–36 Fr (Ciaglia technique) or by a guided forceps dilating tool (Schachner–Ovill technique). In the former case, the tracheostomy tube is introduced over an appropriate sized dilator, and in the latter through the open dilating tool. A CXR should be performed post-procedure.

Complications

The main early complication is haemorrhage from vessels anterior to the trachea. This is usually controlled with direct pressure or, occasionally, sutures. Bleeding into the trachea may result in clot obstruction of the airway; ET suction is usually effective. As bleeding may be gradual, obstruction may not occur until several hours post insertion. The upper airway should be regularly irrigated and suctioned. Paratracheal placement should be promptly recognized by inability to ventilate the lungs and end-tidal CO_2 monitoring.

Later complications include tube displacement, stomal infection, and tracheal stenosis. Patients with large necks or deep-lying tracheas are more at risk of tube displacement especially when being rolled or with vigorous coughing. Such patients benefit from particular caution when being turned/rolled. Insertion of an adjustable flange tracheotomy tube to alter tube length should be considered.

Stenosis is often related to low-grade infection. Rare complications include tracheo-oesophageal fistula or erosion through the lateral tracheal wall into a blood vessel.

Further reading

Young D, Harrison D, Cuthbertson B, et al. for the TracMan Collaborators. 2013. 'Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial'. *JAMA* 309: pp2121–9. doi: 0.1001/jama.2013.5154

Kidane B, Pierre A. 2018. 'From open to bedside percutaneous tracheostomy'. *Thorac Surg Clin* 208: pp263–76.

'Improving tracheostomy care'. National Tracheostomy Safety project. Accessed June 2023. http://tracheostomy.org.uk/healthcare-staff/improving-tracheostomy-care

See Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Tracheotomy—maintenance, p88; Mini-tracheotomy, p90; Airway obstruction, p368; Respiratory failure, p370.

Tracheotomy—maintenance

Since the upper air passages have been bypassed by the tracheotomy tube, good humidification is necessary. This can be achieved in several ways such as a heated water bath humidifier or HME placed in the ventilator circuit, ± regular nebulization or installation of normal saline. A 'Swedish nose' is an HME filtered cap attached to the end of the tracheostomy tube in a non-mechanically ventilated patient.

Cough is less effective without a functioning larynx so regular tracheal suction will be necessary. Laryngeal PEEP is lost with a tracheostomy. The risk of basal atelectasis can be overcome with CPAP or attention to respiratory exercises that promote deep breathing.

The tube may be exchanged if necessary within 5–7 days following percutaneous tracheostomy, or 2–3 days following surgical tracheostomy. However, this should be done cautiously as a tract from skin to trachea will have not yet formed. It may be difficult to re-insert a tube so aids such as a bougie should be available. Tube change should be performed by skilled operators, especially if concerned about upper airway patency. Airway equipment and intubation drugs should be readily available in case complications arise.

Tracheotomy tubes

Standard high-volume, low-pressure cuff

Tracheotomy tubes usually have an inner cannula that can be temporarily removed for cleaning/removal of debris and secretions that may cause obstruction.

Adjustable flange tube

An adjustable flange accommodates variations in skin to trachea depth while ensuring the cuff remains central in the trachea. It is also used when the patient's neck anatomy results in the tip of a standard-length tracheotomy tube abutting against the anterior tracheal wall, compromising ventilation and/or passage of a suction catheter.

Fenestrated with or without cuff

Such tubes have holes in the side wall to reduce work of breathing and assist phonation (with the cuff down). Cuffless tubes can be used where airway protection is not a primary concern.

Fenestrated with inner tube

As above, but with an inner tube to facilitate closure of the fenestration during intermittent mechanical ventilation. The fenestration enables phonation provided the cuff is deflated. The inner tube can be removed for cleaning.

Fenestrated with speaking valve

Expiration through the larynx, via the fenestration, allows speech.

Passy Muir® speaking valve

This expiratory occlusive valve is placed onto the tracheostomy tube to permit inspiration through the tracheostomy and expiration through the glottis. The tracheostomy tube cuff must be first deflated. The valve allows phonation, facilitates swallowing, and may reduce aspiration. The valve may reduce the work of breathing. The potential drop in V_T from cuff deflation

makes this valve only suitable in those patients requiring low-level or no invasive ventilatory support.

Silver tube

An uncuffed tube used occasionally in ear, nose, and throat practice to maintain a long-term tracheostomy fistula.

Removal of the tracheotomy tube

Before removing the tube, ensure the upper airway is patent either by ensuring exhalation can still occur with the tracheostomy tube temporarily occluded, or by direct visualization.

Further reading

'Improving tracheostomy care'. National Tracheostomy Safety project. Accessed June 2023. http://tracheostomy.org.uk/healthcare-staff/improving-tracheostomy-care

See Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Tracheotomy—indications & technique, p86; Mini-tracheotomy, p90; Airway obstruction, p368; Respiratory failure, p370.

Mini-tracheotomy

The technique of placing a small-diameter, uncuffed plastic tube through the cricothyroid membrane under local anaesthetic.

Indications

- Removal of retained secretions, usually if patient's cough is weak.
- Emergency access to lower airway. FONA with 'scalpel, bougie, ET tube' is now, however, recommended as first-line management.

Contraindications/cautions

- Coagulopathy.
- Non-compliant, agitated patient (unless sedated).

Technique

Some kits rely on blind insertion of a blunt introducer; others use a Seldinger technique with an introducer passed over the wire.

1. Use an aseptic technique. Cleanse site with antiseptic. Locate cricothyroid membrane (midline 'spongy' area between cricoid and thyroid cartilages).
2. Infiltrate local tissues with 1% lidocaine + epinephrine. Advance introducer needle into deeper tissues, aspirating to confirm absence of blood. Infiltrate with lidocaine until cricothyroid membrane is pierced and air is easily aspirated.
3. If using Seldinger technique, insert guidewire through the membrane into the trachea. Tether thyroid cartilage with one hand, incise skin and tissues vertically in midline (alongside wire) using a short-bladed guarded scalpel. Insert scalpel to blade guard level to make adequate hole through cricothyroid membrane. Remove scalpel.
4. Insert introducer through incision site into trachea (or over guidewire). Angle caudally. Relatively light resistance is felt during correct passage—do not force introducer if resistance is excessive.
5. Lubricate plastic tube and slide over introducer into trachea.
6. Remove introducer (+ wire), leaving plastic tube *in situ*.
7. Confirm correct position by placing own hand over tube and feeling airflow during breathing. Suction down tube to aspirate intratracheal contents (check pH if in doubt). Cap opening of tube. Suture to skin.
8. Perform CXR (unless very smooth insertion and no change in cardiorespiratory variables).
9. O_2 can be entrained through the tube, or a catheter mount placed to enable bagging, intermittent positive pressure breathing, and/or short-term assisted ventilation.

When a tracheotomy tube is removed but concerns remain about adequate secretion clearance, a mini-tracheotomy tube can be placed directly through the larger stoma. Gauze pads can be placed around the tube, to reduce air leak from the larger stoma until this closes down naturally over a few days.

Complications

- Blood vessel puncture may cause significant intratracheal or external bleeding. Apply local pressure if this occurs after blade incision. If bleeding continues, inserting the mini-tracheotomy tube may have a tamponading effect. If bleeding persists, insert deep sutures either side of the mini-tracheotomy tube; if this fails, contact a surgeon for assistance.
- Perforation of oesophagus.
- Mediastinitis (rare).
- Pneumothorax.

Further reading

➔ See Tracheotomy—maintenance, p88; Chest physiotherapy, p98; Atelectasis & pulmonary collapse, p372.

Chest drain insertion

Used for drainage of air (pneumothorax), fluid (effusion), blood (haemothorax), or pus (empyema) from the pleural space. The technique requires surgical dissection to the pleural membrane and blunt insertion of the tube to avoid accidental damage to intrathoracic or upper abdominal organs.

Insertion technique

Use 28 Fr drain (or larger) for haemothorax or empyema; 20 Fr will suffice for a pure pneumothorax. Seldinger-type drains are also available. The drain is usually inserted through the fifth intercostal space in the mid-axillary line, first anaesthetizing skin and pleura with 5 mL 1% lidocaine. Ensure that air (for pneumothorax) or fluid (effusion) is aspirated.

1. Ultrasound may be used to assist drain placement.
2. Under aseptic technique, make a 1–1.5 cm skin crease incision, create a track with a gloved finger (or forceps) to separate muscle fibres, and open the pleura.
3. Insert drain through the open pleura either using forceps placed through a side-hole of the drain, or with the sharp trochar withdrawn several cm.
4. Angle and insert drain to correct position (toward lung apex for pneumothorax and lung base for haemothorax/effusion). Ultrasound or computed tomography scan are useful for directing placement for small collections.
5. Connect tubing to an underwater seal. Keep the bottle below the level of heart in a spontaneously breathing patient.
6. Secure drain to chest wall by properly placed sutures and gauze swabs for patient comfort and to reduce peri-drain air/fluid leaks.
7. Perform CXR to ensure correct siting and lung reinflation.
8. Place on 3–10 cmH_2O (0.4–1.3 kPa) negative pressure (low-pressure wall suction) if the lung has not fully expanded or a bronchopleural fistula is present.

Subsequent management

- Do not clamp drains prior to removal or during transport of the patient.
- Drains may be removed when the lung has re-expanded and no air leak is present off suction (no respiratory swing in fluid level nor air leak on coughing).
- Unless long-term ventilation is necessary, a drain inserted for a pneumothorax is usually left *in situ* during IPPV.
- Remove drain at end-expiration. Cover hole with ample gauze swabs and adhesive tape; a purse-string suture is not usually necessary. Repeat CXR if clinically indicated.
- Pneumothorax may become loculated and multiple drains required.

Complications

- Puncture of an intercostal vessel may cause significant bleeding.
- Consider:
  - correcting any coagulopathy
  - placing deep tension sutures around drain
  - removing drain
  - inserting a Foley catheter, inflating the balloon and applying traction to tamponade the bleeding vessel.
  - surgical referral may be necessary.
- Puncture of lung tissue may cause a bronchopleural fistula. Consider suction (up to 5–10 cmH_2O), pleurodesis, a double-lumen endobronchial tube, or surgery. Extubate once feasible as positive pressure ventilation will keep the fistula open.
- Perforation of major vessel (often fatal)—clamp but do not remove drain, resuscitate, contact thoracic surgeon, consider double-lumen ET tube.
- Infection—take cultures; antibiotics (staphylococcal ± anaerobic cover); consider removing/re-siting drain.
- Local discomfort/pain from pleural irritation may impair cough. Consider simple analgesia, subcutaneous lidocaine, instilling local anaesthetic, local or regional anaesthesia, etc.
- Drain dislodgement—if needed, replace/re-site new drain. Do not advance old drain (infection risk).
- Lung entrapment/infarction—avoid milking drain if placed for pneumothorax.

Further reading

See Pleural aspiration, p94; Basic resuscitation, p358; Pneumothorax, p398; Haemothorax, p400.

Pleural aspiration

Drainage of fluid from the pleural space using needle, cannula, or flexible small-bore drain. Increasingly being performed under ultrasound guidance. Blood/pus often requires a large-bore drain.

Indications

- Improvement of blood gases.
- Symptomatic improvement of dyspnoea.
- Diagnostic 'tap'.

Contraindications/cautions

Coagulopathy.

Technique

1. Confirm presence of effusion by CXR or ultrasound.
2. Select drainage site either by maximum area of stony dullness under percussion, or under ultrasound guidance.
3. Use an aseptic technique. Clean area with antiseptic and infiltrate skin and subcutaneous tissues with 1% lidocaine ± epinephrine. Advance into deeper tissues, aspirating to confirm absence of blood, then infiltrate with local anaesthetic until pleura is pierced and fluid can be aspirated.
4. Advance drainage needle/cannula/drain slowly through chest wall and intercostal space (above upper border of rib to avoid neurovascular bundle). Apply gentle suction until fluid is aspirated.
5. Withdraw 50 mL for microbiological (e.g. microscopy, culture, and sensitivity, tuberculosis stain, etc.), biochemical (e.g. protein, glucose, lactate dehydrogenase) and histological/cytological (e.g. pneumocystis, malignant cells) analysis, as indicated.
6. Either leave drain *in situ* connected to a drainage bag, or connect needle/cannula by a three-way tap to a drainage apparatus.
7. Continue aspiration/drainage until no further fluid can be withdrawn or if patient becomes symptomatic (pain/dyspnoea). Dyspnoea or haemodynamic changes may occur due to removal of large volumes of fluid (>1–2 L) and subsequent fluid shifts. If this is considered to be a possibility, remove no more than 1 L at a time, either by clamping/de-clamping drain or repeating needle aspiration after an equilibration interval (e.g. 4–6 h).
8. Remove needle/drain. Cover puncture site with firmly applied gauze dressing.

Complications

- Puncture of lung or subdiaphragmatic viscera.
- Bleeding.

Fluid biochemistry

Protein

- Protein >30 g/L (NB: this should be viewed in the context of the plasma protein level) is an exudate—causes: inflammatory, e.g. pneumonia, pulmonary embolus, neoplasm, collagen vascular diseases.
- Protein <30 g/L is a transudate—caused by (i) raised venous pressure (e.g. heart failure, fluid overload), (ii) decreased colloid osmotic pressure (e.g. critical illness leading to reduced plasma protein from capillary leak and hepatic dysfunction, hepatic failure, nephrotic syndrome).

Lactate dehydrogenase

- Can be elevated in infection, malignancy, or rheumatoid arthritis.

Cholesterol

- Elevated in exudates independent of serum levels.

Further reading

➔ See Chest drain insertion, p92; Basic resuscitation, p358; Pneumothorax, p398; Haemothorax, p400.

Fibreoptic bronchoscopy

Indications

Diagnostic

- Collection of microbiological ± cytological specimens (by BAL, protected brush specimen, biopsy).
- Cause of bronchial obstruction (e.g. clot, foreign body, neoplasm, stenosis, extrinsic compression).
- Extent of inhalation injury.
- Diagnosis of ruptured trachea/bronchus, tracheo-oesophageal fistula.

Therapeutic

- Clearance of secretions, inhaled vomitus, soot, or other toxic materials.
- Removal of obstructing matter (e.g. mucus plug, blood clot, food, tooth). Proximal obstruction rather than consolidation is suggested by the X-ray appearance of a collapsed lung/lobe and no air bronchogram.
- Directed placement of balloon catheter to arrest pulmonary bleeding.
- To aid difficult ET intubation.

Contraindications/cautions

- Coagulopathy.
- Severe hypoxaemia.
- Both reducing the effective ET tube lumen and regular suctioning during bronchoscopy reduces V_T and PEEP and can cause lung derecruitment. As this can lead to significant hypoxaemia and hypercapnia, carefully monitor the patient.

Procedure

1. Pre-oxygenate with FiO_2 1.0. Monitor with pulse oximetry.
2. Increase pressure alarm limit on ventilator.
3. Lubricate scope with lubricant gel/saline.
4. If not intubated, apply lidocaine gel to nares ± spray to pharynx.
5. Administer short-term intravenous sedation ± paralysis, as needed.
6. Insert scope nasally in a non-intubated patient, or via the catheter mount port if intubated. Care should be taken to not damage the bronchoscope outer sleeve when inserting it through the latex rubber seal of the catheter mount. If needed, make a small slit in the port to widen the aperture and thus protect the scope. An assistant should support the ET tube during the procedure to minimize trauma to the trachea and scope.
7. If needed, inject 2% lidocaine into trachea to prevent coughing and haemodynamic effects from tracheal/carinal stimulation. This may however impair growth of micro-organisms in the lab.
8. Perform thorough inspection and any necessary procedures. If SpO_2 ≤85% or haemodynamic disturbance occurs, remove scope from the airway to allow stabilization, re-oxygenation, and to blow off accumulated CO_2 for several minutes before continuing.
9. BAL is performed by instillation of at least 60 mL of (preferably warm) isotonic saline into affected lung areas followed by aspiration of fluid into a sterile catheter trap. BAL samples should be sent promptly to the laboratory for analysis.

10. After the procedure, reset ventilator as appropriate. A recruitment procedure may be necessary, especially if oxygen requirements have increased significantly. Consider a chest radiograph to assess any benefit (e.g. lung expansion after removal of occluding mucus plug, blood clot, or foreign body) or complications arising from the procedure.

Complications

- Hypoxaemia ± hypercapnia—e.g. from suctioning, loss of PEEP, non-delivery of V_T.
- Haemodynamic disturbance, e.g. hypoxaemia, agitation.
- Bleeding.
- Perforation—unusual though more common if biopsy taken.

Further reading

➔ See Endotracheal intubation—indications & equipment, p44; Chest physiotherapy, p98; Atelectasis & pulmonary collapse, p372; Haemoptysis, p402; Inhalation injury, p404.

Chest physiotherapy

Aims are to expand collapsed alveoli, mobilize chest secretions, and reinflate collapsed lung segments. Though anecdotal experience shows benefit, no scientific validation of effectiveness has yet been reported.

Indications

- Mobilization of secretions.
- Re-expansion of collapsed lung/lobes.
- Prophylaxis against alveolar collapse and secondary infection.
- Table 3.3 lists situations where chest physiotherapy is considered urgent.

Contraindications/cautions

- Aggressive hyperinflation in already hyperinflated lungs, e.g. asthma, emphysema—though can be very useful in removing mucus plugs.
- Undrained pneumothorax.
- Raised ICP.
- Haemodynamic instability.

Techniques

Hyperinflation

Hyperinflating to 50% above ventilator-delivered V_T, aims to expand collapsed alveoli and mobilize secretions. V_T is rarely measured so either excessive or inadequate hyperinflations may be given depending on lung compliance and operator technique. Pressure-limiting devices ('blow-off valves') or manometers can avoid excessive airway pressures. A recommended technique is slow inspiration, a 1–2 s plateau phase, and then rapid release of the bag to simulate a 'huff' and mobilize secretions. Preoxygenation may be needed as PEEP may be lost and the delivered V_T may be inadequate. Sedation may blunt adverse haemodynamic responses. Full deflation avoids air trapping.

Suctioning

Removes secretions from trachea and main bronchi (usually right). A cough reflex may be stimulated to mobilize secretions further. Tenacious secretions may be loosened by instillation or nebulization of 2–5 mL normal or hypertonic saline, or mucolytics such as carbocisteine. Falls in SaO_2 and cardiovascular disturbance may be avoided by pre-oxygenation.

Percussion and vibration

Drumming and shaking actions on chest wall mobilizes secretions.

Inspiratory pressure support (Bird ventilator)

Aims to increase FRC and expand collapsed alveoli.

Postural drainage

Positioning the patient according to the anatomical location of the affected lung area(s) assists drainage of secretions.

Complications of chest physiotherapy

- Hypoxaemia—from suction, loss of PEEP, etc.
- Haemodynamic disturbance (high V_T, airway pressure, hypoxaemia, agitation, tracheal stimulation, etc.).

- Direct trauma from suctioning.
- Barotrauma/volutrauma including pneumothorax.

Prophylactic measures

- Adequate humidification to avoid tenacious sputum and mucus plugs.
- Pain relief to encourage good chest excursion and cough.
- Position semi-recumbent to optimize use of respiratory muscles.
- Ensure adequate nutrition to help maintain/restore muscle strength.
- Early mobilization to maintain/restore muscle bulk and strength, and to decrease infection risk.
- Encourage deep breathing to decrease infection risk.

Requesting urgent physiotherapy

Table 3.3 Situations where urgent physiotherapy should or should not be requested

Request	Don't request
Collapsed lung/lobe with no air bronchogram visible, i.e. suggesting proximal obstruction rather than consolidation	Clinical signs of chest infection with no secretions being produced
Mucus plugging causing subsegmental collapse, e.g. asthma	Radiological consolidation with air bronchogram but no secretions present

Further reading

➔ See Mini-tracheotomy, p90; Fibreoptic bronchoscopy, p96; Atelectasis & pulmonary collapse, p372.

Chapter 4

Cardiovascular therapy

Electrical cardioversion

Indications

Electrical conversion is used to convert a tachyarrhythmia to normal sinus rhythm. This may be:

- Emergency—when the circulation is absent or severely compromised, e.g. ventricular fibrillation (VF) or ventricular tachycardia (VT).
- Semi-elective—when circulatory status is worsened acutely by the tachyarrhythmia ± not responding to antiarrhythmic agents, e.g. new-onset hypotension.
- Elective—when synchronized cardioversion is performed to restore sinus rhythm for a non-compromising supraventricular tachycardia (SVT). This also reduces the risk of thrombus formation.

Adverse features of a tachyarrhythmia

Adverse features (reflection of poor perfusion) include:

- Clinical signs: hypotension, pallor, clammy, cold, confused.
- Syncope: transient loss of consciousness.
- Myocardial ischaemia: typical chest pain or electrocardiogram (ECG) changes.
- Ventricular dysfunction: pulmonary oedema, worsening lactate levels, rising B-type natriuretic peptide (BNP) levels.

In patients with underlying normal heart function, a ventricular rate <150/min is unlikely to cause adverse problems in the short term. However, if there is underlying cardiac impairment, structural heart disease, or another severe medical condition (e.g. lung disease), then adverse signs and symptoms may be present with ventricular rates >100/min.

Contraindications/cautions

- Aware patient.
- Severe coagulopathy.
- Caution with recent thrombolysis.
- Digoxin levels in toxic range.

Technique

- Figure 4.1 describes the procedure for cardioversion.
- Synchronization requires connection of ECG leads from the patient to the defibrillator, as well as the gel pads. An electric shock is delivered on the R wave to minimize the risk of VF. Newer, biphasic defibrillators require approximately half the energy setting of monophasic defibrillators.
- The chances of maintaining sinus rhythm are increased if K^+ >4.5 mmol/L and plasma Ca^{2+} and Mg^{2+} levels are normal.
- Prior to defibrillation, ensure self and onlookers are not in contact with the patient or bed, and remove oxygen.
- To reduce the risk of superficial burns, replace gelled pads after every three shocks.
- Consider re-siting paddle position (e.g. anteroposterior) if defibrillation fails.

Complications

- Surface burn.
- Pericardial tamponade.

- Electrocution of bystanders.
- Fire from concentrated oxygen flow in close proximity to gel pads.

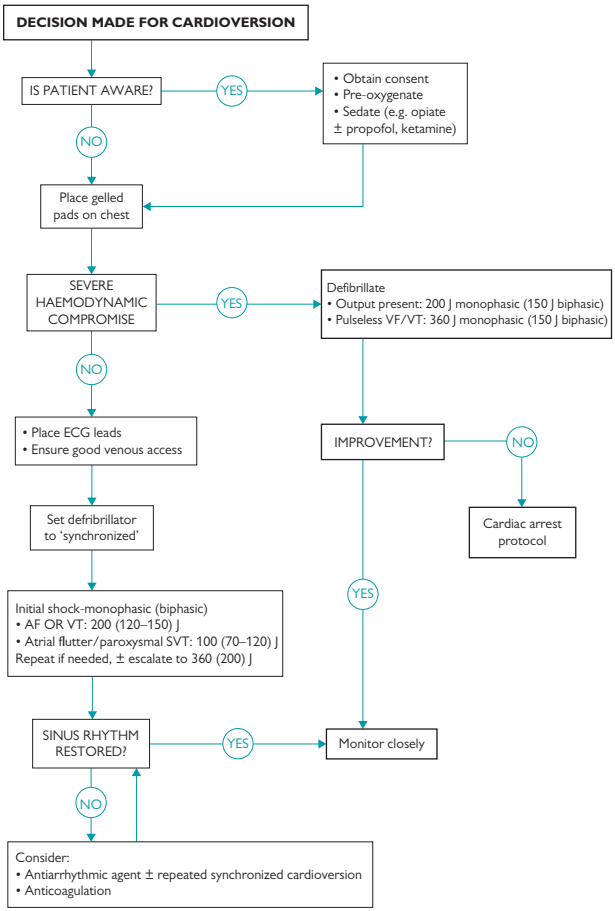

Fig. 4.1 Algorithm for use of electrical cardioversion.

Further reading

Soar J, Nolan J, Bottiger B, et al. 2015. 'European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support'. *Resuscitation* 95: pp99–146. doi: 10.1016/j.resuscitation.2015.07.016

See Chronotropes, p296; Cardiac arrest, p360; Tachyarrhythmias, p412.

Temporary pacing

When the heart's intrinsic pacemaking ability fails, temporary internal or external pacing can be instituted. Internal electrodes can be endocardial (inserted via a central vein) or epicardial (placed on the external surface of the heart at thoracotomy). The endocardial wire may be placed under fluoroscopic control or placed 'blind' using a balloon flotation catheter. External pacing can be rapidly performed by placement of two electrode pads on the front and rear chest wall when asystole or third-degree heart block has produced acute haemodynamic compromise. It is often used as a bridge to temporary internal pacing. It can also be used as a prophylactic measure, e.g. for Mobitz type II second-degree heart block.

Indications

- Third-degree heart block.
- Mobitz type II second-degree heart block when the circulation is compromised, or an operation is planned. Over-pacing (rarely; more successful with internal pacing).

Complications

Internal pacing

- As for central venous catheter insertion.
- Arrhythmias.
- Infection (including endocarditis).
- Myocardial perforation (rare).

Troubleshooting

- No pacemaker spikes seen—check connections, check battery.
- No capture (pacing spikes but no QRS complex after)—poor wire positioning or wire dislodged. Increasing the output may regain capture. If necessary, reposition/replace internal pacing wire.

General

- Check threshold daily as it will rise slowly over 48–96 h, probably due to fibrosis occurring around the electrodes.
- Over-pacing may be used for a tachycardia unresponsive to antiarrhythmic therapy or cardioversion. For SVT, pacing is usually attempted with the wire sited in the right atrium. Pace at rate 20–30/min above patient's heart rate for 10–15 s then either decrease rate immediately to 80/min or slowly, by 20/min every 5–10 s.
- If over-pacing fails, under-pacing may be attempted with the wire situated in either atrium (for SVT) or, usually, ventricle (for either SVT or VT). A paced rate of 80–100/min may produce a refractory period sufficient to suppress the intrinsic tachycardia.
- Epicardial pacing during cardiac surgery uses either two epicardial electrodes or one epicardial and one skin electrode (usually a hypodermic needle). The pacing threshold of epicardial wires rises quickly and may become ineffective after 1–2 days.

Technique for endocardial electrode placement

1. If using fluoroscopy, move patient to X-ray suite or place lead shields around bed area. Staff should wear lead aprons.
2. Use aseptic technique throughout. Insert 6 Fr sheath in internal jugular or subclavian vein. Suture in position.
3. Connect pacing wire electrodes to pacing box (black = negative polarity—distal, red = positive polarity—proximal). Set pacemaker to demand. Check box is working and battery charge is adequate. Set pacing rate to 30/min above patient's intrinsic rhythm. Set voltage to 4 V.
4. Insert pacing wire through sheath into central vein. If using balloon catheter, insert to 15–20 cm depth then inflate balloon. Advance catheter, viewing ECG monitor for change in ECG morphology and capture of pacing rate. If using screening, direct wire towards the apex of the right ventricle. Approximate insertion depth from a neck vein is 35–40 cm.
5. If pacing impulses are not captured, deflate balloon, withdraw wire to 15 cm insertion depth, then repeat step 4.
6. Once pacing is captured, decrease voltage by decrements to determine the threshold at which pacing is no longer captured. Ideal position is determined by a threshold ≤0.6 V. If not achieved, reposition wire.
7. If possible, ask patient to cough to check wire does not dislodge.
8. Set voltage at 3× threshold and desired heart rate on 'demand' mode. Tape wire securely to patient to prevent dislodgement.

Technique for external pacing

1. Connect pacing wire gelled electrodes to pacemaker. Place black (= negative polarity) electrode on the anterior chest wall to the left of the lower sternum and red (= positive polarity) electrode to the corresponding position on the posterior hemithorax.
2. Connect ECG electrodes from ECG monitor to external pacemaker and another set of electrodes from pacemaker to patient.
3. Set pacemaker to demand. Turn pacing rate to 30/min above patient's intrinsic rhythm. Set current to 70 mA.
4. Start pacing. Increase current (by 5 mA increments) until pacing rate captured on monitor.
5. If pacing rate not captured at current of 120–130 mA, re-site electrodes and repeat steps 3–4.
6. Once pacing captured, set current at 5–10 mA above threshold.

Further reading

➔ See Central venous catheter—insertion, p190; Chronotropes, p296; Cardiac arrest, p360; Bradyarrhythmias, p414.

Targeted temperature management

Targeted temperature management (TTM), previously known as therapeutic hypothermia, is the process of actively inducing and maintaining a predetermined core temperature, usually 32–34°C after cardiac arrest. The aim is to achieve neuro- and/or cardioprotection in ischaemia–reperfusion insults such as cardiac arrest, traumatic head injury, subarachnoid haemorrhage, stroke, and haemorrhagic shock as well as sepsis. Proposed mechanisms include reducing metabolism and production of reactive oxygen species.

Trial results for these conditions are too conflicting to make any firm recommendation. The disparate results may relate to the rapidity with which the targeted temperature is attained. In some studies, this has taken 1–2 days. The main harm from reperfusion injury is, however, likely to occur within the first few minutes to hours. Nonetheless, avoidance of hyperpyrexia is likely beneficial.

Recent European guidelines now recommend actively preventing fever (>37.7°C) for at least 72 h, but could offer no recommendation regarding TTM or early cooling after cardiac arrest. Guidelines also recommend comatose patients with mild hypothermia after return of spontaneous circulation should not be actively rewarmed to achieve normothermia.

Timing and duration

The optimal duration for which outcomes may be positively influenced by TTM is uncertain. Current recommendations are to avoid fever for at least 72 h.

Cooling techniques

Various cooling systems are currently available, each with specific advantages and disadvantages. These can be subdivided into non-invasive and invasive.

Non-invasive

- Air- or water-circulating cooling blankets or pads.
- Ice packs in groins and axillae.
- Covering body in wet sheets or spraying with alcohol.

Invasive

- Infusion of cold fluids.
- Irrigating (or instilling and draining at regular intervals) bladder and/or stomach and/or peritoneum with iced water.
- Specialized endovascular catheters placed in a central vein, with iced sterile saline pumped through integral cooling balloons (rapid), e.g. Thermoguard XP.
- Extracorporeal circulation (rapid).

Other aspects

Managing shivering should be considered if aiming for therapeutic hypothermia or normothermia. Heavy sedation ± paralysis may be required.

Potential side effects

- Infection.
- Pressure sores.
- Electrolyte disorders and hyperglycaemia.
- Arrhythmias (low risk if core temperature kept >30°C), bradycardia.
- Increased bleeding tendency.
- Alterations in drug metabolism.
- Thrombocytopenia, leucopenia.

Further reading

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Nolan J, Sandroni C, Böttiger B, et al. 2021. 'European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care'. *Intensive Care Med* 47: pp369–421. doi: 10.1007/s00134-021-06368-4

See Cardiac arrest, p360; Coma, p466; Hypothermia, p652.

Intra-aortic balloon pump

Principle

The intra-aortic balloon pump (IABP) consists of a 30–40 mL balloon placed in the descending aorta. The balloon is inflated with helium during diastole, increasing diastolic blood pressure above the balloon, which improves coronary and cerebral perfusion. The balloon is deflated during systole, decreasing peripheral resistance and increasing stroke volume. Figure 4.2 shows the pressure waveform produced. No drug therapy exists that can increase coronary blood flow while reducing peripheral resistance. Intra-aortic balloon counterpulsation may improve cardiac performance in situations where drugs are ineffective.

Indications

An IABP can support the circulation where a structural cardiac defect is to be repaired surgically. It may also be used for acute circulatory failure where resolution of the cause of the cardiac dysfunction is expected. The use of an IABP may provide temporary circulatory support and promote recovery by improving myocardial blood flow. Other indications include acute myocarditis and poisoning with myocardial depressants. It should not be used in aortic regurgitation as the rise in diastolic blood pressure would increase regurgitant flow. A large, randomized control trial (IABP-SHOCK II) showed no short- or long-term benefit.

Insertion of the balloon

The usual route is via a femoral artery. An introducer sheath is sited percutaneously using a Seldinger technique to provide a rapid, safe, and sterile approach with usually minimal arterial trauma and bleeding. Open surgical catheterization may be needed in elderly patients with atheromatous disease. Check the balloon position on a chest X-ray to ensure the radio-opaque tip is at the level of the second intercostal space.

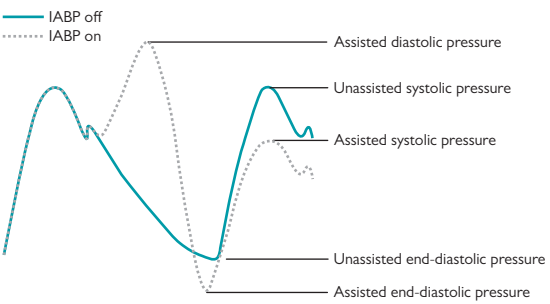

Fig. 4.2 Arterial waveform with and without intra-aortic counterpulsation.

Anticoagulation

The presence of a large foreign body in the aorta requires systemic anticoagulation to prevent thrombosis. The balloon should not be left deflated for longer than a few minutes while *in situ*, otherwise thrombosis may develop despite anticoagulation.

Control of balloon inflation and deflation

Helium is used to inflate/deflate the balloon rapidly. Inflation is commonly timed to the 'R' wave of the ECG, although timing may be taken from an arterial pressure waveform. Minor adjustment may be made to the timing to ensure that inflation occurs immediately after closure of the aortic valve (after the dicrotic notch of the arterial pressure waveform) and deflation occurs at the end of diastole. The filling volume of the balloon can be varied to the maximum balloon volume. A greater filling volume increases circulatory augmentation. The rate may coincide with every cardiac beat or every second or third beat. Slower rates are necessary in tachyarrhythmias. Weaning of intra-aortic balloon counterpulsation may be achieved by reducing augmentation or the rate of inflation.

Further reading

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➔ See Inotropes, p286; Vasopressors, p290; Anticoagulants—parenteral, p334; Acute coronary syndrome—management, p418; Heart failure—assessment, p420; Decompensated heart failure—management, p422.

Ventricular assist device

Ventricular assist devices (VADs) partially or fully support the failing heart. Initially introduced as a bridge to heart transplantation, but with advances in technology, portability, durability, and user-friendliness, these are now utilized in patients with cardiogenic shock and during cardiac surgery. Continuous flow devices have replaced first-generation pulsatile devices, so no peripheral pulse is palpable. Increasingly these are used for long-term cardiac support so intensivists may meet such patients in the immediate post-insertion period, or when the device is already *in situ* long term. Currently, three types of device exist:

- Left (LVAD) or right ventricular assist device (RVAD), e.g. Impella.
- Biventricular assist device (BiVAD).
- Total artificial heart.

Contraindications

- Severe right heart failure (for LVAD).
- Restrictive cardiomyopathy.
- Intractable angina.
- Ventricular arrhythmias.

Immediate post-insertion management

Carefully monitor both left and right ventricular function to optimize support settings.

- Airway, breathing, circulation (ABC); blood gases; markers of organ perfusion and function.
- Patient may not have a palpable pulse so auscultate over heart to hear if mechanical motor working.
- Invasive arterial monitoring; usual aim for mean arterial pressure ≥65 mmHg.
- Echocardiography.

Complications

- Arrhythmias: high risk of sustained VF/VT—if not cardioverted, high risk of decompensated heart failure.
- Bleeding—anticoagulation, bleeding diatheses.
- Increased risk of acquired von Willebrand disease.
- Increased risk of gastrointestinal and intracranial bleeds.
- Infection—prompt treatment is needed to reduce risk of seeding. If source unclear, assume a driveline infection. Cover Gram-negative and Gram-positive bacteria with antibiotics appropriate for known hospital flora and their resistance patterns.
- Right ventricular failure: pulmonary hypertension, pulmonary embolus, LVAD pump speed too high.
- Left ventricular failure: pump thrombosis, cannula obstruction, motor failure, battery failure.
- Chronic hypercoagulable state with thrombus formation, even despite adequate anticoagulation.
- Aortic valve stenosis can develop over time.
- CPR is controversial; if performed, conduct with care to reduce risk of dislodgement of device.

Further reading

See Anticoagulants—parenteral, p334; Tachyarrhythmias, p412; Acute coronary syndrome—management, p418; Heart failure—assessment, p420; Decompensated heart failure—management, p422.

Coronary revascularization techniques

Principle

Early restoration of blood flow through an obstructed coronary vessel will prevent irreversible infarction and/or ongoing ischaemia. Revascularization leads to mortality and morbidity benefits, reduced reinfarction rates, and need for coronary artery bypass grafting (CABG). Time from symptom onset to intervention is key to reducing mortality.

Techniques

Percutaneous

Percutaneous coronary intervention (PCI) has evolved since the 1980s, when stenotic lesions were simply dilated by transluminal coronary angioplasty (PTCA). PCI now includes stenting of narrowed or occluded areas using bare-metal and drug-eluting stents. Drug-eluting stents reduce the risk of restenosis and the need for repeat PCI. They carry an increased risk of 'very late stent thrombosis' plus undesired effects related to the stent polymer; it is thus important to continue dual antiplatelet therapy (DAPT) for 6–12 months post-stent insertion. Next-generation stents using new drugs, polymers, and drug delivery systems are in development to improve upon current devices.

Pharmacological

Thrombolytic agents remain indicated if PCI is not available within 120 min of symptom onset. Older drugs such as streptokinase have been replaced by recombinant tissue plasminogen activators (rtPAs) such as alteplase, reteplase, and tenecteplase which are easier to administer and appear more effective. However, the rate of recanalization at 90 min is only 55–60% and there is a 5–15% risk of early or late reocclusion. There is also a 1–2% risk of intracranial haemorrhage (with 40% mortality) and an increased risk of bleeding elsewhere (e.g. gastrointestinal tract, cannula sites). Other anticoagulant agents are administered including heparin, warfarin, and antiplatelet agents aspirin, ticagrelor, or the glycoprotein IIb/IIIa inhibitors (e.g. abciximab, eptifibatide, and tirofiban).

Surgical

CABG has an important role to play in bypassing stenotic lesions not amenable for PCI. While PCI is targeted at the 'culprit' lesion(s), CABG is directed at the epicardial vessel, including the 'culprit' lesion(s) and possible future culprits.

Patients with single-vessel disease are more likely to have PCI, while those with triple-vessel disease are more likely to undergo CABG. Mortality is similar to PCI.

The advantages of CABG over PCI are better relief of angina and a lower likelihood of subsequent reocclusion. The magnitude of the latter benefit may decrease with drug-eluting stents. However, the increase in the rate of stroke with CABG offsets these advantages.

Critical care issues

- Continue DAPT unless contraindicated, e.g. bleeding or requirement for major surgery.
- Prolonged action of DAPT on platelet function (lasting 5–7 days after discontinuation) will heighten the risk of bleeding, both perioperatively and during critical illness. Fresh platelet transfusions may be needed to restore platelet functionality. Similarly, warfarin has a prolonged duration of action that can be reversed with fresh frozen plasma, prothrombin complex concentrates (e.g. Octaplex®), or recombinant factor VIIa. A balance has to be sought between bleeding risk (or severity of an existing haemorrhage) and stent thrombosis from discontinuation of the drug(s). Discussion with cardiology should be undertaken to determine the risk–benefit for that patient.
- Myocardial 'stunning'—acute, reversible heart failure related to myocardial reperfusion; may last several days after the intervention.
- Arrhythmias—commonly related to reperfusion and may occasionally be life-threatening.
- Mishaps related to PCI including coronary artery rupture plus restenosis and acute occlusion of the stent.
- Complications related to CABG include stroke, bleeding (and tamponade), and transient myocardial depression.

Further reading

Bonaa K, Mannsverk J, Wiseth R, et al. for the NORSTENT investigators. 2016. 'Drug eluting or bare metal stents for coronary artery disease'. *N Engl J Med* 375: pp1242–52. doi: 10.1056/NEJMoa1607991

➲ See Anticoagulants—parenteral, p334; Thrombolytics, p338; Acute coronary syndrome—diagnosis, p416; Acute coronary syndrome—management, p418.

Chapter 5

Renal & blood therapy

Continuous renal replacement therapy—techniques & indications

Continuous renal replacement therapy (CRRT) involves extracorporeal removal of intravenous fluid through a circuit, usually running continuously. Blood passes through a filter that allows removal of fluid, electrolytes, and low-molecular-weight compounds (<30–35 kDa). In comparison, intermittent haemodialysis (HD) or peritoneal dialysis (PD) may be undertaken for 4 h three times weekly (HD) or with PD overnight or 24 h a day. The major difference between intermittent dialysis and CRRT is the speed of removal of water and waste products with CRRT causing much less haemodynamic instability.

Indications

- Azotaemia (uraemia).
- Hyperkalaemia.
- Anuria/oliguria; to make space for nutrition.
- Severe metabolic acidosis.
- Fluid overload.
- Drug removal.
- Hypothermia/hyperthermia.

Techniques

- Continuous veno-venous haemofiltration (CVVH) relies on convection (bulk transfer of solute and water) to clear solute.
- Continuous veno-venous haemodiafiltration (CVVHD)—dialysate flows countercurrent to the blood allowing small molecules to diffuse according to their concentration gradients across a semi-permeable membrane. Concentration gradients are dependent on low potassium and high bicarbonate dialysate composition (no urea or creatinine in dialysate).
- Sustained low-efficiency dialysis (SLED) is haemodialysis performed at lower flow rates over 8–12 h rather than 3–4 h. It provides more haemodynamic stability and can be used without anticoagulation.
- Slow continuous ultrafiltration (SCUF)—predominantly removes fluid with little solute clearance due to lower filtration rates. Used mainly in patients with fluid overload, e.g. heart failure resistant to diuretics without azotaemia.

Complications

- Disconnection leading to haemorrhage.
- Infection risk (sterile technique must be employed).
- Electrolyte, acid–base, or fluid imbalance (due to excess input or removal).
- Haemorrhage related to systemic anticoagulation therapy. Heparin-induced thrombocytopenia may occur rarely.
- About 200 mL blood is lost when the filter circuit clots.

Cautions

- Haemodynamic instability related to hypovolaemia (especially at the start of CRRT).
- Drug dosages may need to be revised (consult pharmacist).
- Vasoactive drug removal by the filter (e.g. catecholamines).
- Membrane biocompatibility problems (more so with cuprophane membranes than polyacrylonitrile).
- Amino acid losses through the filter.
- Heat loss leading to hypothermia.
- Masking of pyrexia.

Further reading

➔ See Haemo(dia)filtration, p118; Peritoneal dialysis, p120; Oliguria, p426; Acute kidney injury—diagnosis, p428; Acute kidney injury—management, p430.

Haemo(dia)filtration

Historically, haemo(dia)filtration was performed via an arterio-venous circuit. The driving pressure was the patient's blood pressure but this was often problematic in the sick intensive care unit (ICU) population. Modern systems utilize a pump for blood removal using double-lumen veno-venous catheters, generally 15–20 cm long with 10–12 Fr lumens (Figure 5.1). The devices have inbuilt safety features for detecting disconnection, high pump pressures, or large air bubbles. Permanent catheters are generally utilized for long-term CRRT.

Membranes

Membranes are usually hollow-fibre polyacrylonitrile (or rarely, polyamide or polysulphone with a surface area of 0.6–1 m^2). Both CVVH and CVVHD are effective for small molecule clearance (e.g. urea). CVVH is better at larger molecule clearance and can remove substances up to the membrane pore size (often 30–35 kDa). Filtrate is usually removed at 20–35 mL/kg/h; fluid balance is adjusted by varying the rate of fluid replacement. High-volume haemofiltration involves higher ultrafiltration rates (e.g. 50–100 mL/kg/h, usually for short periods, e.g. 4 h) in an effort to remove more inflammatory mediators. Outcome studies have, however, not shown benefit.

Creatinine and K^+ clearances are higher with CVVHD, but filtration alone is usually sufficient if ultrafiltrate volume is adequate and the patient is not too catabolic (1000 mL/h filtrate equates to creatinine clearance 16 mL/min). CVVHD is preferred for resistant hyperkalaemia.

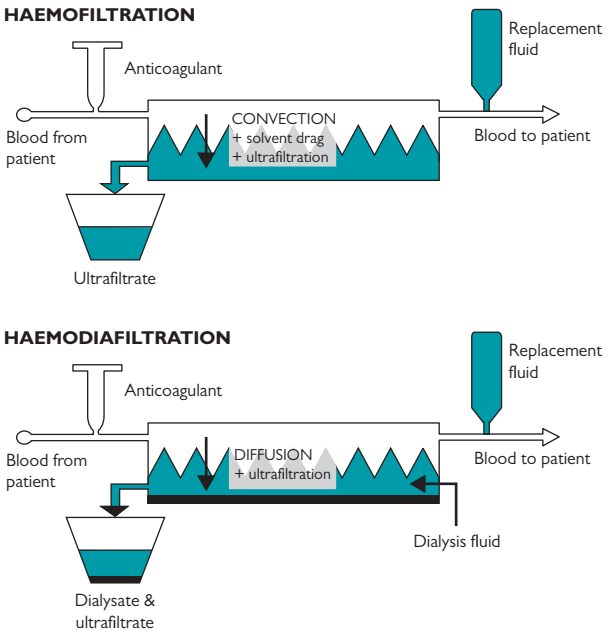

Fig. 5.1 Circuit arrangement for haemo(dia)filtration.

Replacement fluid

Balanced electrolyte solutions buffer acidaemia and can be titrated to the desired fluid and electrolyte balance. Buffers include lactate (liver-metabolized to bicarbonate) and bicarbonate. Acetate (muscle-metabolized) causes more haemodynamic instability and is now infrequently used. Bicarbonate is increasingly used and may be more efficient than lactate at reversing severe acidosis; however, no outcome benefit has yet been shown. Care is needed when giving Ca^{2+} since calcium bicarbonate may crystallize. With liver dysfunction, lactate may be inadequately metabolized.

Increasing metabolic alkalosis may be due to excessive buffer so low buffer (30 mmol/L lactate) replacement fluid can be used. In addition, potassium is readily filtered; although hyperkalaemia may be a problem with acute kidney injury, often K^+ is added to the dialysate to maintain normokalaemia (20 mmol KCl in 4.5 L provides a concentration of 4.44 mmol/L). K^+ clearance is increased by reducing the concentration within replacement fluid or dialysate.

Filter blood flow

Flow through the filter is usually 150–200 mL/min. Too slow a flow rate promotes clotting. Too high a flow rate increases transmembrane pressures and decreases filter lifespan without significantly improving clearance of 'middle molecules' (e.g. urea).

Anticoagulation

The method of choice is regional citrate anticoagulation with less systemic absorption, reduced bleeding risk, and prolonged filter life. Citrate is infused pre-filter and calcium is infused post-filter to correct citrate-induced anticoagulation and prevent systemic effects. Dose is titrated by ionized calcium (Ca^{2+}) measurement. Citrate toxicity may be an issue, especially in patients with liver disease. Toxicity is suggested by a total:ionized Ca ratio >2.5, low [Ca^{2+}], and worsening metabolic acidosis. Alternatives include systemic anticoagulation with unfractionated heparin (200–2000 IU/h) and/or a prostanoid (epoprostenol 2–10 ng/kg/min). The low-molecular-weight heparinoid danaparoid, or direct thrombin inhibitors (e.g. lepirudin, argatroban) may have cross-sensitivity with heparin. Their longer half-lives and difficulty in reversal make them generally unsuitable for critical care.

Premature clotting may be due to mechanical kinking/obstruction of the circuit, insufficient anticoagulation, inadequate blood flow, or lack of endogenous anticoagulants such as antithrombin through which heparin acts.

Usual filter lifespan is 4–5 days but is often decreased in septic patients receiving heparin. In this situation, consider fresh frozen plasma or a synthetic protease inhibitor (e.g. aprotinin, antithrombin).

Further reading

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Honore P, Spapen H. 2018. 'What a clinician needs to know about renal replacement membrane'. *J Transl Int Med* 6: pp62–5.

See Continuous renal replacement therapy—techniques & indications, p116; Oliguria, p426; Acute kidney injury—diagnosis, p428; Acute kidney injury—management, p430.

Peritoneal dialysis

A slow form of dialysis, utilizing the peritoneum as the dialysis membrane. It has been largely superseded by continuous haemofiltration in the ICU. The technique does not require complex equipment although continuous flow techniques do require continuous generation of dialysate. Treatment can be labour intensive involving specialist renal nurses and there is considerable risk of peritoneal infection. Automated PD devices are increasingly used in patients' homes and will reduce workload if needed in an ICU setting.

Peritoneal access

For acute PD, a PD catheter is inserted percutaneously into the peritoneum through a small skin incision (usually midline, 1 cm below the umbilicus) using aseptic technique and under local anaesthetic. The cannula is advanced towards the pouch of Douglas. PD catheter insertion can be performed radiologically under screening, with more immediate use compared to surgical insertion.

Dialysis technique

1–2 L of warmed peritoneal dialysate is infused into the peritoneum. During the acute phase, fluid is flushed in and drained continuously. Once biochemical control is achieved, fluid can be left in the peritoneal cavity for 4–6 h before draining. Heparin (500 IU/L) may be added to the first six cycles to prevent fibrin catheter blockage. Thereafter, it is only necessary if there is blood or cloudiness in the drainage fluid.

Peritoneal dialysate

The dialysate is a sterile balanced electrolyte solution with glucose at 75 mmol/L for a standard fluid solution, or 311 mmol/L for a hypertonic solution used for greater fluid removal. The fluid is usually potassium free since potassium exchanges slowly in PD. Potassium may be added, if necessary.

Complications

- Fluid leak—poor drainage, obese or elderly patients, small defects such as hernias will be exacerbated, requiring repair with a switch in RRT modality.
- Catheter blockage or poor placement—bleeding, omental encasement, poor drainage.
- Infection—white cells >50/mL, cloudy drainage fluid.
- Hyperglycaemia—absorption of hyperosmotic glucose.
- Diaphragm splinting.

Treatment of infection

Appropriate antibiotics may be added to the dialysate. Suitable regimens include:

- Cefuroxime 500 mg/L for two cycles then 250 mg/L for 10 days.
- Gentamicin 8 mg/L for one cycle daily dosing as per levels.
- Dosing depends on native urine output.

Further reading

See Oliguria, p426; Acute kidney injury—diagnosis, p428; Acute kidney injury—management, p430.

Plasma exchange

Indications

Plasma exchange (plasmapheresis) may be used to remove circulating toxins or to replace missing plasma factors. It is mainly used in immune-mediated disease (e.g. anti-glomerular basement membrane (GBM) disease), Guillain–Barré syndrome, thrombotic thrombocytopenic purpura). There is some suggestion of benefit in acute liver failure (transplant-free survival) and sepsis (reduction in vasopressor use and Sequential Organ Failure Assessment (SOFA) score). Conditions for which plasma exchange may be considered are listed in Table 5.1.

Most diseases require a daily 3–4 L plasma exchange repeated for at least four further occasions over 5–10 days.

Techniques

Cell separation by centrifugation

Blood is separated into components in a centrifuge. Plasma (or other specific blood components) are discarded and a plasma replacement fluid (usually fresh frozen plasma) is infused in equal volume. Centrifugation may be continuous where blood is withdrawn and returned by separate needles or intermittent where blood is withdrawn, and separated then returned via the same needle.

Membrane filtration

Plasma is continuously filtered through a large pore filter (molecular weight cut-off typically 1,000,000 Da). Plasma is discarded and replaced by infusion of an equal volume of replacement fluid (usually fresh frozen plasma). The technique is similar to haemofiltration and uses the same equipment.

Table 5.1 Conditions in which plasma exchange can be considered

Autoimmune disease	Anti-GBM disease
	Guillain–Barré syndrome
	Myasthenia gravis
	Pemphigus
	Antinuclear cytoplasmic antibody (ANCA)-associated vasculitis
	Thrombotic thrombocytopenic purpura
Immunoproliferative disease	Cryoglobulinaemia
	Waldenstrom's macroglobulinaemia
Poisoning	Paraquat
Infection	Meningococcaemia
	Sepsis
Other	Acute liver failure
	Reye's syndrome

Complications

- Circulatory instability—intravascular volume changes, removal of circulating catecholamines, hypocalcaemia.
- Reduced intravascular colloid osmotic pressure—if replacement with crystalloid.
- Infection—reduced plasma opsonization.
- Bleeding—removal of coagulation factors.

Further reading

Larsen F, Schmidt L, Bernsmeier C, et al. 2016. 'High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial'. *J Hepatol* 64: pp69–78.

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David S, Bode C, Putensen C, et al. 2021. 'Adjuvant therapeutic plasma exchange in septic shock'. *Intensive Care Med* 47: pp352–4. doi: 10.1007/s00134-020-06339-1

➲ See Guillain–Barré syndrome, p486; Myasthenia gravis, p488; Platelet disorders, p508; Vasculitis, p620.

Other blood purification techniques

Haemoperfusion (haemadsorption) is an extracorporeal system whereby anticoagulated blood is passed through a specialized filter or column containing adsorbent particles that remove poisons, drugs, toxins, or mediators.

Indications

Poisons and drugs

The original technique employed was charcoal haemoperfusion. This removed specific water-soluble drugs such as phenobarbital, theophylline, paraquat, valproate, and carbamazepine that are readily absorbed to activated charcoal and have small volumes of distribution. This technique has been supplanted by more efficient haemodialysis devices and is now rarely used.

Exogenous toxins

Charcoal haemoperfusion was also used to remove circulating bacterial toxins, e.g. endotoxin (lipopolysaccharide) from Gram-negative bacteria. This indication has also been superseded by cartridges containing resins with greater affinity for lipid-soluble molecules, such as polymyxin B-immobilized polystyrene derivative fibres (Toraymyxin™). However, the Euphrates multicentre RCT utilizing this system failed to show outcome benefit in patients with presumed Gram-negative sepsis.

Endogenous toxins and mediators

Acute liver failure is associated with an increase in circulating toxins that have not been detoxified and/or excreted by the failing liver, and a rise in inflammatory mediators. Different haemadsorption techniques have been trialled in patients, e.g. charcoal haemoperfusion, Molecular Adsorbent Recirculating System (MARS™) that utilizes albumin dialysis, Cytosorb™ (that adsorbs excessive amounts of circulating inflammatory mediators non-specifically), and bio-artificial liver support systems, e.g. Extracorporeal Liver Assist Device (ELAD™) where blood passes over functional hepatocytes within a bioreactor. None, however, have yet demonstrated clear outcome benefit.

Similarly, for sepsis and in COVID-19 disease, several devices have been used to remove excess inflammatory mediators (Cytosorb™), or inflammatory mediators, endotoxin, fluid, and uraemic toxins simultaneously (oXiris™, coupled plasma filtration and adsorption). While inflammatory mediator levels and, often, vasopressor levels are reduced, no clear outcome benefit has been seen. In some cases, harm was reported.

Extracorporeal devices in development are using magnetic beads to remove specific anti-inflammatory or pro-inflammatory mediators, or polymer beads conjugated with proprietary human recombinant histone H1.3 protein to remove excess neutrophil extracellular traps (NETs). Engineering of the porous structure of these particles produces columns with varied adsorption properties. Toxins with molecular weights ranging from 100 to 40,000 Da bind to the particles and are removed as blood exits the column. There are two major types of adsorbent particles, including activated charcoal and resins (e.g. hydrocarbon polymer, polystyrene). Charcoal has greater affinity for water-soluble molecules, while resins have greater affinity for lipid-soluble molecules.

Further reading

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➔ See Extracorporeal liver support, p136; Acute liver failure, p454.

Chapter 6

Gastrointestinal therapy

Nasogastric & nasojejunal tubes

Types of tube

A nasogastric (NG) tube is a flexible tube inserted nasally into the stomach for delivery of feed, fluid, and/or medication, or drainage of gastric contents. Nasojejunal (NJ) tubes have the tip placed within the jejunum to bypass the stomach if there are issues with gastric emptying. Feeding tubes are usually fine bore (9 Fr or less in adults), whereas wide bore (Ryles) tubes are used for drainage and can be up to 24 Fr in diameter. Ryles tubes are usually made of PVC and should only be used for up to 10 days. Feeding tubes are either polyurethane (30–90 days *in situ*), or silicone for longer-term feeding.

NJ tubes may be plain or adapted to aid insertion, e.g. the self-propelling Tiger Tube™ has small distal flaps that aid forward advancement during peristalsis, or the Cortrak® tube that uses an electromagnetic sensor at the tip to enable external visualization.

Insertion

1. Awake patients with capacity should consent verbally beforehand. If anxious, they may require some light sedation. Ventilated patients may require a short-term increase in sedation to facilitate placement. Do not attempt insertion in agitated patients unless they are calm and/or sedated because of an increased risk of failure and complications. Such patients are also more likely to pull out tubes after placement with potential risk of self-injury.
2. Measure NEX (length of tube from nose to ear lobe to xiphisternum). This is an estimate of the minimum insertion distance for a NG tube, but correct placement requires other checks as described below.
3. Lubricate the tube and gently insert via a nostril into the oropharynx. If the patient is awake ask them to swallow as the tube is being advanced to aid oesophageal placement. If excessive resistance is encountered do not force the tube further; either retract the tube and re-try or utilize the other nostril. The presence of an orotracheal tube with an inflated cuff may hinder passage into the oesophagus resulting in coiling of the NG tube within the mouth. Insertion using Magill's forceps guided by direct laryngoscopy may be needed. Do not insert finger(s) into the mouth to aid placement.
4. Advance the tube to the assumed correct position using the markings on the outside of the tube. Some fine-bore tubes have a guidewire that should be left in place until correct positioning is confirmed.

Confirmation of correct insertion

Auscultating over the epigastrium while air is injected through the NG tube ('whoosh test') is not considered reliable.

Confirmation by pH of aspirate

- Aspirate contents using a 60 mL enteral syringe.
- Check pH is ≤5.5 to confirm placement within the stomach.
- If no aspirate can be obtained inject air via the syringe to dislodge any debris and try to aspirate again.

Confirmation by chest X-ray

If still uncertain about the tip position, perform a chest X-ray to check for correct positioning, namely:

- The NG tube should bisect the carina (approximately level of T4).
- The NG tube should remain in the midline with the tip visible below the left hemidiaphragm.
- The person confirming placement should have appropriate competencies as per local hospital policy.
- If in doubt consult a radiologist but do not use the tube prior to confirmation of correct placement.
- On occasion, the chest X-ray may need to be repeated with injection of contrast to better delineate the tip position.

Fixation of tube

To stop displacement/removal the NG/NJ tube should be attached securely, usually with tape to the nose ± clips ± adhesive dressings on the cheek. A nasal bridle (a fixation tube going into one nostril and exiting from the other, guided by a magnet at the tip) can be used to deter removal by agitated patients.

Absolute or relative contraindications

Input from a specialist surgeon or gastroenterologist may be needed to determine whether nasal tube placement is safe/appropriate under high-risk circumstances. Placement can be performed endoscopically or by radiological screening to reduce risk. Insertion may need to be delayed until a severe coagulopathy is corrected. Orogastric or percutaneous tubes may be used in patients in whom a nasal approach is considered unsafe.

- Epistaxis.
- Tracheo-oesophageal fistula.
- Maxillofacial disorders/trauma/surgery.
- Base-of-skull fracture.
- Oesophageal or pharyngeal pouch or stricture or neoplasm.
- Actively bleeding oesophageal and/or gastric varices.
- Unstable cervical spine injuries.
- Significant coagulopathy.

Complications

- Epistaxis.
- Perforation.
- Rhinitis.
- Pharyngitis.
- Maxillary sinusitis.
- Oesophageal and/or gastric erosion/ulceration ± bleeding.
- Increased reflux.
- Patient discomfort.
- Dysphagia.
- Accidental placement in lung and feeding.

Further reading

➔ See Percutaneous gastrostomy & jejunostomy feeding tubes, p130; Enteral nutrition, p142; Vomiting/gastric stasis, p434.

Percutaneous gastrostomy & jejunostomy feeding tubes

These are percutaneous tubes placed through the anterior abdominal wall into the stomach (percutaneous gastrostomy), jejunum (percutaneous jejunostomy), or advanced from the stomach into the jejunum (percutaneous gastro-jejunostomy). The catheters can be placed under endoscopic (percutaneous gastrostomy (PEG) or jejunostomy (PEJ)) or radiological (fluoroscopic) (radiologically inserted gastrostomy) guidance. These tubes are primarily used for long-term feeding when the oral route cannot be utilized safely, if at all, or as an alternative to long-term NG tube feeding.

Different tubes can be employed. Loop (pigtail) catheters are inserted directly under fluoroscopic control using a Seldinger technique. Balloon or mushroom catheters are more durable and less prone to blockage or displacement. These have an inflatable balloon or mushroom-shaped tip, respectively, to aid tethering inside the lumen and reduce leakage of content outside the gut. All catheters require external attachment to the skin to reduce the risk of accidental removal/displacement.

Absolute contraindications to insertion include an uncorrectable coagulopathy or absence of a safe access route. Relative contraindications include unfavourable anatomy, gastric neoplasm, varices, massive ascites, and active peptic ulcer disease.

The patient should be fasted beforehand as leakage of some gastric/intestinal content is not unusual while a tract forms between gut and skin. Coagulopathy should be corrected pre-insertion, e.g. aiming for platelets $>50 \times 10^9$/L and international normalized ratio <1.5.

Instructions will be given by the endoscopist/radiologist regarding commencement of feed (usually between 4 and 24 h in the absence of complications) and sometimes to start with water before progressing to feed. They will also advise on tube removal if necessary in case of large ongoing leakage, uncorrectable obstruction, or significant infection.

The patient should be monitored for complications. Mild discomfort is expected for several hours to days after insertion. Worsening pain or features of peritonitis should be referred for surgical review. Most can be managed conservatively provided the tube remains correctly positioned within the stomach or jejunum. The site should be observed daily for infection or leakage.

Complications

- Bleeding.
- Displacement of tip outside gut lumen.
- Spillage of gut contents or feed into the peritoneum, potentially leading to peritonitis.
- Skin/soft tissue infection.

Further reading

See Nasogastric & nasojejunal tubes, p128; Enteral nutrition, p142.

Sengstaken-type or Minnesota tube

Used to manage oesophageal variceal haemorrhage that continues despite pharmacological ± per-endoscopic therapy.

The Sengstaken–Blakemore (SB) tube has a large-bore rubber tube containing two balloons (oesophageal and gastric) and gastric aspiration lumen. This device works usually by the gastric balloon alone compressing the varices at the cardia. Inflation of the oesophageal balloon is rarely necessary. A Minnesota tube has a fourth lumen enabling oesophageal aspiration (Figure 6.1).

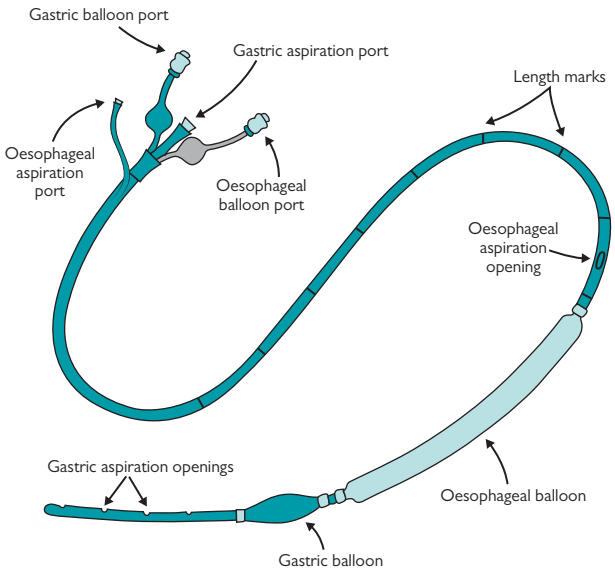

Fig. 6.1 The Minnesota tube.

Insertion technique

The tubes are usually kept in the fridge to stiffen for easier insertion.

1. The patient often requires airway protection with intubation, sedation, and mechanical ventilation prior to insertion.
2. Check balloons inflate properly before insertion. Check volumes with manufacturer's guidance (usually 200–300 mL for SB; up to 500 mL for a Minnesota tube). Check inflated balloon pressure and document. Lubricate end of tube.
3. Insert via mouth; may require direct laryngoscopy. Place to depth of 55–60 cm to ensure gastric balloon is in stomach prior to inflation.
4. Inflate gastric balloon with 50 mL aliquots water to the volume instructed by manufacturer. A small amount of radio-opaque contrast

may be added. Negligible resistance to inflation should be felt. If balloon pressure is >15 mmHg higher than the pre-insertion pressure the balloon may be in the oesophagus. Deflate, advance tube, and re-start. Clamp gastric balloon lumen.
5. Pull tube back until resistance is felt, i.e. gastric balloon is at the cardia, and note length at lips. Fix tube in place by applying countertraction at the mouth.
6. Perform X-ray to check satisfactory position of gastric balloon.
7. If bleeding continues (continued large aspirates from gastric or oesophageal lumens), inflate oesophageal balloon (~50 mL). This is rarely required and should not be inflated on its own.

Subsequent management

- The gastric balloon is usually kept inflated for 12–24 h and deflated prior to endoscopy ± sclerotherapy. Adequate traction on the tube should be tested hourly. The oesophageal lumen should be placed on continuous drainage while enteral nutrition and administration of drugs can be given via the gastric lumen.
- If the oesophageal balloon is used, deflate for 5–10 min every 1–2 h to reduce the risk of oesophageal pressure necrosis. Do not leave the oesophageal balloon inflated for >12 h after sclerotherapy.
- The tube may need to stay *in situ* for 2–3 days though periods of deflation should then be allowed.

Complications

- Haemorrhage—may occur on cuff deflation. Ensure balloon inflated and correct coagulopathy.
- Aspiration—ensure patient intubated, keep head up 35–45°.
- Perforation—avoid inflation of oesophageal balloon and ensure gastric balloon correctly placed.
- Ulceration/oesophageal necrosis—avoid prolonged inflation of balloon(s). In general do not leave inflated >36 h.
- Pain—ensure adequate sedation and analgesia.

Further reading

➔ See Upper gastrointestinal haemorrhage, p438; Bleeding varices, p440.

Upper gastrointestinal endoscopy

Oesophago-gastro-duodenoscopy (OGD) is performed identically in ventilated and non-ventilated patients. Additional sedation may be needed, especially if the patient is awake and/or agitated. A protected airway facilitates the procedure and also offers additional safety if the patient's conscious level is obtunded and there is a high risk of aspiration of gastric contents (blood if haemorrhaging, or food/liquid if ileus or obstruction is present).

Indications

- Investigation of upper gastrointestinal (GI) signs/symptoms, e.g. bleeding, pain, mass, obstruction.
- Therapeutic, e.g. sclerotherapy and/or banding for varices, local epinephrine injection or heat probe (thermocoagulation) for discrete bleeding points, e.g. in peptic ulcer base, removal of foreign body.
- Placement of NJ tube (when gastric atony prevents enteral feeding) or PEG or PEJ.
- Endoscopic retrograde cholangiopancreatography—for bile duct/pancreatic duct obstruction.

Complications

- Local trauma causing haemorrhage or perforation.
- Abdominal distension with gas, compromising respiratory function.
- Aspiration of gastric contents.

Contraindications/cautions

- Severe coagulopathy should be corrected.
- Caution with upper GI tract pathology as risk of perforation.

Procedure

Endoscopy should be performed by an experienced operator to minimize the duration and trauma of the procedure, and to minimize gaseous distension of the gut.

1. The patient is usually placed in a lateral position.
2. Increase fraction of inspired oxygen (FiO_2) and ventilator pressure alarm settings. Consider increasing sedation and adjusting ventilator mode.
3. Monitor electrocardiogram, pulse oximetry oxygen saturation (SpO_2), airway pressures, and haemodynamic variables throughout. If patient is on pressure support or pressure control ventilatory modes also monitor tidal volumes. The operator should cease the procedure, at least temporarily, if the patient becomes compromised.
4. At the end of the procedure the operator should aspirate as much air as possible out of the GI tract to decompress the abdomen, and re-site a NG tube which often becomes displaced.

Further reading

See Upper gastrointestinal haemorrhage, p438; Bleeding varices, p440.

Extracorporeal liver support

The metabolic, synthetic, detoxification, and excretory functions of the liver make the development of a device to support these complex roles challenging. Current management of acute liver failure or acute-on-chronic liver failure remains largely supportive until liver regeneration occurs, or as a bridge to transplantation.

Several extracorporeal liver assist devices (e.g. ELAD™) have been developed. Most utilize albumin dialysis, using fresh albumin to bind and remove toxins to reduce the risk of hepatic encephalopathy, hepatorenal syndrome, and/or cardiovascular failure. Other membranes/filters can be used to remove cytokines, endotoxins, and other pathogen- (PAMPs) or damage-associated molecular proteins (DAMPs).

Extracorporeal bioartificial liver devices containing hepatoma cell lines or hepatocytes remain experimental.

Single-pass albumin dialysis (SPAD)

Utilizes a standard renal replacement therapy (RRT) machine with dialysate containing albumin. Albumin-bound toxins are removed by diffusion. Large quantities of albumin are required. The optimal concentration of albumin, flow rates, and evidence of benefit remain unknown.

Molecular Adsorbent Recirculation System (MARS®)

Similar to SPAD, requiring a continuous RRT machine and albumin- rich dialysate. It also enables removal of water-soluble toxins. Consists of a blood circuit, albumin solution with an activated charcoal resin column, an anion-exchange membrane filter, and a dialysate circuit. Does not remove molecules >50 kDa in mass.

Fractionated plasma separation and adsorption system (FPSA) (Prometheus®)

Uses an albumin-permeable membrane and a high-flux haemodialysis circuit. The patient's filtered albumin is cleansed of bound toxins through a secondary circuit with resin and anion exchange adsorption matrices before being returned to the primary dialysis circuit. Albumin is not therefore required in the dialysate.

Cytosorb®

This extracorporeal cartridge is compatible with various extracorporeal blood-pump circuits. It contains polymer beads that remove hydrophobic molecules up to 55 kDa including cytokines, bilirubin, and myoglobin.

Further reading

Tandon R, Froghi S. 2021. 'Artificial liver support systems'. *J Gastroenterol Hepatol* 36:1164–79. doi: 10.1111/jgh.15255

'Interventional procedure overview of extracorporeal albumin dialysis for acute liver failure'. National Institute for Health and Care Excellence. Accessed June 2023. https://www.nice.org.uk/guidance/ipg316/documents/extracorporeal-albumin-dialysis-for-acute-liver-failure-interventional-procedures-overview2

See Continuous renal replacement therapy—techniques & indications, p116; Haemo(dia)filtration, p118; Other blood purification techniques, p124; Acute liver failure, p454; Hepatic encephalopathy, p456; Decompensated chronic liver failure, p458.

Chapter 7

Nutrition

Nutrition—use & indications

Malnutrition leads to an increased infection risk due to immune compromise, inability to wean/mobilize due to loss of muscle bulk and increased fatiguability, and poor wound healing (Table 7.1). Gut mucosal atrophy occurs within days of non-feeding and may compromise the ability to feed enterally.

Adequate nutritional support should, in general, be provided during critical illness. However, apart from very malnourished patients (body mass index (BMI) ≤15), no large trial evidence supports early versus delayed (e.g. up to 5–7 days) feeding, enteral (EN) versus parenteral nutrition (PN) routes, or hypocaloric versus normocaloric feeds in terms of stay or outcomes in general intensive care unit (ICU) patients. Improved outcomes from early nutritional support do exist for patients with trauma and burns. Enteral feed is also a gastric protectant. However, the patient should be resuscitated and stabilized before starting enteral feeding (other than, perhaps, small-volume 'trophic feeding') as gut hypoperfusion compromises the ability to absorb, and feeding may render the gut more ischaemic. Increasing abdominal distension, increasing intra-abdominal pressures, pain/discomfort, large gastric aspirates, and diarrhoea may suggest the need for a period of bowel rest or continued low-rate feeding, rather than persisting with feeding and addition of prokinetics.

Consider EN when swallowing is inadequate or impossible but gut function is otherwise intact. PN is indicated when the gut cannot be used to provide adequate nutritional support, e.g. obstruction, ileus, high small bowel fistula, or malabsorption. PN may be used exclusively or to supplement EN where indicated.

Calorie requirements

Optimal day-to-day intake is not known for individual patients, particularly in the early phase of acute critical illness. Various formulae estimate basal metabolic rate but are inaccurate in critical illness. Metabolic rate can be measured by indirect calorimetry but this is not commonplace in clinical practice. In the absence of indirect calorimetry, predictive or weight-based equations are generally used. As very high caloric intake is associated with worse outcomes, less (~70% of resting energy expenditure, or estimated requirements) is initially recommended in the acute phase especially if there is a period of prolonged starvation or the patient is very underweight because of the perceived risk of refeeding syndrome. Burn-injured patients generally receive more calories in the recovery phase.

Table 7.1 Consequences of malnutrition

Underfeeding	Overfeeding
Loss of muscle mass	Increased VO_2
Reduced respiratory function	Increased VCO_2
Reduced immune function	Hyperglycaemia
Poor wound healing	Fatty infiltration of liver
Gut mucosal atrophy	
Reduced protein synthesis	

VCO_2 = volume of carbon dioxide produced; VO_2 = volume of oxygen consumed.

Nitrogen requirements

Nitrogen excretion can be calculated in the absence of renal failure using 24 h urea excretion.

$$\text{Nitrogen } (\text{g}/24\text{ h}) = 2 + \text{urinary urea } (\text{mmol}/24\text{ h}) \times 0.028$$

As with most formulae, this method lacks accuracy and does not account for other losses in critically ill patients. Multiple studies have looked at optimal protein requirements in critical illness with varying results. A range of 1.2–2.0 g/kg/day is documented. Depending on pre-morbid status, BMI, level of sarcopenia, and admission reason (e.g. trauma/burns), this can be of actual or adjusted weight.

Other requirements

Most long-term ICU patients require folic acid and vitamin supplementation. Trace elements are usually supplemented in parenteral formulae but are not generally required with EN unless the patient has a chronic deficiency.

Further reading

See Enteral nutrition, p142; Parenteral nutrition, p144; Indirect calorimetry, p146; Refeeding syndrome, p148.

Enteral nutrition

Routes include nasogastric, nasojejunal, gastrostomy, and jejunostomy. Nasal tube feeding should be via a soft, fine-bore tube to aid comfort and avoid ulceration of nose or oesophagus. Prolonged EN may be accomplished via a percutaneous or radiologically inserted gastrostomy or jejunostomy. EN is preferred over PN if oral intake is not possible as it maintains structural integrity of the gut, improves bowel adaptation after resection, and reduces infection risk. However, no outcome benefit has been shown comparing enteral and parenteral routes.

Feed composition

Most patients tolerate iso-osmolar, non-lactose feed. Carbohydrates are provided as sucrose or glucose polymers; protein as whole protein or oligopeptides (may be better absorbed than free amino acids in 'elemental' feeds); fats as medium-chain or long-chain triglycerides. Medium-chain triglycerides are better absorbed. Standard feed is formulated at 1 kcal/mL. Special feeds are available, e.g. high fibre, high protein-calorie, restricted salt, high fat, or concentrated (1.5 or 2 kcal/mL) for fluid restriction. Immune-enhanced feeds, e.g. glutamine-enriched or Impact® (feed supplemented with nucleotides, arginine, and fish oil) have failed to demonstrate outcome benefit.

Management of enteral nutrition

No optimal regimen has been identified. Below is our approach.

1. Start with low rate (from 10 mL/h) polymeric standard feed unless otherwise indicated. Starter regimens incorporating dilute feed are not necessary.
2. After 4 h of low-rate feeding, stop feed for 30 min prior to aspiration of the stomach. Aspirate volumes <200 mL can be accepted as evidence of gastric emptying. If so, increase the infusion rate.
3. Repeat this process until target feed rate is achieved.
4. Thereafter, aspiration of the stomach can be reduced to 8-hrly.
5. If gastric aspirate volumes remain >200 mL, continue feeding at prior rate and do not increase infusion rate. Consider bowel rest If aspirates remain high (especially if abdominal distension/discomfort increases), nasoduodenal/jejunal (if ileus is considered to be proximal), or parenteral feeding. Prokinetics such as metoclopramide and erythromycin (motilin agonist) are sometimes used though utility is debatable. Continuing to feed gut-intolerant patients has been associated with worse outcomes.

Complications

- Tube misplacement: tracheobronchial, nasopharyngeal perforation, intracranial penetration (basal skull fracture), oesophageal perforation.
- Reflux and pulmonary aspiration.
- Nausea and vomiting.
- Abdominal distension is occasionally reported with a tender, distended abdomen ± an increasing metabolic acidosis.

- Refeeding syndrome.
- Diarrhoea: large volume, bolus feeding, high osmolality, infection, lactose intolerance, antibiotic therapy, high-fat content.
- Constipation.
- Metabolic: dehydration, hyperglycaemia, electrolyte imbalance.

Further reading

Atkinson S, Sieffert E, Bihari D. 1998. 'A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill'. *Crit Care Med* 26: pp1164–72. doi: 10.1097/00003246-199807000-00013

➔ See Nutrition—use & indications, p140; Refeeding syndrome, p148; Antiemetics & gut motility agents, p308; Vomiting/gastric stasis, p434; Diarrhoea & constipation, p436.

Parenteral nutrition

Feed composition

The majority of PN currently used is based on commercially prepared 'all-in-one' bags containing specific amounts of amino acids, a lipid emulsion, glucose, electrolytes, and water. Carbohydrate is normally provided as concentrated glucose. Calories are usually given as combination lipids including fish oil (30–40% of total). The nitrogen source is synthetic with crystalline L-amino acids that should contain appropriate quantities of all essential and most non-essential amino acids. Carbohydrate, lipid, and nitrogen sources are usually mixed into a large bag in a sterile pharmacy unit, or as multi-chamber bags available on critical care units. Vitamins, trace elements, and appropriate electrolyte concentrations can be achieved within the same infusion bag, thus avoiding multiple connections. Volume, protein, and calorie content of the feed should be determined on a daily basis in conjunction with the dietitian.

Choice of parenteral feeding route

Central venous catheter (CVC)

A dedicated catheter (or lumen of a multi-lumen catheter) is placed under sterile conditions. For long-term feeding a subcutaneous tunnel is often used to separate skin and vein entry sites. This reduces risk of infection and identifies the special purpose of the catheter. Ideally, blood samples should not be taken nor other injections or infusions given via the feeding lumen. The central venous route allows infusion of hyperosmolar solutions, providing an adequate energy intake in reduced fluid volumes.

Peripherally inserted central catheter (PICC)

PICCs are increasingly used for long-term administration of PN as the infection risk is reduced.

Peripheral venous catheter (PVC)

PN via the peripheral route requires a solution with osmolality <800 mOsm/kg. Either the volume must be increased or the energy content (particularly from carbohydrate) reduced. Peripheral cannula sites must be changed frequently due to an increased infection risk.

Complications

- Catheter related—misplacement, infection, thromboembolism.
- Fluid excess.
- Hyperosmolar, hyperglycaemic state.
- Electrolyte imbalance.
- Refeeding syndrome.
- Metabolic acidosis—hyperchloraemia, metabolism of cationic amino acids.
- Rebound hypoglycaemia (from high endogenous insulin levels).
- Vitamin deficiency—folate (pancytopenia), thiamine (encephalopathy, neuropathy, heart failure), vitamin K (hypoprothrombinaemia).
- vitamin excess—A (dermatitis), D (hypercalcaemia).
- Fatty liver.

Further reading

➔ See Nutrition—use & indications, p140; Indirect calorimetry, p146; Refeeding syndrome, p148; Electrolyte management, p512; Metabolic acidosis, p534; Hyperglycaemia, p538.

Indirect calorimetry

Calorimetry refers to the measurement of energy production. Direct calorimetry measures heat production in a sealed chamber and so is impractical for patients. Indirect calorimetry measures the rate of oxidation of metabolic fuels by measuring the volume of O_2 consumed and CO_2 produced. The ratio of CO_2 production to O_2 utilization (respiratory exchange ratio (RER)) estimates the whole body respiratory quotient (RQ), i.e. which fuels are being utilized (see below). The RER depends on the fuel or combination of fuels being utilized. In health, fat and carbohydrate are predominantly utilized with an RQ of ~0.8 but this can alter in critical illness due to increased metabolism of lipids, amino acids, ketones, and lactate.

The RER is a whole-body measure whereas different organs utilize different fuel sources and adapt differently under the stress of critical illness. For example, the healthy heart mainly uses fatty acids but increases utilization of glucose, lactate, and ketones in disease states. The healthy brain mainly uses glucose but also metabolizes ketones and lactate when injured. Whole body RER cannot therefore be extrapolated to individual organs.

Technique of indirect calorimetry

Inspiratory and mixed expiratory gases must be sampled. O_2 concentration is measured by a fuel cell sensor or fast response paramagnetic sensor while CO_2 is usually measured by infrared absorption. Sensors may need to be calibrated to known concentrations of standard gases. Measurements are usually made at ambient temperature, pressure, and humidity prior to conversion to standard temperature, pressure, and humidity. Table 7.2 lists factors that may contribute to erroneous measurement.

To calculate metabolic rate (energy expenditure), inspired and expired minute volumes are required. It is common for one minute volume to be measured and the other derived from a Haldane transformation. The nitrogen concentration is assumed to be the concentration of gas that is neither O_2 nor CO_2.

$$V_I = V_E \times \frac{N_E}{N_I}$$

Calculation of energy expenditure utilizes a modified Weir formula:

$$\text{Energy expenditure} = \left(3.94\ VO_2 + 1.11\ VCO_2\right) \times 1.44$$

Table 7.2 Measurement errors associated with indirect calorimetry

Underestimates VCO_2	H^+ ion loss, haemodialysis, renal replacement therapy
Overestimates VCO_2	Hyperventilation, bicarbonate infusion
Underestimates VO_2	Free radical production, unmeasured O_2 supply
FiO_2 >0.6	Small difference between inspired and expired O_2
Loss of volume	Circuit leaks, bronchopleural fistula

Use of indirect calorimetry

Can be used to match nutritional intake to energy expenditure. Feeding critically ill patients appropriately, avoiding both underfeeding and overfeeding, appears a rational aim. Limited studies suggest outcome benefit when nutritional needs are tailored to metabolic requirements. However, results obtained from different indirect calorimeters are often quite variable and there are no conclusive randomized controlled trials (RCTs) to demonstrate outcome benefit.

Indirect calorimetry may also be used to assess work of breathing by assessing the change in VO_2 during weaning from mechanical ventilation. The VO_2 change may also be used to assess appropriate levels of sedation and analgesia.

Whole body RER depends on the fuel or combination of fuels being utilized (Table 7.3). Normally, a combination of fat and carbohydrate are utilized with a RQ of ~0.8.

Table 7.3 Respiratory quotients for various metabolic fuels

Ketones	0.63
Fat	0.71
Protein	0.80
Carbohydrate	1.00

Further reading

Oshima T, Delsoglio M, Dupertuis Y, et al. 2020 'The clinical evaluation of the new indirect calorimeter developed by the ICALIC project'. *Clin Nutr* 39: pp3105–11. doi: 10.1016/j.clnu.2020.01.017

Singer P, De Waele E, Sanchez C, et al. 2021. 'TICACOS international: a multi-center, randomized, prospective controlled study comparing tight calorie control versus Liberal calorie administration study'. *Clin Nutr* 40: pp380–7. doi: 10.1016/j.clnu.2020.05.024

See Nutrition—use & indications, p140; Enteral nutrition, p142; Parenteral nutrition, p144.

Refeeding syndrome

Refeeding syndrome can affect patients who are severely malnourished and/or have starved for prolonged periods. Fluid and metabolite shifts can result in significant electrolyte disturbances such as hypocalcaemia, hypomagnesaemia and hypophosphataemia, fluid overload. Heart (arrhythmias, failure), lung, neurological (seizures) and haematological complications are occasionally seen. This may be fatal in extreme cases so cautious re-feeding with very close monitoring of blood chemistry and fluid balance is advised in such patients. In addition, multi-vitamins, especially thiamine, should be given and energy expenditure restricted with limited mobilization.

Rationale

During fasting the body predominantly uses fat and protein as its main energy substrates. Insulin secretion is suppressed and glucagon secretion elevated. On refeeding, insulin secretion rises with an increase in synthesis of fat, protein and glycogen, a rise in basal metabolic rate and salt and water retention. There are compartmental shifts of metabolites resulting in falls in plasma potassium, magnesium, calcium and phosphate, and depletion of vitamins such as thiamine.

It is postulated that intracellular ATP levels may be depleted with effects on muscle weakness, immune function and infection risk, and low levels of 2,3 DPG affecting O_2 release from erythrocytes. However, this is largely associative and may simply reflect the degree of unwellness of the patient as phosphate levels often drop acutely in critical illness. Plasma levels account for 1% of total body phosphate. What constitutes hypophosphataemia is uncertain, with definitions ranging from as low as 0.32 mmol/L to as high as 1 mmol/L. Alcoholics and patients on dialysis programmes may have chronically severely low levels without obvious problem. Studies showing outcome improvement through correcting hypophosphataemia are lacking.

Whether catabolic ICU patients behave similarly to otherwise healthy patients with refeeding syndrome is unknown. Outcome studies in ICU populations show widely inconsistent outcomes. The largest trial to date involved 339 ICU patients who developed hypophosphataemia (<0.65 mmol/L) within 72 h of initiating feed as a proxy for refeeding syndrome. They were randomized to receive either standard nutritional support or protocolized caloric restriction (20 kcal/h for 2 days with a gradual increase thereafter, adjusted according to serum phosphate levels). No significant differences were noted between groups in duration of mechanical ventilation, performance status or length of ICU stay. Hospital stay was longer in the calorie restriction group. At 90 days mortality was lower in the calorie restriction group though quality of life scores were worse.

An RCT of 111 adolescent and young adult patients with anorexia nervosa compared higher calorie feeding (starting at 2000 kcal/day and increasing by 200 kcal/day) against lower-calorie refeeding (starting at 1400 kcal/day and increasing by 200 kcal every other day) resulted in a median 4-day reduction in hospital stay and no difference in electrolyte abnormalities or other complications.

Further reading

Doig G, Simpson F, Heighes P, et al. 2015. '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* 3: pp943–52. doi: 10.1016/S2213-2600(15)00418-X

Koekkoek W, Van Zanten A. 2018. 'Is refeeding syndrome relevant for critically ill patients?" *Curr Opin Clin Nutr Metab Care* 21: pp130–7. doi: 10.1097/MCO.0000000000000449

Garber A, Cheng J, Accurso E, et al. 2021. 'Short-term outcomes of the study of refeeding to optimize inpatient gains for patients with anorexia nervosa'. *JAMA Pediatr* 175: pp19–27. doi: 10.1001/jamapediatrics.2020.3359

➲ See Nutrition—use & indications, p140; Enteral nutrition, p142; Parenteral nutrition, p144; Electrolyte management, p512; Hypocalcaemia, p528; Hypomagnesaemia, p524; Hypophosphataemia, p530.

Chapter 8

Wound & pressure area management

Wound management principles

Wound management attempts to promote healing, prevent contamination and breakdown, and reduce pain and discomfort.

A wound heals through the phases of haemostasis, inflammation, granulation, and maturation. The first two processes arrest bleeding and help remove contamination.

- Granulation involves rebuilding of the tissues, angiogenesis, contraction, and epithelialization. This process normally takes about 21 days but may be delayed by age, infection, dehydration, or poor nutrition.
- Maturation may take several years and involves remodelling of the dermis to increase the strength of the healed wound.

A wound that fails to complete these processes may become chronic. It is important to keep the wound warm and moist since all human cells (with the exception of dead keratinized superficial skin cells) require moisture to survive, and warmth to grow and divide. An exudate provides the best environment for healing by supporting cells involved in wound repair with nutrients. Although angiogenesis is increased in a low-oxygen environment (e.g. under occlusive dressings), large randomized trials show both positive and negative outcomes on the incidence of postoperative wound infection through administration of supplemental oxygen.

Wound cleansing

Wounds should be cleaned by irrigation with isotonic saline. Soaps irritate the wound but may be useful on the surrounding skin. Iodine and peroxide both irritate the wound, are unnecessary and best avoided.

Wound infection

The hallmarks of wound infection are:

- Pain.
- Redness.
- Increased warmth.
- Tenderness.
- Oedema.
- Purulent discharge.
- Foul odour.
- Systemic or spreading signs of infection (e.g. cellulitis)

The wound should be swabbed and any pus collected for microbiological analysis prior to commencing antibiotics (if indicated). If concerned, request from the surgical team ± wound care nurse specialists. Some sutures may need to be removed to facilitate external drainage of pus or fluid discharge. Local treatments may be sufficient e.g. silver preparations, topical antibiotic (e.g. flamazine). The latter should only be used for short-term treatment in mild cases. Surgical debridement may be needed.

Pressure sores

Pressure sores occur due to compression of tissue between bone and the support surface or shearing forces, friction, and maceration of tissues against the support surface. Pressure sores should be prevented by regular turning, skin care (e.g. barrier cream), and use of special high-specification foam mattresses or a dynamic support surface, e.g. alternating pressure

mattress. Any patient can develop pressure sores. Recognized risk factors include old age, immobility, malnutrition, decreased sensation, severe obesity, diabetes, and acute and/or chronic circulatory deficiency.

A developed pressure sore requires cleansing, debridement of eschar or necrotic tissue, staging (Table 8.1), and packing of any crater. Packing should occlude the ulcer but should be loose to avoid adding to pressure damage. Dressings (e.g. film, gauze, gel, foam) should keep the ulcer moist to promote healing.

Deep ulcers over bony prominences should raise the possibility of underlying osteomyelitis.

Table 8.1 Staging of pressure injury

Stage 1	Intact skin with a localized area of non-blanchable erythema
Stage 2	Partial thickness skin loss with exposed dermis
Stage 3	Full thickness skin loss with visible adipose and granulation tissue and rolled skin edges
Stage 4	Full thickness skin and tissue loss with exposed fascia, muscle, tendon, ligament, cartilage, or bone in the ulcer
Unstageable	Ulcer bed cannot be visualized due to slough or eschar

Modified from the Revised National Pressure Ulcer Advisory Panel, November 2016.

Photographs

The progress of wounds and/or pressure sores can be monitored by taking repeated medical photographs (with prior patient consent). Images should be stored in the patient's case records.

Further reading

Edsberg L, Black J, Goldberg M, et al. 2016. 'Revised National Pressure Ulcer Advisory Panel Pressure Injury Staging System'. *J Wound Ostomy Continence Nurs* 43: pp585–97. doi: 10.1097/WON.0000000000000281

'Pressure ulcers'. National Institute for Health and Care Excellence (NICE). March 2023. https://cks.nice.org.uk/topics/pressure-ulcers/

See Dressing techniques, p154; Special support surfaces, p156.

Dressing techniques

Wound dressings serve to reduce pain, protect the wound from further injury and infection, and reduce moisture loss. Dressings should be non-adherent, sterile, and cover the wound completely. Adherent dressings delay wound healing. When dressings are applied to wounds an aseptic technique must be used.

Bio-occlusive dressings

These allow air and water vapour to permeate thus accelerating healing, are transparent to allow wound assessment, and are waterproof.

Calcium alginate

Calcium exchanges with sodium from the wound to convert exudates to a gel. This reduces moisture loss. They are not effective for dry wounds since they depend on absorption of exudates to be active.

Foam dressing

Foam dressings absorb excessive exudates while allowing air and vapour permeation to accelerate healing. They require absorption of exudates to be effective. They are thermally insulating and non-adherent.

Hydrocolloids

Hydrocolloid dressings provide slow absorption of exudates to create a soft, non-adherent gel which occludes the wound and retains moisture. They are effective when exudates are low volume. They should not be used in infected wounds as growth of anaerobes may be encouraged by their occlusive properties.

Hydrogels

Hydrogels have hydrophilic sites to enable absorption of excess exudates. They retain moisture.

Vacuum-assisted closure (VAC)

A foam dressing is placed in the ulcer absorbing excessive exudates. The ulcer is sealed with an adhesive drape and negative pressure is applied for up to 24 h per day. The VAC dressing reduces oedema and improves local blood supply while removing surface debris and exudate. Intermittent treatment may be more effective than continuous. Use of VAC dressings are advantageous in perineal pressure sores because the vacuum helps keep the dressing in place.

Properties of wound dressings

- Maintain warmth.
- Maintain moisture.
- Remove exudates.
- Allow vapour and gas permeation.
- Minimize contamination.
- Non-adherent.

Further reading

See Wound management principles, p152.

Special support surfaces

The use of special support surfaces attempts to reduce the pressure at the contacting skin surface to a level below capillary occlusion pressure. In most cases it is sufficient to use postural changes to minimize the time the support surface contacts with any one area of skin.

Factors suggesting need for special support surfaces

- Patients with severely restricted mobility due to external traction or cardiorespiratory instability cannot be turned frequently, if at all.
- Patients with decreased skin integrity, e.g. burns, pressure sores already present, chronic corticosteroid use, diabetes mellitus.
- Patients on vasoactive drug infusions and/or poor tissue perfusion.

Types of special support surface

High-specification foam mattress

These are superior to standard-specification foam mattresses in redistributing body pressure and reducing the incidence of pressure sores. They relieve pressure via better patient immersion and envelopment while still enabling changes in patient position.

Air mattress

This mattress either replaces or is placed on top of a standard hospital bed mattress. Although providing minimum reduction in contact pressure, they are superior to standard foam mattresses.

Dynamic support mattress

These include alternating pressure mattresses, low air loss beds, and air-fluidized beds:

- Alternating pressure mattress—these mattresses contain lateral air cells that alternately expand and contract, relieving and redistributing pressure through a dynamic lying surface.
- Low air loss bed—these purpose-built, pressure-relieving beds allow easier patient mobility than other support surfaces. Contact pressure may still be higher than capillary occlusion pressure so positioning is still required. Patients who are haemodynamically unstable should be considered for a low air loss bed, particularly if receiving vasoconstrictor drugs. The presence of pressure sores with intact skin is an indication to consider a low air loss bed.
- Air-fluidized bed—this is the only support surface that consistently lowers contact pressure to below capillary occlusion pressure. Consequently, most benefit is seen in patients with severe cardiorespiratory instability who cannot be turned, and in those with pressure sores and broken skin. The additional ability to control temperature of the immediate environment is advantageous in hypothermic patients and those with large surface area burns. Any exudate from the skin is adsorbed into the silicone beads on which the patient floats. This drying effect is particularly useful in major burns (although this must be taken into account for fluid replacement therapy). The air fluidized bed also has a role in pain relief.
- Rotation therapy beds—rotation therapy beds continuously change the pressure with the contacting surface by lateral turning to each side. This reduces shear and minimizes pain and discomfort associated with manual repositioning. They may also facilitate chest drainage.

Extravasation injuries

Extravasation may occur from either central or peripheral venous catheters. As these injuries occur sporadically there is no consensus on management, but early recognition is key to minimizing tissue injury.

The stage of injury and the vesicant's mechanism of tissue injury dictate subsequent management.

Mechanism of injury

- Cytotoxicity with concentration-dependent toxicity, e.g. chemotherapeutics.
- Vasoconstriction, e.g. catecholamines, calcium, large fluid volumes causing mechanical compression.
- pH (fluid pH <5 or >9), e.g. amiodarone, aciclovir, gentamicin, vancomycin, phenytoin, 5% glucose.
- Osmolarity (infusion osmolality <112 or >900 mOsm/L), e.g. phosphate, 10% calcium chloride.
- Absorption-refractory—relates to toxicity from delayed absorption, e.g. lipids, propofol.

Management

No strong evidence base is available to determine optimal therapy. The following are recommendations but local guidelines may differ.

- The infusion site of at-risk patients should be frequently monitored, e.g. when peripheral access is poor, use of peripheral vasopressors.
- Small volume extravasation with less potent vesicants are likely to cause mild injury whereas more potent vesicants and/or larger volumes often cause severe complications with skin and soft tissue necrosis and breakdown.
- For severe injuries, time is of the essence and a surgical team (preferably plastic surgery) should be rapidly involved.
- For mild injury, remove cannula, elevate limb, apply warm or cold compresses. Warm compresses are used for refractory vasoconstricting, pH- or osmolarity-mediated, and absorption injuries to 'disperse and absorb'. Cold compresses are used to 'localize and limit' vesicant spread, e.g. with most cytotoxics, valproate. Consider antidote if no improvement after 30 min.
- For severe injury:
  - initially leave cannula in place, attempt to aspirate as much fluid as possible, then remove cannula unless needed to administer antidote
  - apply warm/cold compresses as above
  - elevate limb; give local antidote promptly (within 30–60 min) as appropriate.
- May require urgent decompression if tissue swelling is tense/skin blanched—either saline flush or open incision and irrigation.
- For pH, osmolarity, and absorption-refractory extravasations, dilute through absorption and dispersal, using hyaluronidase to break down local connective tissue. Animal studies show that best results are obtained if given within 1 h.

- For vasopressor extravasations use an intradermal vasodilator such as phentolamine, terbutaline, or topical glyceryl trinitrate. Give at five multiple sites around the periphery of the blanching and repeat every 30–60 min as needed.

Further reading

See Wound management principles, p152; Dressing techniques, p154.

Chapter 9

Respiratory monitoring

Pulse oximetry

Continuous non-invasive monitoring of arterial oxygen (O_2) saturation is achieved by placing a probe emitting red and near-infrared light over a pulse on a digit, earlobe, cheek, or bridge of the nose. May be affected by skin pigmentation, high bilirubin, or profound anaemia.

Physics

Blood colour varies with O_2 saturation due to the optical properties of the haem moiety. As haemoglobin gives up O_2, it becomes less permeable to red light and takes on a blue tint. Saturation is determined spectrophotometrically by measuring light adsorption at specific wavelengths (650 and 940 nm) to permit the relative quantities of reduced and oxyhaemoglobin (oxyHb) to be calculated. The arterial pulse is used to provide timepoints to allow subtraction of the constant absorption of light by tissue and venous blood. The accuracy of pulse oximetry is ±2% at values above 70% arterial oxygen saturation (SaO_2).

Indications

- Continuous monitoring of SaO_2.

Cautions

- As only two wavelengths are used, pulse oximetry measures functional rather than fractional oxyHb saturation. Erroneous readings may be given with carboxyhaemoglobin (COHb; falsely high), methaemoglobin (metHb: gives fixed values of ~85% regardless of the metHb level), and skin pigmentation (falsely high in >10% of dark-skinned people).
- The reading may be lost or affected by poor peripheral perfusion, intense vasoconstriction, motion artefact, and high levels of ambient lighting.
- Erroneous signals may be produced by significant venous pulsation from tricuspid regurgitation or venous congestion. Venous pulsatility accounts for differences between ear and finger pulse oximetry oxygen saturation (SpO_2).
- Ensure a good LED signal indicator or a pulse waveform (if available) is seen on the monitor.
- Nail varnish and vital dyes (e.g. methylthioninium chloride (methylene blue), indocyanine green) may affect SpO_2 readings.

Further reading

Sjoding M, Dickson R, Iwashyna T, et al. 2020. 'Racial bias in pulse oximetry measurement'. *N Engl J Med* 383: pp2477–8. doi:10.1056/NEJMc2029240

Burnett G, Stannard B, Wax D, et al. 2022. 'Self-reported race/ethnicity and intraoperative occult hypoxemia: a retrospective cohort study'. *Anesthesiology* 136: pp688–96. doi: 10.1097/ALN.0000000000004153

➲ See Oxygen therapy, p40; Ventilatory support—indications, p48; Invasive ventilation—adjustments, p54; Vasopressors, p290.

CO_2 monitoring

Capnography

Respiratory gases are sampled continuously by a rapid response device attached to (sidestream sampling) or within (mainstream sampling) the breathing circuit. Carbon dioxide (CO_2) tension is usually measured by infrared absorption. It should be used during elective intubation to confirm tracheal placement, and continuously monitored in a mechanically ventilated patient to rapidly identify airway obstruction or tube displacement.

The capnogram

The CO_2 concentration of exhaled gas consists of four phases (Figure 9.1). The presence of significant concentrations of CO_2 in phase 1 implies rebreathing of exhaled gas, e.g. inadequate flow of fresh gas into a rebreathe bag. The slope of phase 3 depends on the rate of alveolar gas exchange. A steep slope may indicate ventilation–perfusion mismatch since alveoli that are poorly ventilated but well perfused discharge late in the respiratory cycle. A steep slope is seen in patients with significant auto-(intrinsic) positive end-expiratory pressure (PEEP).

Colorimetric devices

These small devices fit onto an endotracheal tube or the ventilator circuit and respond rapidly to changes in CO_2 (up to 60 breaths/min). The change in pH produced by different CO_2 concentrations in solution changes the colour of an indicator. These devices can be affected by excessive humidity and generally only work in the range 0–4% CO_2. They are useful to confirm tracheal intubation during cardiac arrest and while transferring patients.

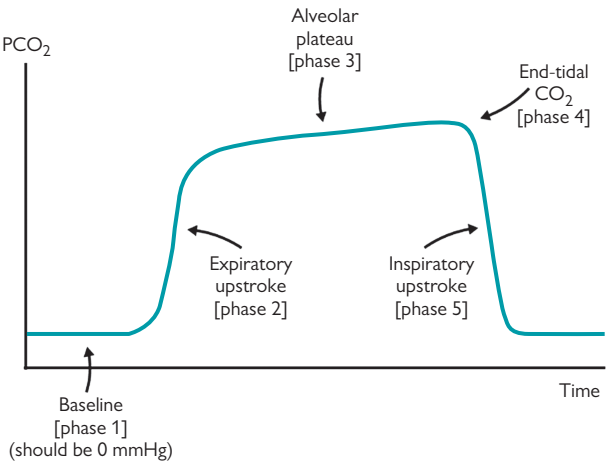

Fig. 9.1 The components of the normal capnogram.

End-tidal partial pressure of CO_2 (PCO_2)

End-tidal PCO_2 approximates to arterial partial pressure of CO_2 ($PaCO_2$) in patients with normal lung function. In intensive care unit patients, pulmonary function is often abnormal, thus end-tidal PCO_2 is less reliable. Large differences may represent an increased dead space to tidal volume (V_T) ratio, poor pulmonary perfusion, or intrapulmonary shunting. A progressive rise in end-tidal PCO_2 may represent hypoventilation, airway obstruction, or increased CO_2 production due to an increased metabolic rate. End-tidal PCO_2 falls with hyperventilation and in low cardiac output states. It is absent with ventilator disconnection and during cardiac arrest, but rises with effective cardiopulmonary resuscitation or restoration of a spontaneous circulation.

Dead space to tidal volume ratio

The arterial to end-tidal PCO_2 difference may be used to calculate the physiological dead space (V_D) to V_T ratio via the Bohr equation:

$$\frac{V_D}{V_T} = \left(\frac{PaCO_2 - PetCO_2}{PaCO_2} \right)$$

In health, a value between 30% and 45% should be expected.

Phase 1

During early exhalation, both anatomical and sampling device dead space gas are sampled. There is negligible CO_2 in phase 1.

Phase 2

As alveolar gas begins to be sampled, CO_2 concentration rapidly rises.

Phase 3

Phase 3—the alveolar plateau—represents the CO_2 concentration in mixed expired alveolar gas. There is normally a slight increase in PCO_2 during phase 3 as alveolar gas exchange continues during expiration. Airway obstruction or a high rate of CO_2 production will increase the slope. End-tidal PCO_2 is lower than the PCO_2 of ideal alveolar gas since the sampled exhaled gas is mixed with alveolar dead space gas.

Phase 4

As inspiration begins, there is a rapid fall in sample PCO_2.

Further reading

➲ See Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Invasive ventilation—adjustments, p54; Tracheotomy—indications & technique, p86; Blood gas analysis, p174.

Pulmonary function tests

Pulmonary function tests rarely impact directly upon clinical management of the critically ill, particularly if the patient has to be moved to a laboratory. Table 9.1 shows clinically relevant tests and Figure 9.2 describes lung volumes and capacities.

- Alveolar–arterial oxygen difference (A–aDO_2) is <2 kPa in youth and <3.3 kPa in old age.
- Normal V_D/V_T is <30%.
- Shunt (the proportion of blood shunted past poorly ventilated alveoli (Q_S)) compared to total lung blood flow (Q_T) is normally <15%.

Table 9.1 Clinically relevant tests

Measurement	Test	Common clinical use
PaO_2, SaO_2, $PaCO_2$	Arterial blood gases	
SpO_2	Pulse oximetry	
End-tidal PCO_2	Capnography	
VC, tidal volume	Spirometry, electronic flowmetry	Serial measurement of borderline function (VC <10–15 mL/kg) e.g. Guillain–Barré syndrome
Peak expiratory flow rate	Wright peak flow meter	(Spontaneous ventilation) asthma
FEV_1, FVC	Spirometry, electronic flowmetry	(Spontaneous ventilation) asthma, obstructive/ restrictive disease
Lung/chest wall compliance	The change in pressure litre increase in volume above FRC	Ventilator adjustments, monitoring disease progression
Flow–volume loop, pressure–volume loop	Pneumotachograph, manometry	Ventilator adjustments

FEV_1 = forced expired volume in 1 s; FRC = functional residual capacity; FVC = forced vital capacity; VC = vital capacity.

Equations

Alveolar gas equation

$$P_AO_2 = (FIO_2 \times 94.8) - \left(\frac{PaCO_2}{RQ}\right)$$

Respiratory quotient (RQ) is often approximated to 0.8. FiO_2 = fraction of inspired O_2.

Alveolar–arterial oxygen difference

$$A - aDO_2 = (FiO_2 \times 94.8) - (PaCO_2 / RQ) - PaO_2$$

Dead space to tidal volume ratio (Bohr equation)

$$\frac{V_D}{V_T} = \left(\frac{PaCO_2 - PetCO_2}{PaCO_2} \right)$$

Shunt equation

$$\frac{Q_S}{Q_T} = \left(\frac{CcO_2 - CaO_2}{CcO_2 - CvO_2} \right)$$

CcO_2 = end-capillary O_2 content, a = arterial, v = mixed venous.

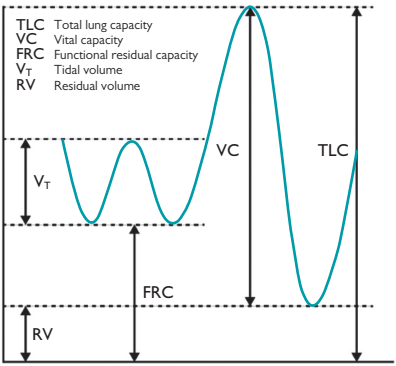

Fig. 9.2 Lung volumes and capacities.

Further reading

See Pulse oximetry, p162; CO_2 monitoring, p164.

Volume–pressure relationship

This is determined by the compliance of lungs and chest wall. The inspiratory volume–pressure relationship has three components (Figure 9.3):

- An initial rise in pressure with no significant volume change.
- A linear increase in volume as pressure increases (the slope of which represents respiratory system compliance).
- A further period of pressure increase with no volume increase.

These three phases are separated by two inflection points, the lower representing the opening pressure of the system after flow resistance has been overcome in smaller airways, and the upper approximating to total lung capacity. The expiratory pressure–volume relationship should normally approximate the inspiratory curve, returning to FRC. In patients with small airway collapse, separation of the inspiratory and expiratory curves occurs (hysteresis) as gas is trapped in smaller airways at the end of expiration.

Dynamic measurement

A pressure–volume loop can be viewed on most modern mechanical ventilators. A square wave inspiratory waveform (constant flow) and no inspiratory pause are necessary for waveform interpretation.

Static measurement

Small incremental lung volumes (200 mL) are delivered with a calibrated syringe. The pressure measurement after each increment is taken under zero flow conditions allowing construction of a pressure–volume curve. A quasi-static curve can be constructed by setting incremental tidal volumes (e.g. between 100 and 1000 mL) for successive ventilator breaths and measuring pressure during an inspiratory pause.

Use of volume–pressure curves

Since respiratory muscle activity can alter intrathoracic pressure, the volume–pressure curve is more easily obtained in the relaxed, fully ventilated patient. Both static and dynamic respiratory system compliance can be determined as the slope of the linear portion of the curve, i.e. where

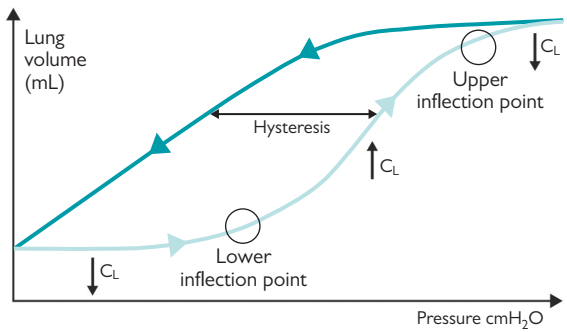

Fig. 9.3 Volume–pressure curve. C_L = compliance.

incremental pressure inflates the lungs. Below the lower inflection point the small airways are closed and expiration does not reach FRC. The lower inflection point therefore represents the appropriate setting for external PEEP to avoid gas trapping. Above the upper inflection point the lungs cannot inflate further. The upper inflection point therefore represents the maximum setting for peak airway pressure.

Compliance: calculations

$$\text{Lung compliance (L/cm}H_2O) = \frac{\Delta V_L}{\Delta P_L}$$

where L, the litre above FRC, is the slope of the linear portion of the curve. Total respiratory system compliance is derived from the equation:

$$\left(\frac{1}{\text{total compliance}}\right) = \left(\frac{1}{\text{lung compliance}}\right) + \left(\frac{1}{\text{wall compliance}}\right)$$

Total compliance can be calculated in well-sedated, ventilated patients as:

$$\frac{\text{tidal volume}}{(\text{end-inspiratory pause pressure minus PEEP})}$$

Further reading

See Invasive ventilation—adjustments, p54; Invasive ventilation—lung recruitment, p60; Positive end-expiratory pressure—principles, p70; Positive end expiratory pressure—management, p72.

Electrical impedance tomography

Electrical impedance tomography (EIT) is a bedside imaging technique that constructs images of the lung based on the electrical conductivity of biological tissue. EIT can be used to monitor lung ventilation and perfusion continuously. It can be used to detect recruited or de-recruited lung, as well as overdistension. It has been used in studies to assess responses to PEEP and lung recruitment manoeuvres, and may be used to guide ventilatory settings of V_T and PEEP. EIT can also detect pneumothorax and ventilator dyssynchrony. and estimate pulmonary artery pressure and lung fluid.

Interpretation of EIT images can be challenging due to its low spatial resolution and the superposition of varied physiological phenomena.

Principles

Devices usually have 16–32 surface electrodes placed above the sixth intercostal space. Below this level may introduce interference from diaphragm and abdominal contents. A high-frequency, low-intensity, alternating current circulating between the electrodes produces different surface voltages that generates a cross-sectional image of the lungs during the respiratory cycle. Tissue allows passage of current with little resistance, whereas gas/air is poorly conductive (Table 9.2).

As lung tissue impedance varies with air content, lung ventilation and changes in expiratory lung volume will alter the voltages measured by the body surface electrodes. Lung perfusion and the pathological presence of lung fluid will also alter conductivity distribution within the thorax.

Further reading

Putensen C, Hentze B, Muenster S et al. 2019. 'Electrical impedance tomography for cardiopulmonary monitoring.' *J Clin Med* 8: pp1176. doi: 10.3390/jcm8081176

See Invasive ventilation—lung recruitment, p60; Positive end expiratory pressure—management, p72.

Table 9.2 Different tissue resistivities

Tissue	Resistivity (Ω•cm)
Blood	150
Lungs, inspiration	2400
Lungs, expiration	700
Heart muscle (longitudinal)	125
Heart muscle (transverse)	1800
Skeletal muscle (longitudinal)	160–575
Skeletal muscle (transverse)	420–5200
Fat	2000–2700
Bone	16,600

Blood gas analyser

A small amount of heparinized blood is either injected from a syringe or aspirated from a capillary tube into the machine. The blood contacts three electrodes that measure pH, PO_2, and PCO_2.

- pH—measured by the potential across a pH-sensitive glass membrane separating a sample of known pH and the test sample.
- PO_2—the partial pressure of O_2—is measured by applying a polarizing voltage between a platinum cathode and a silver anode (Clark electrode). O_2 is reduced, generating a current proportional to PO_2.
- PCO_2—the partial pressure of CO_2—utilizes a pH electrode with a Teflon membrane (Severinghaus electrode) that allows through uncharged molecules (CO_2) but not charged ions (H^+). CO_2 alone thus changes the pH of a bicarbonate electrolyte solution, the change being linearly related to PCO_2.
- Hb—estimated photometrically, though not as accurate as co-oximetry (see below).
- Bicarbonate—calculated by the Henderson–Hasselbach equation. Actual HCO_3^- includes bicarbonate, carbonate, and carbamate.

$$pH = 6.1 + \log_{10} \frac{\text{arterial}\left[HCO_3^-\right]}{PaCO_2 \times 0.03}$$

- Actual base excess (deficit)—the difference in concentration of strong base (acid) in whole blood and that titrated to pH 7.4, PCO_2 5.33 kPa, and 37°C.
- Standard base excess (deficit)—base excess (deficit) at Hb 50 g/L.
- Standard bicarbonate—plasma concentration of hydrogen carbonate equilibrated at PCO_2 5.33 kPa, PO_2 13.3 kPa, and temperature 37°C.

Blood gas values can be given as 'pHstat' or 'alphastat'. The former corrects for body temperature by shifting the calculated Bohr oxyHb dissociation curve to the right with hyperthermia and to the left with hypothermia. Alphastat measures true blood gas levels in the sample.

Co-oximeter

This differs from a standard blood gas analyser as blood is haemolysed to calculate total Hb, fetal Hb oxyHb, COHb, metHb, and sulphaemoglobin by utilizing absorbance at six wavelengths (535, 560, 577, 622, 636, 670 nm).

Cautions

- Too much heparin causes dilution errors and is acidic.
- Intravenous lipid administration may affect pH values.
- Abnormal (high/low) plasma protein concentrations may affect the base deficit value.

Further reading

See Blood gas analysis, p174.

Blood gas analysis

A heparinized (arterial, venous, capillary) blood sample can be inserted into a blood gas analyser or handheld point-of-care device to measure gas tensions and saturations, acid–base status, and electrolytes (Table 9.3).

Table 9.3 Normal arterial blood gas values

pH	7.35–7.45
$PaCO_2$	4.6–6 kPa (34.5–45 mmHg)
PaO_2	10–13.3 kPa (75–100 mmHg)
HCO_3^-	22–26 mmol/L
Base excess	−2.4 to +2.2
Arterial O_2 saturation	95–98%
Mixed venous O_2 saturation	70–75%

Table 9.4 Causes of acid–base disturbances

Respiratory acidosis	pH↓, $PaCO_2$↑	Excess CO_2 production and/or inadequate excretion, e.g. hypoventilation, excess narcotic
Respiratory alkalosis	pH↑, $PaCO_2$↓	Reduction in $PaCO_2$ due to hyperventilation
Metabolic acidosis	pH↓, $PaCO_2$↔ or ↓	Usually related to elevated lactate or keto-acids, as well as renal and hepatic dysfunction. Consider diabetic ketoacidosis, ingestion of acids (e.g. aspirin), loss of alkali (e.g. diarrhoea, renal tubular acidosis), tissue hypoperfusion, high plasma chloride (e.g. from excess saline infusion) resulting in a hyperchloraemic acidosis.
Metabolic alkalosis	pH↑, $PaCO_2$↔ or ↑	May be due to excess alkali (e.g. bicarbonate or buffer infusion), loss of acid (e.g. large gastric aspirates, renal), hypokalaemia, drugs (e.g. diuretics)

Measurements

- Identification of both high and low O_2 and CO_2 levels enables monitoring of disease progression and efficacy of treatment. Ventilator and FiO_2 adjustments can be made precisely.
- pH, $PaCO_2$, and base deficit (or bicarbonate) values can be reviewed in parallel for diagnosis of acidosis and alkalosis, whether it is respiratory or metabolic in origin, and whether any compensation has occurred (Table 9.4 and Figure 9.4).

- Modern analysers now incorporate co-oximeters with multiple wavelengths able to measure oxyHb, total Hb level, and the fractions of metHb, COHb, deoxyHb, and fetal Hb.
- Measurement of mixed or central venous O_2 saturation enables calculation of O_2 consumption and monitoring of whole body O_2 supply:demand balance.

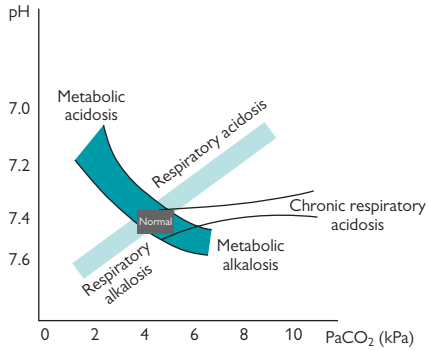

Fig. 9.4 Relationship between $PaCO_2$ and pH in various acid–base disturbances.

Further reading

See Oxygen therapy, p40; Ventilatory support—indications, p48; Invasive ventilation—adjustments, p54; Pressure & stroke volume variation, p212; Respiratory failure, p370; General acid-base principles, p532; Metabolic acidosis, p534; Metabolic alkalosis, p536.

Extravascular lung water measurement

The chest X-ray provides a qualitative assessment of pulmonary oedema and changes slowly in response to clinical treatment. Assessment of cardiac filling pressures does not take into account the degree of capillary permeability nor lymphatic adaptation. Consequently, a relatively low central venous pressure or pulmonary artery wedge pressure may be associated with pulmonary oedema formation. High filling pressures in chronic heart failure may be associated with no oedema and be entirely appropriate. Extravascular lung water (EVLW) measurement provides a technique for quantifying pulmonary oedema and the response to treatment.

Measurement technique

The normal value of 4–7 mL/kg for EVLW has been derived by gravimetric techniques performed postmortem.

A double indicator technique can be used in patients whereby two indicators are injected via a central vein; one distributes within the vascular space and the other throughout the intra- and extravascular space. The volume of distribution of the indicators is derived from the dilution curves detected at the femoral artery. Cooled 5% glucose is used as a thermal indicator for intra- and extravascular volume, and indocyanine green bound to albumin as a colorimetric indicator for intravascular volume. Detection at the femoral artery is by a fibreoptic catheter with a thermistor tip. The cardiac output (CO) is measured by thermodilution at the femoral artery.

The rate of exponential decay of the thermodilution curve allows derivation of the volume of distribution between the injection and detection sites (the heart and lungs).

> Pulmonary thermal volume = thermodilution CO x rate of exponential decay of thermodilution curve (intra- and extravascular volume)

Similar principles may be applied to the dye dilution curve produced on injection of indocyanine green which is assumed to distribute within the vascular space only.

> Pulmonary blood volume = dye dilution CO x rate of exponential decay of dye dilution curve (intravascular volume)

EVLW may be calculated by subtracting pulmonary blood volume from pulmonary thermal volume.

Limitations of EVLW measurement

Since albumin can exchange across capillary membranes, pulmonary blood volume is overestimated by this technique and EVLW is therefore underestimated. However, the corresponding error is small and not clinically significant. Treatment of pulmonary oedema by diuresis and ultrafiltration have been shown to be less effective at reducing EVLW in capillary leak from inflammatory conditions, compared to congestive heart failure.

Further reading

See Cardiac output—central thermodilution, p200; Cardiac output—peripheral thermodilution, p202; Acute respiratory distress syndrome—diagnosis, p384; Acute respiratory distress syndrome—management, p386.

Respiratory imaging

Chest X-ray

This can be performed at the bedside of a critically ill patient. It yields useful information on pathologies within and outside the lung parenchyma (e.g. consolidation, pulmonary oedema, collapse, pleural effusion, pneumothorax); confirmation of suitable positioning of intratracheal, intravascular, and nasogastric/oesophageal tubes and catheters; soft tissue and bony abnormalities; cardiac contour and size; vascular abnormalities (e.g. aortic diameter, oligaemic lung field suggestive of a pulmonary embolus); and free air under the diaphragm. Pitfalls include:

- The position of the patient is usually supine (anteroposterior image). This overestimates ventricular dimensions and can camouflage the presence of a pneumothorax that sits in front of, or behind, normal lung tissue. Look for an 'inverted diaphragm' and increased lucency compared to the other lung.
- Underestimation of the size of pleural effusion and pneumothorax.

Lateral chest X-rays may be useful in diagnosing a pneumothorax that is not obviously apparent on a supine film. However, this is more difficult to perform at the bedside.

Computed tomography (CT) scan

CT scan is the definitive imaging procedure for pathology within the thorax. Injection of contrast highlights vascular structures and the presence of pulmonary emboli in subsegmental arteries (with high-resolution scanning). It enables improved discrimination of pulmonary shadows (e.g. fluid, fibrosis, consolidation, atelectasis, abscess, and empyema) and can be used to guide drainage procedures of air and fluid collections.

Ultrasound

Point-of-care ultrasound (POCUS) can detect lung pathology at the bedside, e.g. diagnosis of pleural effusions, peripheral areas of consolidated lung, and peripheral pneumothorax. It can aid safe performance of invasive procedures, e.g. intravascular line placement, and drainage of fluid or air collections. Recent studies indicate potential utility in monitoring lung aeration, optimizing ventilator settings and strategies such as PEEP recruitment and pronation, assisting weaning, and for outcome prediction.

The ultrasound probe is initially oriented longitudinally (perpendicular to the ribs) to identify the pleura. Switching to a transverse approach aligned to the intercostal space will visualize a wider area but is more prone to artefact so should only be performed by experienced operators.

Nearly all ultrasound waves are reflected back to the probe at soft tissue–air interfaces. Structures beneath the soft tissue pleura are poorly visualized in normal air-filled lung and mainly seen as artefact. Real images are seen with pathological change, e.g. effusion and consolidation. Appearances depend on the relative amount of air and fluid present (normal lung has 98% air; interstitial syndromes ~90%; alveolar syndromes ~10%; atelectasis ~5%).

There are several limitations and cautions to use of POCUS:

- The learning curve is relatively steep; proper training and regular practice are crucial to enhance diagnostic accuracy. Accredited training courses and certification are now well established.
- Interposition of chest drain, dressing, and air (e.g. subcutaneous emphysema) prevents penetration of the ultrasound waves.

Further reading

➔ See Interpreting point-of-care respiratory ultrasound, p180; Airway obstruction, p368; Atelectasis & pulmonary collapse, p372; Pneumonia—diagnosis, p374; Acute respiratory distress syndrome—diagnosis, p384; Asthma—general management, p390; Pulmonary embolus—diagnosis, p394; Pneumothorax, p398; Haemothorax, p400; Heart failure—assessment, p420; Intra-hospital transport, p698.

Interpreting point-of-care respiratory ultrasound

Rapid assessment

Focus is initially concentrated on 'A-' and 'B-lines' for rapid assessment of a sick patient. 'A'-lines are horizontal hyperechoic lines indicating a high gas:volume ratio below the pleura and thus seen with normal or hyperinflated lung or pneumothorax. 'B'-lines are vertical hyperechoic lines that look like comet tails. These artefacts arise from the pleura and move in tandem with lung sliding. Their number suggests the following:

- >2 are compatible with an interstitial syndrome.
- 3–4 indicate thickened subpleural septa.
- ≥5 with ground-glass areas indicate severe interstitial syndrome.

The Lung Ultrasound Score (LUS) is commonly used to identify progressive loss of aeration (Table 9.5). Six regions are visualized per hemithorax: anterior, lateral, and posterior fields identified by sternum, anterior, and posterior axillary lines; each field is then divided into superior and inferior regions. Lung aeration loss can be overestimated in acute respiratory distress syndrome, ventilator-associated pneumonia, and other non-homogeneous diseases.

Specific ultrasound features

These indicate anatomical landmarks or pathologies, e.g.:

- 'Bat sign'—a line 0.5 cm below the rib that identifies parietal pleura.
- 'Sliding sign'—the pleural line moves with ventilation, indicating normal apposition of parietal and visceral pleura.
- 'Seashore sign'—a sandy pattern seen on M-mode represents normal sliding of visceral pleura and excludes pneumothorax at this intercostal space. Loss of sandy pattern (i.e. no sliding) plus movement synchronous with cardiac beats ('lung pulse') suggests pneumothorax.
- 'Stratosphere sign'—M-mode shows straight lines above and below the pleural line. Together with a lack of lung sliding plus a 'lung point' (alternating seashore and stratosphere signs where collapsed lung contacts with parietal pleura during inspiration) suggests pneumothorax.
- Pneumothorax is also suspected when there is no lung sliding and straight lines are seen on M-mode above and below the pleural line ('stratosphere sign'). Pneumothorax is confirmed by a 'lung point', seen on M-mode as alternating seashore and stratosphere signs where collapsed lung contacts with parietal pleura during inspiration.
- 'Shred sign'—small subpleural hypoechoic images with irregular boundaries seen with consolidation.
- A 'tissue-like' appearance is seen with lobar consolidation. Air bronchograms within can be seen as hyperechoic white spots that move with tidal ventilation.
- Pleural effusions are seen as anechoic spaces. Homogeneous appearance suggests transudate while non-homogeneity is seen with blood or exudate. The 'sinusoid sign' is where the distance between parietal and visceral pleura varies with respiration when separated by an effusion. The 'jellyfish sign' shows atelectatic lung 'swimming' within a large effusion.

Table 9.5 Lung Ultrasound Score

Score	
0	Normal aeration (A-lines or ≤2 B-lines)
1	Moderate loss of aeration (≥3 well-spaced B-lines)
2	Severe loss of aeration (coalescent B-lines)
3	Complete loss of aeration (tissue-like pattern)

Total LUS is computed as the sum of each regional score (range 0–36).

Further reading

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Mongodi S, DeLuca D, Colombo A, et al. 2021. 'Quantitative lung ultrasound: technical aspects and clinical applications'. *Anesthesiology* 134: pp949–65. doi: 10.1097/ALN.0000000000003757

➔ See Respiratory imaging, p178; Atelectasis & pulmonary collapse, p372; Pneumonia—diagnosis, p374; Haemothorax, p400.

Chapter 10

Cardiovascular monitoring

ECG monitoring

Continuous electrocardiogram (ECG) monitoring is routinely used in the majority of patients. The standard technique is to display a three-lead ECG (commonly lead II). Other limb leads may be used although the electrodes are placed at the shoulders and left side of the abdomen. Other lead configurations can be used for specific purposes:

- Chest–shoulder–V5: early detection of left ventricular (LV) strain.
- Chest–manubrium–V5: early detection of LV strain.
- Chest–back–V5: P-wave monitoring.

Modern monitors include alarm functions for bradycardia and tachycardia monitoring, and software routines for arrhythmia detection or ST segment analysis.

Causes of changes in heart rate or rhythm

Changes in heart rate or rhythm may be an indication of:

- Increased sympathetic/parasympathetic activity:
  - circulatory insufficiency
  - pain
  - anxiety
  - hypoxaemia
  - hypercapnia
  - sepsis.
- Adverse drug effects:
  - antiarrhythmics
  - sedatives.
- Electrolyte imbalance.
- Fever.

Further reading

See Tachyarrhythmias, p412; Bradyarrhythmias, p414; Acute coronary syndrome—diagnosis, p416; Acute coronary syndrome—management, p418.

Blood pressure monitoring

Non-invasive techniques

Non-invasive techniques are intermittent but automated. They include oscillotonometry (detection of cuff pulsation at the systolic pressure), detection of arterial turbulence under the cuff, ultrasonic detection of arterial wall motion under the cuff, and detection of blood flow distal to the cuff. Use a cuff large enough to cover two-thirds of the upper arm surface.

Invasive (direct) arterial monitoring

Pressure measured in a distal artery is higher than from a central vessel. Although blood pressure (BP) monitoring from larger limb arteries, e.g. femoral or brachial, is more representative, damage to these arteries risks compromising the distal limb. It is generally safer to use radial, ulnar, or dorsalis pedis arteries.

1. Connect the arterial cannula to an appropriate fluid-filled pressure monitoring system via a short length of non-compliant tubing. This system contains a transducer and continuous flush device connected to a 500 mL bag of normal saline pressurized to 200–300 mmHg.
2. Zero the transducer to atmospheric pressure and position it at the level of the fourth intercostal space in the mid-axillary line.
3. The transducer, tubing, and cannula is continuously flushed with 2–3 mL/h normal saline. Small-volume manual flushes can be given after blood draws to remove blood from the tubing.

Damping errors

The arterial transducer is composed of an oscillating membrane that detects the changes in BP at high frequency.

The arterial waveform values may be spuriously represented if there is either underdamping or overdamping of the system. The amplitude of the oscillations will be reduced by any factor that reduces energy within the system. Overdamping can result from the use of three-way taps, bubbles, clots or kinks in the tubing, vasospasm, the catheter tip sited against the vessel wall, or excessively long tubing. The waveform will appear small and flattened and the systolic pressure will be under-read while diastolic is spuriously elevated. Conversely, an underdamped system will cause big swings in the BP trace, resulting in spuriously high systolic and low diastolic values. Underdamping may result from too short tubing or patient conditions such as high cardiac output and tachycardia. In both instances, the mean arterial pressure (MAP) will be more reliable.

Over- and underdamping can be detected by performing a 'square wave' test, i.e. flushing the arterial line for a few seconds and then watching the waveform return to baseline. A normal waveform should oscillate no more than twice before returning to baseline; an overdamped waveform is signified by a slow return to baseline; whereas an underdamped waveform is shown by multiple oscillations.

Limitations of BP monitoring

It is important not to rely on arterial BP monitoring alone in the critically ill. A normal BP does not guarantee adequate organ blood flow. Conversely, a low BP may be acceptable if perfusion pressure is adequate for all organs and blood flow is high. Measurement of cardiac output and markers

of organ perfusion, in addition to BP, is necessary where adequacy of the circulation is doubted.

Interpretation of waveform

The shape of the arterial pressure waveform gives useful qualitative information about the state of the heart and circulation (Table 10.1 and Figure 10.1).

Further reading

See Arterial cannulation, p188; Hypotension, p408; Hypertension, p410.

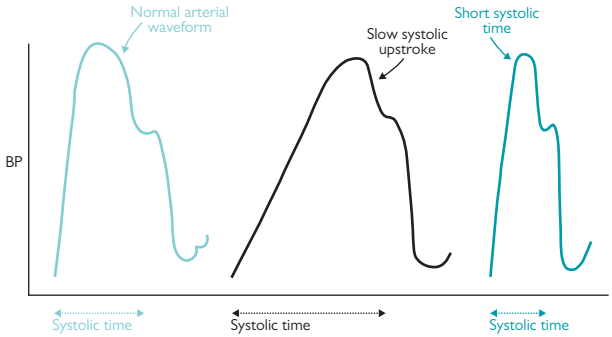

Fig. 10.1 Examples of arterial waveform shape.

Table 10.1 Interpretation of blood pressure waveform

Short systolic time	Hypovolaemia High peripheral resistance
Marked respiratory swing	HypovolaemiaPericardial effusion Airways obstruction High intrathoracic pressure
Slow systolic upstroke	Poor myocardial contractility High peripheral resistance

Arterial cannulation

Performed correctly, arterial cannulation is a safe technique allowing continuous monitoring of BP and frequent blood sampling. It is indicated in patients with unstable, or potentially unstable, haemodynamic or respiratory status.

Radial artery cannulation

The radial artery is most frequently chosen because it is accessible and has good collateral blood flow. Allen's test, used to confirm ulnar blood supply, is not reliable.

Technique of cannulation

1. Use an aseptic technique.
2. After skin cleansing, inject local anaesthetic (1% plain lidocaine) into the skin and subcutaneous tissue over the most prominent pulsation.
3. Hyperextend the wrist and abduct the thumb. Ultrasound may be used to help identify the artery and aid placement. Note the course of the artery and insert a 20 G cannula along the line of the vessel. Enter the vessel in similar fashion to an intravenous cannula. Alternatively, use a Seldinger approach. Here a guidewire is first inserted into the vessel through a rigid needle and the indwelling plastic cannula is then passed over the guidewire.
4. There is usually some resistance to skin puncture. To avoid accidentally puncturing the posterior wall of the artery, puncture the skin and artery as two distinct manoeuvres. Alternatively, a small skin nick may be made to facilitate skin entry.
5. In elderly patients with mobile, atheromatous vessels, consider a technique involving deliberate transfixation of the artery. The cannula is passed through the anterior and posterior walls of the vessel, thus immobilizing it. The needle is removed and the cannula withdrawn slowly into the vessel lumen, before being advanced.
6. After successful puncture, connect the cannula to 0.9% saline-filled tubing connected to a pressure monitoring system with an integral continuous flush device. Flush cannula with normal saline to prevent clotting and maintain cannula patency.
7. Attach the cannula securely to skin with an appropriate dressing.
8. Zero the transducer then position it at the level of the fourth intercostal space, mid-axillary line.
9. Clearly identify/label the tubing to prevent accidental injection of drugs and other fluids.

Alternative sites for cannulation

- Brachial artery—end-artery supplying whole distal limb; thrombosis or occlusion have potentially severe consequences.
- Femoral artery—may be difficult to keep clean. Also supplies a large volume of tissue. A longer catheter should be used to avoid displacement.
- Dorsalis pedis artery—BP will be at least 10–20 mmHg higher than in central vessels, if not higher.

Complications

- Digital ischaemia due to arterial spasm, thrombosis, or embolus.
- Bleeding (particularly in cases with altered coagulation status).
- Infection (with prolonged cannulation).
- False aneurysm.
- Extravasation of fluid.

Further reading

➲ See Blood gas analysis, p174; Blood pressure monitoring, p186; Routine changes of disposables, p586.

Central venous catheter—insertion

Ultrasound-guided placement is generally recommended, especially for difficult placements. The technique with ultrasound guidance is different to the landmark technique; operators should be able to identify a patent vein and manipulate both probe and cannula simultaneously. There will be situations where an ultrasound device may be unavailable, so placement using anatomical landmarks alone should still be learnt.

Landmarks

- Internal jugular—halfway between mastoid process and sternal notch, lateral to carotid pulsation and inside medial border of sternocleidomastoid. Aim toward ipsilateral nipple, advancing under body of sternocleidomastoid until vein entered.
- Subclavian—3 cm below junction of lateral third and medial two-thirds of clavicle. Turn head to contralateral side. Aim for point between jaw and contralateral shoulder tip. Advance needle to hit clavicle. Scrape needle around clavicle and advance further until vein entered.
- Femoral—locate femoral artery in groin. Insert needle 3 cm medially to artery and angled rostrally. Advance slowly until vein entered.

Ultrasound guidance

- Use a linear array transducer.
- Place the patient supine/head down for a jugular vein approach with the head turned slightly contralaterally.
- Place the transducer transversely just below the apex of the sternocleidomastoid triangle. The internal jugular vein and the neighbouring carotid artery (Figure 10.2) can be distinguished by size (the vein is generally larger unless the patient is very hypovolaemic), shape (the vein is more ellipsoid in shape while the artery is circular and pulsatile), and compressibility (veins are easily compressed). The thyroid gland lies medial and has a light-grey echo appearance.
- Move the transducer so it lies over the jugular vein.
- Follow the needle as it is advanced through skin and soft tissues; it appears as a small, bright, hyperechoic dot. Follow the dot until it enters the vein and is mid-cavity. A Seldinger wire can then be advanced through the needle, or, if using a non-guidewire technique, the cannula can be advanced down the vein.
- For a subclavian approach, place the patient supine/head down with the head in a neutral position. Place the transducer transversely just below the mid-portion of the clavicle. The hyperechoic clavicle is seen superiorly whereas the vein is dark and sits just inferiorly and deep to the clavicle. The lung lies directly posteriorly.
- Move the transducer 1–2 cm laterally towards the shoulder with the probe face below the clavicle to obtain an optimal view of the vein. Site over centre of vein.
- Insert the needle laterally pointing towards the suprasternal notch. Then proceed as above when needle tip is visualized.

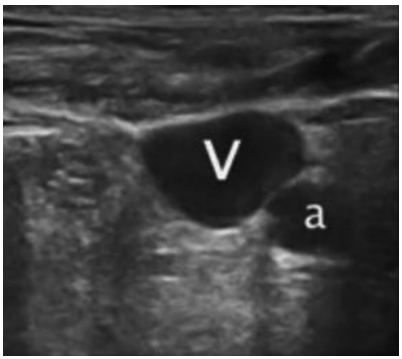

Fig. 10.2 Identification of internal jugular vein (v) and carotid artery (a) on transverse placement of probe.

Insertion technique

The Seldinger technique should generally be used in intensive care unit patients.

1. Use aseptic technique throughout. Clean area with antiseptic (2% chlorhexidine) and surround with sterile drapes. Anaesthetize locally with 1% lidocaine. Flush lumen(s) of catheter with saline.
2. If available, use a sterile sheathed ultrasound probe to distinguish the vein from an adjacent artery by its compressibility, thinner wall, and ovoid shape (see above). The internal jugular and femoral veins are the easiest to locate by ultrasound.
3. Use a metal needle or cannula to locate the central vein. Confirm by easy aspiration of non-pulsatile blood into attached syringe or direct ultrasound visualization of the needle entering the vein.
4. Pass wire (with 'J' or floppy end leading) through needle into vein. Only minimal resistance should be felt. If not, remove wire and confirm needle tip is still within vein lumen. If arrhythmias occur, the wire tip may be at the tricuspid valve so withdraw wire by a few cm.
5. Remove needle leaving wire extruding from skin puncture site.
6. Depending on size/type of catheter, a rigid dilator (± a prior scalpel nick to enlarge puncture site) may be passed over the wire to form a track through subcutaneous tissues to vein. Remove the dilator.
7. Thread catheter over wire. Ensure end of wire extrudes from catheter to prevent accidental loss of wire into the vein. Insert catheter into vein to depth of 15–20 cm. Remove wire.
8. Check for flashback of blood in each lumen and respiratory swing, then flush with saline.
9. Attach catheter to skin using appropriate fixation device. Suturing is not generally recommended in view of an increased risk of infection. Clean and dry area. Use a sterile transparent semi-permeable dressing.
10. A chest X-ray is usually performed to verify correct positioning of the tip (junction of superior vena cava and right atrium) and to exclude pneumothorax.

Further reading

See Central venous catheter—use, p192; Central venous catheter—complications, p194.

Central venous catheter—use

Types of catheter

- One- to five-lumen catheters are available.
- Sheaths are used for insertion of a pulmonary artery (PA) catheter or pacing wire.
- Tunnelled catheter for long-term use.
- Multi-lumen catheters allow multiple infusions to be given separately ± continuous pressure monitoring. Minimizes accidental bolus risk.
- Large-bore, double-lumen catheters for venovenous dialysis/filtration.
- Common routes are internal jugular, subclavian, and femoral.

Uses

- Invasive haemodynamic monitoring.
- Infusion of drugs that can cause peripheral phlebitis or tissue necrosis if tissue extravasation occurs (e.g. total parenteral nutrition, epinephrine, amiodarone).
- Rapid volume infusion; NB: rate of flow is inversely proportional to the length of the cannula.
- Access, e.g. for pacing wire insertion.
- Emergency access when peripheral circulation is 'shut down'.
- Renal replacement therapy, plasmapheresis, exchange transfusion.

Contraindications/cautions

- Coagulopathy.
- Undrained pneumothorax on contralateral side.
- Agitated, restless patient.

Central venous pressure measurement

An electronic pressure transducer is preferable to fluid manometry. After 'zeroing', place the pressure transducer at the level of the left atrium (approximately fourth intercostal space, mid-axillary line) rather than the sternum which is more affected by patient position (supine/semi-erect/prone). Venous pulsation and some respiratory swing should be seen in the trace but not a right ventricular (RV) pressure waveform (i.e. catheter inserted too far).

Further reading

➔ See Temporary pacing, p104; Parenteral nutrition, p144; Central venous catheter—insertion, p190; Central venous catheter—complications, p194; Pulmonary artery catheter—insertion, p196; Routine changes of disposables, p586.

Central venous catheter—complications

Risk of infection is greater with femoral then jugular then subclavian approaches. The risk of pneumothorax is greater with subclavian insertion compared with jugular.

Infection

The incidence of local infection (usually coagulase negative Staphylococci or *S. aureus*) rises after 5 days. The catheter site should be kept clean with an occlusive dressing that should be changed within 7 days, using 2% chlorhexidine in alcohol to clean the site. Strict asepsis should be used for dressing changes.

The need to keep the catheter *in situ* should be questioned daily.

Unless new catheter insertion is high risk (e.g. marked coagulopathy, anatomical issues), catheter exchange over a wire is not advised.

Catheter-related sepsis should be considered if the patient develops an unexplained pyrexia or neutrophilia. Antibiotics may not be needed if mild, localized infection is present.

Removal of the catheter is necessary if the site looks infected, shows spreading cellulitis, or blood cultures taken through the catheter are positive. If removing the catheter, send the tip to the laboratory for culture.

Other complications

- Arterial puncture—apply firm pressure directly over puncture site for 5–10 min (sometimes longer). If continues, consider infusing clotting factors. Rarely, vascular surgical assistance may be needed.
- Note with subclavian arterial puncture cannot directly apply pressure.
- Haemorrhage—may occur from around puncture site, or from a previously failed attempt at insertion. Direct pressure for 5–10 min is usually successful though clotting factor infusion may be needed if bleeding persists., If post-thrombolysis, consider tranexamic acid.
- Arrhythmias—usually related to catheter tip 'tickling' the tricuspid valve; normally resolves on withdrawing catheter by a few cm.
- Pneumothorax—if significant (e.g. >1/3 of hemithorax) or compromising cardiorespiratory status, drain air through catheter or chest drain. Otherwise, observe closely and drain subsequently, if necessary.
- Air embolism—avoid by ensuring all Luer lock connections are not loosely attached. If air embolism does occur, roll patient to left-hand side and place head down (Trendelenburg position) to prevent air entering the pulmonary artery. Give fraction of inspired oxygen (FiO_2) 1.0 to speed resorption of air. Try aspirating air through central line or consider angiography-guided aspiration if very large.
- Venous thrombosis—suggested by unilateral swelling of the distal limb, which can be confirmed by ultrasound. Remove catheter and anticoagulate (unless contraindicated).
- Haemothorax—drain if necessary and monitor blood loss. Usually self-resolves. If bleeding persists, correct any coagulopathy. Seek a cardiothoracic surgical opinion if blood loss is substantial (>1 L).

- Chylothorax (rare)—losses can exceed 1 L/day. Often resolves spontaneously within 5–7 days. If persists, surgical ligation of the lymphatic duct may be necessary. The volume of loss may be reduced with total parenteral nutrition or a low-fat enteral diet.

Further reading

➲ See Central venous catheter—insertion, p190; Central venous catheter—use, p192; Pneumothorax, p398; Haemothorax, p400; Routine changes of disposables, p586.

Pulmonary artery catheter—insertion

Insertion

1. Insert an 8 Fr central venous introducer sheath into the internal jugular or subclavian vein under aseptic technique.
2. Prepare catheter pre-insertion—place three-way taps on all lumens, flush lumens with crystalloid, inflate balloon with 1.6 mL air and check for concentric inflation and leaks, place transparent sleeve over catheter to maintain future sterility, pressure transduce distal lumen, and zero to reference point (usually mid-axillary line). Other pre-insertion calibration steps may be required, e.g. for oxygen saturation.
3. Insert catheter beyond the length of the introducer sheath before inflating balloon. Advance catheter smoothly through the right heart chambers, pause to record pressures and note waveform shape in right atrium (RA), RV, and PA (Figure 10.3). When a characteristic pulmonary artery wedge pressure (PAWP) waveform is obtained, stop advancing catheter, deflate balloon, and ensure that the PA waveform reappears. If not, withdraw catheter by a few cm.
4. Slowly reinflate balloon, observing waveform trace. The wedge recording should not be obtained until at least 1.3 mL of air has been injected into the balloon. If 'overwedged' (pressure climbs on inflation), catheter is inserted too far and balloon has occluded distal lumen. Immediately deflate, withdraw catheter 1–2 cm, and repeat.
5. After insertion, a chest X-ray is usually performed to verify catheter position and to exclude a pneumothorax.

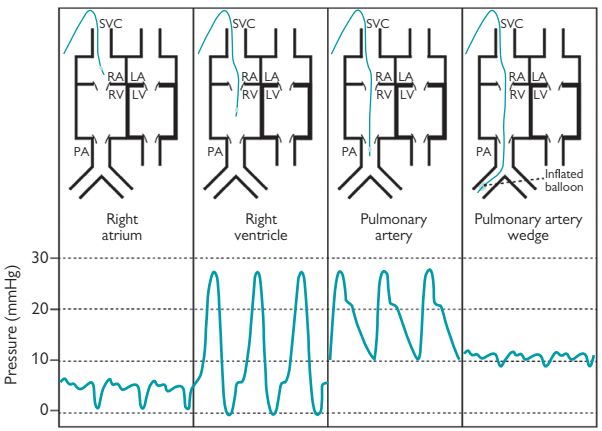

Fig. 10.3 Waveforms as the pulmonary artery catheter is advanced from the right atrium through the right ventricle to the pulmonary artery, and finally to the wedge position.

Contraindications/cautions

- Coagulopathy.
- Tricuspid valve prosthesis or disease.

Complications

- Problems of central venous catheterization.
- Arrhythmias (especially when traversing tricuspid valve).
- Infection (including endocarditis).
- PA rupture.
- Pulmonary infarction.
- Knotting of catheter.
- Valve damage (do not withdraw catheter unless balloon deflated).

Troubleshooting

Excessive catheter length in a heart chamber causes coiling and a risk of knotting. No more than 15–20 cm should be passed before the waveform changes. A knot can be managed by (i) 'unknotting' with an intraluminal wire, (ii) pulling taut and removing catheter and introducer sheath together, or (iii) surgical or angiographic intervention.

If catheter fails to advance to next chamber, consider 'stiffening' catheter by injecting iced crystalloid through the distal lumen, rolling patient to left lateral position, or advancing catheter slowly with balloon deflated.

Arrhythmias on insertion usually occur when the catheter tip is at the tricuspid valve. These usually resolve on withdrawing the catheter.

Further reading

➔ Pulmonary artery catheter—use, p198.

Pulmonary artery catheter—use

No impact on mortality has been demonstrated with catheter use in critically ill or decompensated heart failure patients. Other studies have reported inadequate knowledge of insertion and data interpretation so proper training in its use is mandated.

Uses

- Direct measurements (see Table 10.2 for normal ranges):
  - pressure monitoring—RA, RV, PA, PAWP
  - flow monitoring—(RV) cardiac output
  - oxygen saturation—'mixed venous' (i.e. in RV outflow tract/PA), determination of left-to-right shunts (ASD, VSD).
- Derived variables (Table 10.3)—SVR, PVR, LVSW, RVSW, DO_2, VO_2, O_2ER.

Specialized catheters

- Continuous mixed venous oxygen saturation measurement.
- Continuous cardiac output measurement.
- RV end-diastolic volume, RV ejection fraction calculation.

Management

Monitor PA pressure continuously to identify catheter migration and a wedged trace. If present, pull back catheter immediately to prevent pulmonary infarction due to arterial occlusion.

The risk of local infection rises after 5 days. Consider daily the need for the catheter. Removal ± change of site is needed if the site is infected or positive cultures are grown from either line tip or blood.

For mixed venous blood sampling withdraw samples of PA blood slowly from the distal lumen to prevent 'arterialization', i.e. pulmonary venous sampling.

Table 10.2 Normal values for direct measurements

Stroke volume (SV)	70–100 mL
Cardiac output (CO)	4–6 L/min
Right atrial pressure (RAP)	0–5 mmHg
Right ventricular pressure (RVP)	20–25/0–5 mmHg
Pulmonary artery pressure (PAP)	20–25/10–15 mmHg
Pulmonary artery wedge pressure (PAWP)	6–12 mmHg
Mixed venous oxygen saturation	70–75%

Wedge pressure measurements

- Inflate balloon slowly, monitoring the waveform to avoid potential vessel rupture, especially in elderly and/or pulmonary hypertension. The trace should only 'wedge' after ≥1.3 mL air fills the balloon.
- Measure at end expiration when intrathoracic pressure is closest to atmospheric pressure. For ventilated patients end expiration ≡ lowest wedge reading; during spontaneous breathing end expiration ≡ highest reading. In the dyspnoeic patient a 'mean' wedge reading may be used.
- PAWP cannot be higher than PA diastolic pressure.

- CVP, PAWP, and cardiac output (CO) should not be measured during rapid volume infusion but after a period of equilibration (5–10 min).
- PAWP does not equal LV end-diastolic pressure (LVEDP) in mitral stenosis. In mitral regurgitation, measure PAWP at the end of the 'a' wave.

Table 10.3 Derived variables

Variable	Calculation	Normal range
Cardiac index (CI)	$\frac{CO}{\text{Body surface area}}$	2.5–3.5 L/min/m^2
Stroke index (SI)	$\frac{SV}{\text{Body surface area}}$	40–60 mL/m^2
Systemic vascular resistance (SVR)	$\frac{MAP - RAP}{CO} \times 79.9$	960–1400 dyne.sec/cm^5
Pulmonary vascular resistance (PVR)	$\frac{PAP - PAWP}{CO} \times 79.9$	25–125 dyne.sec/cm^5
LV stroke work (LVSW) index	(MAP − PAWP) × SI × 0.0136	44–68 g-m/m^2
RV stroke work (RVSW) index	(MPAP − RAP) × SI × 0.0136	4–8 g-m/m^2
O_2 delivery (DO_2)	$CO \times 0.134 \times Hb_a \times SaO_2$	950–1300 mL/min
O_2 consumption (VO_2)	$CO \times 0.134 \times (Hb_a \times SaO_2) - CO \times 0.134 \times (Hb_v \times SvO_2)$	180–320 mL/min
O_2 extraction ratio (O_2ER)	$1 - \frac{SaO_2 - SvO_2}{SaO_2}$	0.25–0.30

West's zones

The catheter tip should lie in a zone III region (where PA pressure > pulmonary venous pressure > alveolar pressure). i.e. below left atrial level on a lateral chest X-ray.

Suspect a non-zone III position if (i) PAWP rises by >50% of an increment in positive end-expiratory pressure (PEEP), (ii) the wedge trace shows no detectable cardiac pulsation and/or excess respiratory variation.

A non-zone III position is more likely with high PEEP and/or hypovolaemia.

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See Pulmonary artery catheter—insertion, p196; Cardiac output—central thermodilution, p200.

Cardiac output—central thermodilution

Thermodilution is utilized by the PA catheter to measure RV cardiac output. The principle is a modification of the Fick indicator dilution principle whereby a bolus of cooled 5% glucose is injected through the proximal lumen into the central circulation (RA) and the temperature change is detected by a thermistor at the catheter tip, some 30 cm distal. A modification of the Hamilton–Stewart equation, utilizing the volume, temperature, and specific heat of the injectate, enables cardiac output to be calculated by an online computer from a curve measuring temperature change in the PA.

Continuous thermodilution measurement uses a modified catheter emitting heat pulses from a thermal filament lying 14–25 cm from the tip. 7.5 W of heat are added to the blood intermittently every 30–60 s and these temperature changes are measured by a thermistor 4 cm from the tip. Though updated frequently, the cardiac output displayed is usually an average of the previous 3–6 min.

Thermodilution is also used by the PiCCO (pulse contour cardiac output) device, injecting cooled 5% glucose through a central vein and measuring temperature change in the femoral artery (see following topic).

Thermodilution injection technique

The computer constant must be set for the volume and temperature of the 5% glucose used. Ice-cold glucose (10 mL) provides the most accurate measure. Room temperature injectate (5 mL) is sufficiently precise for normal and high output states; however, its accuracy worsens at low outputs.

1. Press 'Start' button on computer.
2. Inject fluid smoothly over 2–3 s.
3. Repeat at least twice more at random points in the respiratory cycle.
4. Average three measurements falling within 10% of each other. Reject outputs gained from curves that are irregular/non-smooth.

Erroneous readings

- Valve lesions—tricuspid regurgitation allows some of the injectate to reflux back into the RA. Aortic incompetence produces a higher LV output; however, a proportion will regurgitate back into the LV.
- Septal defects.
- Loss of injectate. Check that connections are tight and do not leak.

Disadvantages

- Non-continuous (by injection technique).
- 5–10% inter- and intra-observer variability.
- Erroneous readings with tricuspid regurgitation, intracardiac shunts.
- Frequently repeated measurements may result in considerable volumes of 5% glucose being injected.

Further reading

See Pulmonary artery catheter—insertion, p196; Pulmonary artery catheter—use, p198.

Cardiac output—peripheral thermodilution

The PiCCO device utilizes thermodilution measured peripherally. The most frequent artery used is the femoral into which a catheter (usually 5 Fr in adults) is inserted. Specialized catheters are also available for axillary and radial artery insertion. A bolus of cold saline injected into a central vein is detected by a thermistor in the arterial catheter.

Advantages

- Reasonably accurate and less invasive than PA placement.
- Other information derived.

Disadvantages

- Can underestimate low output values.
- Inaccurate with moderate/severe valvular regurgitation, intracardiac shunts, aortic aneurysm, aortic stenosis, pneumonectomy, pulmonary embolism, rapidly changing temperature, extracorporeal circulations.
- Large-diameter catheter can compromise distal leg perfusion.

Derived indices

As the injectate is administered centrally and the temperature difference is measured in a proximal artery, most of the temperature change occurs in the intrathoracic compartment. Hence volumetric variables such as intrathoracic blood volume (ITBV) and extravascular lung water (EVLW) can be estimated.

- Global end-diastolic volume (GEDV) = volume of blood within the four heart chambers.
- ITBV = GEDV + blood volume within the pulmonary vessels.
- ITBV and GEDV are measures of cardiac preload that studies suggest are comparable, if not superior, to standard cardiac filling pressures (CVP, PAWP), as they are less influenced by mechanical ventilation.
- EVLW = water content in the lungs.

EVLW provides a bedside measure of the degree of pulmonary oedema. It correlates with the severity of acute respiratory distress syndrome and outcomes. No randomized controlled trials have been performed to show its utility in guiding treatment to improve outcomes.

Further reading

➔ See Extravascular lung water measurement, p176; Cardiac output—central thermodilution, p200; Hypotension, p408; Heart failure—assessment, p420.

Cardiac output—indicator dilution

Dye dilution

Mixing of a given volume of indicator to an unknown volume of fluid allows calculation of this volume from the degree of indicator dilution. The time elapsed for the indicator to pass some distance in the cardiovascular system yields a cardiac output value, calculated as

$$\frac{60 \times I}{C_m \times t}$$

where I = amount of indicator injected, C_m = mean concentration of the indicator, and t = curve duration. Traditionally, indocyanine green was injected into a central vein with arterial blood repeatedly sampled to construct a time–concentration curve with a rapid upstroke and an exponential decay. Plotting the dye decay curve semi-logarithmically and extrapolating values to the origin produces cardiac output.

The LiDCO™ device is based on a similar principle, though using lithium as the 'dye'. This can be injected into a peripheral vein and sampled from the radial artery.

Advantages

- Reasonably accurate and less invasive than PA placement.
- Other information derived.

Disadvantages

- Accumulation of lithium with multiple repeated measurements.
- Measurement/calibration takes >10 min. At least two or three lithium time–concentration curves should be performed per calibration to improve the coefficient of variation and accuracy.
- Can underestimate low output values.
- Inaccurate with moderate/severe valvular regurgitation, major pulmonary embolism, intracardiac shunt.
- Paralysing agents and severe hyponatraemia interfere with lithium measurement.
- Lithium should not be used in pregnant patients.

Further reading

See Cardiac output—central thermodilution, p200; Hypotension, p408; Heart failure—assessment, p420.

Cardiac output—Doppler ultrasound

Doppler ultrasound

An ultrasound beam of known frequency is reflected by moving blood corpuscles with a shift in frequency proportional to blood flow velocity. Actual velocity is calculated from the Doppler equation; this requires the cosine of the vector between the direction of the ultrasound beam and that of blood flow. This can be applied to blood flow in ascending aorta and aortic arch (via a suprasternal approach), descending thoracic aorta (oesophageal approach), and intracardiac flow (e.g. transmitral from an apical approach). Spectral analysis of the Doppler frequency shifts produces velocity–time waveforms, the area of which represents 'stroke distance', i.e. the distance travelled by a column of blood with each LV systole. (Figure 10.4). The product of stroke distance and aortic (or mitral valve) cross-sectional area is stroke volume. Cross-sectional area can be measured echocardiographically. This additional measurement can be assumed from nomograms to provide a reasonable *estimate* of stroke volume.

- Corrected flow time (FTc) = flow time corrected to heart rate of 60/min (normal range 330–360 ms).
- FTc is inversely related to systemic vascular resistance. Thus, FTc falls with decreased preload or increased afterload (e.g. hypovolaemia, vasoconstriction, obstruction such as pulmonary embolism or tamponade) while FTc increases with vasodilatation.
- Peak velocity and acceleration indicate LV contractility. They are age dependent (Table 10.4). Values increase with positive inotropy and fall with negative inotropic states (e.g. heart failure, beta blockade).

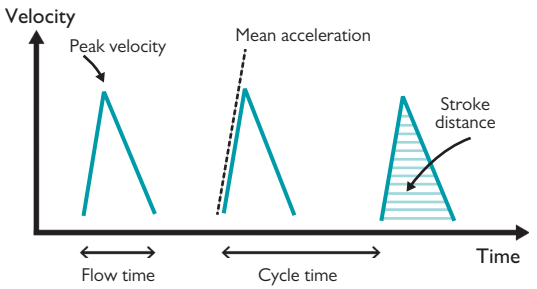

Fig. 10.4 Doppler velocity–time waveform.

Table 10.4 Normal range for peak velocity according to age

Age (years)	20	50	70
Normal peak velocity (cm/s)	90–120	60–80	50–70

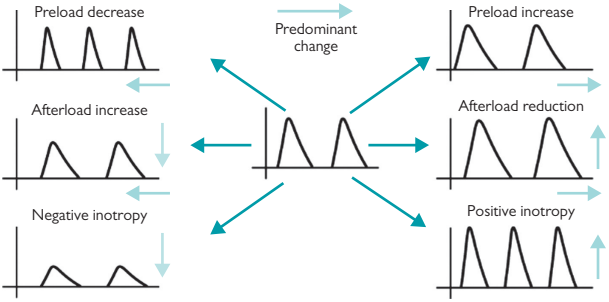

Fig. 10.5 Effect of haemodynamic changes on Doppler velocity time waveform shape.

Advantages

- Quick and minimally invasive.
- Reasonably accurate if performed properly.
- Measures left heart output, unaffected by mitral (unless measured transmitrally) or tricuspid regurgitation, or by intracardiac shunts.
- Continuous (via oesophageal approach)—may need repositioning.
- Other information on contractility, preload and afterload from waveform shape (Figure 10.5).
- Multiple studies showing outcome benefit in high-risk surgical patients from guided fluid optimization intra- or postoperatively.

Disadvantages

- Non-continuous (unless via oesophagus).
- Learning curve to ensure correct signal is insonated (5–10 patients for oesophageal, 15–20 for suprasternal, and 30+ for intracardiac).
- Unreliable with turbulent flow conditions e.g. intra-aortic balloon counterpulsation (oesophageal), aortic stenosis or regurgitation (suprasternal or intracardiac from aortic outflow tract), mitral regurgitation (transmitral).
- Oesophageal approach assumes proportionality of flow between upper and lower body is maintained (~30:70); this changes during aortic cross-clamping (vascular surgery) or use of epidural.
- Suprasternal measurements can be hampered by short neck or obesity (probe has to get behind sternum to insonate ascending aorta or arch correctly), mediastinal air (e.g. post cardiac surgery), and other co-located vessels, e.g. innominate artery.

Further reading

See Basic resuscitation, p358; Fluid challenge, p362; Hypotension, p408; Heart failure—assessment, p420.

Cardiac output—pulse contour analysis

Pulse contour analysis

The contour of the arterial pressure waveform is assumed to be proportional to stroke volume thereby allowing continuous monitoring of cardiac output. However, this relationship is heavily influenced by arterial compliance (relationship between pressure and volume) and aortic impedance. Thus, the major challenges for such technologies are to assess arterial compliance consistently and accurately, and to track changes in cardiac output when there are concurrent changes in compliance, e.g. during rapid blood loss, vasodilatation, or altering vasopressor dosing.

Users should also be aware of the changing morphology of the BP waveform from the central to peripheral circulation during alterations in blood flow redistribution, e.g. severe vasoconstriction. It is also essential to ensure an appropriately damped pressure waveform and non-kinking of the arm (radial) or groin (femoral).

Several commercial devices have their own proprietary algorithms to estimate stroke volume. The LiDCO™plus and PiCCO systems use an alternative cardiac output measuring technique (lithium dye dilution and peripheral thermodilution, respectively) for initial calibration and subsequent recalibration. The Flotrac® and LiDCO™rapid systems derive an estimate of cardiac output without a calibrating device using the patient's BP, sex, age, and body surface area. The overall accuracy of these systems and their ability to follow trends, especially if not calibrated against a reference technique, is questionable with an unstable circulation. Frequent recalibration (1–4-hrly), or more frequently, must be performed if circulatory status changes to any significant extent.

Advantages

- Continuous flow monitoring.
- Uses data from an arterial cannula *in situ* for pressure monitoring.
- Assessment of fluid responsiveness using pulse pressure, systolic pressure, or stroke volume variation.

Disadvantages

- Changes in vascular compliance (e.g. with changes in BP, cardiac output, vascular resistance, body temperature) affect accuracy, thus regular recalibration is needed.
- Cannot confirm accuracy of non-calibrated devices (stroke volume estimation or trend following) unless a reference technique is used.
- Requires a good quality, non-obstructed, non-damped waveform.
- Ongoing debate about relative signal quality from radial versus femoral.
- Unreliable with arrhythmias.
- Unreliable with aortic stenosis, severe peripheral vascular disease.
- Cannot be used with intra-aortic balloon counterpulsation.

Further reading

See Fluid challenge, p362; Hypotension, p408; Heart failure—assessment, p420.

Cardiac output—other techniques

Thoracic bioimpedance

Impedance changes originate in the thoracic aorta when blood is ejected from the LV. This is used to determine stroke volume from formulae utilizing the electrical field size of the thorax, baseline thoracic impedance, and fluctuation related to systole and ventricular ejection time. A correction factor for sex, height, and weight is used. The technique utilizes four pairs of electrodes placed in proscribed positions on the neck and thorax; these are connected to a dedicated monitor which measures thoracic impedance to a low-amplitude, high- (70 kHz) frequency 2.5 mA current applied across the electrodes.

Advantages

Quick, non-invasive, accurate in spontaneous breathing normal people.

Disadvantages

Discrepancies in critically ill patients, (especially if arrhythmias, intrathoracic fluid shifts, anatomical deformities, aortic regurgitation, metal within the thorax). Inability to verify signal.

Thoracic bioreactance

This technology increases signal-to-noise ratio by ~100-fold over bioimpedance. Four pairs of double electrodes are sited on the thorax just below the sternum and the mid-axial line just below the shoulders. The upper electrodes emit a low-level electrical current sensed by their lower pairs. The signal uses both bioimpedance and the relationship between the amount of thoracic fluid at any given timepoint and frequency shifts occurring as the electric current crosses the thorax. This produces the haemodynamic reactance waveform. Clinical experience, particularly in critically ill patients, is limited at present.

Direct Fick

The amount of substance passing into a flowing system equals the difference in concentration of the substance on each side of the system multiplied by flow. Cardiac output can be calculated by dividing total body oxygen consumption (VO_2) by the difference in O_2 content between arterial and mixed venous blood. Alternatively, carbon dioxide (CO_2) production can be used as the indicator. Arterial CO_2 can be derived non-invasively from end-tidal CO_2 while mixed venous CO_2 can be determined by rapid rebreathing into a bag until CO_2 levels have equilibrated.

Advantages

'Gold standard' for cardiac output estimation.

Disadvantages

- Requires measurement of mixed venous blood, leak-free open circuit, or a closed-circuit technique.
- VO_2 measurements via a metabolic cart are unreliable if FiO_2 is high.
- Lung O_2 consumption is not measured and may be high in acute respiratory distress syndrome and pneumonia.
- For CO_2—non-invasive but requires normal lung function.

Further reading

➔ Fluid challenge, p362; Hypotension, p408; Heart failure—assessment, p420.

Pressure & stroke volume variation

These can be used, within strict limitations (see below), to assess the likelihood of response of the circulation to a fluid challenge. The principle is based on the variation in size and height of the arterial pressure waveform during the respiratory cycle (Figure 10.6). In spontaneously breathing subjects, BP decreases on inspiration due to decreased left heart output. The range in normal subjects is 5–10 mmHg. The reverse is seen during positive pressure ventilation where BP decreases on expiration. Pulsus paradoxus is an exaggeration of this phenomenon seen with marked changes in intrathoracic pressure (e.g. severe asthma) or impaired left heart filling (e.g. pericardial tamponade).

Stroke volume variation (SVV)

$$\frac{SV_{max} - SV_{min}}{0.5(SV_{max} + SV_{min})}$$

Pulse pressure variation (PPV)

$$\frac{PP_{max} - PP_{min}}{0.5(PP_{max} + PP_{min})}$$

Variation >10–15% (the optimal positive and negative predictive values vary between studies) suggests a high likelihood of preload responsiveness. It can also indicate deleterious effects of PEEP on the circulation.

Systolic pressure variation (SPV)

The difference between maximal and minimal values of systolic pressure during one breath. As well as SPV, the delta down (Δdown) component (difference between systolic pressure during a short period of apnoea and the lowest value during a breath) >5 mmHg also predicts volume responsiveness.

No clear superiority is demonstrated for one technique over any other.

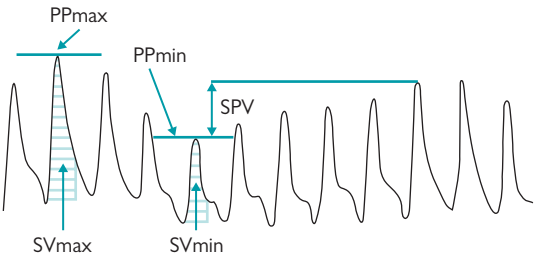

Fig. 10.6 Pulse pressure, systolic pressure and stroke volume variation. PP, pulse pressure; SPV, systolic pressure variation; SV, stroke volume.

Limitations of PPV, SPV, and SVV

- Unreliable in patients taking spontaneous breaths and/or high respiratory rates.
- Unreliable if tidal volume is <8 mL/kg.
- Unreliable with arrhythmias.
- Risk of volume overload in non-hypovolaemic conditions that cause LV underfilling, e.g. obstruction (e.g. pulmonary embolus, tamponade, atrial myxoma) or right heart failure (e.g. RV infarction).
- Vasodilatation may increase SVV.

Further reading

See Fluid challenge, p362.

Echocardiography—use & indications

Widely used as a bedside tool (point-of-care ultrasound (POCUS)) for rapid diagnosis and assessment of cardiac function and structural abnormalities in unstable patients. Echocardiography images (ultrasound reflected off various interfaces) can be misinterpreted so adequate training is crucial. Recognized courses with formal accreditation at basic and more advanced levels (Table 10.5) are now mandated to achieve necessary competencies.

Indications

TTE or TOE probes provide information on valve disease and function, global (systolic and diastolic) and regional ventricular function, chamber volumes, wall thickness, pericardial fluid or disease, aortic dissection, intracardiac shunt, pulmonary pressures, and cardiac output. It can be used to diagnose outflow tract obstruction, intracardiac masses (e.g. myxoma, thrombus), endocarditis, and pulmonary embolism.

Different areas of the heart are best imaged from different approaches, e.g. apical four-chamber, left parasternal long axis, subcostal (Figure 10.7). The inferior vena cava (IVC) (or superior vena cava for TOE) can be imaged to aid assessment of intravascular volume status.

Echocardiography is used in single- (M-mode), two-, or three-dimensional modes, and combined with continuous or pulse wave Doppler for functional and abnormal valve assessments. Analytical software (with AI) or formulae can estimate cardiac output and more detailed aspects of cardiac function.

Advantages

- Non-invasive, safe.
- Relatively quick.
- Provides useful data on cardiac structure, function, and pathologies.

Disadvantages

- Inter-observer variability, especially with novice operators.
- Not used for continuous monitoring.
- Body shape or pathology (e.g. emphysema) may impair image quality.
- TTE has access issues with drains, surgical wound dressings, and subcutaneous air.
- TOE is more invasive with (low) risk of oesophageal damage.

Table 10.5 Echocardiography competency levels

Focused	Point of care; recognize major causes of cardiac arrest/shock
Level 1	Differentiate normal from abnormal; diagnose common abnormalities; mentoring role
Level 2	Perform comprehensive transthoracic (TTE) and transoesophageal echocardiography (TOE); diagnose all cardiovascular abnormalities; supervisor role
Level 3	Perform specialist exams; use in invasive procedures

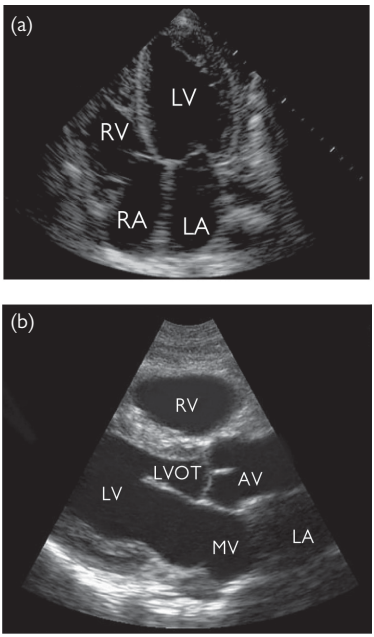

Fig. 10.7 (a) Apical four-chamber view. (b) Parasternal long-axis view. AV, aortic valve; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; MV, mitral valve; RA, right atrium; RV, right ventricle.

Assessment of hypotension/shock/acute dyspnoea

Consider:

- Severe hypovolaemia.
- Evidence of massive pulmonary embolism.
- LV dysfunction: identify causes and sequelae.
- RV dysfunction: identify causes and sequelae.
- Pericardial fluid.
- Aortic dissection.
- Acute valvular pathology.

Further reading

McLean A, Huang S, Hilton A (Eds). 2020. *Oxford Textbook of Advanced Critical Care Echocardiography*. Oxford: Oxford University Press.

Flower L, Madhivathanan P (Eds). 2022. *Point-of-Care Ultrasound in Critical Care*. Banbury: Scion Publishing.

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See Cardiac output—Doppler ultrasound, p206; Echocardiography—functional measurements, p216; Echocardiography—diagnosis, p218.

Echocardiography—functional measurements

Left ventricular systolic function

Ejection fraction (EF)

$$\text{Ejection fraction} = 100 \times \frac{\text{EDV} - \text{ESV}}{\text{EDV}}$$

EDV = end-diastolic volume; ESV = end-systolic volume.

Normal range 55–65%. EF falls with increasing dysfunction. A low EF may still generate a normal stroke volume if EDV is increased; and vice versa. EF can be derived by formulae, e.g. biplane Simpson's method using two- and four-chamber views to trace the endocardial contour. These overestimate compared to magnetic resonance imaging or ventriculography, and can be unreliable with poor image quality, arrhythmias, and regional wall motion abnormalities.

Cardiac output

Stroke volume calculated as product of (i) blood flow velocity–time integral (stroke distance) measured at left ventricular outflow tract (LVOT) or transmitrally and (ii) measurement of aortic diameter at LVOT to compute aortic cross-sectional area (πr^2).

Contractility (dP/dt)

Assessed using gradient of the upstroke of mitral regurgitant flow. This is taken to represent instantaneous LV systolic pressure (with left atrial pressure neglected). Normal >1200 mmHg/s.

Myocardial velocities, strain, and strain rate

These can be assessed in expert hands by tissue Doppler or speckle tracking. Changes can occur before EF falls.

Left ventricular diastolic function

Several tests are used to assess changes in left atrial and left ventricular end-diastolic pressures. The mitral inflow signal reflects the pressure difference between atrium and ventricle. Abnormal diastolic pressure affects the velocity and shape of the Doppler inflow signal, seen as:

- Altered early and late filling (E and A waves, Figure 10.8). Normally, most blood fills the ventricle in early diastole so the E wave is taller. Normal E:A ratio is 0.8–1.5. This increases in fit, young individuals, those with restrictive filling and severe mitral regurgitation. The ratio falls with impaired relaxation.
- Speed of relaxation of medial (med e′) and lateral (lat e′) LV muscle.
- E/e′ = ratio of early filling (E) to mean muscle relaxation velocity (e′). Normal <8, significantly abnormal if ≥14. Used to estimate left ventricular end-diastolic pressure (LVEDP).
- Consequences of raised left atrial pressures e.g. raised pulmonary pressures, dilated left atrium.

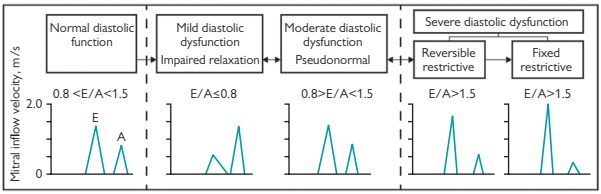

Fig. 10.8 E and A waves on the echocardiogram.

Right ventricular function

The RV shape limits estimates of volume. Estimates of size and function are thus limited to dimensions and area assessed by two-dimensional echo. RV contraction is complex and affected by LV function. It can be considered in both longitudinal and radial function terms.

- Tricuspid annular plane systolic excursion (TAPSE) is the distance travelled by the base of the RV on M-mode echo.
- Fractional area change:

$$\text{Fractional area change} = \frac{\text{RV diastolic area} - \text{RV systolic area}}{\text{RV diastolic area}}$$

Normal values: male >30%, female >35%.

Further reading

McLean A, Huang S, Hilton .(Eds). 2020. *Oxford Textbook of Advanced Critical Care Echocardiography*. Oxford: Oxford University Press.

Flower L, Madhivathanan P (Eds). 2022. *Point-of-Care Ultrasound in Critical Care*. Banbury: Scion Publishing.

See Cardiac output—Doppler ultrasound, p206; Echocardiography—use & indications, p214; Echocardiography—diagnosis, p218.

Echocardiography—diagnosis

Valvular disease (including prosthetic valves)

- Aortic stenosis—valve is usually thickened and calcified with reduced cusp separation and valve area. The degree of stenosis is calculated from the transvalvular jet velocity.
- Aortic regurgitation—identified by early closure of mitral valve, aortic dilatation, diastolic flow reversal in descending aorta, and regurgitant jet seen on continuous wave and colour flow Doppler.
- Mitral stenosis—narrowed valve area and increased mean gradient.
- Table 10.6 shows the measurements for diagnosis of aortic, mitral, and tricuspid stenosis.
- Mitral regurgitation—degenerative (primary) or functional (secondary to LV dysfunction). May see flail leaflet or ruptured papillary muscle. A dense central regurgitant jet reaches up to the posterior wall of the left atrium. Systolic flow reversal seen in pulmonary veins.
- Tricuspid regurgitation—central jet or eccentric wall impinging jet seen on Doppler, systolic flow reversal in hepatic vein.
- Infective endocarditis identified by:
  - presence of vegetations—mobile echo-dense masses on a valve or mural endocardium within the trajectory of a regurgitant jet and with no other anatomical explanation
  - presence of abscesses
  - new dehiscence of a valvular prosthesis.

Table 10.6 Criteria for definition of severe valve stenosis

	Aortic stenosis	Mitral stenosis	Tricuspid stenosis
Valve area (cm^2)	<1.0	<1.5	≤1.0
Indexed valve area (cm^2/m^2/BSA)	<0.6	–	–
Mean gradient (mmHg)	>40	≥10	≥5
Maximum jet velocity (m/s)	>4.0	–	–
Maximum gradient (mmHg)	>64	–	–

BSA = body surface area.

Structural abnormalities

- Regional wall motion abnormality—hypokinesia, akinesia, dyskinesia.
- Heart muscle disease:
  - dilated cardiomyopathy—LV dilation, systolic and diastolic dysfunction, impaired global contractility, but normal wall thickness
  - restrictive cardiomyopathy—biatrial dilatation, hypertrophied ventricles, cavities initially small, normal to depressed systolic function
  - hypertrophic obstructive cardiomyopathy (HOCM)—LV wall thickness ≥15 mm in ≥1 myocardial segment and no other cause of LV hypertrophy; systolic anterior motion of mitral valve

- Takotsubo (stress) cardiomyopathy—resembles an octopus trap with akinesia of LV apical and mid-ventricular segments and hypercontractile base. The apex is dilated (apical ballooning). LV dysfunction may vary
- pericardium—effusion, tamponade, constrictive pericarditis
- acute RV overload/pulmonary embolism—interventricular septum is D-shaped, bulging into LV; RV wall hypokinesis and dilatation; dilated PAs with systolic pressure >30 mmHg; severe tricuspid regurgitation; elevated right atrial pressure; dilated IVC with no respiratory collapse
- peak PA pressure calculated from continuous wave Doppler of tricuspid regurgitant (TR) jet where $P = 4(TRmax^2)$. Values ≥2.8 m/s are abnormal. Mean PA pressure estimated as 0.61 × systolic PA pressure + 2 mmHg
- intracardiac shunt or patent foramen ovale diagnosed by injecting microbubbles or contrast.

Determining fluid status and responsiveness

- Respiratory variations in transpulmonary pressure transmit to the right heart, affecting venous return and IVC diameter. In spontaneously breathing patients (or making spontaneous efforts on mechanical ventilation), the negative transpulmonary pressure at the onset of inspiration induces a variable degree of IVC collapse depending on volaemic status. A normal diameter (1.2–1.7 cm measured distal to the hepatic vein) with a 50% decrease on inspiration suggests a normal RA pressure. A small IVC (<1.2 cm) with spontaneous collapse suggests hypovolaemia, whereas a dilated IVC with collapsibility <50%—or even absent—suggests increasingly high right heart pressures.
- By contrast, patients receiving controlled intermittent mandatory ventilation who are volume-deplete have significant IVC distension during inspiration.
- Transmitral/aortic Doppler flow velocity variation during the respiratory cycle is also suggestive of LV underfilling. This may be due to hypovolaemia or to flow obstruction, e.g. pulmonary embolus, tamponade.

Further reading

McLean A, Huang S, Hilton A (Eds). 2020. *Oxford Textbook of Advanced Critical Care Echocardiography*. Oxford: Oxford University Press.

Flower L, Madhivathanan P (Eds). 2022. *Point-of-Care Ultrasound in Critical Care*. Banbury: Scion Publishing.

See Cardiac output—Doppler ultrasound, p206; Echocardiography—use & indications, p214; Echocardiography—functional measurements, p216.

Tissue perfusion monitoring

Near-infrared spectroscopy (NIRS)

This non-invasive technique utilizes near-infrared light to quantify tissue oxyhaemoglobin concentration (StO_2) or, more accurately, microvascular oxygenation in arterioles, capillaries, and venules. It may measure oxymyoglobin though to what extent this influences the measurement is uncertain. It is usually measured in a peripheral muscle, e.g. thenar eminence or deltoid. As normal resting values vary widely (70–95%), it is a poor indicator of mild to moderate shock states. It can be useful in detecting peripheral compartment syndrome. More utility can be gained from the rate of fall in StO_2 during proximal arterial occlusion (and/or rise in StO_2 on release of occlusion). A reduced rate of fall suggests decreased tissue O_2 utilization ± microvascular perfusion. A slow rate of recovery suggests poor perfusion.

Specialized spectrophotometers can detect mitochondrial cytochrome oxidase redox states—this has been studied in neonatal brains though there is potential for extrapolation to other organs.

Cautions

- Reliability poor if used in muscle groups with significant overlying adipose tissue, e.g. pectoral muscle in females, deltoid in the obese.
- Dark skin pigmentation may affect the readings.

Microvascular circulation visualization

This non-invasive technique uses sidestream dark field imaging (SDF) to visualize the microcirculation. An earlier technique used orthogonal polarization spectroscopy (OPS) but this is no longer commercially available. Briefly, OPS utilized polarized light scattered by the tissue and collected by the objective lens. High-quality images of the microcirculation were obtained by absorbing surface structures lit up by depolarized light returning from deeper structures. SDF uses the same principle but, rather than polarized light, uses light-emitting diodes that are isolated from its inner image-conducting core.

The technique is mainly used sublingually, but can be applied to other areas, e.g. rectum or bowel stoma. The software enables off-line (and more recently online) semi-quantitative analysis of microcirculatory alterations affecting capillary density and heterogeneity of blood flow. The proportion of perfused capillaries may vary as may flow characteristics within separate capillaries, e.g. continuous or stop-go. Plasma and cellular factors, e.g. viscosity, red cell rheology, degree of platelet and neutrophil rolling, and endothelial swelling all affect microvascular flow characteristics.

Persisting abnormalities are a good prognostic indicator in shock. Applicability of changes in the sublingual circulation to other beds is uncertain; discrepancy has been demonstrated with the intestinal microcirculation in sepsis.

Cautions

- Excess probe pressure will affect the microcirculation especially when arterial pressure is low.

Chapter 11

Neurological monitoring

Intracranial pressure monitoring

Indications

Used to monitor intracranial pressure (ICP) and response to treatment. May be used in cases of traumatic brain injury (TBI), Glasgow Coma Scale score ≤8, or with an abnormal computed tomography (CT) scan showing mass lesions, oedema, midline shift, or compressed basal cisterns. Up to 50% of patients who subsequently develop raised ICP may have a normal CT scan on admission. Also used to manage patients with encephalopathy, post neurosurgery, and intracranial haemorrhage. Though a raised ICP can be related to poor prognosis after TBI the converse is not true. Use of ICP monitoring has not been shown to reduce mortality in TBI.

Methods of monitoring ICP

Ventricular monitoring

A catheter is inserted into the lateral ventricle via a burr hole. The catheter may be connected to a pressure transducer or may contain a fibreoptic pressure monitoring device. Both catheters require regular recalibration. Systems should be tested for patency and damping by temporarily raising ICP (e.g. with a cough or by occluding a jugular vein). Cerebrospinal fluid may be drained through the ventricular catheter to reduce ICP (external ventricular drain).

Subdural monitoring

The dura is opened via a burr hole and a hollow bolt inserted into the skull. The bolt may be connected to a pressure transducer or admit a fibreoptic or hi-fidelity pressure monitoring device. A subdural bolt is easier to insert than ventricular monitors. The main disadvantages of subdural monitoring are a tendency to underestimate ICP and damping effects. Again, calibration and patency testing should be done regularly.

Complications

- Infection: particularly after 5 days.
- Haemorrhage: particularly with coagulopathy or difficult insertion.

Using ICP monitoring

Normal ICP is <10 mmHg. A raised ICP is usually treated when >25 mmHg in TBI. There may be sustained or fluctuating rises in ICP to 50–100 mmHg which are associated with worse outcomes. Cerebral perfusion pressure (CPP) is the difference between mean blood pressure (BP) and mean ICP. Treatment aimed at reducing ICP may also reduce mean BP. Target CPP is >50–60 mmHg.

Further reading

Chesnut R, Temkin N, Carney N, et al. 2012. 'Global Neurotrauma Research Group. A trial of intracranial-pressure monitoring in traumatic brain injury'. *N Engl J Med* 367: pp2471–81. doi:10.1056/NEJMoa1207363

See Intracranial haemorrhage, p478; Subarachnoid haemorrhage, p480; Raised intracranial pressure, p484; Head injury—general management, p632.

Jugular venous bulb saturation

Retrograde passage of a fibreoptic catheter from the internal jugular vein into the jugular bulb enables continuous monitoring of jugular venous bulb oxygen saturation (SjO_2). This represents the balance between global brain oxygen delivery and consumption. It can be used in conjunction with other monitors of cerebral haemodynamics such as middle cerebral blood flow (CBF), cerebral arterio-venous lactate difference, and ICP to direct management. It only gives information about global not regional cerebral metabolism. If both CBF and oxygen consumption fall, the SjO_2 may remain unchanged.

Principles of SjO_2 management

- The normal range is 55–75%.
- In the absence of anaemia and with normal SaO_2, SjO_2 >75% suggests luxury perfusion (hyperaemia) or global infarction.
- SjO_2 values of 50–55% correspond to cerebral hypoperfusion.
- SjO_2 values <50% suggest global ischaemia and are usually associated with increased cerebral lactate production.
- Knowledge of SjO_2 allows optimization of brain blood flow to avoid excessive or inadequate perfusion and iatrogenic hypoperfusion induced through treating raised ICP aggressively with diuretics and hyperventilation.
- Studies in brain trauma have found higher mortality if jugular venous desaturation occurs, and a significant relationship between CPP and SjO_2 when CPP <70 mmHg. A falling SjO_2 may be an indication to increase CPP. No prospective randomized trial has yet been performed to study impact on outcomes.
- Approximately 85% of cerebral venous drainage passes down one of the internal jugular veins (usually right). SjO_2 usually represents drainage from both hemispheres and is equal on both sides. After focal injury, this pattern of drainage may alter.

Insertion technique

1. Insert introducer sheath rostrally in internal jugular vein.
2. Calibrate fibreoptic catheter pre-insertion.
3. Insert catheter via introducer sheath; advance to jugular bulb.
4. Withdraw introducer sheath.
5. Confirm (i) free aspiration of blood via catheter, (ii) satisfactory light intensity reading, (iii) satisfactory positioning of catheter tip by lateral cervical X-ray (high in jugular bulb, above second cervical vertebra).
6. Perform *in vivo* calibration, repeat calibration 12-hrly.

Troubleshooting

If the catheter is sited too low in the jugular bulb, erroneous SjO_2 values may result from mixing of intra- and extracerebral venous blood. This could be particularly pertinent when CBF is low.

Ensure light intensity reading is satisfactory; if too high the catheter may be abutting against a wall and if low the catheter may not be patent or have a small clot over the tip.

Before treating the patient, always confirm the veracity of low readings against a blood sample drawn from the catheter and measured in a co-oximeter confirming.

Complications

- Complications of internal jugular line insertion.
- Venous thrombosis potentially leading to infarction.

Formulae

$$CMRO_2 = CBF \times 1.34 \times [Hb] \times (SaO_2\text{-}SjO_2)$$

where $CMRO_2$ = cerebral metabolism of oxygen; CBF = cerebral blood flow; Hb = haemoglobin; SaO_2 (%) = arterial oxygen saturation; SjO_2 = jugular bulb oxygen saturation.

$$\text{Cerebral oxygen extraction ratio} = \left(\frac{SaO_2 - SjO_2}{SjO_2} \right)$$

$$\text{Cerebral perfusion pressure} = \text{systemic BP} - \text{intracranial pressure}$$

Further reading

See Intracranial pressure monitoring, p224; Other neurological monitoring, p230; Intracranial haemorrhage, p478; Subarachnoid haemorrhage, p480; Raised intracranial pressure, p484; Head injury—general management, p632.

Electroencephalogram (EEG)

EEG monitoring

The EEG uses electrodes placed over the scalp and measures voltage fluctuations in ionic currents in neurones. This reflects changes in cortical electrical function, dependent on cerebral perfusion and oxygenation.

Bispectral index (BIS) monitor

BIS is a statistical index derived from the EEG and expressed as a score between 0 and 100. Scores below 50 have been reliably associated with anaesthesia-induced unconsciousness. Assessment in the critically ill patient is complicated by confounding factors such as septic encephalopathy, brain trauma, and hypoperfusion. A low score is related to deep or excessive sedation and may allow dose reduction (or cessation) of sedative agents, especially in paralysed patients.

Cerebral function monitor (CFM)

The CFM is a single channel, filtered trace from two recording electrodes placed over the parietal regions of the scalp. A third electrode may be used in the midline to help with interference detection. The parietal recording electrodes are usually placed close to watershed areas of the brain in order to allow maximum sensitivity for ischaemia detection. Voltage is displayed against time on a chart running at 6–30 cm/h.

Use of CFM

CFM detects cerebral ischaemia; increasingly prolonged electrical silence (burst suppression) gives early warning (Figure 11.1).

Sedation produces a fall in baseline to <5 μv, equivalent to burst suppression. This indicates maximum reduction in cerebral O_2 consumption and that no further benefit would be gained from additional sedation. Subclinical seizure activity may be detected where muscle relaxants have been used (Figure 11.2). Other patterns are shown in Figure 11.3.

Further reading

See Sedatives, p322; Tranquillizers, p324; Coma, p466; Generalized seizures, p472; Head injury—general management, p632; Hypothermia, p652; Brainstem death, p714.

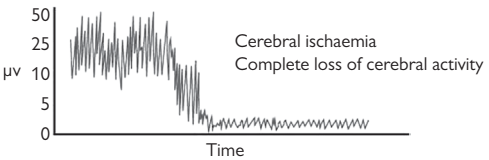

Fig. 11.1 Typical CFM recording in cerebral ischaemia.

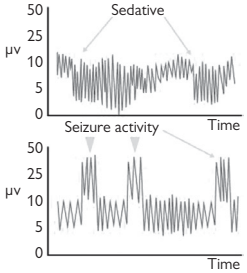

Fig. 11.2 Typical CFM recording in sedation or seizure.

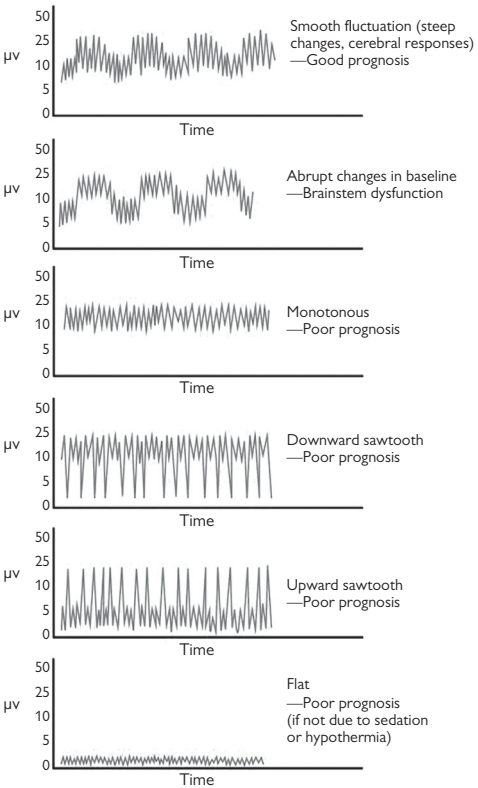

Fig. 11.3 Typical CFM patterns.

Other neurological monitoring

Cerebral blood flow

CBF can be measured by radioisotope techniques utilizing tracers such as ^{133}Xenon given intravenously or by inhalation. This remains a research tool in view of the radioactivity exposure and the usual need to move the patient to a gamma-camera.

Transcranial Doppler

Middle cerebral artery (MCA) blood flow can be assessed non-invasively by transcranial Doppler (TCD) ultrasonography. The pulsatility index (PI) relates to cerebrovascular resistance with a rise in PI indicating a rise in resistance and cerebral vasospasm. Normal PI is <1.2. PI values >2.13 correlate with ICP >22 mmHg, a cut-off often used to denote raised ICP.

$$PI = \frac{(PSV - EDV)}{MV}$$

PSV = peak systolic velocity; EDV = end-diastolic velocity; MV = mean velocity.

ICP can be estimated by the formula:

$$ICP = (10.93 \times PI) - 1.28$$

Normal MCA blood flow velocity is <80 cm/s. Vasospasm is inferred with values >120 cm/s and severe vasospasm when >200 cm/s. Low values of common carotid end-diastolic blood flow and velocity can predict brain death. Impaired reactivity of CBF to changes in PCO_2 (in normal brains 3–5% per mmHg PCO_2 change) is another marker of poor outcome.

Midline shift and diagnosis of circulatory arrest and brain death can be suggested by changes in the TCD flow signal.

Pupillometer

Automated pupillometry provides a more accurate measurement of pupillary size, symmetry, and reactivity via measurement of the light reflex.

Near-infrared spectroscopy (NIRS)

- Near-infrared (700–1000 nm) light passed across the head is absorbed by Hb (oxy- and deoxyHb), myoglobin, and oxidized cytochrome aa_3 (the terminal part of the electron transport chain).
- The sum of (oxy + deoxy) Hb is considered an index of cerebral blood volume (CBV) change, and the difference as an index of change in Hb saturation assuming no variation occurs in CBV. CBV and flow can be quantified by measuring the response to changes in the Fraction of inspired oxygen (FiO_2).

- CBF is measured by a modification of the Fick principle. OxyHb is used as the intravascular non-diffusible tracer, its accumulation being proportional to the arterial inflow of tracer. Good correlations have been found with the ^{133}Xenon technique.
- Cytochrome aa_3 cannot be quantified by NIRS but its redox status may be followed to provide an indication of mitochondrial function.
- Movement artefact must be avoided.

Lactate

The brain normally utilizes lactate as a fuel. However, in states of severely impaired cerebral perfusion, the brain may become a net lactate producer with venous lactate rising above the arterial value. A lactate oxygen index can be derived by dividing the venous-arterial lactate difference by the arterio-jugular venous oxygen difference. Values >0.08 are consistently seen with cerebral ischaemia.

Cerebral microdialysis

Microdialysis catheters may be placed in the brain during surgery to assess brain metabolism. Extracellular fluid chemicals diffuse into the catheter and are sampled for bedside analysis of, e.g. glucose, lactate, and pyruvate. An elevated extracellular fluid lactate:pyruvate ratio is a sensitive marker of ischaemia following acute brain injury. The technique can monitor tissue at risk of ischaemia, e.g. due to vasospasm or to determine the safe lower limit of CPP.

Further reading

Lau V, Arntfield R. 2017. 'Point-of-care transcranial Doppler by intensivists'. *Crit Ultrasound J* 9: 21. doi:10.1186/s13089-017-0077-9

See Tissue perfusion monitoring, p220; Lactate, p246.

Chapter 12

Laboratory & point-of-care monitoring

Renal function

Biomarkers can be measured in blood, urine, as well as other fluids such as abdominal drain fluid (e.g. if ureteric disruption is suspected). For normal ranges see Table 12.1.

Urea

A product of the urea cycle resulting from ammonia breakdown depends upon adequate liver function for synthesis and adequate renal function for excretion. Low levels are seen in cirrhosis and high levels in renal failure or gastrointestinal haemorrhage (from absorption of blood).

Uraemia is a clinical syndrome including lethargy, drowsiness, confusion, pruritus, and pericarditis resulting from high plasma levels of urea or, more correctly, nitrogenous waste products (azotaemia).

The ratio of urine:plasma urea may help distinguish between oliguria of renal or pre-renal origin. Higher ratios (>10:1) occur in pre-renal conditions, e.g. hypovolaemia and low levels (<4:1) with direct renal causes.

Previously, 24 h measurement of urinary urea (or nitrogen) excretion was used as a guide to nutritional protein replacement, but is no longer considered a useful routine tool.

Creatinine

A product of creatine metabolism, creatinine production depends on creatine generated in liver, kidneys, and pancreas, ingestion (e.g. red meat), and muscle mass and function. Muscle phosphocreatine acts as a reserve of high-energy phosphate that can be rapidly mobilized. Production decreases in critical illness. Low levels occur with malnutrition and high levels with muscle breakdown (rhabdomyolysis) and impaired excretion (renal failure). In renal failure, plasma creatinine >120 μmol/L suggests reduced creatinine clearance (<25 mL/min). Plasma half-life increases from 4 h to 24–72 h with a falling glomerular filtration rate (GFR).

The usual plasma urea (mmol/L):creatinine (μmol/L) ratio is ~1:10. Lower ratios in a critically ill patient suggest rhabdomyolysis while higher ratios are seen in cirrhosis, malnutrition, hypovolaemia, and hepatic failure.

The ratio of urine:plasma creatinine may help distinguish between oliguria of renal or pre-renal origin. Higher ratios (>40) are seen in pre-renal conditions and low levels (<20) with direct renal causes.

Table 12.1 Normal serum ranges

Urea	2.5–6.5 mmol/L
Creatinine	70–120 μmol/L (depends on lean body mass)
Creatinine clearance	85–125 mL/min (male) 75–115 mL/min (female)

Creatinine clearance

Creatinine clearance is a measure of glomerular filtration. Once filtered, only small amounts of creatinine are re-absorbed.

$$\text{Creatinine clearance} = \frac{U \times V \times 1000}{P \times T}$$

where U = urine creatinine (mmol/L), V = urine volume (mL), P = plasma creatinine (μmol/L) and T = time of urine collection (min).

Glomerular filtration rate

GFR is calculated as:

$$\frac{\text{Urine Y (mg/ml)} \times \text{Urine flow (ml/min)}}{\text{Plasma Y mg/ml}}$$

where Y = a substance that is completely excreted.

Creatinine clearance approximates to GFR as the glomerulus freely filters creatinine. However, as creatinine is also secreted by peritubular capillaries this overestimates GFR by 10–20%.

Laboratories increasingly report estimated GFR (eGFR). This is calculated from complex equations such as the CKD-EPI Creatinine equation (2021) or the MDRD equation. Normal GFR is >90 mL/min/1.73 m². The eGFR may be inaccurate in the severely malnourished and morbidly obese. The eGFR equations assume steady-state plasma creatinine levels so are not valid if changing acutely, e.g. during acute kidney injury (AKI) or patients receiving dialysis.

Other biomarkers

In addition to urea and creatinine, >30 novel biomarkers have been proposed to assess renal injury or dysfunction. They can be stratified into markers reflective of:

- Glomerular integrity (albuminuria, proteinuria).
- Glomerular filtration (serum cystatin C).
- Tubular damage (e.g. blood or urine neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), *N*-acetyl-D-glucosaminidase (NAG)).
- Tubular stress (e.g. insulin-like growth factor binding protein 7 (IGFBP-7), tissue inhibitor metalloproteinase 2 (TIMP-2)).
- Intra-renal inflammation (e.g. interleukin (IL)-18).

Many of these biomarkers rise in advance of urea and creatinine and can prognosticate for the development of AKI. However, no large prospective studies have yet shown any outcome improvement through their use.

Further reading

Ostermann M, Joannidis M. 2016. 'Acute kidney injury 2016: diagnosis and diagnostic workup'. *Crit Care* 20:299. doi: 10.1186/s13054-016-1478-z

Ostermann M, Zarbocl A, Goldstein S, et al. 2020. 'Recommendations on acute kidney injury biomarkers from the Acute Disease Quality Initiative Consensus Conference: a consensus statement'. *JAMA Network Open* 3:e2019209. doi: 10.1001/jamanetworkopen.2020.19209

See Oliguria, p426; Acute kidney injury—diagnosis, p428.

Urinalysis

Techniques

- Biochemical/metabolic (Table 12.2):
  - colorimetric 'dipsticks' read manually from reference chart or by an automated machine within 15–120 s of dipping in urine (see manufacturer's instructions). Usually performed at the bedside
  - can be measured in some point-of-care analysers used for plasma electrolyte measurement. Recalibration of the machine or special dilution techniques may be required
  - laboratory analysis, e.g. urea, osmolality, electrolytes, creatinine, myoglobin
  - toxicology.
- Haematological dipstick or laboratory testing for haemoglobin (Hb), white cells.
- Microbiological—microscopy, culture, sensitivity; antigen testing (e.g. pneumococcus, *Legionella*).
- Renal disease—usually by microscopy and laboratory testing.

Associated tests

Some of the above investigations are performed in conjunction with a blood test, e.g. urine:plasma ratios of urea, creatinine, and osmolality to distinguish renal from pre-renal causes of oliguria; 6 h or 24 h urine collection plus plasma creatinine for creatinine clearance estimation.

Cautions

- White blood cells, proteinuria, and mixed bacterial growth often occur in catheterized patients and do not necessarily indicate infection.
- Urinary nitrite may indicate a possible urinary tract infection.
- A 'positive' dipstick test for blood does not differentiate between haematuria, haemoglobinuria, or myoglobinuria.
- Only conjugated bilirubin is excreted into the urine; unconjugated bilirubin is not water-soluble.
- Urinary sodium and potassium levels are increased by diuretic usage.
- Urinary ketones test only detects acetoacetate whereas blood ketones also measure β-hydroxybutyrate, the predominant ketone produced by fat metabolism.

Further reading

➔ See Virology, p258; Diabetic ketoacidosis, p542; Hyperosmolar diabetic emergencies, p544.

Table 12.2 Common urinalysis tests

Biochemical/metabolic	
pH	Dipstick
Glucose	Dipstick
Ketones	Dipstick
Protein	Dipstick, laboratory
Bilirubin	Dipstick
Nitrite	Dipstick
Sodium, potassium	Electrolyte analyser, laboratory
Urea, creatinine, nitrogen	Laboratory
Osmolality	Laboratory
Specific gravity	Bedside gravimeter, laboratory
Myoglobin	Laboratory, positive dipstick to blood
Drugs, poisons	Send to Poisons Reference Laboratory
Haematological	
Red blood cells	Microscopy, positive dipstick to blood
Haemoglobin	Laboratory, positive dipstick to blood
Neutrophils	Dipstick, laboratory
Microbiological	
Bacteriuria	Microscopy, culture
Tuberculosis (TB)	Microscopy, culture(early morning specimens)
Legionnaire's disease	Laboratory
Pneumococcus	Laboratory
Nephro-urological	
Haematuria	Microscopy
Granular casts	Microscopy
Protein	Laboratory
Sodium, potassium	Electrolyte analyser, laboratory
AKI biomarkers	Laboratory
Malignant cells	Cytology

Electrolytes (Na^+, K^+, Cl^-, HCO_3^-)

Measured accurately in plasma or urine by direct ion-selective electrodes (DISE), though these are sensitive to interference by excess liquid heparin.

Plasma levels of sodium and potassium poorly reflect intracellular levels where concentrations are reversed. Likewise, they do not necessarily reflect total body levels. Patients can become symptomatic and experience life-threatening problems with extreme changes in either direction. For normal ranges see Table 12.3.

Table 12.3 Normal plasma ranges

Sodium	135–145 mmol/L
Potassium	3.5–5.3 mmol/L
Chloride	95–105 mmol/L
Bicarbonate	23–28 mmol/L
Anion gap	<11 mmol/L

Sodium

Urinary excretion depends on intake, total body balance, acid–base balance, hormones (including antidiuretic hormone, aldosterone, corticosteroids, atrial natriuretic peptide), drugs (particularly diuretics, non-steroidal anti-inflammatories, and angiotensin-converting enzyme inhibitors), and renal function.

In oliguria, urinary Na^+ levels <10 mmol/L suggest a pre-renal cause whereas >20 mmol/L is seen with direct renal damage. This does not apply if diuretics have been given previously.

True hyponatraemia (<135 mmol/L) is associated with a low serum osmolality (<280 mOsm/kg). Pseudohyponatraemia is a laboratory artefact due to the presence of another abnormal solute that affects the measurement. This solute can be lipid (hyperlipidaemia), protein (e.g. high immunoglobulin or light/heavy chain levels, haematological malignancy), or other (e.g. mannitol). Some include hyperglycaemia as a cause; however, this is real rather than artefactual because of the hypertonic hyperosmolar shift in fluid resulting in a true dilutional hyponatraemia. With pseudohyponatraemia, serum osmolality is normal (280–300 mOsm/kg). DISE potentiometry, as used in point-of-care blood gas analysers, is not prone to this artefactual error as opposed to many formal laboratory analysers that utilize indirect ion-selective electrode (IISE) potentiometry that requires a correction factor affected by a solute load higher than the normal 7% found in plasma.

Potassium

Plasma K^+ levels are affected by plasma H^+ levels; a metabolic acidosis reduces urinary potassium excretion and displaces potassium from the cells into the bloodstream. The opposite occurs with a metabolic alkalosis.

Serum (but not plasma) potassium levels may be spuriously elevated by tight tourniquets, thrombocytosis (0.15 mmol/L rise for every 10×10^9/L

elevation in the platelet count), or leukocytosis due to increased potassium release during clot formation. Blood taken upstream of an infusion containing potassium may also cause spurious hyperkalaemia.

Chloride and bicarbonate

Bicarbonate levels vary with acid–base balance. In the kidney, Cl^- reabsorption is increased when HCO_3^- reabsorption is decreased, and vice versa. Plasma [Cl^-] tends to vary inversely with plasma [HCO_3^-], keeping total anion concentration normal. A raised [Cl^-] (producing a hyperchloraemic metabolic acidosis) is seen with excess administration of saline solutions.

Anion gap

The anion gap (AG) is the difference between unestimated anions (e.g. phosphate, ketones, lactate) and cations.

$$AG = \left(Na^+ + K^+\right) - \left(Cl^- + HCO_3^-\right)$$

With modern ion-selective electrodes, the normal AG is <11 mmol/L. Previous normal ranges (<20 mmol/L) were measured by older technologies.

In metabolic acidosis, an increased AG occurs with renal failure, ingestion of acid, ketoacidosis, and hyperlactataemia whereas a normal gap (usually associated with hyperchloraemia) is found with excess saline administration, decreased acid excretion (e.g. Addison's disease, renal tubular acidosis), or loss of base (e.g. diarrhoea, pancreatic/biliary fistula, acetazolamide, ureterosigmoidostomy).

Further reading

Theis S, Khandhar P. 2022. 'Pseudohyponatremia'. In: *StatPearls* [*Internet*]. StatPearls Publishing: Treasure Island (FL). Accessed September 2023. www.ncbi.nlm.nih.gov/ books/NBK553 207/

➲ See Blood gas analysis, p174; Electrolyte management, p512; Hypernatraemia, p514; Hyponatraemia, p516; Hyperkalaemia, p518; Hypokalaemia, p520; General acid–base principles, p532; Metabolic acidosis, p534.

Calcium, magnesium, & phosphate

For normal ranges see Table 12.4.

Calcium

Measurement of the ionized fraction is more relevant than total plasma levels (or total plasma corrected for albumin) as the ionized fraction is responsible for the extracellular actions of calcium and symptomatology.

High calcium levels occur with hyperparathyroidism, sarcoidosis, and certain malignancies, while low levels are seen in renal failure, severe pancreatitis, hypomagnesaemia, and hypoparathyroidism. Increasing use of regional citrate anticoagulation (and calcium reversal) for renal replacement therapy requires regular monitoring of ionized calcium.

Magnesium

Plasma levels poorly reflect intracellular or whole-body stores, 65% of which is in bone and 35% in cells. The ionized fraction is ~50% of the total plasma level.

High magnesium levels are seen with renal failure and excessive administration; this rarely requires treatment unless serious cardiac conduction problems or neurological complications (respiratory paralysis, coma) intervene. Low levels occur following severe diarrhoea, diuretic therapy, and alcohol excess and may induce tachyarrhythmias and hypocalcaemia.

Magnesium is used therapeutically for conditions including ventricular and supraventricular arrhythmias, pre-eclampsia, seizures, and asthma. Supranormal plasma levels of 1.5–2.0 mmol/L are often sought (2.0–2.5 mmol/L for pre-eclampsia).

Magnesium levels tend to follow potassium levels. Hypokalaemia may be resistant to treatment unless magnesium is corrected first.

Phosphate

Serum only contains 1% of total body phosphate. Low levels (sometimes <0.1 mmol/L) can occur acutely with critical illness but may be chronically low with alcoholism, malnutrition, and chronic diuretic usage. High levels are seen with renal failure and bowel ischaemia.

Both hypo- and hyperphosphataemia are associated with an increased mortality risk (especially hyper-) in critical illness. This likely relates to the underlying condition rather than the phosphate level per se.

Although hypophosphataemia is claimed to cause muscle weakness, failure to wean, and myocardial dysfunction, an evidence base is lacking. No studies have been performed to show benefit from correction. Plasma levels usually correct spontaneously concurrent with clinical improvement.

Table 12.4 Normal plasma ranges

Calcium	2.2–2.6 mmol/L
Ionized calcium	1.05–1.2 mmol/L
Magnesium	0.7–1.0 mmol/L
Phosphate	0.7–1.4 mmol/L

Further reading

Hofmaenner DA, Singer M. 2022. 'Challenging management dogma where evidence is non-existent, weak or outdated'. *Intensive Care Med* 48: pp548–58. doi: 10.1007/s00134-022-06659-4

See Hypomagnesaemia, p524; Hypercalcaemia, p526; Hypocalcaemia, p528; Hypophosphataemia, p530; Pre-eclampsia & eclampsia, p686.

Cardiac function & injury

The diagnosis of myocardial infarction (MI) (acute coronary syndrome) has been redefined as a typical rise then fall in troponin, or a more rapid rise and fall in creatine kinase myocardial band (CK-MB), with one or more of:

- Ischaemic symptoms.
- Development of pathological Q waves on electrocardiogram (ECG).
- ECG ST elevation or depression.

Troponins

Troponins are bound to the actin filament within muscle and involved in excitation–contraction coupling. Cardiac troponin T and I are coded by specific genes and are distinct from skeletal muscle troponins. Neither is detectable in healthy individuals, but both are released into the bloodstream from cardiomyocytes damaged by necrosis, toxins, and inflammation. They become detectable by 4–6 h after myocardial injury, peak at 14–18 h, and can persist for up to 12 days (Figure 12.1). Current assays are highly specific as they use recombinant human cardiac troponin T (Trop T) as a standard. High-sensitivity troponin (hs-Trop T) assays are increasingly being used as levels rise more rapidly following cardiac injury. Troponin can be measured with point-of-care devices.

Troponin levels can also rise markedly with other cardiac insults, e.g. tachycardia (supraventricular/ventricular tachycardia), pericarditis, myocarditis, sepsis, heart failure, severe exertion, and pulmonary embolism (PE). Levels are elevated in renal failure due to delayed excretion. The degree of rise post-MI or during critical illness correlates with a worse outcome.

A positive test is when the cardiac troponin exceeds the 99th percentile of values for a control group on ≥1 occasion during the first 24 h after the index clinical event. The negative predictive value after an acute MI is probably strongest after 6 h. Sensitivity peaks at 12 h but with lower specificity. With renal dysfunction, higher levels are needed to diagnose myocardial damage due to impaired excretion.

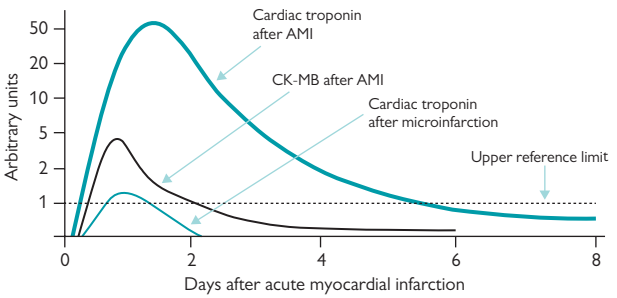

Fig. 12.1 Pattern of troponin and cardiac iso-enzyme change after myocardial infarction. AMI, acute myocardial infarction.

Cardiac enzymes

CK is detectable in plasma within a few hours of myocardial injury. The cardiac-specific CK-MB isoform can be measured if there is concurrent skeletal muscle injury. CK and aspartate aminotransferase (AST) peak by 24 h and fall over 2–3 days whereas the rise and subsequent fall in plasma lactate dehydrogenase takes 1–2 days longer (Figure 12.1).

Brain (or B-type) natriuretic peptide (BNP)

Cardiomyocytes produce and secrete natriuretic peptides. Plasma levels rise in various conditions, but generally suggest left and/or right ventricular dysfunction associated with heart failure (sensitivity 90–100% and specificity 70–80%). BNP levels rise with increasing dysfunction. Numerous commercial assays for BNP or N-terminal (NT)-proBNP are now available, each with their own diagnostic range. NT-proBNP has a longer half-life and therefore remains in the bloodstream in higher concentrations. Can be useful as a screening tool for patients with dyspnoea, prognostication, and for titration of therapy. Levels increase with age and are higher in females. Levels also rise in renal failure in the absence of fluid overload (due to lack of excretion), and pulmonary disease with right ventricular strain (e.g. pulmonary embolus).

Further reading

Alpert J, Thygesen K, Antman E, et al. 2000. 'Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction'. *J Am Coll Cardiol* 36: pp959–69. doi: 10.1016/S0735-1097(00)00804-4

McCullough P, Nowak R, McCord J, et al. 2002. 'B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study'. *Circulation* 106: pp416–22. doi: 10.1161/01.CIR.0000025242.79963.4C

McLean A, Huang S, Salter M. 2008. 'Bench-to-bedside review: the value of cardiac biomarkers in the intensive care patient'. *Crit Care* 12:215. doi: 10.1186/cc6880

➲ See Acute coronary syndrome—diagnosis, p416; Acute coronary syndrome—management, p418; Heart failure—assessment, p420.

Liver function tests

Hepatic metabolism proceeds via phase I enzymes (oxidation and phosphorylation), and subsequently, phase II enzymes (glucuronidation, sulphation, acetylation). Phase I enzyme reactions involve cytochrome P450. Liver functions is assessed through enzyme assays and the effect products of liver function. For normal ranges see Table 12.5.

Markers of hepatic injury

- Alanine aminotransferase (ALT).
- Aspartate aminotransferase (AST).
- Lactate dehydrogenase (LDH).

Patterns and ratios of various enzymes are variable. Measurement of ALT is usually sufficient. It is more liver specific but less sensitive than AST and has a longer half-life. AST is not liver specific but is a sensitive indicator of hepatic damage. Low levels occur in extrahepatic obstruction and inactive cirrhosis. LDH is non-specific and isoenzymes are needed to distinguish cardiac or skeletal muscle injury or haemolysis from liver injury.

Acute phase reactants such as C-reactive protein (CRP) and ferritin are produced by the liver and rise in inflammatory states.

Markers of cholestasis

- Bilirubin.
- Alkaline phosphatase.
- Gamma-glutamyl transferase (γGT).

Bilirubin derives from Hb released during erythrocyte breakdown. It is conjugated with glucuronide by hepatocytes. Conjugated bilirubin is water-soluble and unconjugated lipid-soluble. Levels increase with intra- and extrahepatic biliary obstruction (predominantly conjugated), hepatocellular damage, and haemolysis. Jaundice is detectable clinically when bilirubin levels are >45 μmol/L.

Alkaline phosphatase is released from bone, liver, intestine, and placenta. In the absence of bone disease (check Ca^{2+} and PO_4^{3-}) and pregnancy, raised levels usually indicate intra- or extrahepatic biliary tract dysfunction.

A raised γGT is a highly sensitive marker of hepatobiliary disease. Increased synthesis is induced by obstructive cholestasis, alcohol, various drugs and toxins, and acute and chronic hepatic inflammation.

Markers of reduced synthetic function

- Albumin.
- Clotting factors.

Albumin levels fall during critical illness due to protein catabolism, capillary leak, decreased synthesis, and dilution with artificial colloids.

Coagulation factors II, VII, IX, and X are liver synthesized. Over 33% of functional hepatic mass must be lost before any abnormality is seen.

Markers of liver failure

- Ammonia.

Ammonia is produced in the gut and transported to the liver. Here the urea cycle converts it to urea which is then renally excreted. Hyperammonaemia occurs in cirrhotic liver failure (90% of cases) or when portal blood is diverted to the systemic circulation (transjugular intrahepatic portosystemic stented shunt (TIPSS) procedure). It occurs in urea cycle disorders and with infection by certain microorganisms. Elevated levels can cause abnormal neurological signs and symptoms. It is implicated in hepatic encephalopathy, though 10% do not have raised levels.

Table 12.5 Normal plasma ranges

Albumin	35–53 g/L
Bilirubin	3–17 μmol/L
Conjugated bilirubin	0–6 μmol/L
Alanine aminotransferase	5–50 U/L
Alkaline phosphatase	100–280 U/L
Aspartate aminotransferase	11–55 U/L
Gamma-glutamyl transferase	5–37 U/L
Lactate dehydrogenase	230–460 U/L
Ammonia	11–32 μmol/L

Further reading

Ali R, Nagalli S. 2023. 'Hy\perammonemia'. In *StatPearls [Internet]*. StatPearls Publishing: Treasure Island (FL). Accessed September 2023. www.ncbi.nlm.nih.gov/books/NBK557504/

See Jaundice, p452; Acute liver failure, p454; Hepatic encephalopathy, p456; Decompensated chronic liver failure, p458; Paracetamol poisoning, p558; HELLP syndrome, p688.

Lactate

Lactate is an important fuel source in critical illness. Pyruvate, the end-product of glycolysis, is taken up from the cytosol into the mitochondria by pyruvate dehydrogenase and metabolized to acetyl CoA, the entry point into the Krebs cycle. Electrons are donated from the Krebs cycle to the electron transport chain via NADH and $FADH_2$ (Figure 12.2). Pyruvate not taken up by mitochondria goes into equilibrium with lactate (Figure 12.3). This reaction is catalysed in either direction by lactate dehydrogenase. Lactate can be recycled back to glucose by the liver through the Cori cycle (Figure 12.4).

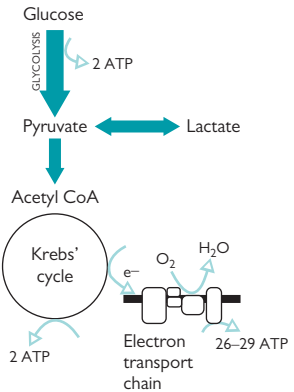

Fig. 12.2 Bioenergetic pathway from oxidation of glucose.

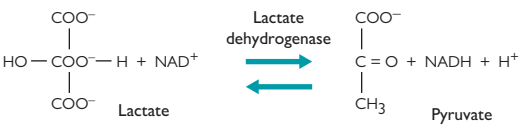

Fig. 12.3 Pyruvate–lactate equilibrium.

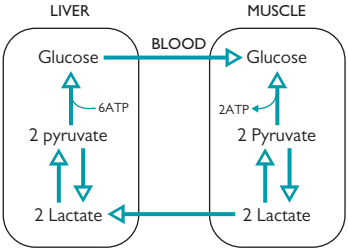

Fig. 12.4 Cori cycle (lactate–glucose between liver and muscle).

Causes of raised lactate

Lactic acidosis is a misnomer. The hydrogen ion production is not directly related to lactate production but arises from ATP hydrolysis and increased glycolysis. Indeed, conversion of pyruvate to lactate uses a hydrogen ion (Figure 12.3). 'Lactic acidosis' is traditionally classified as type A or type B. Type A refers to excess production when tissue oxygenation is inadequate. Type B occurs where there is no systemic tissue hypoxia. Severe, persistent type A lactic acidosis is associated with a poor outcome.

Increased lactate production is thus not due only to tissue hypoxia. It can be generated either by excess glycolysis in relation to downstream requirements (e.g. excess stimulation by exogenous or endogenous epinephrine), or by a downstream block, e.g. of pyruvate dehydrogenase (sepsis), oxygen insufficiency (any cause of tissue hypoxia), or mitochondrial electron transport chain dysfunction (e.g. sepsis, metformin, carbon monoxide poisoning). In stress situations, lactate levels rise in part due to increased activity of the skeletal muscle Na^+ pump driven by epinephrine-stimulated glycolysis.

A further cause of hyperlactataemia is decreased utilization or clearance. This is particularly apparent with liver (± kidney) dysfunction, especially when exogenous lactate is being administered, e.g. lactate-buffered renal replacement fluid. Lactate is a buffer not an acid so a high blood lactate is not, therefore, synonymous with lactic acidosis.

Measurement of blood lactate

Point-of-care devices or blood gas analysers enable rapid measurement of blood. Normal blood lactate <2 mmol/L.

Further reading

Totaro R, Raper R. 1997. 'Epinephrine-induced lactic acidosis following cardiopulmonary bypass'. *Crit Care Med* 25: pp1693–9.

Levy B, Gibot S, Franck P, et al. 2005. 'Relation between muscle Na^+K^+ ATPase activity and raised lactate concentrations in septic shock: a prospective study'. *Lancet* 365: pp871–5.

See Blood gas analysis, p174; Metabolic acidosis, p534.

Biomarkers

An increasing number of biomarkers are becoming available to aid diagnosis, to monitor disease progression, and to monitor response to treatment (theranostics). Biomarkers can also be used to prognosticate. Biomarkers are distinct from specific tests to directly identify, for example, a pathogen by blood culture, a drug overdose by toxicology screening, and therapeutic drug monitoring aiming to optimize drug effectiveness and reduce toxicity.

Increasingly, biomarker results are becoming available within minutes using point-of-care devices. Considerable research effort is also being made into biomarker-guided personalized treatments. A description of the various uses of biomarkers in critical care with examples of more novel biomarkers (rather than traditional markers such as arterial partial pressure of O_2, CRP, procalcitonin, lactate, creatinine, and bilirubin) are given below.

Diagnosis

- Infection—identification of pathogens in blood or other body fluids (e.g. DNA, RNA) or their constituents (e.g. endotoxin for Gram negative bacteria, (1,3)-β-d-glucan (BDG) for fungi).
- Sepsis, e.g. transcriptomic panels using polymerase chain reaction (PCR).
- Inflammation, e.g. panels including cytokines, markers of endothelial activation.
- Immune suppression, e.g. human leukocyte antigen (HLA)-DR.

Organ injury and dysfunction

- Heart, e.g. troponin (injury), BNP (dysfunction).
- Brain, e.g. S100B, neurone-specific enolase (NSE).
- Kidney, e.g. NGAL (tubular damage), cystatin C (glomerular filtration).
- Liver, e.g. ammonia (dysfunction).

Prognosis

- Brain injury, e.g. NSE.
- Heart failure, e.g. BNP.

Theranostic

- Titration of heart failure treatment, e.g. BNP.

Personalized medicine (research tools at present)

- Hyperferritinaemia for use of anakinra (IL-1 receptor blocker) in macrophage activation-like syndrome
- HLA-DR or lymphopenia for use of immune stimulants such as interferon gamma.

Further reading

➔ See Acute coronary syndrome—diagnosis, p416; Heart failure—assessment, p420; Acute kidney injury—diagnosis, p428; Acute liver failure, p454; Hepatic encephalopathy, p456; Decompensated chronic liver failure, p458; Coma, p466; Infection—diagnosis, p588.

Full blood count

Normal ranges for a full blood count are shown in Table 12.6.

Haemoglobin

A raised Hb occurs in polycythaemia and haemoconcentration. Anaemia may be due to reduced red cell mass (decreased red cell production, survival, or loss) or haemodilution (from excess intravascular fluid administration). Anaemia may cause a hyperdynamic circulation which, if very severe, may lead to cardiac failure. In this case, blood transfusion must be performed with extreme care to avoid fluid overload. For differential diagnosis of anaemia, see Table 12.7.

Table 12.6 Normal ranges

Haemoglobin	130–170 g/L (men), 120–160 g/L (women)
MCV	80–100 fL
MCH	28–32 pg/cell
White cell count	4–11 × 10^9/L
Neutrophils	2–7.5 × 10^9/L
Lymphocytes	1.3–3.5 × 10^9/L
Eosinophils	0.04–0.44 × 10^9/L
Basophils	0–0.1 × 10^9/L
Monocytes	0.2–0.8 × 10^9/L
Platelets	150–400 × 10^9/L

MCH = mean corpuscular haemoglobin; MCV = mean corpuscular volume.

Table 12.7 Differential diagnosis of anaemia

Reduced MCV	Iron deficiency
Raised MCV	Vitamin B_{12} or folate deficiency Alcohol excess or liver disease Hypothyroidism
Normal MCV	Anaemia of chronic disease Bone marrow failure (e.g. acute folate deficiency) Haemolysis (increased reticulocytes and bilirubin)

White blood cells

A raised white cell count is common in critical illness (Table 12.8).

Table 12.8 Causes of a raised white cell count in critical illness

Neutrophilia	**Lymphocytosis**	**Eosinophilia**
Bacterial infection	Brucellosis	Asthma
Trauma, surgery, & burns	Typhoid	Allergic conditions
Haemorrhage	Myasthenia gravis	Parasitaemia
Inflammation	Hyperthyroidism	
Corticosteroid therapy	Leukaemia	
Leukaemia	Inflammation	
Pregnancy		
Neutropenia	**Lymphopenia**	
Sepsis	Sepsis	
Viral infections	Corticosteroid therapy	
Bone marrow failure	Viral & fungal infections	
Adverse drug reactions	Chemotherapy	
Autoimmune disease	Radiation toxicity	
Hypersplenism	Systemic lupus erythematosus	
Chemotherapy		
Typhoid, brucellosis, TB		
Radiation toxicity		

Platelets

Thrombocytopenia is due to decreased production (bone marrow failure, vitamin B_{12} or folate deficiency), decreased survival (sepsis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura (TTP), hypersplenism, heparin-induced thrombocytopenia syndrome (HITS)), increased consumption (haemorrhage, disseminated intravascular coagulation (DIC)). *In vivo* aggregation may result in an apparent thrombocytopenia; this should be checked on a blood film by looking for platelet clumps. Spontaneous bleeding is associated with platelet counts $<10 \times 10^9$/L or $<20 \times 10^9$/L in sepsis.

Further reading

See Anaemia, p500; Sickle cell disease, p502; Haemolysis, p504; Platelet disorders, p508.

Coagulation monitoring

The traditional description of the extrinsic, intrinsic, and common coagulation pathways has little *in vivo* validity but remains useful for interpreting laboratory results. In the cell-based model the major event initiating haemostasis *in vivo* is the action of factor VIIa and tissue factor at the site of injury (Figure 12.5).

The basic screen consists of a platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT). Drawing blood from indwelling catheters runs the risk of dilution or contamination with heparin. The correct volume of blood must be placed in the sample tube to avoid dilution errors.

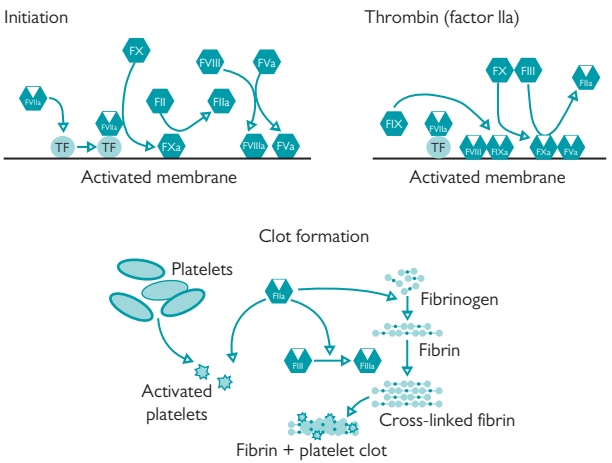

Fig. 12.5 The coagulation cascade. TF, tissue factor.

Specific coagulation tests

Activated clotting time (ACT)

The time to clot formation. Less precise than APTT, it is mainly used for point-of-care testing, e.g. cardiac surgery, extracorporeal membrane oxygenation (ECMO). The collection tube contains a surface activator which activates coagulation via factor XII pathway. The ACT is prolonged by thrombocytopenia, heparin, hypothermia, haemodilution, and fibrinolysis. Aspirin and clopidogrel have a variable effect. Warfarin and inhibitors of GpIIb/IIIa, Xa and thrombin significantly prolong the ACT. Normal range is 100–140 s.

Thrombin time (TT)

The sample tube contains lyophilized thrombin and reflects conversion of fibrinogen to fibrin. TT is prolonged by fibrinogen depletion, e.g. DIC, liver disease, fibrinolysis or thrombolysis, and unfractionated heparin via

anti-thrombin-dependent interaction with thrombin. Low-molecular-weight heparin (LMWH) and warfarin usually have no effect. Normal is 12–16 s.

Prothrombin time (PT)

The sample tube contains tissue factor and calcium. As it measures activity of the extrinsic and common coagulation pathways, it depends on the functional activity of factor II, V, VII, X, and fibrinogen. PT is prolonged with warfarin, liver disease, clotting factor or vitamin K deficiency, malabsorption, direct oral anticoagulants, or dilutional coagulopathy. Normal = 12–16 s. International normalized ratio (INR) relates PT to control and is normally ~1.

Activated partial thromboplastin time (APTT)

The sample tube contains kaolin or other activator, and cephalin to activate the intrinsic pathway. It measures activity of intrinsic and common pathways. APTT is prolonged by heparin, liver disease, DIC, severe fibrinolysis, von Willebrand factor, or severe deficiencies of factor VIII, IX, XI, or XII. Normal range is 30–40 s. If heparin contamination is suspected to be the cause of a prolonged APTT, a reptilase test can be performed.

Fibrinogen

Produced by the liver, levels may be reduced in liver disease and rise in inflammation. High levels of fibrin degradation products (FDPs) may impair conversion to fibrin.

D-dimers and fibrin degradation products (FDPs)

D-dimers are produced when cross-linked fibrin is degraded, but not when fibrinogen is broken down. They thus differ from FDPs which are released following plasmin degradation of fibrinogen. D-dimers are raised in DIC and have a high negative predictive value for exclusion of deep vein thrombosis and PE. They have a low positive predictive value for PE as they can be raised in multiple conditions, e.g. postoperatively, sepsis, trauma, renal failure. Raised levels do not distinguish between fibrinogenolysis and fibrinolysis.

Coagulation factor and other assays

Assays are available for all coagulation factors and other molecules involved in clotting such as von Willebrand factor, antithrombin, protein S, and protein C. These may be measured for diagnosis of specific defects.

Anti-Xa factor assays

As heparins inhibit factor Xa activity, the factor Xa assay is the most specific method of controlling LMWH therapy.

ADAMTS13 assay

A-disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) is an enzyme that degrades large von Willebrand factor into smaller multimers. Normal activity ranges between 50% and 160%. ADAMTS13 deficiency (<5%) results in TTP with intravascular blood clots and bleeding secondary to depletion of clotting factors. ADAMTS13 can fall to lesser degrees in other inflammatory conditions such as sepsis.

Further reading

See Intra-aortic balloon pump, p108; Haemo(dia)filtration, p118; Plasma exchange, p122; Anticoagulants—parenteral, p334; Thrombolytics, p338; Coagulants & antifibrinolytics, p340; Pulmonary embolus—management, p396; Acute liver failure, p454; Bleeding disorders—causes & diagnosis, p494; Clotting disorders, p498.

Thromboelastography & rotational thromboelastometry

Point-of-care viscoelastic haemostatic assays measure whole-blood clot formation. Testing during cardiac and liver surgery is well established. Increasingly it is used in acute settings, e.g. trauma, obstetrics. This enables prompt modification of treatment as rapid assessment of clot initiation time, clot strength, and breakdown enables better utilization of blood products and may reduce blood loss. However, no benefit in mortality has yet been demonstrated in randomized studies. The test should be utilized in conjunction with the clinical situation, e.g. ongoing blood loss.

Several devices now exist, mainly thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) that utilize different terminology. Interpreting the shape of the curve often provides more information than individual absolute values; see Table 12.9 and Figure 12.6.

Thromboelastography (TEG®)

Clot formation is stimulated by a wire moving within a cup containing a fresh whole blood sample. As this happens, the physical properties of the clot are measured. Kaolin and tissue factor can be used as activators.

- R value—reaction time from start of test to initial fibrin formation (amplitude 2 mm); this value depends on clotting factors.
- K value—time to achieve clot strength of 20 mm amplitude; this value depends on the fibrinogen level.
- α angle—slope of line between R and K assesses rate of clot formation ('thrombin burst'); depends on fibrinogen.
- MA—maximum amplitude reflects overall stability of clot, depends on both platelets (80%) and fibrin (20%).
- LY30—percentage decrease in amplitude at 30 min post MA.

Rotational thromboelastometry (ROTEM®)

Reagents are added to a blood sample to initiate clot formation mimicking extrinsic (EXTEM) or intrinsic (INTEM) pathways. Additional reagents can be added to assess specific issues.

- Clotting time (CT)—reflects clot initiation; >80 s suggests falls in factor II, VII, and X levels.
- Clot formation time (CFT)—similar to K value for TEG®.
- Maximal clot firmness (MCF)—reflects clot strength which depends on functional platelets and adequate fibrinogen levels. The platelet count alone does not highlight platelet dysfunction. Increasing fibrinogen with cryoprecipitate may reduce the need for platelet transfusion. With severe coagulopathy, it may take >30 min to achieve MCF. Clot amplitude (CA) at 5 and 10 min can be used to predict the final MCF in emergency situations.
- Clot lysis (CL)—describes the % decrease in MCF after 60 min.

The impact of hypothermia and/or hypocalcaemia will be missed as standardized testing is performed at 37°C with calcium added to the sample. The impact of antiplatelet agents (aspirin, clopidogrel) is not detected by ROTEM®.

Comparing TEG® and ROTEM®

Results are not directly comparable, but variables represent similar factors.

TEG®		ROTEM®		
Test	Normal	Test	EXTEM normal	INTEM normal
R	4–8 min	CT	38–79 s	100–240 s
K	1–4 min	CFT	34–159 s	30–110 s
α angle	47–74°	α angle	63–83°	70–83°
MA	55–73 mm	MCF	50–72 mm	50–72 mm
LY30	0–8%	CL	<15%	<15%

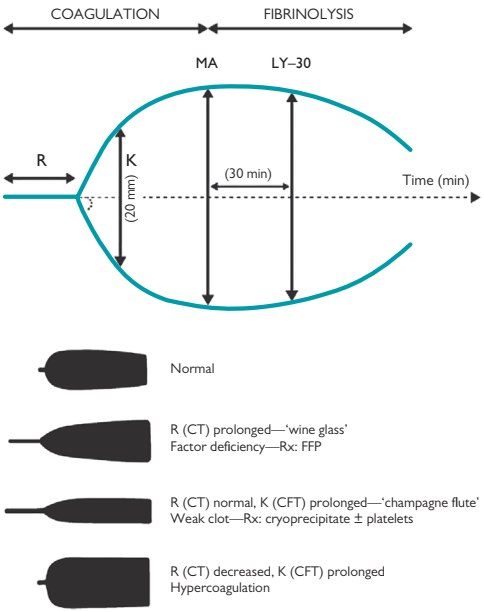

Fig. 12.6 Common TEG® and ROTEM® patterns.

Further reading

Whiting D, DiNardo J. 2014. TEG and ROTEM: technology and clinical applications. *Am J Hematol* 89:228–32. doi: 10.1002/ajh.23599

Shaydakov M, Sigmon D, Blebea J. 2023. 'Thromboelastography'. In *StatPearls [Internet]*. StatPearls Publishing: Treasure Island (FL). Accessed September 2023. https://www.ncbi.nlm.nih.gov/books/NBK537061/

See Bleeding disorders—causes & diagnosis, p494; Clotting disorders, p498; Multiple trauma—initial management, p628; Multiple trauma—ongoing management, p630.

Bacteriology

Microbiology samples should, if possible, be taken prior to commencement of antimicrobial therapy. Sampling sites include those suspected clinically of harbouring infection or, if a specific site cannot be identified, blood, urine, and sputum samples. In severe infection, consider replacing intravascular catheters. Samples should be sent promptly for Gram stain and cell count for appropriate fluid, e.g. cerebrospinal fluid (CSF), ascites, and set-up for cultures. See Table 12.9 for typical organisms.

Blood cultures

Sample by a peripheral venous stab as catheters often include contaminants such as coagulase-negative Staphylococci. Clean the skin with alcohol/chlorhexidine and allow to dry thoroughly before venepuncture. Withdraw at least a 20 mL blood sample (yield increases by 30% compared to a 10 mL sample) and divide into anaerobic and aerobic culture bottles. If catheter-related sepsis is suspected, a through-catheter sample may be also taken. Clearly label all samples. Culture bottles are incubated within automated systems which alarm when bacterial growth is detected. Antibiotic sensitivities can take a further 12–24 h to obtain.

Interpret positive cultures alongside the clinical picture; an early, pure, heavy growth from multiple bottles is likely significant whereas a mixed growth could be less relevant. Cultures may grow late, or not at all, if the patient is receiving antibiotics. Any Gram-negative or *S. aureus* growth is generally taken as significant.

Techniques such as matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry and PCR systems accelerate identification of bacteria or fungi and identify antibiotic-resistant genes from positive blood cultures within 1–2 h. Technologies are now available to identify limited numbers of organisms and resistance genes directly from blood or other samples within 2–6 h.

Urine

Catheter specimens are usually obtained from an aseptically prepared sampling site. Urine is plated onto culture medium with a calibrated loop and incubated for 18–24 h prior to examination. Bacteria $\geq 10^5$/mL are considered significant. If the catheter has been in place for >2 days all urine specimens will show bacterial growth so a positive test is of dubious value. Isolation of the same organism from blood, however, confirms a significant culture. Urine can also be used for antigen testing (e.g. pneumococcus, *Legionella pneumophilia*).

Table 12.9 Typical intensive care unit-acquired infections

Pneumonia	*Pseudomonas aeruginosa*, *Staph aureus*, *Enterobacter* spp., *Klebsiella* spp., *Acinetobacter* spp.
Urinary infection	*Escherichia coli*, *Ps aeruginosa*, *Klebsiella* spp., *Proteus* spp.
Catheter-related sepsis	*Staph aureus*

Sputum/bronchial samples

Sputum samples are easily contaminated during collection, particularly from non-intubated patients. Suction specimens from intubated patients can be taken via a sterile suction catheter, protected catheter brush, or from specific lung segments via a bronchoscope. Gram-negative bacteria are frequently isolated from tracheal aspirates of intubated patients; only deep suction specimens are significant. Blood cultures should accompany respiratory tract specimens if pneumonia is suspected.

Pus samples and wound swabs

Aspirated pus must be sent to the lab immediately, or a swab taken and sent in transport medium. The lab should be asked to perform an urgent Gram stain. Pus is preferable for bacterial isolation.

Antibiotic assays

Antibiotic assays are usually performed for drugs such as aminoglycosides and vancomycin to avoid complications such as nephrotoxicity and ototoxicity and to verify the calculated dose (based on weight and eGFR) is within the therapeutic range (Table 12.10).

Depending on the dosing strategy (e.g. intermitted or continuous), the timing of sampling will vary and local guidelines should be consulted. Although therapeutic drug monitoring for other antibiotic classes is being promoted, this is rarely performed at present. Suboptimal dosing is associated with worse clinical outcomes.

Table 12.10 Antibiotic therapeutic levels

	Trough (mg/L)	Peak (mg/L)
Amikacin	<8	30
Gentamicin	<2	4–10*
Tobramycin	<2	4–10
Vancomycin	<8	20–30

* Seek microbiological advice if once-daily gentamicin is used. Advice will differ for continuous infusion.

Further reading

Roberts J, Paul S, Akova M, et al. 2014. 'DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients?' *Clin Infect Dis* 58: pp1072–83. doi: 10.1093/cid/ciu027

See Pleural aspiration, p94; Fibreoptic bronchoscopy, p96; Chest physiotherapy, p98; Urinalysis, p236; Virology, p258; Pneumonia—diagnosis, p374; Infection—diagnosis, p588.

Virology

Serology and virus detection

A clotted blood specimen allows either molecular detection of viral particles with PCR and/or measurement of antiviral antibodies. Convalescent (14 days) serum can be sent to determine rising IgM antibody titres and/or PCR. Single sample titres may be used to determine previous exposure and carrier status.

Hepatitis B

The hepatitis B surface antigen (HBsAg) is used as a screening test. The presence of the hepatitis B core antigen (HBcAg) is used to determine infectivity. Hepatitis B e antigen (HBeAg) may also indicate enhanced infectivity. Individuals that remain HBsAg positive for 6 months are considered to be carriers. The anti-HB immunoglobulin (Ig)-G antibody directed against either the surface or core antigen indicates prior infection. Anti-HBs antibody detection may also indicate prior vaccination.

PCR tests can also be used to detect viral load in acute infection and to monitor the response to treatment. Serology should be sent in all patients suspected with deranged liver function tests. Serology should be sent in staff who suffer accidental exposure to body fluids, e.g. needlestick injury. Those who are not immune may be treated with immunoglobulin.

HIV

The viral load (measure of activity) and CD4 count may be used to assess the likelihood of symptomatology being AIDS-related, although the CD4 will fall with acute critical illness. Consent should usually be sought pretesting. High-risk patients should be considered for testing. In critically ill patients, such consent can rarely be obtained and unconsented testing may be used where management may change with knowledge of the HIV status, or where organ donation is being considered. Most AIDS-related infections can be adequately treated without knowledge of HIV status. Patients or staff who are recipients of a needlestick injury can be treated with antiretroviral therapies if the donor is known to be HIV positive; unconsented testing may be reasonable.

Rapid respiratory viral screen (COPAN)

This test provides rapid identification of common respiratory viruses, i.e. adenovirus, influenza A, influenza B, parainfluenza 1, parainfluenza 2, parainfluenza 3, and respiratory syncytial virus (RSV) using an immunofluorescence technique.

Severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2)

The gold standard test is PCR from a deep nasal/pharyngeal swab sample. Lateral flow assays have an appreciable false-negative rate, but a low false-positive rate. The PCR test indicates the presence of virus particles but does not demonstrate viral viability. Anti-SARS-CoV-2 against the spike (S) and nucleocapsid (N) proteins usually develop within 2 weeks of exposure.

Cytomegalovirus (CMV)

PCR test to determine the degree of CMV replication is used frequently in immunocompromised patients. Critically ill patients in the intensive care

unit may show evidence of CMV reactivation, but the clinical significance of this is still uncertain.

Other viruses

PCR testing can be used to identify specific viruses depending on the presumptive diagnosis. Examples include herpes simplex, varicella zoster, Epstein–Barr virus (EBV), and viral haemorrhagic fevers.

Viral microscopy and culture

Now less commonly performed, but can be used on samples of blood, urine, CSF, or bronchial aspirate. These may also be sent for DEAFF (detection of early antigen fluorescent foci). Herpesvirus infections may be detected by electron microscopy of samples (including pustule fluid) and adenovirus in immunosuppressed patients with a chest infection.

Common serology for critically ill patients

- Hepatitis A.
- Hepatitis B.
- Hepatitis C.
- HIV.
- CMV.
- EBV.
- *Mycoplasma pneumoniae*.
- *Legionella pneumophila*.

Further reading

'Needlestick injuries and blood-borne viruses: decisions about testing adults who lack the capacity to consent'. British Medical Association. Accessed June 2023. https://www.bma.org.uk/media/1411/bma-guidance-on-needlestick-injuries-guidance-may-2016.pdf

➔ See Urinalysis, p236; Bacteriology, p256; Pneumonia—diagnosis, p374; Infection control—blood-borne viruses, p582; Infection—diagnosis, p588; HIV-related disease, p610; Viral Critical Illness, p612.

Mycology

Direct detection

Yeasts such as *Candida* and *Aspergillus* spp. were traditionally difficult to identify and relied upon either culture or from microscopy or histology of fluid or tissue samples (e.g. silver stain for *Aspergillus*, India ink stain for *Cryptococcus* spp.). Blood cultures often yielded negative results due to low numbers of circulating yeasts, fastidious pathogens that were difficult to grow, or inadequate blood sample volumes. Even when grown, time to positivity frequently took several days.

These tests were later complemented by antigen tests for *Candida* (e.g. mannan test) and *Cryptococcus*. More recently, multiplex molecular PCR panels have become available to rapidly detect fungal DNA in blood and other body fluids, e.g. bronchoalveolar lavage (BAL), CSF. The major fungal pathogens such as *Candida albicans*, *C. krusei*, *C. glabrata*, and *Cryptococcus neoformans* can be readily identified, often within a few hours. Increasingly, multiplex panels are incorporating diagnostic capability for less common pathogens such as *Rhizopus* spp., *Candida parapsilosis*, and *C. auris*.

Biomarkers

Galactomannan (GM) is a polysaccharide component of the cell wall of *Aspergillus* spp. released into serum and other bodily fluids during early growth, where it can persist for up to 8 weeks. Enzyme-linked immunosorbent assay (ELISA) detection in blood and BAL can be used to diagnose invasive aspergillosis. Though reasonably sensitive, false-positive tests are reported with some β-lactam antibiotics (e.g. piperacillin–tazobactam, co-amoxiclav), fluids containing gluconate or citrate, e.g. some platelet transfusions and parenteral nutrition solutions, and other fungal species, e.g. *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus* spp.

(1,3)-β-d-glucan (BDG) is a cell wall polysaccharide found in pathogenic fungi including *Candida* spp., *Aspergillus* spp., *Pneumocystis jirovecii*, and *Histoplasma capsulatum*. It can survive in the body for up to 7 weeks despite negative cultures. The ELISA test has a very low level of detection. Sensitivity is reported at 50–90% and specificity at 75–90% so is often used as a rule-out test that can be performed serially in high-risk patients. False-positive results are reported with use of cellulose membranes (such as used in renal replacement therapy), surgical packing, recent use of albumin or immunoglobulins, and β-lactam antibiotics.

Because of the high cross-over in fungal detection between GM and BDG, the two tests are often measured together with BDG-positive and GM-negative results being more suggestive of a *Candida* spp. infection.

Further reading

Hage C, Carmona E, Epelbaum O, et al. 2019. 'Microbiological laboratory testing in the diagnosis of fungal Infections in pulmonary and critical care practice. An official American Thoracic Society clinical practice guideline'. *Am J Respir Crit Care Med* 200: pp535–50. doi: 10.1164/rccm.201906-1185ST

See Pneumonia—diagnosis, p374.

Toxicology

Purpose

Samples taken from blood, urine, vomitus, or gastric lavage (depending on drug or poison ingested) for:

- Monitoring of therapeutic drug levels (usually plasma) and avoidance of toxicity, e.g. ciclosporin, vancomycin, digoxin, aminoglycosides, lithium, phenytoin, theophylline.
- Identification of possible toxic substances, e.g. ethylene glycol, cyanide, amphetamines, opiates, causing symptomatology and/or pathology. Always take a urine sample for analysis.
- Confirmation of toxic plasma levels and monitoring of treatment effect, e.g. paracetamol levels with *N*-acetylcysteine treatment, aspirin with forced dialysis.
- Medicolegal, e.g. alcohol, recreational drugs following road traffic collisions.
- Unusual situations such as chemical terrorism need to go to specialist laboratories.

Samples

Confirm with chemistry laboratory ± local poisons unit as to which, how, and when body fluid samples should be taken for analysis, e.g. peak/trough levels for aminoglycosides, urine samples for out-of-hospital poisoning, repeat paracetamol levels to monitor efficacy of treatment.

Further reading

See Antibacterials, p344; Poisoning—general principles, p554; Paracetamol poisoning, p558.

Chapter 13

Fluids

Crystalloids

Types

- Balanced electrolyte, e.g. Ringer's lactate, Hartmann's solution, Plasma-Lyte®.
- Saline, e.g. 0.9% saline, 0.18% saline in 4% glucose, 1.8%, 2.7%, 0.45%.
- Glucose, e.g. 5%, 10%, 20%, 50%.
- Sodium bicarbonate, e.g. 1.26%, 8.4%.
- See Table 13.1 for ion content of crystalloid fluids.

Uses

- To provide daily requirements of water and electrolytes, supplement fluids given during feeding, or to carry drugs.
- To correct hypovolaemia.
- To replace fluid loss through wounds, fistulae, or drainage tubes. See Table 13.2 for ion content of gastrointestinal fluids.
- Higher-concentration glucose infusions may be used to prevent hypoglycaemia.
- Crystalloid fluids may contain potassium chloride supplements.
- Sodium bicarbonate may be used to correct metabolic acidosis, for urinary alkalinization, etc.

Table 13.1 Ion content of crystalloids (mmol/L)

	Na^+	K^+	HCO_3^-	Cl^-	Ca^{2+}	Lactate	Acetate/ gluconate
0.9% saline	154	0	0	154	0	0	0
Hartmann's	131	5	0	111	4	29	0
Ringer's lactate	130	4.5	0	109	2.7	28	0
Plasma-Lyte®	140	5	0	98	0	0	27/23
0.18% saline/ 4% glucose	31	0	0	30	0	0	0

Table 13.2 Ion content of gastrointestinal fluids (mmol/L)

	H^+	Na^+	K^+	HCO_3^-	Cl^-
Gastric	40–60	20–80	5–20	150	100–150
Biliary	0	120–140	5–15	30–50	80–120
Pancreatic	0	120–140	5–15	70–110	40–80
Small bowel	0	120–140	5–15	20–40	90–130
Large bowel	0	100–120	5–15	20–40	90–130

Route

- Intravenous (IV).

Notes

- The sodium content of 0.9% saline is equivalent to that of extracellular fluid. Salt-containing solutions therefore distribute throughout the extracellular fluid space.
- Hypertonic or hypotonic saline solutions are rarely needed; use should be guided by plasma Na^+ levels and clinical indication.
- Excessive amounts of saline can result in a hyperchloraemic acidosis which may adversely affect renal function and possibly increase mortality risk. Monitor plasma Na^+ and Cl^- levels and adjust fluid type accordingly. The usual difference between plasma Na^+ and Cl^- is 35–40 mmol/L; a smaller value suggests excessive Cl^- relative to Na^+.
- Use of Ringer's lactate or Hartmann's solution avoids hyperchloraemic acidosis caused by the relative excess chloride infused with 0.9% saline. However, large amounts may induce mild hyponatraemia.
- A daily requirement of 70–80 mmol sodium is normal although there may be excess loss in sweat and from the gastrointestinal tract. This can be provided as saline or balanced electrolyte solution.
- 5% glucose is used to supply IV water requirements. It is isotonic in the bag but hypotonic in the patient as the glucose is quickly metabolized, leaving just water. Since there are no electrolytes to favour distribution to one space or another, water distributes uniformly throughout the extra- and intracellular spaces. The 50 g/L glucose content only provides 200 kcal/L. Normal requirements are ~1.5–2 L/day.
- Water loss in excess of electrolytes is uncommon but occurs in excess sweating, fever, hyperthyroidism, diabetes insipidus and hypercalcaemia. Choice and volume of replacement fluid should be guided by regular monitoring of electrolytes and renal function.
- 0.9% saline is preferred over balanced solutions for brain injury.
- Potassium chloride must be given slowly since rapid injection may cause fatal arrhythmias. No more than 40 mmol/h should be given, and even this may be dangerous in some patients. Up to 20 mmol/h is safer. The frequency of infusion is dictated by measuring plasma K^+.

Further reading

Finfer S, Bellomo R, Boyce N, et al. for the SAFE Study Investigators. 2004. 'A comparison of albumin and saline for fluid resuscitation in the intensive care unit'. *N Engl J Med* 350: pp2247–56. doi: 10.1056/NEJMoa040232

Hammond N, Zampieri F, Di Tanna G, et al. 2022. 'Balanced crystalloids versus saline in critically ill adults—a systematic review with meta-analysis'. *NEJM Evid* 1(2). doi: 10.1056/evidoa2100010

See Nutrition—use & indications, p140; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Sodium bicarbonate, p268; Colloids, p270; Electrolyte management, p512; Hyponatraemia, p516; Hypokalaemia, p520; Metabolic acidosis, p534; Hypoglycaemia, p540.

Sodium bicarbonate

Types

- Isotonic sodium bicarbonate 1.26%.
- Hypertonic sodium bicarbonate 8.4%.

Uses

- Correction of metabolic acidosis.
- Alkalinization of urine, e.g. for salicylate overdose, treatment of rhabdomyolysis.
- Alkalinization of blood, e.g. for treatment of tricyclic antidepressant overdose.

Route

- IV.

Notes

- Isotonic (1.26%) sodium bicarbonate may be used to correct acidosis associated with renal failure, to replace excess alkali loss from the gut (diarrhoea, fistulae), for urinary alkalinization (e.g. for salicylate overdose), and to correct hyponatraemia when plasma Cl^- levels are normal or high. It should not be used simply to correct a low blood pH without looking for and treating the underlying cause.
- Bicarbonate may not be necessary if fluid and potassium deficits are corrected.
- The hypertonic 8.4% solution (1 mmol HCO_3^-/mL) can be used when infusion volumes need to be restricted. It should ideally be given through a central vein as extravasation may result in extensive skin necrosis.
- Bicarbonate increases CO_2 production. The partial pressure of CO_2 ($PaCO_2$) may rise if bicarbonate is given quickly and the minute volume is not increased.
- Bicarbonate cannot cross the cell membrane without dissociation so the increase in $PaCO_2$ may result in intracellular acidosis and depression of myocardial cell function.
- A decrease in plasma ionized calcium as a result of alkalinization may also cause a decrease in myocardial contractility.
- There are no patient data to indicate bicarbonate improves myocardial contractility or responsiveness to circulating catecholamines in severe acidosis. Acidosis secondary to myocardial depression is related to intracellular changes that are not accurately reflected by arterial blood chemistry.
- Excessive administration may cause hyperosmolality, hypernatraemia, hypokalaemia, and sodium overload.
- Bicarbonate may decrease tissue oxygen availability through a left shift of the oxyhaemoglobin dissociation curve.

Table 13.3 Ion content of sodium bicarbonate (mmol/L)

	Na^+	K^+	HCO_3^-	Cl^-	Ca^{2+}
1.26% sodium bicarbonate	150	0	150	0	0
8.4% sodium bicarbonate	1000	0	1000	0	0

Further reading

See Blood gas analysis, p174; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Electrolyte management, p512; Hypernatraemia, p514; Hypokalaemia, p524; Metabolic acidosis, p534.

Colloids

Types

- Albumin, e.g. 4.5–5%, 20–25% human albumin solution.
- Dextran, e.g. 6% dextran 70.
- Gelatin, e.g. 3.5% polygeline, 4% succinylated gelatin.
- Hydroxyethyl starch, e.g. 6% hetastarch.

Uses

- Fluid resuscitation.
- Correction of hypoalbuminaemia.
- Reduction of peripheral oedema.

NB: use of synthetic colloids (starches, gelatins, dextrans) has decreased over the last decades due to concerns regarding renal dysfunction with use of large volumes, and no evidence of outcome benefit compared to cheaper crystalloid solutions.

Route

- IV.

Side effects

- Dilution coagulopathy.
- Anaphylaxis.
- Interference with blood cross-matching (dextran 70).
- Renal dysfunction (starch).
- Pruritus (starch, gelatin).

Notes

- Smaller volumes of colloid (~10–20%) are required for resuscitation compared to crystalloids with less contribution to oedema through maintaining plasma colloid osmotic pressure.
- Colloids contain no clotting factors or other plasma enzyme systems.
- 20–25% albumin (often in conjunction with a diuretic) is used to correct severe hypoalbuminaemia or reduce tissue oedema. However, clear evidence of outcome benefit is lacking.
- Polygeline is a 3.5% gelatin solution and contains calcium (6.25 mmol/L). The calcium content prevents use of the same administration set for blood transfusions. Succinylated gelatin is a 4% solution and does not contain calcium.

Features of albumin

- Main provider of plasma colloid osmotic pressure.
- Transport of various molecules.
- Free radical scavenging.
- Binding of toxins.
- Inhibition of platelet aggregation.

Further reading

Finfer S, Bellomo R, Boyce N, et al. for the SAFE Study Investigators. 2004. 'A comparison of albumin and saline for fluid resuscitation in the intensive care unit'. *N Engl J Med* 350: pp2247–56. doi: 10.1056/NEJMoa040232

Brunkhorst F, Engel C, Bloos F, et al. 2008. 'Intensive insulin therapy and pentastarch resuscitation in severe sepsis'. *N Engl J Med* 358: pp125–39. doi: 10.1056/NEJMoa070716

Myburgh J, Finfer S, Bellomo R, et al. 2012. 'Hydroxyethyl starch or saline for fluid resuscitation in intensive care'. *N Engl J Med* 367: pp1901–11. doi: 10.1056/NEJMoa1209759

Perner A, Haase N, Guttormsen A, et al. 2012. 'Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis'. *N Engl J Med* 367: pp124–34. doi: 10.1056/NEJMoa1204242

Caironi P, Tognoni G, Masson S, et al. 2014 'Albumin replacement in patients with severe sepsis or septic shock'. *N Engl J Med* 370: pp1412–21. doi: 10.1056/nejmoa1305727

➔ See Crystalloids, p266; Basic resuscitation, p358; Fluid challenge, p362; Anaphylactoid reactions, p624.

Blood transfusion

Types

- Packed red cells.
- Whole blood.

Uses

- Correction of low haemoglobin due to blood loss (including frequent phlebotomy), haemodilution, or reduced red cell production.
- The evidence base for patients in the intensive care unit suggests a target haemoglobin >70 g/L is adequate for most patients. Transfusing above this threshold offers no added benefit, but a risk of transfusion-related complications.
- A higher transfusion trigger, e.g. target haemoglobin of 90–100 g/L, may be considered in patients with cardiac and/or respiratory morbidity, though the evidence base for benefit is weak.

Route

- IV.

Notes

Blood storage

Red blood cells (RBCs) can be stored for 35 days at 4°C.

Blood for transfusion is leukodepleted to reduce the risk of acute non-haemolytic transfusion reactions and transmission of pathogens such as variant Creutzfeldt–Jakob disease. Microaggregate formation is associated with platelets, white cells, and fibrin and range in size from 20 to 170 μm. The risk of microaggregate damage is reduced with packed red cells. In addition to spherocytosis and haemolysis, prolonged storage depletes ATP and 2,3-DPG levels thus decreasing the O_2 binding affinity of the red cells. There is, however, no strong evidence to support the use of fresh packed red cells over stored in the critically ill.

Compatibility

With modern laboratory procedures it is possible to obtain ABO compatibility for group-specific transfusion within 5–10 min and a full cross-match in 30 min.

In an emergency, with massive blood loss that threatens life, O-negative packed cells can be transfused but a sample must be taken for grouping prior to transfusion.

Hazards of blood transfusion

- Stored blood is anticoagulated with citrate 3 g/unit RBC. This acts by chelating calcium. Citrate toxicity may occur from massive blood transfusion causing metabolic alkalosis (related to citrate conversion to bicarbonate in the liver), compensatory respiratory acidosis, and hypocalcaemia. In particular, transfusion rates exceeding a unit of blood given over 5 min, or large transfusion in patients with coexisting liver dysfunction or severe hypothermia, can result in increased plasma citrate and reduced ionized calcium levels. Prophylactic use of calcium supplementation is not generally needed but plasma calcium and acid–base balance should be regularly monitored and treated if necessary. Ionized Ca^{2+} should be maintained above 0.9 mmol/L.

- Potassium load—potassium returns to cells rapidly but hyperkalaemia may be a problem if blood is stored at room temperature and given rapidly.
- Jaundice—haemolysis of incompatible or old blood.
- Pyrexia—immunological transfusion reactions to incompatible red or white cells or platelets or blood products.
- Disseminated intravascular coagulation—partial activation of clotting factors and destruction of stored cells, either in old blood or when transfusion is incompatible.
- Anaphylactoid reaction—urticaria is common and probably due to a reaction to transfused plasma proteins; if severe, it may be treated by slowing the transfusion and giving chlorphenamine 10 mg IV/intramuscularly. In severe anaphylaxis, in addition to standard treatment, the transfusion should be stopped and saved for later analysis. A sample should be taken for further cross-matching.
- Transmission of disease—including viruses, parasites (malaria), and prions.
- Transfusion-related acute lung injury and immune reactions.

Further reading

Hebert P, Wells G, Blajchman M, et al. for the Transfusion Requirements in Critical Care Investigators. 1999. 'A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care'. *N Engl J Med* 340: pp409–17. doi:10.1056/NEJM199902113400601

Rossaint R, Afshari A, Bouillon B, et al. 2023. 'The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition'. *Crit Care* 27:80. doi: 10.1186/s13054-023-04327-7

'Transfusion Handbook 3.3: Blood products'. Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC). Accessed June 2023. https://www.transfusionguidelines.org/transfusion-handbook/3-providing-safe-blood/3-3-blood-products

'Serious Hazards of Transfusion (SHOT)' website. Accessed June 2023. https://www.shotuk.org

➔ See Basic resuscitation, p358; Upper gastrointestinal haemorrhage, p438; Bleeding varices, p440; Lower intestinal bleeding & colitis, p442; Jaundice, p452; Anaemia, p500; Sickle cell disease, p502; Haemolysis, p504; Hyperkalaemia, p518; Anaphylactoid reactions, p624.

Blood products

Types

- Plasma, e.g. fresh frozen plasma (FFP). Octaplas® is a commercial solvent detergent FFP which inactivates encapsulated viruses such as HIV, hepatitis viruses.
- Platelets.
- Concentrates of coagulation factors, e.g. prothrombin complex concentrate (PCC, factor IX complex, Octaplex™), factor VIII concentrate.
- Cryoprecipitate—centrifuged plasma to collect clotting factors, especially rich in factor VIII.
- Recombinant technologies, e.g. factor VIIa, factor VIII.

Uses

- Vitamin K deficiency (FFP, PCC).
- Thrombocytopenia or platelet dysfunction (platelets).
- Haemophilia (cryoprecipitate, factor VIII, recombinant factor VIIa).
- Von Willebrand's disease (cryoprecipitate).
- Fibrinogen deficiency (cryoprecipitate).
- Christmas disease (factor IX complex).

Route

- IV.

Notes

- A unit (150 mL) of FFP is usually collected from one donor and contains all coagulation factors including 200 units of factor VIII, 200 units of factor IX, and 400 mg fibrinogen. It is stored at −30°C, can be kept for 24 h at 4°C, and should be infused within 2 h once defrosted.
- Platelet concentrates are viable for 5–7 days when stored at room temperature. Viability decreases if they are refrigerated. They must be infused quickly via a short giving set with no filter.
- Indications for platelet concentrates include platelet count $<10 \times 10^9$/L, or $<50 \times 10^9$/L with spontaneous bleeding or to cover invasive procedures and spontaneous bleeding with platelet dysfunction. Generally avoid transfusions. in conditions associated with immune platelet destruction (e.g. TTP) unless life-threatening bleeding occurs.
- A 15 mL vial of cryoprecipitate contains 100 units of factor VIII, 250 mg fibrinogen, factor XIII and von Willebrand factor. It can be stored at −18°C for 12 months. After thawing it can be stored at room temp for up to 6 h. In haemophilia, cryoprecipitate is given to achieve a factor VIII level >30% of normal.
- Factor VIII concentrate contains 300 units of factor VIII per vial. In severe haemorrhage due to haemophilia, 10–15 units/kg is given 12-hrly.
- Recombinant factor VIIa may be considered for control of bleeding in trauma, surgery, and patients with haemophilia. It forms complexes with exposed tissue factor and is independent of factors VIII or IX.
- PCC contains factors II, VII, IX, and X in treatment or prophylaxis of hereditary and acquired coagulation factor disorders, e.g. warfarin overdose. Heparin may be added so caution in patients with heparin-induced thrombocytopenia.

Further reading

Rossaint R, Afshari A, Bouillon B, et al. 2023. 'The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition'. *Crit Care* 27:80. doi: 10.1186/s13054-023-04327-7

➔ See Plasma exchange, p122; Full blood count, p250; Coagulation monitoring, p252; Colloids, p270; Blood transfusion, p272; Anticoagulants—parenteral, p334; Coagulants & antifibrinolytics, p340; Bleeding disorders—causes & diagnosis, p494; Clotting disorders, p498; Platelet disorders, p508.

Chapter 14

Respiratory drugs

Bronchodilators

Types

- β_2 adrenergic agonists, e.g. salbutamol, epinephrine, terbutaline.
- Anticholinergics, e.g. ipratropium.
- Theophyllines, e.g. aminophylline.
- Others, e.g. magnesium, ketamine, isoflurane.

Uses

- Relief of bronchospasm.

Routes and dosages

- Inhaled (salbutamol, epinephrine, terbutaline, ipratropium, isoflurane).
- Nebulized (salbutamol, epinephrine, terbutaline, ipratropium).
- Intravenous (IV) (salbutamol, epinephrine, terbutaline, ipratropium, aminophylline, magnesium, ketamine).
- Oral (PO) (aminophylline).

For drug dosages see Table 14.1.

In extremis, epinephrine may be given as 0.1–0.5 mg subcutaneously, injected down the endotracheal tube or by IV infusion.

Side effects

- Central nervous system stimulation (salbutamol, epinephrine, terbutaline, aminophylline).
- Tachycardia (salbutamol, epinephrine, terbutaline, aminophylline, ketamine).
- Hypotension (salbutamol, terbutaline, aminophylline, isoflurane).
- Hyperglycaemia (hydrocortisone, prednisolone, epinephrine).
- Hypokalaemia (salbutamol, epinephrine, terbutaline).
- Lactic acidosis (salbutamol)—rare.
- Mucus thickening and plugging (ipratropium).

Table 14.1 Drug dosages

	Aerosol*	Nebulizer*	IV bolus	IV infusion
Salbutamol	100–200 µg	2.5–5 mg		3–20 µg/min
Terbutaline	250–500 µg	5–10 mg	1.5–5 µg/min	
Epinephrine		0.5 mg		
Ipratropium		250 µg		
Aminophylline			5 mg/kg over 20 min	0.5 mg/kg/h
Magnesium			1.2–2 g over 20 min	
Ketamine			1–2 mg/kg	<0.75 mg/kg/h

*Aerosols and nebulizers are usually given four–six times daily but may be given more frequently if necessary.

Notes

- Selective β_2 agonists are usually given by inhalation via a pressurized aerosol or a nebulizer. Inhalation often gives rapid relief of bronchospasm. The aerosol is of less benefit in severe asthma unless used with a spacer device. They can be given by IV infusion.
- Nebulized drugs require a minimum volume of 4 mL and a driving gas flow of 6–8 L/min (higher or lower flow creates the wrong particle size for drug delivery).
- As epinephrine is not selective, arrhythmias are more likely. However, the α agonist effect may reduce mucosal swelling by vasoconstriction further improving airflow.
- Ipratropium bromide does not depress mucociliary clearance but may thicken sputum due to its anticholinergic effect. It is synergistic with β_2 agonists but has a slower onset of action. There is minimal evidence of benefit in critical care.
- Aminophylline is synergistic with β_2 agonists. Dosages must be adjusted according to plasma levels (range 10–20 mg/L) since toxic effects may be severe. Dose requirements are lower with heart failure, liver disease, chronic airflow limitation, fever, and erythromycin, and higher in children, smokers, and those with a moderate to high alcohol intake.
- Magnesium is a useful adjunctive therapy for severe asthma.
- Ketamine or isoflurane may be useful for sedation and bronchodilatation in the ventilated asthmatic.

Further reading

➔ See Chest physiotherapy, p98; Pulmonary function tests, p166; Corticosteroids, p352; Pneumonia—general management, p378; Chronic obstructive pulmonary disease, p388; Asthma—general management, p390.

Respiratory stimulants

Types

- Drug antagonists, e.g. naloxone, flumazenil.
- Central nervous system stimulants, e.g. doxapram.

Uses

- Acute respiratory failure due to failure of ventilatory drive.
- Drug-induced ventilatory failure, e.g. as a result of excessive sedation or postoperatively.

Routes and dosages

- IV.

For drug dosages see Table 14.2.

Modes of action

- Naloxone—short-acting opiate antagonist.
- Flumazenil—short-acting benzodiazepine antagonist.
- Doxapram—generalized central nervous system stimulant with predominant respiratory stimulation at lower doses. Stimulation of carotid chemoreceptors at very low doses with increased tidal volumes.

Side effects

- Seizures (flumazenil, doxapram).
- Tachyarrhythmias (naloxone, flumazenil).
- Hallucinations (doxapram).

Notes

- Respiratory stimulants are used in patients who develop acute hypercapnic respiratory failure.
- Effects of doxapram are short-lived so infusion is necessary. After about 12 h infusion the effects on ventilatory drive are reduced.
- Naloxone may be used in respiratory depression due to opiate drugs. Since it reverses all opiate effects, it may be better to reverse respiratory depression with non-specific respiratory stimulants, e.g. doxapram leaving pain relief intact. It may need to be repeated where long-acting opiates are involved.
- Most benzodiazepines are long-acting compared to that of flumazenil so repeated doses may be necessary.
- Flumazenil should not be used in mixed overdose.

Table 14.2 Drug dosages

	IV bolus	IV infusion
Naloxone	0.1–0.4 mg	0.1–2.0 mg/h*
Flumazenil	0.2 mg over 15 s (0.1 mg/min to max 2 mg)	0.1–0.4 mg/h
Doxapram	1–1.5 mg/kg over 30 s	2–3 mg/min

* Higher dose for reversing partial agonist opiates with high binding affinity.

Further reading

Greenstone M, Lasserson T. 2003. 'Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease'. *Cochrane Database Syst Rev* 1:CD000223.

➔ See Respiratory failure, p370; Chronic obstructive pulmonary disease, p388; Sedative poisoning, p560; Postoperative complications, p668.

Pulmonary vasodilators

Types

- Inhaled nitric oxide (iNO).
- Prostaglandins—epoprostenol ($PGI_{2\alpha}$), iloprost (PGI_2 analogue).
- Endothelin-1 receptor antagonist—bosentan.
- Glyceryl trinitrate (GTN).
- Phosphodiesterase (PDE) type 3 inhibitor—milrinone.
- Sildenafil.

Modes of action

- Smooth muscle relaxation.

Uses

- Vasodilatation at the site of gas exchange to improve ventilation–perfusion matching, although randomized multicentre studies in patients with acute lung injury revealed no long-term benefit nor outcome improvement from iNO.
- Pulmonary hypertension.
- Right heart failure post-cardiac surgery.
- Primary graft failure post-lung transplant.

Routes and dosages

iNO from cylinders is added to the inspiratory limb of the ventilator circuit by a servo control device to achieve a concentration of 1–20 ppm. Approximately 50% of patients with severe respiratory failure show short-term improvement in arterial partial pressure of oxygen (PaO_2) with iNO. However, the most effective dose varies. It is usual to start at 1 ppm for 10 min and monitor the change in PaO_2/fraction of inspired O_2 (FiO_2) ratio. An increase should be followed by an increase in NO concentration to 5 ppm for a further 10 min. Thereafter, the dose is adjusted according to response at 10 min intervals until the most effective dose is found. It is important to assess the dose response at daily intervals, aiming to keep the dose at the lowest effective level.

Prostaglandins can be given via infusion (epoprostenol) or nebulizers (iloprost, epoprostenol).

GTN and milrinone can be given by nebulization. The half-life of GTN is only 20–30 min.

Bosentan is an endothelin-1 receptor antagonist that is given orally but is generally used for chronic pulmonary hypertension.

Sildenafil is a PDE_5 inhibitor that promotes breakdown of cGMP that is only given orally.

Side effects

NO is immediately bound to haemoglobin ensuring local effects only. For other pulmonary vasodilators:

- Hypotension (if given IV or PO).
- Bleeding (particularly at cannula sites).
- Flushing, headache.

For drug dosages see Table 14.3.

Table 14.3 Drug dosages

Epoprostenol	IV: 2–20 ng/kg/min Nebulization: 10–50 ng/kg/min
Iloprost	Nebulization: 2.5–5 mg 6–9× per day
Milrinone	Nebulization: 4 mg milrinone 4-hrly
Glyceryl trinitrate (nitroglycerine)	Nebulization: 5 mg over 15 min
Bosentan	36.5 mg PO bd increasing to 125 mg PO bd
Sildenafil	10–20 mg PO tds

Notes

- NO and nitrogen dioxide concentrations can be monitored in the inspiratory limb of the ventilator circuit with fuel cell analysers or by chemiluminescence.
- It is extremely rare to see toxic nitrogen dioxide concentrations (>5 ppm). Methaemoglobin is formed when NO binds to haemoglobin. Prolonged inhalation at higher doses may rarely produce significant methaemoglobinaemia (>5%) so this should be monitored daily.
- Excessive humidification of inspired gases may potentially form nitric acid with NO; the use of heat–moisture exchangers rather than water baths is recommended.
- Since concentrations used are so small, dilution of exhaled gases into the atmosphere is unlikely to produce important environmental concentrations. In the air-conditioned intensive care environment air changes are so frequent as to make scavenging unnecessary.
- Tolerance does not develop to NO but patients can become dependent on continued inhalation with rebound pulmonary hypertension and hypoxaemia on withdrawal. For this reason, withdrawal must be gradual.
- Epoprostenol is active on both pulmonary and systemic circulations. In view of its short half-life it must be given continuously. If given by nebulization, an ultrasonic nebulizer should be used. Iloprost nebulization has a much longer half-life.
- Avoid extravasation into peripheral tissues as solution has high pH.
- Effects last up to 30 min following discontinuation of the drug.
- Prostaglandins may potentiate the effect of heparin.
- Efficacy of epoprostenol nebulization appears similar to that of NO inhalation, but not as rapid.

Further reading

Adhikari N, Dellinger R, Lundin S, et al. 2014. 'Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis'. *Crit Care Med* 42: pp404–12.

Farkas J. 'Inhaled pulmonary vasodilators.' In: *Internet Book of Critical Care*. 29 July 2020. Accessed 23 September 2023 https://emcrit.org/ibcc/pulmvaso/

See Acute respiratory distress syndrome—management, p386.

Chapter 15

Cardiovascular drugs

Inotropes

Types

- Catecholamines, e.g. epinephrine, norepinephrine, dobutamine, dopamine.
- Phosphodiesterase (PDE) inhibitors, e.g. milrinone, enoximone.
- Calcium sensitizers, e.g. levosimendan.
- Cardiac glycosides, e.g. digoxin (weak).

Modes of action

- Increased force of myocardial contraction either by activating cardiac β1 adrenoreceptors (catecholamines), decreasing cAMP breakdown (PDE inhibitors), increasing calcium sensitivity (Ca sensitizers), or directly increasing contractility (digoxin). All agents except digoxin have, to greater or lesser degrees, associated dilator or constrictor properties via α1 & β1 adrenoreceptors, dopaminergic receptors, or K_{ATP} channels.
- Digoxin may cause splanchnic vasoconstriction and, for an inotropic effect, usually requires higher plasma levels.
- The increase in cardiac work is partially offset in those drugs possessing associated dilator effects.
- Other than epinephrine (when used for its vasoconstrictor effect in cardiopulmonary resuscitation (CPR)) or digoxin (for long-term use in chronic heart failure), inotropes are usually given by continuous intravenous (IV) infusion titrated to desired effect.

Routes and dosages

See Table 15.1.

Uses

- Myocardial failure, e.g. post-myocardial infarction (MI), myocarditis.
- Myocardial depression, e.g. sepsis.
- Augmentation of oxygen delivery in high-risk surgical patients.

Table 15.1 Routes of administration and drug dosages

Epinephrine	Infusion starting from 0.05 μg/kg/min
Norepinephrine	Infusion starting from 0.05 μg/kg/min
Dobutamine	Infusion from 2.5 to 25 μg/kg/min
Dopamine	Infusion from 2.5 to 30 μg/kg/min
Milrinone	Infusion from 0.375 to 0.75 μg/kg/min
Enoximone	Infusion from 5 to 20 μg/kg/min
Digoxin	0.5 mg given orally (PO) or IV over 10–20 min. Repeat at 4–8 h intervals until loading achieved (assessed by clinical response). Maintenance dose thereafter is 0.0625–0.25 mg/day depending on plasma levels and clinical response
Levosimendan	0.1 μg/kg/min for 24 h

Side effects

- Arrhythmias (usually associated with concurrent hypovolaemia).
- Tachycardia (usually associated with concurrent hypovolaemia).
- Hypotension (dilator properties ± concurrent hypovolaemia).
- Hypertension (related to constrictor properties).
- Anginal chest pain, or ST-segment and T-wave changes on electrocardiography (ECG).
- Catecholamines decrease metabolic efficiency, are immunosuppressive, enhance β-oxidation of fat, and are pro-thrombotic. *In vitro*, they enhance bacterial growth.

Notes

- Epinephrine, norepinephrine, dobutamine, and dopamine should be given via a central vein as tissue necrosis may occur secondary to peripheral extravasation. Norepinephrine may be administered peripherally for a limited period of time.
- The haemodynamic effects of inotropes are shown in Table 15.2.
- Dopamine and dopexamine are now rarely used. A randomized controlled trial in shock patients showed more adverse events with dopamine compared to norepinephrine.

Table 15.2 Haemodynamic effects of inotropic drugs

	BP	HR	CO	SVR
Epinephrine	+	+	+/++	+
Norepinephrine	++	–	+/–	++
Dobutamine	0/–	+	++	–
Dopamine	+/++	–	+	+/++
Milrinone	–	+	++	–
Enoximone	–	+	++	–
Digoxin	0/–	–	+	+
Levosimendan	0/–	+	++	–

BP = blood pressure; CO = cardiac output, HR = heart rate, SVR = systemic vascular resistance.

Further reading

De Backer D, Biston P, Devriendt J, et al. for the SOAP II Investigators. 2010. 'Comparison of dopamine and norepinephrine in the treatment of shock'. *N Engl J Med* 362: pp779–89. doi:10.1056/NEJMoa0907118

Tian D, Smyth C, Keijzers G, et al. 2020. 'Safety of peripheral administration of vasopressor medications: a systematic review'. *Emerg Med Australas* 32: pp220–7.

See Intra-aortic balloon pump, p108; Cardiac output—central thermodilution, p200; Cardiac output—peripheral thermodilution, p202; Cardiac output—indicator dilution, p204; Cardiac output—Doppler ultrasound, p206; Cardiac output—pulse contour analysis, p208; Cardiac output—other techniques, p210; Basic resuscitation, p358; Cardiac arrest, p360; Hypotension, p408; Tachyarrhythmias, p412; Acute coronary syndrome—diagnosis, p416; Acute coronary syndrome—management, p418; Decompensated heart failure—management, p422; Organ donation, p716.

Vasodilators & antihypertensives

Types

- β-blockers.
- Nitrates, e.g. glyceryl trinitrate (nitroglycerine), isosorbide dinitrate.
- Angiotensin converting enzyme (ACE) inhibitors, e.g. ramipril.
- Smooth muscle relaxants, e.g. sodium nitroprusside, hydralazine.
- α-adrenergic antagonists, e.g. phentolamine.
- Calcium channel blockers, e.g. nifedipine, diltiazem.
- PDE inhibitors, e.g. enoximone, milrinone.

Modes of action

- Vasodilatation by smooth muscle relaxation.
- Reduce ventricular preload, afterload, and cardiac work.

Uses

- Myocardial failure, e.g. post-MI, cardiomyopathy.
- Angina/ischaemic heart disease.
- Systemic hypertension (specific causes, e.g. pheochromocytoma).
- Peripheral vascular disease/hypoperfusion.

Routes and dosages

See Table 15.3.

Table 15.3 Routes of administration and drug dosages

Esmolol	A titrated loading dose regimen is commenced followed by infusion (50–200 μg/kg/min)
Metoprolol	IV bolus up to 5 mg (rate 1–2 mg/min), repeat after 5 min if neededIV infusion 0.04–0.1 mg/kg/h
Propranolol	Initially given as slow IV 1 mg boluses repeated at 2 min intervals until effect is seen (to maximum 5 mg)
Labetalol	20–200 mg/h IV
Nitrates	Glyceryl trinitrate 2–40 mg/h IV or patch (5–10 mg)Isosorbide dinitrate 2–40 mg/h IV
Sodium nitroprusside	20–400 μg/min IV
Hydralazine	5–10 mg by slow IV bolus, repeat after 20–30 min. Alternatively, give by infusion starting at 200–300 μg/min and reducing to 50–150 μg/min
ACE inhibitors	Ramipril 1.25 mg PO/SL rising to 10 mg od PO/SL Captopril: 6.25 mg test dose rising to 25 mg tds PO Enalapril: 2.5 mg test dose rising to 40 mg od PO Lisinopril: 2.5 mg test dose rising to 40 mg od PO
Nifedipine:	5–20 mg PO. Capsule fluid can be injected down NG tube or given sublingually
Phentolamine	2–5 mg IV slow bolus. Repeat as necessary
Milrinone	Infusion from 0.375–0.75 μg/kg/min
Enoximone	Infusion from 5–20 μg/kg/min

Side effects/complications

- Heart failure and/or bradycardia (with β-blockers).
- Peripheral hypoperfusion (with β-blockers).
- Bronchospasm (with β-blockers).
- Decreased sympathetic response to hypoglycaemia (with β-blockers).
- Hypotension (often associated with concurrent hypovolaemia).
- Tachycardia (often associated with concurrent hypovolaemia).
- Symptoms include headache, flushing, postural hypotension.
- Renal failure (ACE inhibitors)—especially with renal artery stenosis, hypovolaemia, non-steroidals.
- Tachyphylaxis (with nitrates).
- Cyanide toxicity (with sodium nitroprusside).
- Unpredictable blood pressure lowering with SL nifedipine. Caution when treating a hypertensive emergency.
- Caution if using β-blockers and calcium channel blockers together.

Notes

- β-blockers are increasingly used more for their beneficial effects in heart failure, and for arrhythmia and blood pressure control. Care needs to be taken with regard to negative inotropic and chronotropic effects. Use small doses to begin with, or shorter-acting agents such as esmolol.
- Glyceryl trinitrate and isosorbide dinitrate reduce both preload and afterload. At higher doses, the afterload effect is more prominent.
- Tolerance to nitrates usually commences within 24–36 h unless intermittent oral dosing is used. Progressive increases in dose are required to achieve the same effect.
- Prolonged (>24–36 h) administration of sodium nitroprusside can rarely produce a metabolic acidosis related to cyanide accumulation. The administration set including syringe should be shielded from light.
- ACE inhibitor tablets can be crushed and given SL or by NG tube.

Further reading

➲ See Blood pressure monitoring, p186; Cardiac output—central thermodilution, p200; Cardiac output—peripheral thermodilution, p202; Cardiac output—indicator dilution, p204; Cardiac output—Doppler ultrasound, p206; Cardiac output—pulse contour analysis, p208; Cardiac output—other techniques, p210; Antianginal agents, p298; Hypertension, p410; Acute coronary syndrome—diagnosis, p416; Acute coronary syndrome—management, p418; Decompensated heart failure—management, p422.

Vasopressors

Types

- α-adrenergic, e.g. norepinephrine, epinephrine, metaraminol, ephedrine, phenylephrine, methoxamine.
- Drugs reducing production of cyclic guanosine monophosphate (cGMP) (in septic shock), e.g. methylthioninium chloride (methylene blue).
- Vasopressin or synthetic analogues, e.g. terlipressin.
- Angiotensin II (recombinant).

Modes of action

- Acting on peripheral α-adrenergic, angiotensin or vasopressin V1 receptors.
- Blocking cGMP and nitric oxide (NO) production (methylthioninium chloride).
- SVR is increased by arteriolar vasoconstriction and/or restoration of vascular reactivity. Venoconstriction increases central venous pressure in tandem.

Uses

- To increase organ perfusion pressures, particularly in high-output, low peripheral resistance states, e.g. sepsis, anaphylaxis
- To maintain an adequate cerebral perfusion pressure following neurological injury.
- To raise coronary perfusion pressures in CPR (epinephrine, vasopressin).
- Angiotensin II and methylthioninium chloride are predominantly used when there is resistance to catecholamines.
- Dopamine is less frequently used as has been shown to be less effective than norepinephrine.

Routes and dosages

See Table 15.4.

Table 15.4 Routes of administration and drug dosages

Norepinephrine	Infusion from 0.05 to 1.0 μg/kg/min
Epinephrine	Infusion from 0.05 to 1.0 μg/kg/min
Metaraminol	0.5–2 mg by slow IV bolus or infusion 0.5–10 mg/h
Dopamine	Infusion from 5 to 50 μg/kg/min
Ephedrine	3–30 mg by slow IV bolus
Methylthioninium chloride (methylene blue)	1–2 mg/kg over 15–30 min or 0.5–1 mg/kg/h for up to 6 h
Vasopressin (argipressin)	0.01–0.04 U/min for sepsis
Terlipressin	0.25–0.5 mg bolus, repeated at 30 min intervals as needed to maximum 2 mg, or infusion 0.1–0.3 mg/h
Angiotensin II	Initially 20 ng/kg/min (maximum dose not to exceed 80 ng/kg/min for the first 3 h) and 40 ng/kg/h thereafter

Side effects/complications

- Increased cardiac work.
- Decreased cardiac output.
- Myocardial and splanchnic ischaemia.
- Arrhythmias and tachycardia, especially with concurrent hypovolaemia.
- Decreased peripheral perfusion and distal ischaemia/necrosis.

Notes

- Avoid, if possible, in low cardiac output states as they may further compromise the circulation.
- Methoxamine and phenylephrine are the 'purest' pressor agents; other α-adrenergic agents have some inotropic properties. Ephedrine is similar to epinephrine, but its effects are more prolonged.
- Splanchnic, renal, and cerebral effects are variable and unpredictable.
- Pulmonary vascular resistance is also raised by these agents.
- Methylthioninium chloride (methylene blue) inhibits the NO–cGMP pathway. Its use has only been reported in a few small case series. Vasopressin (short half-life, infusion needed) and terlipressin (longer half-life, can be given by bolus) may be effective in treating catecholamine-resistant vasodilatory shock. Paradoxically, such patients respond to small doses that have no pressor effect in health.
- Large randomized controlled trials in septic shock show no outcome difference between types of catecholamine, nor vasopressin over norepinephrine.
- No outcome studies have been performed to date on angiotensin II.
- Excessive dosing of any pressor agent may lead to regional ischaemia, e.g. cardiac, splanchnic. Digital ischaemia may respond to prompt administration of IV prostanoids (e.g. PGE_1, PGI_2).

Further reading

Annane D, Vignon P, Renault A, et al. for the CATS Study Group. 2007. 'Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial'. *Lancet* 370: pp676–84. doi: 10.1016/S0140-6736(07)61344-0

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Khanna A, English S, Wang X, et al. for the ATHOS-3 Investigators. 2017. 'Angiotensin II for the treatment of vasodilatory shock'. *N Engl J Med* 377: pp419–30. doi: 10.1056/NEJMoa1704154

See Blood pressure monitoring, p186; Cardiac output—central thermodilution, p200; Cardiac output—peripheral thermodilution, p202; Cardiac output—indicator dilution, p204; Cardiac output—Doppler ultrasound, p206; Cardiac output—pulse contour analysis, p208; Cardiac output—other techniques, p210; Tissue perfusion monitoring, p220; Intracranial pressure monitoring, p224; Jugular venous bulb saturation, p226; Other neurological monitoring, p230; Basic resuscitation, p358; Cardiac arrest, p360; Hypotension, p408; Sepsis—management, p594; Anaphylactoid reactions, p624; Head injury—general management, p632; Spinal cord injury, p636; Organ donation, p716.

Diuretics

Types

- Loop diuretics, e.g. furosemide, bumetanide.
- Osmotic diuretics, e.g. mannitol.
- Thiazides, e.g. metolazone.
- Potassium-sparing diuretics, e.g. amiloride, spironolactone, potassium canrenoate.

Modes of action

- Osmotic diuretics reduce distal tubular water reabsorption.
- Thiazides inhibit distal tubular Na^+ loss and carbonic anhydrase and increase Na^+ and K^+ exchange. This reduces supply of H^+ ions for exchange with Na^+ ions producing an alkaline natriuresis with potassium loss.
- Loop diuretics inhibit Na^+ and Cl^- reabsorption in the ascending loop of Henle.
- Potassium-sparing diuretics inhibit distal tubular Na^+ and K^+ exchange.

Uses

- Diuresis.
- Control of chronic oedema (thiazides, loop diuretics).
- Control of hypertension (thiazides).
- Promotion of renal excretion (e.g. forced diuresis, hypercalcaemia).

Routes and dosages

- IV (mannitol, furosemide, bumetanide, potassium canrenoate).
- PO (metolazone, furosemide, bumetanide, amiloride, spironolactone).

For drug dosages see Table 15.5.

Side effects

- Hypovolaemia (all).
- Hypo- or hypernatraemia.
- Hypokalaemia (all except potassium-sparing diuretics).
- Hyperkalaemia (potassium-sparing diuretics).
- Oedema formation (mannitol).
- Reduced catecholamine effect (thiazides).
- Hyperglycaemia (thiazides).
- Metabolic alkalosis (loop diuretics).
- Hypomagnesaemia (loop diuretics).
- Pancreatitis (furosemide).

Table 15.5 Drug dosages

	PO	IV	Infusion
Mannitol		0.25-2 g/kg over 30–60 min, repeated once if needed after 4–8 h	
Metolazone	5–10 mg od		
Furosemide	20–40 mg 6–24-hrly	5–80 mg 6–24-hrly	1–10 mg/h
Bumetanide	0.5–1 mg 6–24-hrly	0.5–2 mg 6–24-hrly	1–5 mg/h
Amiloride	5–10 mg 12–24-hrly		
Spironolactone	100–400 mg od		
K^+ canrenoate		200–400 mg od	

Notes

- Correct pre-renal causes of oliguria before resorting to diuretic use.
- Diuretics do not prevent renal failure but may convert oliguric to polyuric renal failure.
- If there is inadequate glomerular filtration, mannitol is retained and passes to the extracellular fluid to promote oedema formation.
- Potassium-sparing diuretics should generally be avoided with ACE inhibitors due to an increased risk of hyperkalaemia.

Further reading

See Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Fluid challenge, p362; Hypertension, p410; Oliguria, p426; Pancreatitis, p462; Hyponatraemia, p516; Hypokalaemia, p520; Metabolic alkalosis, p536.

Antiarrhythmics

Modes of action

See Table 15.6.

Table 15.6 Modified Vaughan Williams classification

Class	Action	Examples
0	Sino-atrial node blocker	Ivabradine
I	Fast Na^+ channels blockers	
	Ia: intermediate dissociating, prolonged AP	Ia: Disopyramide
	Ib: fast dissociating, shorten AP	Ib: Lidocaine
	Ic: slow dissociating, little effect on duration of AP	Ic: Flecainide
	Id: late Na^+ current blockers	Id: Ranolazine
II	β-blockers. Reduces rate of pacemaker discharge	Propranolol Atenolol
III	K^+ channel blockers. Prolong duration of action potential and hence length of refractory period	Amiodarone Sotalol
IV	Calcium handling modulators	Verapamil Diltiazem
V	Variable mechanisms of action	Adenosine Digoxin $MgSO_4$

Uses

- Correction of supraventricular and ventricular tachyarrhythmias.
- Identify supraventricular arrhythmias (adenosine).

Routes and dosages

- For drug dosages and their routes of administration see Table 15.7.

Side effects/complications

- Hypotension (e.g. verapamil, β-blockers) or bradycardia (e.g. β-blockers, amiodarone, digoxin, lidocaine).
- All atrioventricular blockers are contraindicated in re-entry tachycardia (e.g. Wolff–Parkinson–White syndrome).
- Amiodarone may cause severe bradycardia, acute and chronic pulmonary fibrosis, and thyroid dysfunction.

Notes

- Adenosine is very short-acting and may revert paroxysmal SVT (but not atrial flutter and fibrillation) to sinus rhythm. Ineffective for ventricular tachycardia (VT). Contraindicated in second- and third-degree heart block, sick sinus syndrome, asthma. May cause flushing, bronchospasm and occasional severe bradycardia.
- Amiodarone: effective against most tachyarrhythmias. When converting from IV to oral dosing, initial high oral dosing (200 mg tds) is required. Avoid in patients with thyroid dysfunction. Avoid with other class III agents (e.g. sotalol). Give IV doses centrally to avoid phlebitis.
- Bretylium: may take 15–20 min to take effect; now used predominantly for resistant ventricular fibrillation/VT. Continue CPR for at least 20 min.

- Digoxin: slow-acting, requires loading (1–1.5 mg) to achieve therapeutic levels over 12–24 h. Contraindicated in second- and third-degree heart block. May cause severe bradycardia. Low K^+, Mg^{2+} and raised Ca^{2+} increase myocardial sensitivity to digoxin. Amiodarone raises levels.
- Lidocaine: 10 mL of 1% solution contains 100 mg. No effect on SVT. Contraindicated in second- and third-degree heart block. May cause bradycardia and central nervous system side effects, e.g. drowsiness, seizures.
- Verapamil: caution with β-blockers as profound hypotension and bradyarrhythmias may result. Pre-treatment with 3–5 mL 10% calcium gluconate by slow IV bolus may prevent hypotensive effects.

Table 15.7 Routes of administration and drug dosages

Adenosine	6 mg rapid IV bolus. If no response after 1 min give 12 mg. If no response after 1 min repeat 12 mg
Amiodarone	5 mg/kg IV over 20 min (or 150–300 mg over 3 min in emergency) then IV infusion of 15 mg/kg/24 h in 5% glucose via central vein. Reduce thereafter to 10 mg/kg/24 h (~600 mg/day) for 3–7 days then maintain at 5 mg/kg/24 h (300–400 mg/day)
β-blockers	Esmolol: a titrated loading dose regimen is commenced followed by an infusion rate of 50–200 μg/kg/min Propranolol: initially given as slow IV boluses of 1 mg repeated at 2 min intervals to a maximum of 5 mg Labetalol: 0.25–2 mg/min Sotalol: dosage range is 20–120 mg IV (0.5–1.5 mg/kg) administered over 10 min. Repeat 6-hrly if necessary Metoprolol: 2.5–5 mg injected IV at rate of 1–2 mg per min, repeated at 5 min intervals until satisfactory response is seen or total dose of 10–15 mg given Atenolol: 2.5 mg IV over 2.5 min, repeated at 5 min intervals until response is seen or maximum of 10 mg
Bretylium	In emergency, 5 mg/kg by rapid IV bolus. If no response after 5 min, repeat or increase to 10 mg/kg
Digoxin	500 μg given IV over 10–20 min. Repeat at 4–8 h intervals until loading achieved (assessed by clinical response). Maintenance dose thereafter is 62.5–250 μg/day depending on plasma levels and clinical response
Lidocaine	1 mg/kg slow IV bolus for loading then 2–4 mg/min infusion. Should be weaned slowly over 24 h
$MgSO_4$	10–20 mmol over 1–2 h (over 5 min in emergency)
Verapamil	2.5 mg slow IV. If no response repeat to a maximum of 20 mg. An IV infusion of 1–10 mg/h may be tried. 10% calcium chloride solution should be readily available to reverse hypotension or negative inotropy

Further reading

Lei M, Wu L, Terrar D, et al. 2018. 'Modernized classification of cardiac antiarrhythmic drugs'. *Circulation* 138: pp1879–96. doi: 10.1161/CIRCULATIONAHA.118.035455

See Electrical cardioversion, p102; ECG monitoring, p184; Cardiac arrest, p360; Tachyarrhythmias, p412.

Chronotropes

Types

- Anticholinergic, e.g. atropine, glycopyrronium bromide (glycopyrrolate).
- Non-selective β-adrenergic agonist, e.g. isoprenaline.

Modes of action

- Anticholinergic drugs act by competitive antagonism of acetylcholine at peripheral muscarinic receptors and decreasing atrioventricular conduction time.
- Direct chronotropy via β-adrenergic stimulation.

Uses

- All types of bradycardia, including third-degree heart block.
- Atropine (500 μg repeated every 3–5 min as needed, to a total 3 mg), or isoprenaline as a second-line agent, can be used for life-threatening bradycardia.

Routes and dosages

See Table 15.8.

Table 15.8 Routes of administration and drug dosages

Atropine	0.3–0.6 mg IV bolus, repeated if required to a total 3 mg
Glycopyrronium bromide	0.2–0.4 mg IV bolus.
Isoprenaline	5 μg/min starting infusion rate and titrate upwards
Epinephrine	2–10 μg/min infusion

Side effects/complications

- Anticholinergic drugs produce dry mouth, reduction and thickening of bronchial secretions, and inhibition of sweating. Urinary retention may occur, but parenteral administration does not lead to glaucoma.
- β-agonists can induce tachyarrhythmias or hypo/hypertension.

Notes

- Chronotropes may be used as a bridge to temporary pacing.
- Atropine nebulizers have been used successfully in patients developing symptomatic bradycardia during endotracheal suction.
- Neurological effects are more likely with atropine than glycopyrronium bromide.

Further reading

See Temporary pacing, p104; ECG monitoring, p184; Cardiac arrest, p360; Bradyarrhythmias, p414.

Antianginal agents

Types

- Vasodilators, e.g. nitrates, calcium antagonists.
- β-blockers.
- Potassium channel openers, e.g. nicorandil.
- Antiplatelet/anticoagulant agents, e.g. aspirin, heparin, clopidogrel.

Modes of action

- Calcium channel blockers decrease influx of calcium into cells. This leads to reduced ventricular contraction and relaxation of cardiac and smooth muscle fibres leading to coronary and systemic vasodilatation.
- Nitrates causes efflux of calcium ions from smooth muscle and cardiac cells and increases cGMP synthesis resulting in coronary and systemic vasodilatation.
- β-blockers inhibit β-adrenoreceptor stimulation, reducing myocardial work and oxygen consumption.
- Potassium channel openers vasodilate by relaxing vascular smooth muscle on the arterial circulation while a nitrate-type action provides some venodilatation.
- Other drugs for stable angina include ivabradine (funny channel inhibitor, slows heart rate) and ranolazine (reduces diastolic wall tension, but does not affect heart rate).
- Though aspirin, heparin, fondaparinux, ticagrelor, and clopidogrel have no direct antianginal effect, patients with unstable angina benefit from reduced platelet aggregation and thrombus formation.

Routes and dosages

See Table 15.9.

Table 15.9 Routes of administration and drug dosages

Glyceryl trinitrate	0.3 mg SL, 0.4–0.8 mg by buccal spray, 2–40 mg/h by IV infusion
Isosorbide dinitrate	10–20 mg tds orally, 2–40 mg/h by IV infusion
Nifedipine	5–20 mg PO. The capsule fluid can be aspirated then injected down NG tube or given SL
Metoprolol	50–100 mg 2–3 times per day or 1–2 mg/min up to 5 mg, repeat after 5 min if required
Bisoprolol	5–10 mg od, max 20 mg per day
Nicorandil	10–20 mg PO bd
Clopidogrel	300 mg PO loading dose then 75 mg PO od
Aspirin	75–150 mg PO od
Fondaparinux	2.5 mg SC od
Ticagrelor	180 mg loading dose then 90 mg bd
Ivabradine	5–7.5 mg PO bd
Ranolazine	500–1000 mg PO bd

Side effects/complications

- Hypotension.
- Tachycardia (except β-blockers).
- Heart failure, peripheral hypoperfusion, bronchospasm, bradycardia, and decreased sympathetic response to hypoglycaemia (with β-blockers). Caution if using β-blockers and verapamil together.
- Tachyphylaxis (with nitrates).
- Nicorandil is contraindicated in hypotension and cardiogenic shock. Avoid in hypovolaemia. Rapid-onset hyperkalaemia may occur.
- Ivabradine is contraindicated in cardiogenic shock, acute MI, and heart block. It may cause vision disorders, hypertension, and bradycardia.
- Ranolazine prolongs the QT interval and increases the effect of drugs metabolized by cytochrome P450.

Notes

- Combination therapy involving nitrates, β-blockade, aspirin, antiplatelet drugs ± heparin ± calcium antagonists are used in acute coronary syndromes; thrombolytic therapy confers no added advantage. Local guidelines should be consulted.
- Angina may occasionally be worsened by a 'coronary steal' phenomenon where blood flow is diverted away from stenosed coronary vessels. This does not occur with nicorandil.

Further reading

➔ See Coronary revascularization techniques, p112; Echocardiography—use & indications, p214; Vasodilators & antihypertensives, p288; Acute coronary syndrome—management, p418.

Antiplatelet agents

Types

- Cyclooxygenase/thromboxane A_2 inhibitor, e.g. aspirin.
- ADP receptor inhibitors, e.g. clopidogrel, ticagrelor, prasugrel.
- Thrombin inhibitor, e.g. bivalirudin, argatroban.
- Glycoprotein IIb/IIIa inhibitor (GPI), e.g. abciximab, eptifibatide, tirofiban.
- D/NOACs (direct/novel oral anticoagulants).

Modes of action

- Antiplatelet agents prevent platelet aggregation by directly or indirectly inhibiting activation of GPI by thromboxane A_2, ADP or thrombin.

Uses

- Prevents clot formation after acute MI.
- Prevents clot formation with plaque build-up, e.g. unstable angina.

Routes and dosages

See Table 15.10.

Table 15.10 Drug dosages

Aspirin	300 mg PO stat
Clopidogrel	300–600 mg PO loading then 75 mg PO od
Ticagrelor	180 mg PO loading then 90 mg bd
Prasugrel	60 mg PO loading then 10 mg od
Bivalirudin	0.75 mg/kg IV bolus then 1.75 mg/kg/h
Argatroban	350 µg/kg IV followed by 25 µg/kg/min
Abciximab	50 µg/kg IV over 10–60 min followed by 10 µg/min for 12 h
Eptifibatide	180 µg/kg IV loading followed by 2 µg/kg/min
Tirofiban	25 µg/kg IV followed by 0.15 µg/kg/min for 18 h
Rivaroxaban	10 mg od (prophylaxis), 15 mg bd for 21 days then 20 mg od (treatment dose)

Stat = *statim* (immediately).

Side effects

- Bleeding.
- Hypotension.

Notes

- GPI, e.g. IV eptifibatide or tirofiban, in addition to aspirin and clopidogrel are used in patients at intermediate-to-high risk of MI or death where angiography is likely within 96 h.
- Bivalirudin can be used instead of heparin + GPI for angiography within 24 h where fondaparinux or a GPI have not already been used.

Further reading

See Acute coronary syndrome—management, p418.

Chapter 16

Gastrointestinal drugs

H_2 blockers & proton pump inhibitors

Types

- H_2 antagonists, e.g. ranitidine.
- Proton pump inhibitors (PPIs), e.g. omeprazole, lansoprazole, pantoprazole.

Modes of action

- They inhibit gastric acid secretion, reducing both volume and acid content, either by blocking the histamine H_2 receptor or inhibiting H^+/K^+-ATPase which fuels the parietal cell proton pump on which acid secretion depends.

Uses

- Peptic ulceration, gastritis, duodenitis.
- Reflux oesophagitis.
- Prophylaxis against stress ulceration.
- Upper gastrointestinal (GI) haemorrhage of peptic/stress ulcer origin.
- With non-steroidal anti-inflammatories in patients with dyspepsia.

Routes and dosages

See Table 16.1.

Table 16.1 Routes of administration and drug dosages

Ranitidine	50 mg tds by slow IV bolus, 150 mg bd PO
Lansoprazole	30 mg od PO or NG
Omeprazole	40 mg od (over 20–30 min) or 20–40 mg od PO
Pantoprazole	40 mg od PO or slow IV over at least 2 min For acute GI bleed, 80 mg bolus then infusion 8 mg/h for 72 h

Side effects/complications

- Bacterial over-growth leading to *Clostridioides difficile* (formerly *Clostridium difficile*) colitis and pneumonia.
- Prolonged use of PPI may increase risk of osteoporosis.

Notes

- Though often given, there is no strong evidence that PPI or H_2 blockers given before endoscopy offer any benefit in upper GI bleeding.
- For stress ulcer prophylaxis, a recent study in patients undergoing mechanical ventilation showed a reduced incidence of clinically significant upper GI bleeding with IV pantoprazole compared to placebo.
- In low-risk patients enteral nutrition may be considered as an alternative to drug treatment.
- Dosages should be modified in renal failure.
- Omeprazole can delay elimination of diazepam, phenytoin, and warfarin.

Further reading

Cook D, Deane A, Lauzier F, et al. for the REVISE Investigators. 2024. 'Stress Ulcer Prophylaxis during Invasive Mechanical Ventilation'. *N Engl J Med* 391: pp9–20. doi: 10.1056/NEJMoa2404245

See Upper gastrointestinal haemorrhage, p438.

Antacids

Types

- Sodium bicarbonate.
- Magnesium-based antacids, e.g. magnesium trisilicate.
- Aluminium-based antacids, e.g. aluminium hydroxide (Aludrox®).
- Proprietary combinations, e.g. sodium alginate with calcium carbonate and sodium bicarbonate (Gaviscon®).

Modes of action

- Neutralizes gastric acid.
- Provides protective coating on upper GI mucosa.

Uses

- Symptomatic relief of gastritis, duodenitis, oesophagitis.
- Stress ulcer prophylaxis (contentious).

Routes and dosages

- PO/NG.

For drug dosages see Table 16.2.

Table 16.2 Drug dosages

Magnesium trisilicate	10–30 mL qds
Aluminium hydroxide	10–30 mL qds
Gaviscon®	10–30 mL qds

Side effects/complications

- Possible increased risk of nosocomial pneumonia.
- Aluminium toxicity (if aluminium-containing antacids are used long term in patients with renal dysfunction).
- Diarrhoea (magnesium-based antacids).
- Constipation (aluminium-based antacids).
- Metabolic alkalosis if large amounts are administered.
- Milk-alkali syndrome, resulting in hypercalcaemia, metabolic alkalosis, and renal failure, is very rare.

Notes

- As their main use is for symptomatic relief, antacids are rarely needed in mechanically ventilated patients.

Further reading

➔ See Upper gastrointestinal haemorrhage, p438.

Antiemetics & gut motility agents

Types

- Phenothiazines, e.g. prochlorperazine, levomepromazine.
- Dopamine receptor blocker; e.g. metoclopramide, domperidone.
- Antihistamines, e.g. cyclizine.
- $5HT_3$ receptor antagonists, e.g. ondansetron, granisetron.
- Dexamethasone.
- Erythromycin.

Modes of action

- Phenothiazines increase the threshold for vomiting at the chemoreceptor trigger zone via central DA_2-dopaminergic blockade; at higher doses there may also be some effect on the vomiting centre.
- Metoclopramide acts centrally but also increases gastric motility by blocking peripheral DA_2-dopaminergic receptors.
- Cyclizine increases lower oesophageal sphincter tone and may inhibit the midbrain emetic centre.
- Ondansetron is a highly selective $5HT_3$ receptor antagonist; its precise mode of action is unknown but may act both centrally and peripherally.
- Dexamethasone's antiemetic mechanism is also uncertain but may act through inhibiting prostaglandin synthesis, having anti-inflammatory effects, and decreasing release of endogenous opiates.
- Erythromycin is a motilin agonist acting on antral enteric neurones.

Uses

- Nausea.
- Vomiting and large nasogastric aspirates.
- Ileus.

Routes and dosages

See Table 16.3.

Table 16.3 Routes of administration and drug dosages

Prochlorperazine	5–10 mg tds PO, 12.5 mg qds IM or by slow IV bolus
Levomepromazine	6 mg od PO, increasing up to 25 mg bd6.25 mg SC od, increasing up to 25 mg bd as needed 5–25 mg/24 h infusion
Metoclopramide	10 mg tds by slow IV bolus, IM, or PO
Cyclizine	50 mg tds slow IV bolus, IM, or PO
Ondansetron	4–8 mg tds by slow IV bolus, IM, or PO
Granisetron	1–3 mg by slow IV bolus up to max 9 mg/24 h
Dexamethasone	2.5–10 mg/day
Erythromycin	250–500 mg tds PO or 3 mg/kg IV (rounded to the nearest 50 mg) tds IV

Side effects/complications

- Dystonic or dyskinetic reactions, oculogyric crises (prochlorperazine, levomepromazine, metoclopramide). Metoclopramide dosing should be restricted to <30 mg/24 h for up to 5 days in view of the risk of extrapyramidal side effects.
- Arrhythmias (metoclopramide, prochlorperazine, levomepromazine, erythromycin).
- Headaches, flushing (ondansetron).
- Urticaria, drowsiness, dry mouth, blurred vision, urinary retention (cyclizine).
- Postural hypotension (prochlorperazine, cyclizine).
- Rarely neuroleptic malignant syndrome (prochlorperazine, metoclopramide, levomepromazine).
- Cholestatic jaundice (erythromycin).

Notes

- The initial choice generally falls between prochlorperazine, metoclopramide, cyclizine, or ondansetron.
- Metoclopramide and prochlorperazine dosage should be reduced in renal and hepatic failure.
- Ondansetron and erythromycin dosage should be reduced in hepatic failure.
- Dexamethasone and levomepromazine are mainly used in oncology practice.

Further reading

See Enteral nutrition, p142; Vomiting/gastric stasis, p434.

Antidiarrhoeals

Types

- Loperamide.
- Codeine phosphate.

Modes of action

- Loperamide and codeine phosphate bind to gut wall opiate receptors, reducing propulsive peristalsis and increasing anal sphincter tone.

Uses

- Diarrhoea.

Routes and dosages

See Table 16.4.

Table 16.4 Routes of administration and drug dosages

Loperamide	2 capsules (20 mL) initially, then 1 capsule (10 mL) after every loose stool for up to 5 days
Codeine phosphate	30–60 mg 4–6-hrly PO, IM, or by slow IV bolus

Side effects/complications

- Abdominal cramps, bloating.
- Constipation (if excessive amounts given).

Notes

- Should not be used when abdominal distension develops, particularly with ulcerative colitis or pseudomembranous colitis.
- Avoid in infective diarrhoea as may prolong illness.
- Caution with loperamide in liver failure, and codeine in renal failure.

Further reading

See Enteral nutrition, p142; Diarrhoea & constipation, p436.

Anti-constipation agents

Types

- Laxatives, e.g. lactulose, senna, propantheline, mebeverine.
- Bulking agents, e.g. dietary fibre (bran), hemicelluloses (methylcellulose, ispaghula husk), sodium docusate.
- Suppositories, e.g. glycerine.
- Enemas, e.g. warmed normal saline, olive oil, or arachis oil retention enemata.
- Opioid receptor antagonists, e.g. methylnaltrexone.

Modes of action

- Laxatives include.
  - antispasmodic agents such as anticholinergics (e.g. propantheline and mebeverine, a phenylethylamine derivative of reserpine)
  - non-absorbable disaccharides (e.g. lactulose) which soften the stool by an osmotic effect and by lactic acid production from a bacterial fermenting effect
  - irritants, such as castor oil; this is hydrolysed in the small intestine releasing ricinoleic acid
  - senna stimulates peristalsis via its anthrone component.
- Bulking agents are hydrophilic, increasing water content of the stool.
- Peripheral opioid receptor antagonists reduce opioid-induced constipation without affecting analgesia.

Uses

- Constipation.

Routes and dosages

See Table 16.5.

Table 16.5 Routes of administration and drug dosages

Lactulose	15–50 mL tds PO
Senna	15 mg PO at night
Movicol®	25 mL liquid diluted in 100 mL of water PO/NG
Sodium docusate	50 mg PO od to 100 mg PO qds
Methylnaltrexone	8–12 mg SC given as 4–7 doses/week. Reduce in renal failure

Side effects/complications

- Bloating and abdominal distension.
- Diarrhoea.

Notes

- Surgical causes presenting as constipation such as bowel obstruction must be excluded. Other measures should be taken, if possible, to improve bowel function, e.g. reducing concurrent opiate dosage.
- Larger doses of lactulose are used in hepatic failure as the pH of the colonic contents is reduced; this lowers formation and absorption of ammonium ions and other nitrogenous products into the portal circulation.
- Anthraquinone glycosides (e.g. senna) and liquid paraffin are no longer recommended for routine use.

Further reading

See Diarrhoea & constipation, p436.

Chapter 17

Neurological drugs

Non-opioid analgesics

Types

- Paracetamol (acetaminophen).
- Non-steroidal anti-inflammatory drugs (NSAIDs), e.g. aspirin, ibuprofen, indometacin (indomethacin), diclofenac, ketorolac.
- Gabapentinoids, e.g. gabapentin, pregabalin.
- Ketamine.
- Nitrous oxide.
- Local anaesthetics, e.g. lidocaine, bupivacaine.
- α_2 agonists—clonidine, dexmedetomidine (see under 'Sedatives').

Uses

- Pain associated with inflammatory conditions (aspirin, NSAIDs).
- Postoperative and musculoskeletal pain (aspirin, NSAIDs, paracetamol, gabapentin, ketamine, nitrous oxide, lidocaine, bupivacaine).
- Opiate-sparing effect (aspirin, paracetamol, NSAIDs).
- Antipyretic (aspirin, paracetamol, NSAIDs).

Routes and dosages

- Intravenous (IV) (paracetamol, ketamine).
- Intramuscular (IM) (diclofenac, ketamine).
- Orally (PO) (aspirin, NSAIDs, paracetamol, gabapentin).
- Rectally (PR) (aspirin, diclofenac, paracetamol).
- Local/regional (lidocaine, bupivacaine).
- Inhaled (nitrous oxide).

For drug dosages see Table 17.1.

Table 17.1 Drug dosages

Aspirin	600 mg PO/PR 4-hrly
Ibuprofen	400 mg PO 4–8-hrly
Indometacin	50–100 mg PO/PR 12-hrly
Diclofenac	25–50 mg PO 8-hrly, 100 mg PR 12–24-hrly, 75 mg IM 12-hrly
Ketorolac	10 mg PO 4–6-hrly, 10–30 mg IV/IM 4–6-hrly
Paracetamol	0.5–1 g PO/PR/IV 4–6-hrly
Gabapentin	300 mg PO, increased as necessary to 600 mg PO tds
Ketamine	5–25 μg/kg/min IV or 0.5–1.0 mg/kg IM
Clonidine	100–150 μg/h
Dexmedetomidine	1 μg/kg over 10 min, followed by 0.2–0.7 μg/kg/h infusion
Lidocaine	Up to 3 mg/kg*
Bupivacaine	Up to 2 mg/kg*

* Local anaesthetic doses vary according to area to be anaesthetized. Maximum doses may be increased if epinephrine is used locally.

Side effects

- Gastrointestinal bleeding (aspirin, indometacin, diclofenac).
- Renal dysfunction (indometacin, diclofenac if any hypovolaemia).
- Reduced platelet aggregation (aspirin, indometacin, diclofenac).
- Reduced prothrombin formation (aspirin, indometacin, diclofenac).
- Myocardial depression and cardiac arrest (lidocaine, bupivacaine).
- Hypertension and tachycardia (ketamine).
- Hypotension and bradycardia (clonidine).
- Seizures (lidocaine, bupivacaine).
- Hallucinations and psychotic tendencies (ketamine—may be prevented by concurrent use of benzodiazepines).

Notes

- Mild to moderate pain is managed with simple analgesics, progressing to opioids if pain relief is inadequate.
- Non-steroidal anti-inflammatory agents should be generally avoided in patients with renal dysfunction, gastrointestinal bleeding, or coagulopathy.
- In sub-anaesthetic doses ketamine is a powerful analgesic. It is associated with good airway maintenance, allows spontaneous breathing, is a bronchodilator, and provides cardiovascular stimulation.
- Nitrous oxide is a powerful, short-acting analgesic used with 50% oxygen (Entonox®) to cover short, painful procedures. It should not be used with an undrained pneumothorax since it may lead to tension pneumothorax.
- Clonidine and dexmedetomidine have intrinsic analgesic properties.
- Dexmedetomidine has minimal effects on respiration and can be helpful in weaning.

Further reading

➔ See Opioid analgesics, p318; Rheumatic disorders, p618; Pyrexia, p654; Pain, p660; Perioperative critical care, p666.

Opioid analgesics

Types

- Natural opiates, e.g. morphine, codeine.
- Semi-synthetic, e.g. diamorphine, dihydrocodeine, buprenorphine.
- Synthetic, e.g. pethidine, fentanyl, alfentanil, remifentanil, tramadol.

Uses

- Analgesia.
- Sedation.
- Anxiolysis.
- Antidiarrhoeal (codeine).
- Cough suppressant (codeine).

Routes and dosages

- IV (morphine, diamorphine, pethidine, fentanyl, alfentanil, remifentanil, tramadol).
- IM/subcutaneous (SC)/PO (morphine, codeine, diamorphine, dihydrocodeine, pethidine, tramadol).
- Percutaneous/patch (fentanyl, buprenorphine).

For drug dosages see Table 17.2.

Table 17.2 Drug dosages

Intravenous	Bolus	Infusion
Morphine	0.1–0.2 mg/kg	0.05–0.07 mg/kg/h
Diamorphine	0.05–0.1 mg/kg	0.03–0.06 mg/kg/h
Pethidine	0.5 mg/kg	0.1–0.3 mg/kg/h
Fentanyl	5–7.5 µg/kg	5–20 µg/kg/h
Alfentanil	15–30 µg/kg	20–120 µg/kg/h
Remifentanil	1 µg/kg	0.05–2 µg/kg/min
Buprenorphine	300–600 µg 6–8-hrly	–
Tramadol	50–100 mg 4–6-hrly	0.05–0.07 mg/kg/h
Oxycodone	1–10 mg IV 4-hrly	Start at 2 mg/h

Other routes	IM/SC	PO/SL
Morphine	10 mg IM/SC 4-hrly	5–20 mg PO 4-hrly
Codeine	30–60 mg IM 4-hrly	30–60 mg PO 4-hrly
Diamorphine	5 mg IM/SC 4-hrly	5–10 mg PO 4-hrly
Buprenorphine		200–400 µg SL 6–8-hrly or a once-weekly patch

Table 17.2 (*Contd.*)

Intravenous	Bolus	Infusion
Dihydrocodeine	50 mg IM/SC 4–6-hrly	30 mg PO 4–6-hrly
Pethidine	25–100 mg IM/SC 4-hrly	50–150 mg PO 4-hrly
Tramadol	50–100 mg IM 4–6-hrly	50–100 mg PO 4–6-hrly
Oxycodone	Start at 7.5 mg/24 h SC or 5 mg 4–6-hrly SC	From 5 mg PO 4–6-hrly
Fentanyl	12–100 μg/h percutaneous or 600 μg buccal	

NB: the above doses are a guide only and may need to be altered widely according to individual circumstances. The correct dose of an opiate analgesic is generally enough to ablate pain.

Side effects

- Respiratory depression.
- Central nervous system depression.
- Stimulation of the vomiting centre.
- Decreased gastric emptying and gut motility, constipation.
- Histamine release and itching.
- Dry mouth.
- Increased muscular tone.
- Appetite loss.
- Withdrawal syndrome.
- Addiction (rare in the critically ill).

Notes

- Mild to moderate pain requiring opioids is usually treated with less potent drugs such as codeine, dihydrocodeine, or tramadol.
- As morphine is poorly absorbed from the gastrointestinal tract, it is usually administered parenterally. It is metabolized in the liver to morphine-6-glucuronide which is sixfold more potent than morphine and accumulates in renal failure.
- Pethidine has local anaesthetic properties associated with cardiac depression and vasodilatation. It is metabolized to norpethidine which may lead to seizures on accumulation. Respiratory depression occurs despite maintenance of respiratory rate.
- Fentanyl and alfentanil are good, short-acting analgesics but with less sedative quality. Long-term infusion leads to accumulation. They can cause severe respiratory depression and muscular rigidity.
- Remifentanil is a potent, ultra short-acting agent that should be administered only by infusion. Bolus may lead to apnoea. The patient may experience rebound pain if the infusion is stopped abruptly.

Further reading

See Non-opioid analgesics, p316; Pain, p660; Perioperative critical care, p666.

Epidural analgesics

An epidural catheter is inserted into the epidural space to deliver local anaesthetics and/or opioids, or other analgesics to act locally on nerve roots and the spinal cord. Effective analgesia can be achieved with lower drug doses reducing the risk of side effects from systemic opioids in postoperative or post-trauma analgesia, or for regional anaesthesia.

Types

- Opioid analgesics (morphine, diamorphine, fentanyl, alfentanil).
- Local anaesthetics (bupivacaine).
- Adjuvants (clonidine, bicarbonate).

Uses

- Postoperative analgesia.
- Regional anaesthesia.

Dosages

See Table 17.3.

Table 17.3 Drug dosages

	Concentration	Dose
Fentanyl	2–4 μg/mL	0–40 μg/h
Morphine	50 μg/mL	0–0.5 mg/h
Diamorphine	20 μg/mL	0–0.2 mg/h
Bupivacaine	0.1–0.25%	6.3–18.8 mg/h
Clonidine	2 μg/mL	15–20 μg/h

Side effects

- Hypotension (local anaesthetics, clonidine) can be managed with fluids and vasopressors. Do not automatically assume the epidural is a cause of hypotension; exclude surgical bleeding and hypovolaemia.
- Motor blockade (local anaesthetics).
- Bradycardia (local anaesthetic with a high block above T4).
- Central nervous system and respiratory depression (opioids).
- Urinary retention (opioids, local anaesthetics).
- Stimulation of the vomiting centre (opioids).
- Appetite loss (opioids).
- Dry mouth (opioids).
- Decreased gastric emptying and gut motility (opioids).
- Histamine release and itching (opioids).
- Increased muscular tone (opioids).
- Headache (dural puncture).
- Abscess or haematoma (catheter related).
- Total spinal block (profound hypotension, apnoea, unconsciousness, dilated pupils due to inadvertent spinal injection of epidural dose).

Management of an *in situ* epidural

- Check level of insertion (e.g. T9–L4) and length of catheter at skin. Check for leaks, bleeding, and/or local infection.
- Establish if patient is in pain and location of pain. This may relate to inadequate dosing (low block) rather than failure.
- Assess sensory level and the presence of any motor block.

Notes

- The epidural catheter should typically be placed in the mid-dermatome range of the site of the pain.
- Epidural catheters can remain *in situ* for up to 5 days.
- Clotting should be normal/corrected at time of insertion and removal. Prophylactic low-molecular-weight heparin (LMWH) should not be given for 12 h prior to insertion, and for 4 h after removal, to reduce the risk of epidural haematoma.
- Patients on treatment dose LMWH with an epidural *in situ* should be discussed with pharmacy or haematology. In general, treatment dose LMWH should not be given when an epidural is *in situ*.
- Fentanyl is more lipid-soluble than non-synthetic opioids so gains faster access to opioid receptors.
- Low bupivacaine concentrations are less likely to block larger diameter motor fibres allowing the patient to mobilize.
- Combinations of drugs (e.g. bupivacaine plus fentanyl) are often used in lower doses to maximize the analgesic effect while minimizing side effects.
- Higher volume infusions block a greater range of nerve roots. A bolus of 1–2 mL of local anaesthetic will typically block one dermatome. Age reduces the volume required.
- An inadequate block may respond to a bolus dose or an increase in infusion rate.
- Clonidine may enhance epidural opioid and local anaesthetic analgesia.

Further reading

➲ See Non-opioid analgesics, p316; Opioid analgesics, p318; Respiratory failure, p370; Hypotension, p408; Bradyarrhythmias, p414; Epidural analgesia—management, p662.

Sedatives

Types

- Benzodiazepines, e.g. diazepam, midazolam, lorazepam.
- Anaesthetic agents, e.g. propofol, sevoflurane, ketamine, thiopental.
- α_2 agonists, e.g. clonidine, dexmedetomidine.

Routes and dosages

- IV (benzodiazepines, propofol, α_2 agonists).
- IM (benzodiazepines).
- PO (diazepam, lorazepam, clonidine).
- Inhaled (sevoflurane).

For drug dosages see Table 17.4.

Table 17.4 Drug dosages

	Bolus	Infusion
Propofol	0.5–2 mg/kg IV	1–3 mg/kg/h
Diazepam	0.05–0.15 mg/kg IV/IM	Too long acting
Midazolam	50 µg/kg IV/IM	1–10 mg/h
Lorazepam	1 mg IV	Too long-acting
Clonidine	Slow IV injection 1–2 µg/kg over 10–15 min	100–150 µg/h
Ketamine	1–2 mg/kg IV over >60 sec; 6.5–13 mg/kg IM	Initially 0.5–2 mg/kgMaintenance 10–45 µg/kg/min
Thiopental	100–150 mg/kg IV bolus, repeat if needed after 30–60 sec or up to 4 mg/kg	3–5 mg/kg/h
Dexmedetomidine	Start at 0.7 µg/kg/h; adjust according to response with usual range 0.2–1.4 µg/kg/h	

NB: the above doses are a guide; they may need to be altered according to patient response.

Side effects

- Hypotension (benzodiazepines, propofol, α_2 agonists, thiopental).
- Bradycardia (α_2 agonists).
- Respiratory depression (benzodiazepines, propofol).
- Dry mouth and reduced gut motility (clonidine, dexmedetomidine).
- Rebound agitation on drug withdrawal (benzodiazepines).

Notes

- Benzodiazepines are anxiolytic and amnesic but increase delirium risk.
- Benzodiazepines accumulate in renal failure; avoid excessive dosage by regular reassessment of need.
- Propofol in sub-anaesthetic doses is short-acting but effects are cumulative with prolonged infusion or coexisting hepatic/renal failure.
- Large dose propofol may increase calorie intake, cause hypertriglyceridaemia or the propofol infusion syndrome (bradycardia,

metabolic acidosis, rhabdomyolysis, hyperlipidaemia, enlarged or fatty liver) related to mitochondrial impairment.
- α_2 antagonists offer analgesia, sedation, and opiate synergism.
- Dexmedetomidine causes minimal respiratory depression and enables easy patient rousability. Bradycardia and hypotension may occur.
- Sevoflurane is short acting, although cumulative with a theoretical risk of fluoride toxicity with prolonged use.

Monitoring sedation

- Frequent, objective reassessment of sedation and degree of agitation, with corresponding adjustment of doses is necessary to avoid severe cardiovascular and respiratory depression. Simple sedation scores are available to aid assessment (Table 17.5).
- All sedatives are cumulative so doses must be kept to a minimum to reduce critical care stay.
- Daily sedation holds are another means of assessing potential over-sedation but risk abrupt patient awakening with possible agitation.

Table 17.5 Richmond Agitation–Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative, violent
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Non-purposeful movements, fights ventilator
+1	Restless	Anxious but movements not aggressive vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 s)
−2	Lightly sedated	Briefly awakens with eye contact to voice (<10 s)
−3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
−5	Unrousable	No response to voice or physical stimulation

Further reading

Pandharipande P, Pun B, Herr D, et al. 2007. 'Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial'. *JAMA* 298: pp2644–53. doi: 10.1001/jama.298.22.2644

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Hughes C, Mailloux P, Devlin J, et al. 2021. 'Dexmedetomidine or propofol for sedation in mechanically ventilated adults with sepsis'. *N Engl J Med* 384: pp1424–36. doi:10.1056/NEJMoa2024922

See Invasive ventilation—failure to tolerate ventilation, p56; Invasive ventilation—principles of weaning, p64; Electroencephalogram (EEG), p228; Respiratory stimulants, p280; Delirium, p470.

Tranquillizers

Types

- Major tranquillizers, e.g. haloperidol.
- Antipsychotic agents, e.g. haloperidol, olanzapine, quetiapine, aripiprazole.

Uses

- Reduces agitation and anxiety. All have sedative properties, but phenothiazines cause less suppression of respiratory drive.

Routes and dosages

- IV/IM (haloperidol, aripiprazole).
- PO (aripiprazole, olanzapine, quetiapine).

For drug dosages see Table 17.6.

Table 17.6 Drug dosages

	Bolus
Haloperidol	1–10 mg IV/IM, prn or qds
Olanzapine	5 mg PO/IM, titrate to max 20 mg
Quetiapine	50 mg PO 12-hrly, titrate to max 200 mg

Note that the above doses are a guide only and may need to be altered significantly according to individual circumstances.

Side effects

All antipsychotics may have the following effects

- Hypotension.
- Prolonged QTc—monitor QTc interval regularly.
- Arrhythmias including torsades de pointes.
- Extrapyramidal disorder.
- Neuroleptic malignant syndrome.

Notes

- All tranquillizers are cumulative so doses must be kept to a minimum.
- Consider regular dosing, with prn supplements as needed, in a severely agitated patient to reduce risk of harm both to self and carers.

Further reading

See Invasive ventilation—failure to tolerate ventilation, p56; Invasive ventilation—principles of weaning, p64; Electroencephalogram (EEG), p228; Respiratory stimulants, p280; Delirium, p470.

Muscle relaxants

Types

- Depolarizing: suxamethonium.
- Non-depolarizing: rocuronium, atracurium, vecuronium, pancuronium.

Mode of action

- Suxamethonium is structurally related to acetylcholine and causes initial stimulation of muscular contraction seen clinically as fasciculation. During this process continued stimulation leads to desensitization of the post-synaptic membrane of the neuromuscular junction with efflux of K^+ ions. Subsequent flaccid paralysis is short-acting (2–3 min) and cannot be reversed (is actually potentiated) by anticholinesterase drugs. Prolonged effects occur with pseudo-cholinesterase deficiency (suxamethonium apnoea).
- Non-depolarizing muscle relaxants prevent acetylcholine from depolarizing the post-synaptic membrane of the neuromuscular junction by competitive blockade. They have a slower onset and longer duration of action than depolarizing agents. Reversal of paralysis can be achieved by anticholinesterase drugs, e.g. neostigmine or sugammadex (for rocuronium or vecuronium only).

Uses

- Facilitates endotracheal intubation.
- Facilitates mechanical ventilation where adequate sedation does not prevent patient interference with the function of the ventilator.
- Improves chest wall compliance in severe acute respiratory distress syndrome.

Routes and dosages

- IV.

For drug dosages see Table 17.7.

Table 17.7 Drug dosages

	Bolus	Infusion
Suxamethonium	50–100 mg	2–5 mg/min
Atracurium	0.3 mg/kg*	25–50 mg/h
Rocuronium	0.6 mg/kg (1 mg/kg in RSI)*	300–600 µg/kg/h
Vecuronium	5–7 mg	Excessive half life
Pancuronium	4 mg	1–4 mg/h

* Use ideal body weight; dose adjustment may be required in the elderly.

RSI = rapid sequence induction.

Side effects

- Hypertension (suxamethonium, pancuronium).
- Bradycardia (suxamethonium).
- Tachycardia (pancuronium).
- Hyperkalaemia (suxamethonium).

Reversal

- Paralysis can be assessed using peripheral nerve stimulation (train of four, or double-burst stimulation).
- Neostigmine with glycopyrronium (dose 1–2 mL where 1 mL = 2.5 mg neostigmine + 0.5 mg glycopyrronium). Glycopyrronium is co-administered to counteract muscarinic effects of neostigmine (e.g. bradycardia, dry mouth).
- Sugammadex is a modified cyclodextrin that encapsulates rocuronium or vecuronium. It is indicated when rapid reversal of paralysis is required. Routine reversal 2–4 mg/kg then 4 mg/kg if required or block recurs. For immediate reversal 16 mg/kg.

Notes

- Frequently reassess requirements for muscle relaxants. Ideally, stop relaxant infusions intermittently to assess depth of sedation. If mechanical ventilation proceeds smoothly after relaxants have been stopped they should not generally be restarted.
- Suxamethonium is contraindicated with hyperkalaemia, spinal neurological disease, hepatic disease, and for 5–50 days after burns.
- Atracurium and cisatracurium are non-cumulative and popular choices for infusion. Non-enzymatic (Hoffman) degradation of these agents is independent of renal or hepatic function though effects are prolonged in hypothermia.
- Rocuronium has the fastest onset of the non-depolarizing muscle relaxants.

Further reading

See Endotracheal intubation—indications & equipment, p44; Invasive ventilation—failure to tolerate ventilation, p56; Invasive ventilation—failure to deliver ventilation, p58; Sedatives, p322; Tranquillizers, p324; Critical care neuromyopathies, p490; Perioperative critical care, p668.

Anticonvulsants

Types

- Benzodiazepines, e.g. lorazepam, diazepam, clonazepam.
- Phenytoin, fosphenytoin.
- Valproate.
- Levetiracetam.
- Magnesium sulfate.
- Anaesthetic agents, e.g. thiopental, propofol.

Uses

- Control of status epilepticus.
- Intermittent seizure control.
- Myoclonic seizures (clonazepam, valproate).

Routes and dosages

- IV (lorazepam, diazepam, clonazepam, phenytoin, fosphenytoin, valproate, levetiracetam, magnesium, thiopental).
- PO (diazepam, clonazepam, phenytoin, carbamazepine, valproate, levetiracetam).
- PR (diazepam).

For IV drug dosages see Table 17.8.

Table 17.8 Intravenous drug dosages

	Bolus	Infusion
Lorazepam	4 mg (max 2 mg/min)	
Midazolam/ diazepam	2.5 mg prn every 3 min to max dose of 20 mg	1–10 mg/h
Phenytoin	18 mg/kg at <50 mg/min, then 100 mg tds	
Fosphenytoin	20–30 mg/kg	150–225 mg/ min
Magnesium sulfate	20 mmol over 10–20 min	5–10 mmol/h
Valproate	400-800 mg	
Levetiracetam	For status 60 mg/kg (max dose 4500 mg) over 15 min followed after 12 h by maintenance dose of 500 mg bd	
Clonazepam	1 mg	1–2 mg/h
Propofol	1–2 mg/kg	20–200 μg/ kg/min
Thiopental	1–3 mg/kg	1 mg/kg/h initially

Side effects

- Sedation (benzodiazepines, thiopental).
- Respiratory depression (benzodiazepines, thiopental).
- Nausea and vomiting (phenytoin, valproate).
- Ataxia (phenytoin, carbamazepine).
- Visual disturbance (phenytoin, carbamazepine).
- Hypotension (diazepam, thiopental).
- Arrhythmias (phenytoin, carbamazepine).
- Pancreatitis (thiopental).
- Hepatic failure (valproate).

Notes

- Common insults causing seizures include cerebral ischaemic damage, space-occupying lesions, drugs or drug/alcohol withdrawal, metabolic encephalopathy (including hypoglycaemia) and neurosurgery.
- Anticonvulsants provide control of seizures but the cause should be corrected where possible.
- Onset of seizure control may be delayed by up to 24 h with phenytoin but a loading dose is usually given during the acute seizure phase.
- Magnesium sulfate is especially useful in eclamptic seizures.
- Phenytoin has a narrow therapeutic range and a non-linear relationship between dose and plasma levels. Monitor plasma levels regularly until stable.
- A recent randomized controlled trial (RCT) comparing levetiracetam, fosphenytoin, and valproate as second-line therapy for benzodiazepine-refractory status epilepticus had similar success rates in approximately half of the patients, regardless of age (children, adults, elderly (>65 years))
- Enteral feeding should be stopped while oral phenytoin is given.
- Carbamazepine has a wider therapeutic range than phenytoin and there is a linear relationship between dose and plasma levels. It is not, therefore, critical to monitor plasma levels.
- Plasma concentrations of valproate are not related to its seizure-controlling effect.
- Other drugs, e.g. lacosamide, can be used in resistant cases. Seek neurology advice.

Further reading

Treiman V. Meyers P, Walton N, et al. for the Veterans Affairs Status Epilepticus Cooperative Study Group. 1998. 'A comparison of four treatments for generalized convulsive status epilepticus'. *N Engl J Med* 339: pp792–8. doi: 10.1056/NEJM199809173391202

Altman D, Carroli G, Duley L, et al. for the Magpie Trial Collaboration Group. 2002. 'Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial'. *Lancet* 359: pp1877–90. doi: 10.1016/s0140-6736(02)08778-0

Chamberlain J, Kapur J, Shinnar S, et al. 2020. 'Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, RCT.' *Lancet* 395: pp1217–24. doi: 10.1016/S0140-6736(20)30611-5

See Electroencephalogram (EEG), p228; Generalized seizures, p472.

Neuroprotective agents

Types

- Diuretics, e.g. mannitol, furosemide.
- Corticosteroids, e.g. dexamethasone.
- Calcium antagonists, e.g. nimodipine.
- Barbiturates, e.g. thiopental.

Uses

- Reduction of cerebral oedema (mannitol, furosemide, dexamethasone).
- Prevention of cerebral vasospasm (nimodipine).
- Reduction of cerebral metabolic rate (thiopental).

Routes and dosages

See Table 17.9.

Table 17.9 Drug administration routes and dosages

Mannitol	20–40 g IV 6-hrly
Furosemide	1–5 mg/h IV infusion
Dexamethasone	4 mg 6-hrly or 8–16 mg od
Nimodipine	60 mg PO 4-hrly or 0.5–2.0 mg/h IV infusion
Thiopental	1.5–3 mg/kg slow IV, repeated as needed
Simvastatin	80 mg PO

Notes

- Cerebral protection requires generalized sedation and abolition of seizures to reduce cerebral metabolic rate, cerebral oedema and neuronal damage during ischaemia and reperfusion.
- Mannitol reduces cerebral interstitial water through its osmotic effect. This is transient and most effective with an intact blood–brain barrier. Interstitial water is mainly reduced in normal areas of brain and this may accentuate cerebral shift. Repeated doses accumulate in the interstitium and may eventually increase oedema formation; mannitol should only be given a maximum of 4–5 times in 48 h with regular monitoring of plasma osmolality. In addition to its osmotic effect, there is some evidence of cerebral vasoconstriction due to a reduction in blood viscosity and free radical scavenging.
- The loop diuretic effect of furosemide encourages salt and water loss. It may also reduce cerebrospinal fluid (CSF) chloride transport lowering CSF formation.
- Dexamethasone reduces oedema around space-occupying lesions. Corticosteroids are not currently considered useful after head injury or cerebrovascular accident but benefit has been shown if given early post-spinal injury. Corticosteroids encourage salt and water retention so should be withdrawn slowly to avoid rebound oedema.

- Nimodipine prevents cerebral vasospasm during recovery from cerebrovascular insults. As a calcium channel blocker it also prevents calcium ingress during neuronal injury that is associated with cell death. It is often used for 5–14 days after subarachnoid haemorrhage.
- Thiopental reduces cerebral metabolism. Although it also reduces cerebral blood flow, blood flow is redistributed preferentially to ischaemic areas. Thiopental acutely reduces intracranial pressure and this is probably its main cerebroprotective effect. Seizure control is a further benefit. Despite these effects, barbiturate coma has not been shown to improve outcome in cerebral insults of various causes.
- A large RCT in acute stroke found no benefit from magnesium sulfate given before hospital admission.

Further reading

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Saver J, Starkman S, Eckstein M, for the FAST-MAG Investigators and coordinators. 2015 'Prehospital use of magnesium sulfate as neuroprotection in acute stroke.' *N Engl J Med* 372: pp528–36. doi: 10.1056/NEJMoa1408827.

➔ See Intracranial pressure monitoring, p224; Jugular venous bulb saturation, p226; Electroencephalogram (EEG), p228; Other neurological monitoring, p230; Anticonvulsants, p328; Coma, p466; Generalized seizures, p472; Intracranial haemorrhage, p478; Subarachnoid haemorrhage, p480; Stroke, p482; Raised intracranial pressure, p484.

Chapter 18

Haematological drugs

Anticoagulants—parenteral

Types

- Unfractionated heparin.
- Low-molecular-weight heparin (LMWH), e.g. dalteparin, enoxaparin, tinzaparin, fondaparinux.
- Heparinoids, e.g. danaparoid.
- Direct thrombin inhibitors, e.g. bivalirudin, argatroban.
- Anticoagulant prostanoids, e.g. epoprostenol, alprostadil.
- Sodium citrate.

Modes of action

- Heparin potentiates naturally occurring antithrombin, reduces platelet adhesion to injured vessels, and promotes *in vitro* aggregation.
- LMWH influences factor Xa activity specifically; its simpler pharmacokinetics allow a smaller dose to be effective.
- Heparinoids are similar to heparin, with 10–20% risk of cross-reactivity. Use is mainly restricted to treating heparin-induced thrombocytopenia (HIT) syndrome and for deep vein thrombosis (DVT) prophylaxis. No antidote is available.
- Direct thrombin inhibitors are unrelated to heparin so can be used to treat HIT.
- Prostanoids affect the balance between native pro-thrombotic thromboxane A_2 and antithrombotic prostaglandin I_2.
- Sodium citrate chelates ionized calcium.

Uses

- Maintenance of extracorporeal circulation.
- Prevention or treatment of thromboembolism.

Routes and dosages

- Intravenous (IV) (heparins, heparinoids, prostanoids, sodium citrate).
- Subcutaneous (SC) (heparins).

For drug dosages and indications see Table 18.1.

Side effects

- Bleeding.
- Hypotension (anticoagulant prostanoids).
- HIT.
- Hypocalcaemia and hypernatraemia (sodium citrate).

Notes

- Alprostadil is less potent than epoprostenol. As it is metabolized in the lungs, systemic vasodilatation effects are usually minimal.
- For extracorporeal use, citrate has advantages over heparin as it has no antiplatelet activity, is readily haemofiltered, and readily reversed by calcium. Filter half-life is also prolonged.

Table 18.1 Drug dosages

Unfractionated heparin	Dose is titrated to produce an APTT of 1.5–2.5 × control. This usually requires 500–2000 IU/h with a loading dose of 3000–5000 IU
LMWH	For DVT prophylaxis, give 2500–5000 IU dalteparin, 20–40 mg enoxaparin, or 2.5 mg fondaparinux SC daily For anticoagulation of an extracorporeal circuit, give an IV bolus of 35 IU/kg dalteparin or 0.25 mg/kg enoxaparin, followed by an infusion of 13 IU/kg dalteparin or 0.1 mg/kg enoxaparin. Adjust dose to maintain anti-factor Xa activity at 0.5–1 IU/mL (or 0.2–0.4 IU/mL if high risk of haemorrhage) For DVT or pulmonary embolism, give 200 IU/kg dalteparin daily (or 100 IU/kg bd if at risk of bleeding), 1.5 mg/kg enoxaparin in split dose daily, or 7.5 mg fondaparinux SC daily
Heparinoids	Caution in patients with renal insufficiency For DVT prophylaxis give 750 anti-Xa units danaparoid SC bd For DVT or pulmonary embolism with history of HIT give a loading dose of 2500 anti-Xa units danaparoid IV then infusion of 400 U/h for 2 h, 300 U/h for 2 h, then maintenance of 200 U/h for 5 days. Target a therapeutic anti-Xa level during the infusion of 0.5–0.7 anti-Xa-U/mL. For anticoagulation of an extracorporeal circuit, loading dose 3500 anti-Xa-U danaparoid IV followed by a continuous infusion of 100 anti-Xa-U/h.
Direct thrombin inhibitors	Caution in patients with renal insufficiency Bivalirudin: 0.15–0.2 mg/kg/h IV; adjusted to APTT 1.5–2.5 × baseline Argatroban: 2–10 μg/kg/min, adjusted to APTT 1.5–2.5 × baseline
Anticoagulant prostaglandins	Usual dose range is 2.5–10 ng/kg/min. If used for an extracorporeal circulation, infusion should be started 30 min prior to commencement
Sodium citrate	Infused at 5 mmol/L of extracorporeal blood flow. Monitor Ca^{2+} (ideally ionized levels and treat as needed)

APTT = activated partial thromboplastin time.

Further reading

See Extracorporeal membrane oxygenation, p84; Electrical cardioversion, p102; Intra-aortic balloon pump, p108; Coronary revascularization techniques, p112; Haemo(dia)filtration, p118; Plasma exchange, p122; Coagulation monitoring, p252; Blood products, p274; Coagulants & antifibrinolytics, p340; Pulmonary embolus—management, p396; Acute coronary syndrome—management, p418; Clotting disorders, p498.

Anticoagulants—oral

Types

- Warfarin.
- Direct thrombin inhibitors, e.g. dabigatran.
- Direct factor Xa inhibitors, e.g. rivaroxaban, apixaban.

Modes of action

- Warfarin produces a controlled deficiency of vitamin K-dependent coagulation factors (II, VII, IX, and X).
- Direct thrombin inhibitors prevent thrombin-induced platelet aggregation.

Uses

- Prevention or treatment of thromboembolism.

Dosages

See Table 18.2.

Table 18.2 Drug dosages

Warfarin	Start at 10 mg/day orally for 2 days then 1–6 mg/day adjusted according to INR. For DVT prophylaxis, pulmonary embolus, mitral stenosis, atrial fibrillation, and tissue valve replacements, maintain INR between 2 and 3. For recurrent DVT or pulmonary emboli and mechanical valve replacements, maintain INR at 3.0–4.5
Dabigatran	150 mg PO bd for DVT or pulmonary embolism treatment, or prophylaxis in atrial fibrillation. For prophylaxis against DVT or pulmonary embolus, 110 mg PO then 220 mg PO od for prophylaxis. Reduce dose in renal failure
Rivaroxaban	15 mg PO bd for 21 days then 20 mg PO od for 6 months for DVT or pulmonary embolus treatment. For atrial fibrillation prophylaxis, 20 mg PO od. For prophylaxis against DVT or pulmonary embolus give 10 mg PO od. Reduce dose in renal failure
Apixaban	10 mg PO bd for 7 days, then 5 mg PO bd for 6 months for DVT or pulmonary embolus treatment. For atrial fibrillation prophylaxis, 5 mg PO bd. For prophylaxis against DVT or pulmonary embolus 2.5 mg PO bd. Reduce dose in renal failure

INR = international normalized ratio.

Side effects

- Bleeding.
- Hypotension (anticoagulant prostanoids).
- HIT.
- Hypocalcaemia and hypernatraemia (sodium citrate).

Notes

- Warfarin is given orally and needs 48–72 h to develop its full effect. It can be reversed by vitamin K or prothrombin complex.
- Dabigatran, rivaroxaban, and apixaban have been developed for oral thromboprophylaxis or treatment of thromboembolism without monitoring. There is an antidote (andexanet-α) for reversal of anticoagulation from apixaban and rivaroxaban though it is expensive.

Further reading

➲ See Extracorporeal membrane oxygenation, p84; Electrical cardioversion, p102; Intra-aortic balloon pump, p108; Coronary revascularization techniques, p112; Haemo(dia)filtration, p118; Plasma exchange, p122; Coagulation monitoring, p252; Blood products, p274; Coagulants & antifibrinolytics, p340; Pulmonary embolus—management, p396; Acute coronary syndrome—management, p418; Clotting disorders, p498.

Thrombolytics

Types

- More fibrin-specific, e.g. alteplase (recombinant tissue plasminogen activator (rt-PA)), tenecteplase, reteplase.
- Older agents, e.g. streptokinase, urokinase.

Modes of action

- Activate plasminogen to form plasmin which degrades fibrin.

Uses

- Life-threatening thromboembolism.
- Acute myocardial infarction.
- Acute ischaemic stroke (alteplase).

Routes and dosages

See Table 18.3.

Table 18.3 Routes of administration and drug dosages

Alteplase (rt-PA)	Dose schedule for acute myocardial infarction is 15 mg IV bolus, then 0.75 mg/kg over 30 min, then 0.5 mg/kg over 1 h to a maximal dose of 100 mg over 90 min. This is then followed by heparin for 24–48 h For pulmonary embolism: 10 mg IV over 1–2 min then 90 mg IV over 2 h, followed by heparin For acute ischaemic stroke: 0.1 mg/kg IV over 1–2 min then 0.8 mg/kg IV over 60 min. Avoid heparin for 24 h
Anistreplase	Single IV injection of 30 IU over 4–5 min
Tenecteplase	For acute MI: IV bolus of 0.5 mg/kg over 10 s followed by heparin for 24–48 h
Reteplase	For acute MI: two IV boluses of 10 U given 30 min apart followed by heparin for 24–48 h
Streptokinase	For acute MI: 1.5 MU IV over 60 min. Heparin for the next 24–48 h is optional For major DVT: 250,000 U IV over 30 min followed by 100,000 U/h IV for 24–72 h For pulmonary embolism: 1.5 million units IV over 2 h
Urokinase	For unblocking indwelling vascular catheters a dose ranging from 5000 to 37,500 IU is instilled For thromboembolic disease: 4400 IU/kg IV is given over 10 min followed by 4400 IU/kg/h IV for 12–24 h

Side effects

- Bleeding—treat with tranexamic acid (1 g IV tds).
- Hypotension and arrhythmias.
- Embolization from pre-existing clot as it is broken down.
- Anaphylactoid reactions (anistreplase, streptokinase, urokinase).

Contraindications (absolute)

- Previous intracranial haemorrhage or stroke of unknown origin.
- Structural cerebrovascular lesion or malignant intracranial neoplasm.
- Ischaemic stroke within 6 months (not acute stroke within 3 h).
- Recent major trauma/surgery/head injury (<3 weeks).
- Gastrointestinal bleeding within last month.
- Aortic dissection.
- Active bleeding or bleeding diathesis.

Contraindications (relative)

- Transient ischaemic attack in preceding 6 months.
- Oral anticoagulant therapy.
- Pregnancy within 1 week postpartum.
- Non-compressible vascular puncture.
- Traumatic cardiopulmonary resuscitation.
- Poorly controlled hypertension (systolic blood pressure >180 mmHg).
- Advanced liver disease.
- Infective endocarditis.
- Active peptic ulcer.

Notes

- In acute myocardial infarction thrombolytics are of most value when used within 12 h of onset. Adjuvant therapy may be needed (e.g. aspirin with streptokinase, heparin with rt-PA) to maximize the effect.
- Alteplase may be beneficial in acute ischaemic stroke if initiated within 3 h of clearly defined onset of symptoms. Haemorrhage and diffuse swelling should be excluded by computed tomography scan.
- Anaphylactoid reactions to streptokinase are not uncommon, particularly in those who have had streptococcal infections. Patients should not be exposed twice between 5 days and 1 year of the last dose.

Further reading

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➔ See Coagulation monitoring, p252; Coagulants & antifibrinolytics, p340; Pulmonary embolus—management, p396; Acute coronary syndrome—management, p418.

Coagulants & antifibrinolytics

Types

- Vitamin K.
- Prothrombin complex concentrate, e.g. Octaplex®, Beriplex®.
- Protamine.
- Tranexamic acid.
- Activated factor VII (FVIIa).
- Fresh frozen plasma.

Uses

- To reverse a prolonged prothrombin time, e.g. malabsorption, oral anticoagulant therapy, β-lactam antibiotics or critical illness (vitamin K, Octaplex®, Beriplex®).
- To reverse the effects of heparin (protamine).
- Bleeding from raw surfaces, e.g. prostatectomy, dental extraction (tranexamic acid).
- Bleeding from thrombolytics (tranexamic acid).
- Bleeding from major trauma or haemophilia (FVIIa).

Routes and dosages

- IV (vitamin K, protamine, tranexamic acid, FVIIa).
- PO (vitamin K, tranexamic acid).

For drug dosages see Table 18.4.

Table 18.4 Drug dosages

Vitamin K	5–10 mg IV
Octaplex®	30–50 IU/kg IV
Beriplex®	30 IU/kg IV
Protamine	25–50 mg slow IV
Tranexamic acid	1–1.5 g IV 6–12-hrly
Factor VIIa	90 μg/kg slow IV repeated as necessary 1.5–2-hrly

Notes

- The effects of vitamin K are prolonged so avoid in patients dependent on oral anticoagulant therapy. A 10 mg dose is given PO or by slow IV injection daily. In life-threatening haemorrhage due to warfarin excess, give 5–10 mg by slow IV injection along with other coagulation factor concentrates (Octaplex®, Beriplex®). If INR >7 or in less severe haemorrhage 0.5–2 mg may be given by slow IV injection with a minimum lasting effect on oral anticoagulant therapy.
- Protamine has an anticoagulant effect of its own in high doses. Protamine 1 mg neutralizes 100 IU unfractionated heparin if given within 15 min. Less is required if given later since parenteral heparin is removed rapidly. Protamine should be given by slow IV injection

according to the APTT with a total dose not exceeding 50 mg. Protamine injection may cause severe hypotension.

- Tranexamic acid has an antifibrinolytic effect by antagonizing plasminogen.
- Recombinant FVIIa is licensed for use in haemophilia. A number of case series in major trauma, orthopaedic, and cardiac surgery reported benefit in severe, intractable bleeding non-responsive to standard measures.

Further reading

➔ See Coagulation monitoring, p252; Blood products, p274; Anticoagulants—parenteral, p334; Anticoagulants—oral, p336; Thrombolytics, p338; Bleeding disorders—causes & diagnosis, p494; Clotting disorders, p498.

Chapter 19

Antimicrobial drugs

Antibacterials

Types

- Penicillins, e.g. benzylpenicillin, flucloxacillin, piperacillin, ampicillin.
- Cephalosporins, e.g. cefotaxime, ceftazidime, cefuroxime.
- Carbapenems, e.g. imipenem, meropenem.
- Aminoglycosides, e.g. gentamicin, amikacin, tobramycin.
- Quinolones, e.g. ciprofloxacin.
- Glycopeptides, e.g. teicoplanin, vancomycin.
- Macrolides, e.g. erythromycin, clarithromycin.
- Tetracyclines, e.g. tigecycline.
- Other, e.g. clindamycin, metronidazole, linezolid, co-trimoxazole.

Uses

- Treatment of bacterial infection according to local guidelines that take account of local resistance patterns. See Table 19.1.
- Prophylaxis against bacterial infection, e.g. perioperative.
- Empiric therapy for serious infections should take account of known community and hospital infection and resistance patterns.

Table 19.1 Common choices for specific organisms

Staphylococcus aureus	Flucloxacillin
Meticillin-resistant *Staphylococcus aureus* (MRSA)	Teicoplanin, vancomycin, linezolid
Streptococcus pneumoniae	Cefuroxime, cefotaxime, benzylpenicillin
Neisseria meningitidis	Ceftriaxone, cefotaxime, benzylpenicillin
Haemophilus influenzae	Cefuroxime, cefotaxime
Escherichia coli	Ampicillin, ceftazidime, ciprofloxacin, gentamicin, imipenem, meropenem
Klebsiella spp.	Ceftazidime, ciprofloxacin, gentamicin, meropenem
Pseudomonas aeruginosa	Ceftazidime, ciprofloxacin, gentamicin, imipenem, meropenem, piperacillin–tazobactam

Routes and dosages

- Intravenous (IV) in the critically ill. For drug dosages see Table 19.2.

Side effects

- Hypersensitivity reactions.
- Gastrointestinal disturbance.
- Vestibular damage (aminoglycosides).
- Seizures (penicillins, metronidazole, ciprofloxacin).
- Renal failure (aminoglycosides, glycopeptides, ciprofloxacin, rifampicin).
- Erythema multiforme (co-trimoxazole).
- Leucopenia (co-trimoxazole, metronidazole, ciprofloxacin).
- Thrombocytopenia (linezolid).
- Peripheral neuropathy (metronidazole).

Table 19.2 Drug dosages (IV)

Benzylpenicillin	1.2 g 6-hrly (2-hrly for pneumococcal pneumonia)
Co-amoxiclav	1.2 g 8-hrly
Flucloxacillin	500 mg–2 g 6-hrly (or 2 g 4-hrly for endocarditis)
Ampicillin	500 mg–1 g 6-hrly
Piperacillin–tazobactam	4.5 g 6–8-hrly
Ceftazidime	2 g 8-hrly
Ceftazidime/avibactam	2/0.5 g 8-hrly
Ceftriaxone	2–4 g daily
Cefuroxime	750 mg–1.5 g 8-hrly
Ceftolozane/tazobactam	1.5–3.0 g 8-hrly
Cefiderocol	2 g 6–8-hrly
Meropenem	500 mg–1 g 8-hrly; 2 g tds for brain penetration
Gentamicin	3–5 mg/kg daily in 3 divided doses given 8-hrly, or 5–7 mg stat then adjusted by levels (usually 80 mg 8-hrly)
Amikacin	15 mg/kg stat then by levels (usually 500 mg 12-hrly)
Tobramycin	5 mg/kg stat then by levels (usually 100 mg 8-hrly)
Erythromycin	500 mg–1g 6–12-hrly
Clarithromycin	500 mg 12-hrly
Clindamycin	300–600 mg 6-hrly
Metronidazole	500 mg 8-hrly or 1g 12-hrly PR
Ciprofloxacin	400 mg 8–12-hrly
Co-trimoxazole	960 mg 12-hrly, increased for *Pneumocystis* pneumonia
Tigecycline	100 mg initially then 50 mg 12-hrly
Rifampicin	600 mg daily
Teicoplanin	6 mg/kg 12-hrly ×3, then 6 mg/kg OD. Give 10 mg/kg (max 1g) for endocarditis
Vancomycin	500 mg 6-hrly (monitor levels)
Linezolid	600 mg 12-hrly
Chloramphenicol	1–2 g 6-hrly
Colistin	9 MU loading then 9 MU/day in 2–3 divided doses

Most antimicrobials need dose adjustment for renal or hepatic failure.

Notes

- Risk of cephalosporin allergy in penicillin allergic is about 1%.
- Extended infusion of meropenem (> 3 h) may enhance its activity.
- Ideally, daily therapeutic monitoring should be performed due to variable drug handling in critically ill patients.

Further reading

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Roberts J, Paul S, Akova M, et al. 2014. 'DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients?' *Clin Infect Dis* 58: pp1072–83. doi: 10.1093/cid/ciu027.

See Infection—treatment, p590; Multi-resistant infections, p600.

Antifungals

Types

- Polyenes, e.g. amphotericin B (conventional or liposomal), nystatin.
- Imidazoles, e.g. ketoconazole, clotrimazole.
- Triazoles, e.g. fluconazole, voriconazole, itraconazole, posaconazole.
- Echinocandins, e.g. caspofungin, micafungin, anidulafungin.
- Others, e.g. flucytosine.

Uses

- Candidiasis—fluconazole, amphotericin B, caspofungin, voriconazole.
- Aspergillosis—amphotericin B, caspofungin, voriconazole, itraconazole.
- *Cryptococcus* spp.—amphotericin B, flucytosine, fluconazole.
- Blastomycosis—itraconazole.
- Histoplasmosis—amphotericin B, itraconazole.

Routes and dosages

- Generally given IV in the critically ill although many can be given via the enteral route (PO or NG). For drug dosages see Table 19.3.

Side effects

- Hypersensitivity reactions.
- Gastrointestinal disturbance (amphotericin, flucytosine).
- Renal failure (voriconazole, amphotericin—more common with conventional rather than liposomal).
- Liver toxicity (voriconazole, posaconazole).
- Leucopenia (flucytosine).

Table 19.3 Drug dosages

Amphotericin (liposomal)	3–5 mg/kg daily (1 mg/kg for prophylaxis)
Flucytosine	25–50 mg/kg 6-hrly
Fluconazole	200–400 mg IV daily (50–400 mg for prophylaxis)
Caspofungin	70 mg IV then 50–70 mg daily
Voriconazole	400 mg PO/IV 12-hrly (day 1) then 200–300 mg 12-hrly
Itraconazole	200 mg IV 12-hrly for 2 days then 200 mg daily

Most antimicrobials need dose adjustment for renal or hepatic failure.

Notes

- Some *Candida* spp. (*C. auris*, *C. glabrata*, *C. parapsilosis*) are resistant to fluconazole.
- Gastrointestinal disturbance (amphotericin, flucytosine).
- Renal failure.

Further reading

See Mycology, p260; Infection—treatment, p590; Multi-resistant infections, p600.

Antivirals

Types

- Reverse transcriptase inhibitors such as nucleoside analogues (e.g. aciclovir) block reverse transcription of RNA to DNA.
- Neuraminidase inhibitors (e.g. oseltamivir, zanamivir) block release of viral particles from host cells.
- Adenosine nucleoside triphosphate analogues (e.g.remdesivir) act by inhibiting RNA-dependent RNA polymerase.
- Interferons (e.g. interferon α) inhibit viral synthesis in infected cells.
- Inhibitors of viral DNA polymerases, e.g. ganciclovir.
- Foscarnet is a structural mimic of pyrophosphate that inhibits viral DNA polymerases.

Uses

- Herpes simplex—aciclovir, foscarnet.
- Varicella zoster—aciclovir.
- Cytomegalovirus—ganciclovir, foscarnet,
- Influenza A and B—oseltamivir, zanamivir.
- COVID-19—remdesivir.

Routes and dosages

- Generally given IV in the critically ill although many can be given PO.

For drug dosages see Table 19.3.

Table 19.4 Drug dosages

Aciclovir	5–10 mg/kg IV 8-hrly
Ganciclovir	5 mg/kg IV 12-hrly
Foscarnet	90 mg/kg IV 12-hrly
Oseltamivir	75 mg PO 12-hrly
Zanamivir	600 mg IV 12-hrly
Remdesivir	200 mg loading then 100 mg od

Side effects

- Hypersensitivity reactions.
- Renal failure (foscarnet, aciclovir).
- Leucopenia (aciclovir, ganciclovir).

Further reading

See Virology, p258; Infection—treatment, p590.

Chapter 20

Immunological drugs

Corticosteroids

Uses

- Anti-inflammatory, e.g. asthma, allergic and anaphylactoid reactions, rheumatological and vasculitic disorders, inflammatory bowel disease, some types of hepatitis, dermatological conditions, neurological diseases, neoplasm-related cerebral oedema, acute respiratory distress syndrome, laryngeal oedema (e.g. after intubation), and after spinal cord injury.
- Infection—to reduce the inflammatory response of microbial killing, e.g. miliary tuberculosis, bacterial meningitis, *Pneumocystis jirovecii* pneumonia. In septic shock, 'low-dose' hydrocortisone (50 mg qds) reduces pressor requirements in 'vasopressor-unresponsive' patients.
- COVID-19.
- Haematology, e.g. lymphoma, leukaemia, idiopathic thrombocytopenic purpura, haemolytic anaemia.
- Replacement therapy, e.g. Addison's disease, post-adrenalectomy or pituitary surgery. Fludrocortisone is also usually required long term for its mineralocorticoid effect.
- Immunosuppressive, e.g. after organ transplantation.
- Antiemetic.

Routes and dosages

See Table 20.1.

Table 20.1 Routes of administration and drug dosages

Drug	Replacement dose	Anti-inflammatory dose
Dexamethasone	–	4–20 mg tds IV
Hydrocortisone	20–30 mg daily	100–200 mg qds IV
Methylprednisolone	–	500 mg–1 g IV daily
Prednisolone	2.5–15 mg mane	40–60 mg od PO
Fludrocortisone	0.05–0.3 mg daily	–

Weaning

- Acute use (<3–4 days)—can stop immediately.
- Short-term use (≥3–4 days)—wean over 2–5 days.
- Medium-term use (weeks)—wean over 1–2 weeks.
- Long-term use (months/years)—wean slowly (months to years).

Side effects/complications

- Sodium and water retention (especially with mineralocorticoids).
- Hypoadrenal crisis if stopped abruptly after prolonged treatment.
- Immunosuppressive—increased infection risk (NB: fungi, atypical infections).
- Neutrophilia.
- Impaired glucose tolerance/diabetes mellitus.
- Hypokalaemic alkalosis.

- Neuropsychiatric.
- Osteoporosis, proximal myopathy, dermal atrophy, fat distribution (long-term use).
- Increased susceptibility to peptic ulcer disease and gastrointestinal bleeding.

Notes

- For relative potency of corticosteroids see Table 20.2.
- Oral fungal infection is relatively common with inhaled corticosteroids but systemic and pulmonary fungal infection is predominantly seen in the severely immunocompromised (e.g. AIDS, post-chemotherapy).
- For a short-term anti-inflammatory effect, sufficient dose is more important than choice of drug. Chronic hydrocortisone should be avoided for anti-inflammatory use because of its mineralocorticoid effect but is appropriate for adrenal replacement.
- Prednisone and cortisone are inactive until metabolized by the liver to prednisolone and hydrocortisone, respectively.
- The role of steroids in causing critical illness myopathy is contentious.
- Benefit unproved in cerebral oedema after head injury, cardiac arrest.

Table 20.2 Relative potency and activity

Drug	Glucocorticoid activity	Mineralocorticoid activity	Equivalent anti-inflammatory dose (mg)
Cortisone	++	++	25
Dexamethasone	++++	–	0.75
Hydrocortisone	++	++	20
Methylprednisolone	+++	+	4
Prednisolone	+++	+	5
Prednisone	+++	+	5
Fludrocortisone	+	++++	–

Further reading

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Annane D, Sébille V, Charpentier C, et al. 2002. 'Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock'. *JAMA* 288: pp862–71. doi: 10.1001/jama.288.7.862

de Gans J, van de Beek D, for the European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. 2002. 'Dexamethasone in adults with bacterial meningitis'. *N Engl J Med* 347: 1549–56. doi: 10.1056/NEJMoa021334

Sprung C, Annane D, Keh D, et al. for the CORTICUS study group. 2008. 'Hydrocortisone therapy for patients with septic shock'. *N Engl J Med* 358: pp111–24. doi: 10.1056/NEJMoa071366

➔ See Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Full blood count, p250; Airway obstruction, p368; Acute respiratory distress syndrome—management, p386; Asthma—general management, p390; Meningitis, p474; Raised intracranial pressure, p484; Myasthenia gravis, p488; Platelet disorders, p508; Hypercalcaemia, p526; Hypoadrenal crisis, p548; Sepsis—management, p594; HIV-related disease, p610; Rheumatic disorders, p618; Vasculitis, p620; Anaphylactoid reactions, p624; Spinal cord injury, p636.

Immunomodulatory therapies

Many types of immunomodulatory agents are now being introduced into clinical practice.

Types

- Corticosteroids.
- Immunoglobulins.
- Monoclonal antibodies.
- Immunosuppressants, e.g. azathioprine, mycophenolate, ciclosporin, cyclophosphamide, tacrolimus, methotrexate.
- Others, e.g. anakinra (interleukin (IL)-1 receptor antagonist protein), tocilizumab (IL-6 receptor blocker).

Immunoglobulins (IVIg)

Many indications including:

- Severe infections, e.g. invasive group A streptococcal disease (including necrotizing fasciitis), staphylococcal toxic shock syndrome, necrotizing (Panton–Valentine leukocidin (PVL)-associated) staphylococcal sepsis.
- Neurological conditions, e.g. myasthenia gravis, Guillain–Barré syndrome.
- Others, e.g. rheumatological, poly/dermatomyositis, malignancy, immune-mediated thrombocytopenia.
- Meta-analyses of IVIg trials suggest possible benefit in sepsis and in specific toxin-related conditions.

Dosage

- IVIg—a single dose of 1 g/kg should be given and may be repeated if no improvement is seen after an initial response. If an anaphylactoid reaction occurs, slow down/stop infusion and consider corticosteroids and/or other therapies as indicated.

Immunomodulators

Indications for other immunosuppressive therapies include:

- Autoimmune conditions.
- Transplant rejection.
- Inflammatory bowel disease.
- Graft-versus-host disease (GVHD).
- Haemophagocytic lymphohistiocytosis (HLH).
- Rheumatoid diseases.
- Indications for immunostimulation.
- Post-chemotherapy neutropenia.
- Being trialled to reverse sepsis-related immunosuppression.

Notes

- Some agents suppress the immune/inflammatory response, e.g. steroids, tumour necrosis factor (TNF) inhibitors, whereas others activate a depressed immune system (e.g. granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), interferon-γ).
- Agents may:
  - target pathogen triggers (e.g. endotoxin)

  - target cytokines (e.g. TNF, IL-1, IL-6), and effector cells and their products (e.g. neutrophils, free oxygen radicals, nitric oxide)
  - target other immune pathways such as complement (e.g. eculizumab)
  - target cancer pathways (e.g. B-cell depletion with rituximab, PD1 inhibition with nivolumab)
  - aim to replace or boost often-depleted endogenous anti-inflammatory response systems (e.g. corticosteroids, activated protein C, antithrombin, immunoglobulin).
- All of these agents carry necessary actions (e.g. bone marrow suppression for haem-oncology treatment) or unwanted complications that may precipitate a critical care admission, e.g. cytokine release syndrome (CRS) following chimeric antigen receptor T-cell (CAR-T) therapy, or secondary infection following any immunosuppressive therapy. Furthermore, these agents may interact with other commonly used drugs, modifying their actions.

Complications

There are an ever-increasing number of immunomodulatory agents. To list complications related to each agent is beyond the scope of this book. Many cause *common* complications such as renal or liver dysfunction and bone marrow suppression, whereas some agents can produce specific syndromes such as posterior reversible encephalopathy syndrome (PRES) and CRS.

Further reading

➔ See Corticosteroids, p352; Sepsis—management, p594; Haemophagocytic lymphohistiocytosis (HLH), p616; Rheumatic disorders, p618; Neutropenia & infection, p678; Chimeric antigen receptor T-cell (CAR-T) therapy, p680.

Chapter 21

Resuscitation

Basic resuscitation

For any failure of the cardiorespiratory system, the order of priority should be ABC, namely securing the **A**irway, maintaining adequate **B**reathing (gas exchange), and restoring the **C**irculation (with drugs, external cardiac massage, and defibrillation, if necessary). Initial assessment should include airway patency, respiratory effort, assessment of circulation (including skin colour and capillary refill time, pulse rate, regularity and strength, blood pressure (BP)), conscious level, and a presumptive (differential) diagnosis. It is a priority to call for help at an early stage depending on illness severity and the presence of adequate numbers of staff with appropriate expertise.

Airway

If compromised, the airway should be opened by tilting the head back with one hand on the forehead, lifting the chin with the fingers of the other hand (Figure 21.1). In addition, performing a jaw thrust may improve airway patency (Figure 21.2). The fingers should be placed behind the angle of the mandible on both sides and the mandible lifted forward and upward until the lower teeth (or gum) are in front of the upper teeth (or gum).

If any concerns about neck stability and possible spinal injury (e.g. trauma, severe rheumatoid arthritis) then conduct jaw thrust only.

Mouth and pharynx should be cleared by suction and loose-fitting dentures removed. If necessary (if conscious level depressed) an oropharyngeal (Guedel) airway may be inserted. If conscious level is severely depressed (e.g. in cardiac arrest), the patient may require advanced airway support in the form of an endotracheal tube, tracheostomy, or cricothyroidotomy. Trained airway staff are needed in this instance. In the interim, a supraglottic airway device (e.g. laryngeal mask airway (LMA)) may be inserted by an appropriately trained person.

The Difficult Airway Society and the National Tracheostomy Safety project offer useful advice and emergency algorithms for airway management.

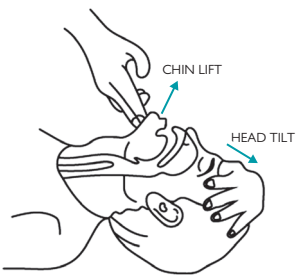

Fig. 21.1 Opening the airway with head tilt and chin lift.

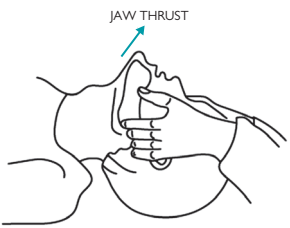

Fig. 21.2 Opening the airway with a jaw thrust.

Breathing

Oxygen should be delivered at a high enough concentration to achieve adequate arterial saturation (94–98%). Hyperoxia, indicated by persistent saturation at 100%, should be avoided as this can be detrimental. Begin ventilatory support if the patien t breathes inadequately (poor arterial saturation, hypercapnia, rapid shallow breathing).

Various oxygen masks are available for spontaneously breathing patients. Standard masks such as Hudson or Venturi masks can deliver a fraction of inspired oxygen (FiO_2) up to 0.6. A non-rebreathe mask with a reservoir bag can increase FiO_2 up to 0.8.

If there is inadequate or no respiratory effort, then manual ventilation needs to be provided, initially via a tight-fitting mask with a self-inflating bag (Ambu bag) or a Mapleson C (Waters) circuit (more commonly used in intensive care units and operating theatres). These require a high-flow oxygen supply (>10 L/min). The Waters circuit has an adjustable pressure valve that can provide an uncertain level of positive end-expiratory pressure.

Circulation

Commence external cardiac compressions and summon appropriate assistance if pulses are impalpable and the patient is unresponsive.

For pulses that are very weak, or if the patient is severely bradycardic, external cardiac compressions may be required if the underlying cause is not promptly corrected. Quickly identify the likely cause and treat appropriately, e.g. oxygen for hypoxaemia, fluid for hypovolaemia, needle decompression for tension pneumothorax, atropine for bradycardia of cardiac origin, epinephrine for cardiac failure or anaphylaxis.

Treatment should not be prolonged without circulatory monitoring to guide resuscitation and ensure adequacy of the circulation.

Venous access

Venous access must be secured early during basic resuscitation. Large-bore (e.g. 14 or 16 G) cannulae are necessary. For managing severe haemorrhage, at least two cannulae are required. Small peripheral veins should be avoided. If venous access difficult, a Seldinger approach to a femoral or neck vein may be necessary. The latter has the advantage of providing central venous monitoring. Alternatively, an interosseous (IO) needle can be sited in an appropriate bone (e.g. tibial plateau below the level of the tibial tuberosity). Various 'gun' devices are now available to assist with IO needle insertion.

Further reading

'Intubation guidelines'. Difficult Airway Society. 2017. Accessed July 2023. https://das.uk.com/guidelines/icu_guidelines2017

'Emergency care (adults)'. National Tracheostomy Safety project. Accessed June 2023. https://tracheostomy.org.uk/healthcare-staff/emergency-care

➔See Oxygen therapy, p40; Airway maintenance, p42; Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Electrical cardioversion, p102; Central venous catheter—insertion, p190; Colloids, p270; Inotropes, p286; Vasopressors, p290; Cardiac arrest, p360; Fluid challenge, p362.

Cardiac arrest

Rapid recognition of cardiac arrest is critical. Summon help, start cardiorespiratory resuscitation (CPR), and, if appropriate, aim to defibrillate as soon as possible.

The focus is on airway, breathing, and circulation with vasoactive drug treatment ± cardioversion. Initial management of airway and breathing is as described for basic resuscitation. Intubation should ideally be attempted by a skilled operator. If intubation is difficult, maintain manual ventilation with a tight-fitting mask, Ambu bag (or Waters circuit), and 100% O_2. Tube placement and return of circulation should be confirmed by capnography.

Cardiac massage

External massage provides minimal circulatory support during cardiac arrest. Aim for a rate of 100–120/min with minimal interruptions, and a 5 cm compression depth. Give 2 breaths after 30 compressions until a protected airway is established. Thereafter, compressions should be continuous with manual breaths at a rate of 10/min. Compressions should not be paused for ventilation. Capnography should be used to confirm endotracheal placement of the airway tube and adequacy of chest compressions.

Cardioversion

Cardioversion is performed urgently with pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF), or if these cannot be excluded. Continue cardiac massage while the defibrillator is charging and restart massage immediately (within 5 s) after shock without waiting to review the electrocardiogram. Cerebral damage continues while there is no blood flow. Repeat single shocks at 2 min intervals where indicated. For refractory or recurrent VF consider increasing shock energy or using different defibrillation pad positions, e.g. anterior–posterior.

Drugs

Drugs should be given via a large vein since vasoconstriction and poor flow delay peripheral injections reaching the central circulation. If early venous access cannot be secured the intraosseous route may be used. The following are considered essential drugs:

Epinephrine

Its α-adrenergic constrictor effect predominates during cardiac arrest, helping to maintain diastolic BP and thus coronary and cerebral perfusion.

1 mg (10 mL of 1:10,000 solution) epinephrine should be given as soon as possible for a non-shockable rhythm.

For a shockable rhythm, 1 mg epinephrine should be given after the third shock.

In both situations, repeat 1 mg boluses should be given every 3–5 min while CPR continues.

Antiarrhythmic drugs

For resistant VF/VT give amiodarone (300 mg) after 3 shocks. A further 150 mg may be given if VF/pulseless VT remains after 5 shocks. Lidocaine (100 mg) can be used as an alternative.

Thrombolytics

Consider systemic thrombolytic agents (e.g. recombinant tissue plasminogen activator (rt-PA), alteplase) if pulmonary embolus is suspected either clinically and/or with echocardiography.

Magnesium

Give magnesium sulfate (2 g or 8 mmol) if torsades de pointes is suspected. Consider administration if patient remains in refractory VF/VT.

Calcium chloride

Used in pulseless electrical activity if there is hyperkalaemia, hypocalcaemia, or prior calcium antagonist use. Give 10 mL 10% solution and repeat if necessary.

Bicarbonate

Only used if cardiac arrest is due to hyperkalaemia or tricyclic poisoning. A dose of 50 mL of 8.4% solution is given.

Post-arrest management

Admit to intensive care for monitoring and management after return of spontaneous circulation (ROSC) and stabilization. Although current UK Resuscitation Council guidelines support targeted temperature management (TTM) lowering core temperature to 32–34°C, the evidence base is inconclusive. However, there is general consensus that hyperthermia should be avoided to protect the brain.

Appropriate investigations and treatment need to be considered depending on the underlying cause of the arrest.

Further reading

The Hypothermia after Cardiac Arrest Study Group. 2002. 'Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest'. *N Engl J Med* 346: pp549–56. doi: 10.1056/NEJMoa012689

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➔ See Electrical cardioversion, p102; Targeted temperature management, p106; ECG monitoring, p184; Sodium bicarbonate, p268; Inotropes, p286; Vasopressors, p290; Basic resuscitation, p358.

Fluid challenge

Hypovolaemia should be treated promptly to prevent/reverse hypoperfusion and reduce the risk of organ dysfunction. In general, aim for an adequate circulating volume before initiating other methods of circulatory support. However, in extremis, catecholamines may be needed to achieve an adequate perfusion pressure. Clinical signs of hypovolaemia (reduced skin turgor, low central venous pressure (CVP), oliguria, tachycardia, and hypotension) are relatively late indicators. Lifting the legs of a supine patient and achieving a positive haemodynamic response is a useful indicator of hypovolaemia, though the BP may increase if this manoeuvre causes pain/discomfort.

A high index of suspicion must be maintained as normal heart rate, BP, and CVP do not exclude hypovolaemia. CVP is particularly unreliable in pulmonary vascular disease, right ventricular disease, isolated left ventricular failure, and valvular heart disease. Absolute CVP or pulmonary artery wedge pressure (PAWP) values are also difficult to interpret since peripheral venoconstriction may maintain CVP despite hypovolaemia; indeed, the CVP may fall in response to fluid. The response to a fluid challenge is the safest method of assessment.

Assessing the response to a fluid challenge

The aim of a fluid challenge (rapid 200–250 mL bolus IV over 5–10 min) is to produce a rapid increase in plasma volume and a concurrent improvement in monitored variables such as BP, heart rate, CVP, PAWP, or stroke volume. Repeat fluid challenges if the response suggests ongoing hypovolaemia and hypoperfusion persists.

CVP (or PAWP) response

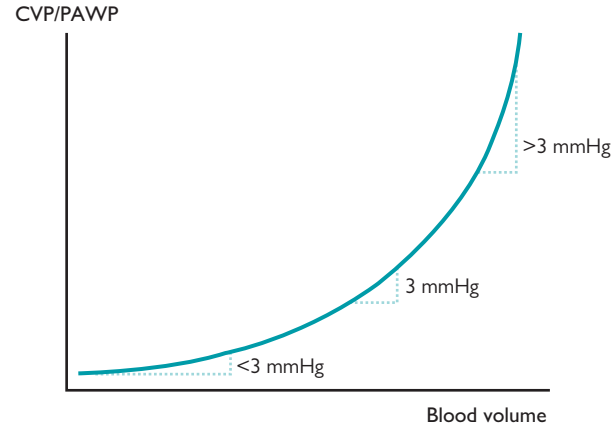
The change in CVP/PAWP after a fluid challenge depends on the starting blood volume (low/normal/elevated) (Figure 21.3). A ≥3 mmHg rise in CVP/PAWP represents a significant increase, suggesting an adequate circulating volume and thus no need to give further fluid. If uncertain, monitor the stroke volume response as this is more precise.

Stroke volume response

In an inadequately filled left ventricle, a fluid challenge will increase stroke volume. Failure to increase stroke volume may be due to a well-filled ventricle (usually accompanied by a ≥3 mmHg rise in filling pressure), ongoing rapid fluid loss (e.g. massive haemorrhage), right heart failure, or obstruction (e.g. pericardial tamponade, massive pulmonary embolus, mitral stenosis). Stroke volume rather than cardiac output should be monitored during a fluid challenge. If heart rate falls in response to a fluid challenge, the cardiac output may not increase, despite an increase in stroke volume.

Further reading

See Central venous catheter—insertion, p190; Central venous catheter—use, p192; Cardiac output—central thermodilution, p200; Cardiac output—peripheral thermodilution, p202; Cardiac output—indicator dilution, p204; Cardiac output—Doppler ultrasound, p206; Cardiac output—pulse contour analysis, p208; Cardiac output—other techniques, p210; Pressure & stroke volume variation, p212; Echocardiography—use & indications, p214; Colloids, p270; Basic resuscitation, p358.



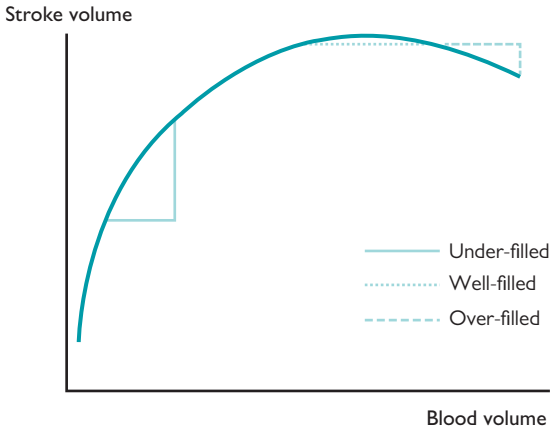


Fig. 21.3 CVP and stroke volume response to fluid challenge.

Chapter 22

Respiratory disorders

Dyspnoea

Defined as difficulty in breathing. The respiratory rate may be increased (or occasionally decreased) while respiratory effort is usually increased with the use of accessory muscles. The patient may show signs of progressive fatigue and impaired gas exchange.

Common causes in the intensive care unit (ICU)

- Table 22.1 shows common ICU causes of dyspnoea.
- A functional cause of dyspnoea (e.g. anxiety) is only made after exclusion of other treatable causes.
- Dual coexisting pathologies should be considered, e.g. chest infection and hypovolaemia.

Table 22.1 Common ICU causes of dyspnoea

Respiratory	Respiratory failure
Circulatory	Heart failure, hypoperfusion, pulmonary embolus, severe anaemia
Metabolic	Acidosis (any cause)
Central	Stimulants, e.g. aspirin
Anaphylactic	Upper airway obstruction, bronchospasm
Functional	Anxiety, psychological stress

Principles of management

1. Oxygen (O_2) therapy to maintain arterial O_2 saturation (SaO_2) (at a level appropriate for the patient).
2. Correct abnormality where possible.
3. Support therapy until recovery:
   - mechanical, e.g. high-flow nasal oxygen (HFNO), continuous positive airways pressure (CPAP), bi-level positive airway pressure (BiPAP)/ non-invasive ventilation (NIV), intermittent positive pressure ventilation
   - pharmacological, e.g. bronchodilators, vasodilators
4. Relieve anxiety.

Further reading

See Airway obstruction, p368; Respiratory failure, p370; Asthma—general management, p390; Pulmonary embolus—diagnosis, p394; Heart failure—assessment, p420; Anaemia, p500; Sickle cell disease, p502; Metabolic acidosis, p534.

Airway obstruction

Causes

- In the lumen, e.g. foreign body, blood clot, vomitus, sputum plug.
- In the wall, e.g. epiglottitis, oedema, anaphylaxis, neoplasm.
- Outside the wall, e.g. trauma (facial, neck), thyroid mass.

Presentation

- Spontaneously breathing: stridor, dyspnoea, fatigue, cyanosis.
- Mechanically ventilated (e.g. due to intraluminal obstruction): inability to pass suction catheter, raised airway pressures, decreased tidal volume (V_T), hypoxaemia, hypercapnia.

Diagnosis

- Chest and lateral neck X-ray.
- Fibreoptic laryngoscopy/bronchoscopy.
- Computed tomography (CT) scan.

Management

Not intubated

- Increase fraction of inspired O_2 (FiO_2) to maintain adequate oxygenation.
- If collapsed or in extremis, attempt removal of any visible obstructing intraluminal lesion by suction, forceps, or flexible/rigid bronchoscopy. Consider immediate orotracheal intubation if proximal obstruction cannot be relieved. If this is not possible, perform emergency cricothyroidotomy or tracheostomy. This may need to be done as an awake procedure. Drain haematoma (e.g. remove neck sutures) if it is the cause of extra-luminal compression.
- Determine and treat cause as appropriate, e.g. remove foreign body, treat anaphylaxis, angio-oedema.
- Elective intubation or tracheostomy may be required to protect the airway if concern that disease may progress (e.g. burn inhalation).
- Laryngeal oedema may occur following inhalation injury, burns, anaphylaxis, or after traumatic, prolonged or repeated intubation. The incidence of post-extubation laryngeal oedema may be reduced by proper tethering of the endotracheal (ET) tube and prevention of excessive coughing. Check for cuff leak before extubation, especially in at-risk patients. Treat with steroids (e.g. dexamethasone 8 mg tds for 24–72 h) ± epinephrine nebulizers to reduce upper airway oedema ± Heliox (79% He/21% O_2) alone or with supplemental O_2 to lower viscosity and improve airflow. Reintubation may be necessary.
- Corticosteroids and Heliox may be useful for other causes of stridor, e.g. pharyngeal tumours, epiglottitis.
- In acute epiglottitis, a tongue depressor or nasendoscopy may precipitate complete obstruction so facilities should be available to perform emergency cricothyroidotomy or tracheostomy. The responsible organism is usually *Haemophilus influenzae* so treat early, e.g. with co-amoxiclav + steroids. Acute epiglottitis can occur in adults.

Intubated

- Increase FiO_2 to maintain adequate O_2 saturation.
- Ensure ET or tracheostomy tube is not displaced.
- Ensure ET tube is not obstructed. Pass suction catheter down the tube, assess ease of passage, and suction out any contents. If the tube is obstructed and cannot be cleared, remove the tube, oxygenate by face mask, then reintubate.
- If the ET tube is patent but obstruction is distal, e.g. at the carina, attempt repeated suction interspersed with 5 mL boluses of 0.9% saline to try to remove distal plug/blood clot. Urgent fibreoptic bronchoscopy may be necessary for diagnosis and, if needed, removal of an obstruction such as a thick sputum plug or blood clot using high-pressure suction, a snare, or biopsy forceps. Failing this, a Fogarty-type catheter may be used to extract a solid plug. Site the catheter through the ET tube, inflate the balloon distally, and then withdraw the catheter through the ET tube, removing the plugs.
- If the obstruction cannot be removed by fibreoptic bronchoscopy, an experienced operator should perform urgent rigid bronchoscopy.
- Correct any underlying precipitant, e.g. coagulopathy for blood clot, mucolytic, and increase humidification for thick sputum plugs.
- A compressing mural or extramural mass (e.g. tumour) may require placement of an intraluminal stent, or laser resection, in a specialist centre.

Further reading

See Endotracheal intubation—indications & equipment, p44; Continuous positive airway pressure (CPAP), p76; Tracheotomy—indications & technique, p86; Fibreoptic bronchoscopy, p96; Corticosteroids, p352.

Respiratory failure

Defined as impaired pulmonary gas exchange leading to hypoxaemia and/or hypercapnia. For causes of respiratory failure see Table 22.2.

Types of respiratory failure

- Type I: hypoxaemic—often parenchymal in origin.
- Type II: hypoxaemic, hypercapnic—often mechanical in origin.

Principles of management

1. Ensure adequate SaO_2.
2. Correct abnormality where possible, e.g. drain pneumothorax, relieve/bypass obstruction.
3. Support therapy until recovery.
   - non-invasive respiratory support (CPAP, NIV, HFNO)
   - positive pressure ventilation
   - pharmacological treatment, e.g. bronchodilators, antibiotics, opiate antagonists, respiratory stimulants
   - general measures, e.g. hydration, airway humidification, removal of secretions, physiotherapy, bronchoscopy
4. If high mean airway pressures are required, unless the patient is symptomatic (e.g. drowsy, dyspnoeic), the arterial partial pressure of carbon dioxide ($PaCO_2$) may be left elevated to minimize ventilator trauma (permissive hypercapnia). If chronically hypercapnic (type II respiratory failure), correction of $PaCO_2$ can be achieved over days.

Table 22.2 Causes of respiratory failure

Central	Cerebrovascular accident, drugs (e.g. opiates, sedatives), raised intracranial pressure, trauma
Brainstem/spinal cord	Trauma (at or above phrenic level), tetanus, motor neurone disease
Neuropathy	Guillain–Barré syndrome, critical illness polyneuropathy
Neuromuscular	Muscle relaxants, organophosphorus poisoning, myasthenia gravis
Chest wall/muscular	Flail chest, myopathy (including critical illness & disuse myopathy), muscle fatigue from heart failure
Airways	Upper airways obstruction, airway disruption, asthma, COPD, anaphylaxis
Parenchymal	Pneumonia, ARDS, fibrosis, pulmonary oedema
Extrapulmonary	Pneumothorax, pleural effusion, haemothorax
Circulatory	Pulmonary embolus, heart failure, Eisenmenger intracardiac shunt

ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease.

Further reading

See Oxygen therapy, p40; Bronchodilators, p278; Respiratory stimulants, p280; Antibacterials, p344; Corticosteroids, p352; Airway obstruction, p368; Atelectasis & pulmonary collapse, p372; Pneumonia—diagnosis, p374; COVID-19—management of severe respiratory failure, p382; Acute respiratory distress syndrome—diagnosis, p384; Acute respiratory distress syndrome—management, p386; Chronic obstructive pulmonary disease, p388; Asthma—general management, p390; Pulmonary embolus—diagnosis, p394; Pneumothorax, p398; Inhalation injury, p404; Heart failure—assessment, p420; Stroke, p482; Guillain–Barré syndrome, p486; Myasthenia gravis, p488; Critical care neuromyopathies, p490; Tetanus, p492; Botulism, p494; Poisoning—general principles, p554; Sedative poisoning, p560; Antidepressant poisoning, p562; Organophosphate poisoning, p576; Multiorgan dysfunction—causes & definitions, p596; HIV-related disease, p610; Multiple trauma—initial management, p628; Head injury—management of complications, p634; Spinal cord injury, p636; Blast injury, p642; Near-drowning, p646; Postoperative complications, p668.

Atelectasis & pulmonary collapse

A collapsed lobe or segment may be seen on chest X-ray, ultrasound or CT scan. Macroatelectasis is evident as volume loss. In microatelectasis the chest X-ray may be normal but the alveolar–arterial O_2 difference will be high. Atelectasis reduces lung compliance and arterial partial pressure of O_2 (PaO_2), and increases work of breathing. This may result in poor gas exchange, high airway pressures, reduced V_T, and, if severe, circulatory collapse.

Causes

- Collapsed lobe/segment—bronchial obstruction (e.g. sputum retention, foreign body, blood clot, vomitus, excess ET tube depth).
- Macroatelectasis—air space compression by oedematous tissue, external compression (e.g. pleural effusion, diaphragmatic splinting), sputum retention.
- Microatelectasis—inadequate depth of respiration.

Sputum retention

Excess mucus (sputum) normally stimulates coughing. If ciliary clearance is reduced (e.g. smoking, sedatives) or mucous volume is excessive (e.g. asthma, bronchiectasis, cystic fibrosis) sputum retention may occur. Sputum retention may also be the result of inadequate coughing (e.g. chronic obstructive pulmonary disease, pain, neuromuscular disease) or increased mucous viscosity (e.g. hypovolaemia, inadequate humidification of inspired gas, anticholinergic drugs).

Preventive measures

- Lung hydration—maintain systemic hydration and humidify inspired gases (e.g. nebulized saline, heated water bath, heat–moisture exchange filter).
- Mucolytics, e.g. acetylcysteine (*N*-acetylcysteine, NAC), may be useful to dissolve thick sputum plugs. Avoid sputum thickening drugs, e.g. anticholinergics (atropine, ipratropium).
- Encourage deep breathing, postural changes, mobilizing.
- Ensure good pain control; avoid oversedation and hypoventilation.
- Physiotherapy—postural drainage, percussion and vibration, intermittent positive pressure breathing, incentive spirometry.
- Maintenance of lung volumes—encourage deep breathing, CPAP, positive end-expiratory pressure (PEEP), adequate V_T.
- Ventilator recruitment procedures.
- If abdomen is distended, decompress with large-bore nasogastric tube and sit up if possible.

Management

Specific management depends on the cause and should be corrective. All measures taken for prevention should continue. If there is lobar or segmental collapse with obstruction of proximal airways, bronchoscopy may be useful to allow directed suction, removal of plugs, and directed saline instillation.

Further reading

➔ See Fibreoptic bronchoscopy, p96; Chest physiotherapy, p98; Bronchodilators, p278; Chronic obstructive pulmonary disease, p388; Acute weakness, p468; Critical care neuromyopathies, p490; Pain, p660; Postoperative complications, p668.

Pneumonia—diagnosis

Definitions

Patients may present with a chest infection (community-acquired pneumonia (CAP)), develop infection after 48 h as an in-patient (hospital-acquired pneumonia (HAP)), or after 48 h on mechanical ventilation (ventilator-associated pneumonia (VAP)).

Features include fever, cough, purulent sputum, dyspnoea, leucocytosis, arterial desaturation, pleuritic pain, and bronchial breathing. However, especially in ventilated patients, such features are non-specific and are often present in the absence of infection.

Clinical features

A history is useful in determining possible causes:

- CAP in previously healthy individuals—*Streptococcus pneumoniae* (pneumococcus) is often lobar and of acute onset.
- Atypical pneumonia is usually insidious. Legionnaire's disease is often associated with community outbreaks, renal failure, electrolyte disturbance, and neurological and gastrointestinal symptoms.
- In chronic disease (e.g. alcoholism, COPD, liver failure)—*Staphylococcus aureus* and *H. influenzae* are more common. *Staph aureus* pneumonia may complicate influenza. Panton–Valentine leukocidin (PVL)-producing *Staph aureus* causes a necrotizing pneumonia, especially in younger patients.
- HAP/VAP—often enteric (Gram negative) organisms such as *Klebsiella* spp., *Pseudomonas* spp., and *Acinetobacter* spp., though *Staph aureus* is responsible for ~20–25%. Pneumococcus is rare.
- Recent aspiration—may be a chemical pneumonitis only, but anaerobic or Gram-negative infection can occur later.
- Immunosuppressed—opportunistic infections (e.g. tuberculosis (TB), *Pneumocystis jirovecii*, herpesviruses, cytomegalovirus (CMV), or fungi).
- Viral pneumonitis presents initially with fever, dry cough, myalgia, headaches. Causes include influenza and respiratory syncytial virus (RSV), coronaviruses (e.g. COVID-19, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS)).
- CURB-65 (Table 22.3) can aid decisions on hospital admission.

Table 22.3 CURB-65 pneumonia severity score

Symptom		Point
Confusion	Yes	1
Urea	≥7 mmol/L	1
Respiratory rate	≥30 min	1
Blood pressure	SBP <90 mmHg and/or DBP ≤60 mmHg	1
Age	≥65 years	1

Risk of 30-day mortality increases with a higher point score, ranging from 0.6% for score 0 (such patients usually managed as outpatients) to 27.8% for score of 5.

DBP = diastolic blood pressure; SBP = systolic blood pressure.

Investigation

Urgent investigation includes arterial gases, electrolytes, chest X-ray, blood count, and microbiological and molecular testing (polymerase chain reaction (PCR), antigen) of blood, urine, and lung fluid. Sputum is generally less helpful as there may be contamination of the sample from upper airway organisms. Further tests may be indicated, e.g. CT scan, bronchoscopy, diagnostic pleural tap.

Test for respiratory viruses, and if indicated TB, especially in immunosuppressed and high-risk patients (malnutrition, recent contacts).

Radiological investigation

- Clear lung fields—acute bronchitis is associated with cough, mucoid sputum, and wheeze. In previously healthy patients, a viral aetiology is most likely, often with an upper respiratory prodrome.
- Consolidation—pneumococcus often causes lobar consolidation.
- Cavitation—consider anaerobic infection (sputum is often foul smelling). Cavitation occurs in 30–50% of pneumonia caused by *Klebsiella pneumoniae*. Also consider pneumococcus, *Staph aureus*, and TB. Consider foreign body or a pulmonary infarct where there is an abscess.
- Some infections may produce characteristic appearances, e.g. peri-hilar reticular shadowing and small pneumatoceles (*Pneumocystis jirovecii* pneumonia); round soft tissue mass within a cavity and outlined by an air crescent (aspergilloma), small nodules (varicella).

Laboratory investigation

Consider the following for laboratory investigations:

- Throat swab for viral PCR.
- Lung fluid (e.g. cough specimen, ET tube aspirate, protected brush specimen, bronchoalveolar lavage specimen, pleural aspirate) for microscopy, culture, and sensitivity, serology, and molecular tests.
- Blood cultures.
- Serology (e.g. viral, atypical such as *Mycoplasma* spp., *Legionella* spp.).
- Urine for antigen (if *Legionella* spp. or pneumococcus suspected).
- Molecular diagnostics, e.g. real-time PCR, bacterial DNA.
- Blood levels of inflammatory markers, e.g. C-reactive protein and procalcitonin, are usually higher in bacterial vs fungal vs viral infection, though positive and negative predictive values are not sufficiently discriminatory.

Microbiological yield from culture is often low, especially if antibiotic therapy has started pre-sampling. Multiple organisms are often cultured, especially from sputum. Separating pathogenic from colonizing organisms may be difficult. In HAP, known nosocomial pathogens are most likely, e.g. local Gram-negative flora.

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Mandell L, Niederman M. 2019. 'Aspiration pneumonia'. *N Engl J Med* 380: pp651–63. doi: 10.1056/NEJMra1714562

➔ See Blood gas analysis, p174; Respiratory imaging, p178; Bacteriology, p256; Virology, p258; Infection—diagnosis, p588; HIV-related disease, p610; Viral critical illness, p612.

Pneumonia—antimicrobial management

Appropriate treatment depends on a careful history plus radiological and laboratory findings. Empiric 'best guess' antimicrobial treatment often needs to be started before culture results are available. If indicated, engage local microbiology or infectious disease expertise to advise.

Principles of antimicrobial prescribing

- A straightforward viral infection does not require antimicrobial treatment. Treat secondary bacterial infection (e.g. by *Staph aureus*) if identified/concerned.
- Choice of antimicrobial depends on type (CAP/HAP/VAP) and known local (community and hospital) resistance patterns. For example, countries may have high levels of penicillin-resistant pneumococci and co-amoxiclav-resistant *H. influenzae*. For nosocomial pneumonia, hospitals may have known multi-resistant Gram –ve (e.g. *Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella* spp.) or Gram +ve organisms (meticillin-resistant *Staph aureus* (MRSA), vancomycin-resistant enterococci).
- Table 22.4 details dosages of common antimicrobials.
- If uncertain, start broad-spectrum antimicrobials to cover likely pathogens and de-escalate promptly once tests become available.
- Guidelines often recommend dual combination antibiotics with a β-lactam and macrolide for patients with moderate-to-high severity CAP. The evidence base supporting this is weak, e.g. the CAP-START study.
- Consider adjusting antimicrobials once sensitivities are available. Deterioration or failure to respond within 72 h, should prompt a further search for the cause and consideration of broader antimicrobial coverage.
- In immunosuppressed patients consider organisms such as fungi (*Candida* spp., *Aspergillus* spp.), viruses (e.g. CMV), and atypical organisms (e.g. *Pneumocystis jirovecii*, atypical mycobacteria).
- Reactivation of CMV is common in critically ill but otherwise immunocompetent patients; benefits of prophylactic treatment with appropriate antivirals in seropositive patients remain uncertain.
- Though few prospective trials have been performed, short-course antimicrobial therapy (e.g. 5 days) appears adequate in most cases. Prolonged duration courses are indicated for specific conditions, e.g. empyema, pulmonary TB.
- Treat early community-acquired viral pneumonitis with appropriate antivirals such as remdesivir for COVID-19 and the neuraminidase inhibitors, zanamivir or oseltamivir for H1N1 influenza.

Further reading

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'Pneumonia (community-acquired): antimicrobial prescribing'. National Institute for Health and Care Excellence. Accessed June 2023. https://www.nice.org.uk/guidance/ng138

See Bacteriology, p256; Virology, p258; Antibacterials, p344.

Table 22.4 Doses of common antimicrobial agents

Drug	Dose	Organism
Aciclovir	10 mg/kg 8-hrly IV	Herpesviruses
Amphotericin B (AmBisome®)	3–6 mg/kg IV daily	Fungi
Benzylpenicillin	1.2 g 2–6-hrly IV	*Strep pneumoniae*
Caspofungin	70 mg IV then 50 mg IV daily	Fungi
Ceftazidime	2 g 8-hrly IV	Gram –ve spp.
Cefuroxime	750 mg–1.5 g 8-hrly IV	*Strep pneumoniae* *H. influenzae*, Gram–ve spp.
Ceftriaxone	1–2 g od IV	Gram +ve/–ve spp.
Ciprofloxacin	400 mg IV 8–12-hrly	Gram +ve/–ve spp.
Clarithromycin	500 mg 12-hrly IV or PO	Atypical pneumonia *Strep pneumoniae*
Co-amoxiclav	1.2 g 6-hrly IV	H. *influenzae* Gram +ve/–ve spp.
Co-trimoxazole	120 mg/kg/day IV	*Pneumocystis carinii* Atypical pneumonia
Erythromycin	0.5–1 g 6–12-hrly	Atypical pneumonia *Strep pneumoniae*
Flucloxacillin	0.5–2 g 6-hrly IV	*Staph aureus*
Ganciclovir	5 mg/kg 12-hrly IV	CMV
Linezolid	600 mg 12-hrly IV or PO	MRSA
Meropenem	0.5–2 g 8-hrly IV	Gram +ve/–ve spp.
Metronidazole	0.5 g 8-hrly IV or 1 g 12-hrly PR	Anaerobes
Oseltamivir	75 mg 12-hrly PO	Influenza viruses
Piperacillin–tazobactam	4.5 g 8-hrly IV	Gram +ve/–ve spp.
Polymyxin E (colistin)	2.5–5 mg/kg/day divided 6–12-hrly IV or IM	MRSA
Remdesivir	200 mg IV loading then 100 mg IV od for up to 9 days	COVID-19
Teicoplanin	400 mg 12-hrly for 3 doses then 400 mg daily	MRSA
Vancomycin	500 mg 6-hrly (monitor levels)	MRSA
Zanamivir	10 mg daily inhaled	Influenza viruses

Pneumonia—general management

Supportive care

- Support the patient's breathing to maintain adequate gas exchange. This can range from increased O_2 concentrations by face mask, through to non-invasive support, intubation and mechanical ventilation, and, rarely, extracorporeal lung support (extracorporeal membrane oxygenation (ECMO)).
- Prevent the patient from tiring as decent sleep, good V_T, and a strong cough facilitate recovery.
- Employ physiotherapy, postural changes, and suction aids to facilitate sputum clearance. Bronchoscopic clearance of sputum may be required, especially if lobar collapse is present.
- Maintain good hydration and airway humidification to avoid sputum thickening.

Adjunctive therapies

- Steroid therapy (e.g. prednisolone 50 mg od) may reduce progression to mechanical ventilation from CAP, but impact on mortality reduction remains uncertain.
- Bronchodilatation with β_2-agonist nebulizers may help ventilation and sputum clearance in patients with bronchospasm.
- Mucolytics may help sputum clearance, but there is no evidence, as yet, that routine nebulization offers additional benefit.
- Surgery or interventional radiology may be needed to drain abscess, empyema, and significant pleural effusions.

Patient isolation

- Isolate the patient if concerned about any infectious pathogen, e.g. viral or TB. Check local policy.
- Staff should don appropriate protective masks and clothing.

Preventive strategies

VAP likely originates from colonized oropharyngeal secretions infecting the lung. Multiple preventive strategies have been proposed including 30° head-up positioning, selective gut decontamination, modified ET tubes enabling continuous subglottic aspiration, and antiseptic or silver-impregnated ET tubes to reduce biofilm formation. An evidence base conclusively showing benefit for most of these procedures is lacking, though strongest for selective digestive decontamination (SDD).

Further reading

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➲See Oxygen therapy, p40; Ventilatory support—indications, p48; Fibreoptic bronchoscopy, p96; Chest physiotherapy, p98; Bronchodilators, p278; COVID-19—general management, p380; Viral critical illness, p612.

COVID-19—general management

First recognized in late 2019 in China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19) has resulted in a global pandemic with millions of deaths and hospital admissions.

Presenting features

Symptoms include cough, fever, myalgia, and fatigue. Other manifestations include headache, diarrhoea, confusion, anosmia, and/or dysgeusia, rash. Increasing shortness of breath occurs in more severe illness. Hypoxaemic patients usually present with normal or low CO_2 levels. Despite severe hypoxaemia, the patient may appear comfortable ('happy hypoxia'); this phenomenon relates to a non-elevated $PaCO_2$.

Diagnosis

Nasal and oropharyngeal swabs (PCR or lateral flow tests), saliva (LAMP method), or lung fluid are used to identify the presence of virus. The current gold standard is PCR.

Laboratory data may reveal lymphopenia, mild neutrophilia, and elevated levels of C-reactive protein, D-dimer, and N-terminal (NT)-pro-B-type natriuretic peptide (BNP).

Radiographic presentation may evolve from a normal chest X-ray through to air-space opacities (ground-glass appearance). It is usually bilateral with peripheral and lower zones predominant. Similar findings may be found on CT scan, as well as septal thickening.

Personal protective equipment (PPE)/universal precautions

The risk of airborne viral spread from aerosol-generating procedures (AGPs), e.g. suction, intubation, non-invasive respiratory support (NIRS), is much lower than originally feared. FFP3 masks and visors should be worn if performing any airway-related procedure or if the patient is spontaneously coughing as particles can be spread up to 7–8 m.

The risk of live virus being present diminishes after 5–10 days. Local infection control measures vary.

Treatment

Early disease can be treated with antiviral treatments such as Paxlovid™ and remdesivir, ± combination monoclonal antibodies, e.g. REGEN-COV (in sero-negative patients).

In the Recovery trial, dexamethasone 6 mg od reduced mortality in patients requiring O_2 or respiratory support, but not in patients receiving no O_2. A Cochrane meta-analysis of all steroid trials reported to date showed a more conservative outcome effect. It is currently not known whether higher-dose steroids are beneficial in those failing to respond to 6 mg dexamethasone. A recent study showed worse outcomes in non-ventilated patients receiving 20 mg dexamethasone compared to 6 mg.

Other immunomodulatory agents may give some added outcome benefit, e.g. interleukin-6 antagonists such as tocilizumab, the Janus kinase (JAK) inhibitor baricitinib, and the tyrosine kinase inhibitor imatinib. More studies, and ideally, biomarkers, are required to establish which patients specifically benefit, especially to avoid potential harm.

Complications

Thromboembolism

A greater risk of venous, arterial, or pulmonary arterial thromboembolism relates to an increased prothrombotic state, though traditional coagulopathy markers such as international normalized ratio, prothrombin time, and activated partial thromboplastin time are usually normal.

Prophylactic anticoagulation, usually with a low-molecular-weight heparin (LMWH), is advised, though the optimal dosing regimen remains uncertain. Full anticoagulation should be given for confirmed thromboembolism.

Pulmonary hypertension and right heart failure

These may result from the underlying disease process and high airway pressures that may be generated by positive pressure ventilation. Although various treatments are used, e.g. inhaled nitric oxide (NO), nebulized epoprostenol, enteral sildenafil, the outcome benefits from such treatments have not been clearly demonstrated.

Extrapulmonary.

Extrapulmonary complications include renal failure, myocarditis, and encephalopathy. These should be managed as per conventional strategies.

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➲ See Continuous renal replacement therapy—techniques & indications, p116; Haemo(dia)filtration, p118; Coagulation monitoring, p252; Virology, p258; Anticoagulants—parenteral, p334; Oliguria, p426; Acute kidney injury—diagnosis, p428; Acute kidney injury—management, p430.

COVID-19—management of severe respiratory failure

Non-invasive respiratory support (NIRS)

The main reason for critical care admission is hypoxaemic respiratory failure. Unless the patient is in extremis, a trial of non-invasive respiratory support should be initiated, although optimal timing of commencement remains uncertain. Although two randomized trials show less need for invasive ventilation using CPAP over HFNO, there remains an important role for HFNO. This can be used effectively in combination with CPAP to allow comfort and oral nutrition and hydration breaks and is especially useful if several days of CPAP are required. Reassurance, sedation, and anxiolysis are important adjuncts to aid compliance.

Prone position

While prone positioning often improves gas exchange and patient comfort, no prospective studies have shown outcome benefit. If tolerated, it should be offered to spontaneously breathing patients requiring O_2 or NIRS and continued, if beneficial for gas exchange, to patients being mechanically ventilated.

Invasive ventilation

Predictors of NIRS failure include older age, underlying comorbidities, illness severity, higher inflammatory markers, lower PaO_2:FiO_2 ratio (or similar scores), and poor response to a trial of NIRS. Optimal timing of intubation remains uncertain but patients should not be allowed to become exhausted or endure prolonged periods of strenuous respiratory effort as this may result in pSILI (patient self-induced lung injury). However, this must be balanced against the potentially greater risk of VILI (ventilator-induced lung injury) and other complications of mechanical ventilation.

No specific mode of ventilation has shown superiority. Standard lung protective strategies utilized in ARDS should be applied. It is also important to maintain adequate hydration and airway humidification. Paralysis may be needed if lung compliance and gas exchange remain poor.

ECMO

Consider if extreme respiratory failure does not respond to conventional ventilatory strategies, including prone positioning. Regional centres have their own referral criteria, including duration of respiratory support, age, comorbidities, and other organ failures. Even with good patient selection, reported mortality is ~40%. The RESP score is commonly used for predicting survival.

Tracheotomy

Often required to facilitate weaning after a prolonged period of ventilation. Optimal timing of tracheotomy plus technique of insertion (percutaneous vs open surgical) also remain uncertain.

Further reading

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➲ See Ventilatory support—indications, p48; Invasive ventilation—modes, p52; Non-invasive respiratory support, p74; High-flow nasal oxygenation (HFNO), p80; Prone positioning, p82; Extracorporeal membrane oxygenation, p84; Tracheotomy—indications & technique, p86.

Acute respiratory distress syndrome—diagnosis

Acute respiratory distress syndrome (ARDS) is the respiratory component of multiple organ dysfunction. It may dominate the clinical picture, or be of lesser importance in relation to dysfunction of other organ systems.

Aetiology

As part of the exaggerated inflammatory response following an insult that may be direct (e.g. chest trauma, inhalation injury) or distant (e.g. peritonitis, haemorrhage, burns). Histology reveals aggregation and activation of neutrophils and platelets, patchy endothelial and alveolar disruption, interstitial oedema, and fibrosis. Classically, the acute phase is characterized by increased capillary permeability and a later fibroproliferative phase by a predominant fibrotic reaction. However, such distinctions are not so clear-cut; evidence of fibrosis is present as early as day 1.

Definitions

The 2012 definitions ('Berlin criteria') were updated in 2023 (Table 22.5) to take account of the increased use of non-invasive support, possible non-availability of arterial blood gases, and to support those in resource-limited settings.

Table 22.5 2023 ARDS global definitions criteria

Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload. Exclude hydrostatic oedema if no risk factor present
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities, not fully explained by effusions, lobar/lung collapse, or nodules
Oxygenation:	
• Not intubated	P:F ratio ≤40 kPa (300 mmHg) or S:F ratio ≤315 if SpO_2 ≤97% on HFNO with flow ≥30 L/min or NIV/CPAP with ≥5 cmH_2O end-expiratory pressure
• Intubated	Mild: P:F 26.7–40 kPa (200–300 mmHg) or S:F 236–315 if SpO_2 ≤97% Moderate: P:F 13.3–26.7 kPa (100–200 mmHg) or S:F 149–235 if SpO_2 ≤97%. Severe: P:F ≤13.3 kPa (≤100 mmHg) or S:F <148 if SpO_2 ≤97%
• Modified	S:F ≤315 if SpO_2 <97% For resource-limited settings. NB: neither PEEP nor minimum O_2 flow rate is needed for diagnosis in these settings

P:F = PaO_2:FiO_2 ratio; S:F = SpO_2:FiO_2 ratio.

Prognosis

Prognosis depends, in part, on the underlying insult, the presence of other organ dysfunctions, and the age and chronic health of the patient. While outcomes are improving, ARDS still carries a hospital mortality of 20–30% and a 1-year mortality of ~40%.

Survivors from ARDS often show some deterioration on lung function testing. A significant proportion of survivors have physical, cognitive and/or psychological sequelae up to 5 years later.

Further reading

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➲ See Acute respiratory distress syndrome—management, p386; Inhalation injury, p404; Multiorgan dysfunction—causes & definitions, p596; Multiple trauma—initial management, p628; Burns—airway & circulatory management, p638; Blast injury, p642.

Acute respiratory distress syndrome—management

General (non-respiratory) management

- Remove the precipitating factor whenever possible, e.g. drain pus, antibiotics, fix long bone fracture.
- Use preventive measures to avoid secondary infection.
- Carefully manage fluid balance to restore and maintain adequate organ perfusion. Avoid excess, unnecessary fluid input. Worse outcomes occur when fluid balance remains positive after the initial fluid resuscitation phase. Diuretic use may be appropriate here.
- Both the ARDS disease process and high ventilator pressures result in pulmonary hypertension that may lead to right ventricular dysfunction/failure and haemodynamic compromise. Pulmonary vasodilators (e.g. sildenafil, epoprostenol, NO) can reduce pulmonary pressures though no outcome benefit trials yet exist.
- Haemodynamic manipulation may improve or worsen oxygenation due to variable effects on shunt and ventilation–perfusion mismatch.
- Sedate to maintain tube tolerance and enable mechanical ventilation. Infusions of an opiate plus propofol are usually given. α_2 agonists (e.g. clonidine) may be added as sparing agents. Titrate doses to the minimum needed to allow comfort ventilation.
- Multicentre trials of adjuvant therapies (e.g. statins, surfactant, inhaled NO) have not shown mortality benefit, or even caused harm (e.g. β_2 agonists). Outcomes from corticosteroid trials are inconsistent.
- No outcome benefit has been shown from either hypocaloric feeding or immunonutrition approaches.

Respiratory management

- Maintain adequate gas exchange with increased FiO_2 and, depending on severity, non-invasive respiratory support (e.g. HFNO, CPAP, NIV) or positive pressure ventilation. Pressure controlled or airway pressure release modes are generally used, though no benefit has been shown for specific modes.
- Target V_T to 4–8 mL/kg predicted body weight and plateau inspiratory pressures ≤30 cmH_2O.
- Target blood gas values at maintaining survival without striving to achieve normality. Permissive hypercapnia, where $PaCO_2$ values are allowed to rise, has been associated with outcome benefit, likely through less ventilator trauma. While some permit hypercapnia providing arterial pH ≥7.2, this threshold was empirically chosen.
- Acceptable levels of SaO_2 are controversial; values ≥90% are targeted but in severe ARDS may be progressively relaxed to 80–85%, or perhaps even lower, providing organ function remains adequate.
- Prone positioning may improve gas exchange. It is recommended for use in moderate–severe ARDS soon after intubation and initial stabilization. Patients should be turned prone for at least 16 h/day. Care must be taken during turning to prevent ET tube displacement, pressure sores, and shoulder injuries.

- Routine use of continuous infusions of neuromuscular paralysis is no longer recommended.
- Though no clear outcome benefit has been demonstrated in randomized controlled trials, patients meeting specific criteria can be referred to a specialist centre for consideration of ECMO. Extracorporeal CO_2 removal (e.g. Novalung™) is no longer recommended.
- Routine recruitment manoeuvres to improve gas exchange are no longer recommended.
- No outcome benefit was seen in studies targeting high PEEP, nor comparing high-frequency oscillation against conventional ventilation.
- Ventilator trauma is ubiquitous so minimizing iatrogenic injury is key. Pneumothoraces may occur requiring chest drains. These may be difficult to diagnose by X-ray or ultrasound. CT scanning may reveal undiagnosed pneumothoraces and aid drain placement.

Further reading

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➲ See Oxygen therapy, p40; Ventilatory support—indications, p48; Positive end-expiratory pressure—principles, p70; Prone positioning, p82; Extracorporeal membrane oxygenation, p84; Pulmonary vasodilators, p282; Corticosteroids, p352; Acute respiratory distress syndrome—diagnosis, p384; Pneumothorax, p398.

Chronic obstructive pulmonary disease

Patients with chronic obstructive pulmonary disease (COPD) may be admitted for management of acute exacerbations, for non-pulmonary reasons, or as a prophylactic measure in view of their limited respiratory function, e.g. for elective postoperative ventilation. An acute exacerbation (which may or may not be infection related) results in decompensation and symptomatic deterioration. Such infections include viruses, bacteria (e.g. *H. influenzae*, *Strep pneumoniae, Staph aureus*), fungi and, rarely, atypical organisms (e.g. *Mycoplasma pneumoniae*, *Legionella pneumophilia*).

Problems in managing COPD patients

- Frailty due to chronic ill health.
- Fatigue, muscle weakness, and decreased physiological reserve leading to earlier need for ventilatory support, weak cough, increased difficulty in weaning, and greater physical dependency on support therapies.
- Psychological dependency on support therapies.
- More prone to pneumothorax.
- Usually have greater levels of sputum production.
- Right ventricular dysfunction (cor pulmonale).

Management considerations

- Ensure good pain control but avoid oversedation.
- Mobilize early and encourage deep breathing.
- Encourage good sleep pattern to reduce risk of fatigue.
- Non-invasive ventilatory support (e.g. CPAP, NIV, HFNO) may avoid the need for intubation. Apply early, especially if patient is showing signs of fatigue.
- Consider respiratory stimulants (e.g. doxapram) if central narcosis from CO_2 retention.
- Accept lower target levels of PaO_2 or SpO_2 (e.g. 88–92%). Higher levels of O_2 saturation are unnecessary and may occasionally be harmful by reducing respiratory drive (in type II failure).
- Accept higher target levels of $PaCO_2$ if patient is known or suspected to have chronic CO_2 retention (e.g. elevated plasma bicarbonate levels on admission to hospital).
- Think ahead as to whether intubation is appropriate if non-invasive strategies fail. The decision should be made in consultation with the patient (if possible), family and, perhaps, a respiratory physician or general practitioner with knowledge of the patient.

Weaning the patient with COPD

- If possible, consider a trial of early extubation to avoid prolonged ventilator dependency.
- Weaning may be prolonged, especially if baseline reserve is poor. Daily trials of spontaneous breathing may reveal faster-than-anticipated progress.
- Consider early extubation to NIV.
- Set realistic daily weaning targets.
- Early mobilization is usually advantageous.

- Prevent over-fatiguing the patient by too rapid weaning or excessive mobilization.
- Ensure a good night's sleep.
- Provide encouragement and psychological support.
- Consider early tracheostomy when difficulty in weaning is expected.
- Consider heart failure as a cause of difficulty in weaning. COPD patients often have cor pulmonale or concurrent ischaemic heart disease.
- Consider periods (1–7 days) of non-weaning to allow rest and focus on physical rehabilitation and muscle strengthening.

Further reading

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See Oxygen therapy, p40; Positive end-expiratory pressure—principles, p70; Non-invasive respiratory support, p74; Continuous positive airway pressure (CPAP), p76; Chest physiotherapy, p98; Blood gas analysis, p174; Bronchodilators, p278; Respiratory stimulants, p280; Antibacterials, p344; Pneumonia—diagnosis, p374; Pneumothorax, p398.

Asthma—general management

Acute bronchospasm and mucus plugging are often secondary to an insult such as infection. The patient may progress to fatigue, respiratory failure and collapse. Onset may develop slowly over days or rapidly within minutes to hours.

Clinical features

- Dyspnoea, wheeze (expiratory ± inspiratory), difficulty in talking, accessory muscle use, fatigue, agitation, cyanosis, coma, collapse.
- Pulsus paradoxus is a poor indication of severity; a fatiguing patient cannot generate significant respiratory swings in intrathoracic pressure.
- A 'silent' chest is a late sign suggesting severely limited airflow.
- Pneumothorax and lung/lobar collapse.

Management of asthma

Asthmatics must be managed in a well-monitored area. If clinical features are severe, they should be admitted to a critical care unit where rapid institution of mechanical ventilation is available. Monitoring should comprise, as a minimum, pulse oximetry, continuous electrocardiogram (ECG), blood pressure monitoring and blood gas analysis. If severe, insert an arterial cannula ± central venous access.

1. Try to keep the patient calm, and nurse in a quiet environment. Small midazolam or morphine boluses (1–2 mg) may offer useful anxiolysis.
2. Adjust FiO_2 to maintain SaO_2 92–98%.
3. Nebulized β_2 agonist (e.g. salbutamol) may be repeated 2–4-hrly or, in severe attacks, given continuously (Table 22.6). Benefit from ipratropium bromide is questionable; it may thicken sputum through its anticholinergic action.
4. IV hydrocortisone for 24–48 h then oral prednisolone.
5. IV bronchodilators, e.g. salbutamol, magnesium sulfate.
6. Exclude pneumothorax and lung/lobar collapse.
7. Ensure adequate hydration and fluid replacement.
8. Commence appropriate antibiotics only if good evidence of bacterial chest infection. Green sputum does not necessarily indicate a bacterial infection.
9. NIV can be used in asthmatics with persistent hypercapnia or an excessive work of breathing. The patient should not be obtunded, haemodynamically unstable, having excess secretions or uncooperative. Monitor carefully in an ICU setting due to an increased risk of pneumothorax.
10. If no response to above measures or in extremis, consider:
    - IV salbutamol infusion
    - epinephrine SC or by nebulizer
    - aminophylline infusion
    - mechanical ventilation
    - anecdotal success is reported with subanaesthetic doses of a volatile anaesthetic agent such as isoflurane or sevoflurane which both calms/sedates and bronchodilates.

Indications for mechanical ventilation

- Increasing fatigue.
- Respiratory failure—rising $PaCO_2$, falling PaO_2.
- Cardiovascular collapse.

Facilitating endotracheal intubation

Summon senior assistance. Pre-oxygenate with 100% O_2. Perform rapid sequence induction. To minimize barotrauma, care should be taken to avoid excess air trapping, high airway pressures, and high V_T.

Table 22.6 Drug dosages in severe asthma

Epinephrine	0.5 mL 1:1000 solution SC or 2 mL 1:10,000 solution by nebulizer
Hydrocortisone	100–200 mg qds IV
Prednisolone	40–60 mg od PO initially
Salbutamol	2.5–5 mg by nebulizer 5–20 μg/min by IV infusion
Magnesium sulfate	1.2–2.0 g IV over 20 min
Aminophylline	6 mg/kg IV loading dose over 20 min; then 0.7 mg/kg/h infusion (lower in elderly, cor pulmonale, heart failure, liver disease). Monitor levels and adjust as necessary

Further reading

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➔ See Oxygen therapy, p40; Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Pulmonary function tests, p166; Blood gas analysis, p174; Bronchodilators, p278; Antibacterials, p344; Corticosteroids, p352; Asthma—ventilatory management, p392; Pneumothorax, p398.

Asthma—ventilatory management

Early period

1. Intubate and bag cautiously as haemodynamic collapse can occur on induction and with high inflation pressures. Consider ketamine as an induction agent for its bronchodilator properties and cardiovascular stability. Note, atracurium may cause histamine release and potentially worsen bronchospasm. Rocuronium, cisatracurium, and vecuronium are considered safe neuromuscular blockers. Fentanyl and propofol are deemed safe sedatives.
2. Initially give low V_T (5 mL/kg) breaths at low rate (5–10/min) to assess degree of bronchospasm and air trapping. Slowly increase V_T (to 6–7 mL/kg) ± increase rate. Monitor with regular blood gas analyses. Avoid air trapping and high inspiratory pressures. Low rates with prolonged inspiratory:expiratory (I:E) ratio (e.g. 1:1) may be advantageous. Avoid short expiratory times and high levels of PEEP. Do not strive for normocapnia. Monitor auto-PEEP levels.
3. Administer muscle relaxants until severe bronchospasm has abated and gas exchange improves.
4. Sedate with either standard medication or with agents such as ketamine or sevoflurane that have bronchodilating properties. Ketamine given alone may cause hallucinations while sevoflurane can excessively vasodilate.
5. If significant air trapping remains, consider ventilator disconnection and forced manual chest compressions every 10–15 min.
6. If severe bronchospasm persists, consider injecting 1–2 mL of 1:10,000 epinephrine down ET tube. Repeat at 5 min intervals, as needed.
7. In very resistant cases or patients with problematic pneumothoraces, consider ECMO support to enable CO_2 removal and/or adequate oxygenation.

Maintenance

1. Ensure adequate rehydration.
2. Give ample humidification to loosen mucus plugs. Use a heated water bath humidifier or, alternatively, a heat–moisture exchanger plus either hourly normal saline nebulizers or regular ET instillation of 5 mL normal saline.
3. Physiotherapy assists mobilization of secretions and removal of mucus plugs. Avoid hyperventilation.
4. With improvement, gradually normalize ventilator settings (V_T, rate, I:E ratio) to achieve normocapnia before allowing patient to waken and breathe spontaneously.
5. Consider pneumothorax or lung/lobar collapse if deteriorating.
6. If mucus plugging constitutes a major problem, consider instillation of a mucolytic (acetylcysteine (*N*-acetylcysteine, NAC) though this may induce further bronchospasm. Bronchoscopic removal of plugs should only be performed by an experienced operator.

Assessment of air trapping (intrinsic PEEP, PEEPi)

- Measure PEEPi by pressing end-expiratory hold button of ventilator.
- No pause between expiratory and inspiratory sounds or waveform phases on the ventilator.
- Disconnection of ventilator and timing of audible expiratory wheeze.
- An increasing $PaCO_2$ may respond to reductions in minute volume as this could lower the level of intrinsic PEEP.

Weaning

- Bronchospasm may increase on lightening sedation due to awareness of ET tube and increased coughing.
- The patient may need a trial of extubation while still on high FiO_2.
- Consider extubation under inhalational or short-acting IV sedation.
- Space out intervals between β_2-agonist nebulizers. Convert other anti-asthmatic drugs to oral medication. Theophylline dose (if used) should be adjusted to ensure therapeutic levels.

Further reading

➔ See Oxygen therapy, p40; Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Invasive ventilation—modes, p52; Invasive ventilation—adjustments, p54; Invasive ventilation—failure to deliver ventilation, p58; Invasive ventilation—complications, p62; Positive end-expiratory pressure—principles, p70; Blood gas analysis, p174; Asthma—general management, p390; Pneumothorax, p398.

Pulmonary embolus—diagnosis

Definition

- Clot in pulmonary vasculature.

Aetiology

- Deep vein thrombosis in femoral and/or pelvic veins.
- Amniotic fluid embolus.
- Fat embolus after pelvic or long bone trauma.
- Right heart source, e.g. mural thrombus.

Clinical features

- Acute pleuritic-type chest pain, dyspnoea, ± haemoptysis.
- The patient with a major embolus often prefers to lie flat. Dyspnoea improves due to increased venous return and right heart loading.
- Deterioration in gas exchange—PaO_2 may be low while $PaCO_2$ may be low, normal, or high.
- Cardiovascular features, e.g. tachycardia, low/high blood pressure, collapse.
- Various scores, e.g. Wells, PERC, and revised GENEVA can be used to identify the clinical probability of pulmonary embolism (PE) and can be used alongside clinical gestalt.

Investigations

- CT pulmonary angiogram (CTPA): investigation of choice.
- Chest X-ray: may be normal, but massive embolus may produce fewer vascular markings (pulmonary oligaemia) in a hemithorax ± a bulging pulmonary hilum. A wedge-shaped peripheral infarct may be seen after a few days following a smaller embolus.
- ECG: acute right ventricular strain, i.e. $S_1Q_3T_3$, tachycardia, right axis deviation, right bundle branch block, P pulmonale.
- Echocardiogram: for evidence of pulmonary hypertension and acute right ventricular strain. Absence does not exclude PE.
- Pulmonary angiography—now supplanted by CTPA.
- Ventilation/perfusion scan: degree of certainty is reduced if area of non-perfused lung corresponds to any chest X-ray abnormality.
- D-dimers: useful rule-out test—if levels are <500 ng/mL, there is a 97–100% negative predictive value for PE. Elevated levels have a low positive predictive value. The normal range of D-dimers increases with age; some authorities argue for age adjustment for cut-off values.
- Troponin and NT-BNP: elevated with significant PE as markers of ventricular injury and strain and can prognostic for poor outcomes. See Table 22.7 for categories of risk.
- Fat globules or fetal cells in pulmonary artery blood may occasionally be found with fat and amniotic fluid embolus, respectively.

Table 22.7 Risk categories

High risk	Haemodynamic instability due to cardiac arrest, obstructive shock, or persisting hypotension not caused by new-onset arrhythmia, concurrent hypovolaemia, or sepsis
Intermediate risk	Presence of right ventricular dysfunction and elevated levels of troponin and NT-BNP
Low risk	Haemodynamically stable with no right ventricular strain and normal cardiac biomarkers

Further reading

Freund Y, Cohen-Aubart F, Bloom B. 2022. 'Acute pulmonary embolism. A review'. *JAMA* 328: pp1336–45. doi: 10.1001/jama.2022.16815

Kahn SR, de Wit K. 2022. 'Pulmonary embolism'. *N Engl J Med* 387: pp45–57. doi: 10.1056/NEJMcp2116489

See Pulmonary embolus—management, p396.

Pulmonary embolus—management

General management

1. Adjust FiO_2 to maintain adequate SpO_2.
2. Lie patient flat (if able) and give a modest fluid challenge (e.g. 200–250 mL) to increase venous return. Assess response and repeat if indicated. Avoid fluid overload as this may worsen right ventricular function.
3. Start epinephrine (or norepinephrine) infusion if circulation remains compromised.
4. Pulmonary hypertension may be decreased by inhaled NO or vasodilators. Care should be taken due to risk of systemic hypotension with IV therapy.
5. Mechanical ventilation if needed and if non-invasive support fails or is not tolerated. Gas exchange and haemodynamics may worsen significantly on induction of anaesthesia and intubation due to loss of preferential shunting, decrease in cardiac output from reduced venous return, and vasodilatation from sedative drugs. Hypoxaemia and cardiovascular collapse may ensue.
6. Use low V_T (6–8 mL/kg predicted body weight) to minimize plateau pressures; use low PEEP.
7. In very severe cases, ECMO may be considered.

Management of blood clot embolus

- See Table 22.8 for drug regimens.
- For high-risk PE give a thrombolytic agent (e.g. alteplase, tenecteplase) followed by LMWH.
- For intermediate- and high-risk PE, give LMWH. Bleeding risk is greater with unfractionated heparin.
- For low-risk PE give a direct oral anticoagulant (DOAC), e.g. apixaban, rivaroxaban or LMWH.
- Routine use of thrombolysis in intermediate-risk PE is discouraged as trial data found no outcome benefit but an increased risk of major haemorrhage and stroke.
- Fondaparinux can be used as an alternative to LMWH.
- If systemic thrombolysis fails or is contraindicated, consider catheter-directed thrombolysis (± thrombectomy) by interventional radiology or surgical thrombectomy.
- After stabilization, a DOAC or vitamin K antagonist can be commenced with a bridging plan to discontinue LMWH.
- An inferior vena cava filter may be sited if anticoagulation is contraindicated.

Table 22.8 Drug dosages in pulmonary embolus

Subcutaneous LMWH regimen	Dalteparin: 200 units/kg (max 18,000 units) every 24 h (*or* 100 units/kg 12-hrly if increased risk of haemorrhage) Enoxaparin: 1 mg/kg 12-hrly or 1.5 mg/kg (150 units/kg) every 24 h Tinzaparin: 175 anti-Xa units/kg once daily
Direct oral anticoagulant (DOAC) regimen	Apixaban: 10 mg bd Rivaroxaban: 15 mg bd
Fondaparinux regimen	Subcutaneously 5 mg (body weight <50 kg), 7.5 mg (weight 50–100 kg) or 10 mg (weight >100 kg)
Thrombolysis regimens	Alteplase: 10 mg IV over 1–2 min then 90 mg infusion given over 2 h (max 1.5 mg/kg if weight <65 kg) Tenecteplase: 0.5 mg/kg IV, with a 5 mg step-up for every 10 kg increase from 60 to 90 kg

NB: central venous catheters should ideally be inserted pre-thrombolysis by an experienced operator to minimize risk of bleeding/haematoma.

Further reading

Freund Y, Cohen-Aubart F, Bloom B. 2022. 'Acute pulmonary embolism'. *JAMA* 328: pp1336–45. doi: 10.1001/jama.2022.16815

Kahn SR, de Wit K. 2022. 'Pulmonary embolism'. *N Engl J Med* 387: pp45–57. doi: 10.1056/NEJMcp2116489

See Ventilatory support—indications, p48; Blood gas analysis, p174; Coagulation monitoring, p252; Pulmonary vasodilators, p282; Anticoagulants—parenteral, p334; Anticoagulants—oral, p336; Thrombolytics, p338; Basic resuscitation, p358; Cardiac arrest, p360; Pulmonary embolus—diagnosis, p394.

Pneumothorax

Significant collection of air in the pleural space that may occur spontaneously with no underlying lung disease (primary pneumothorax), or following trauma (including iatrogenic), asthma, and chronic lung disease (secondary pneumothorax). It can also occur from ventilator trauma.

Clinical features

- May be asymptomatic.
- Dyspnoea, pain.
- Decreased breath sounds, hyper-resonant, asymmetric chest expansion.
- Respiratory failure and deterioration in gas exchange.
- Increasing airway pressures and difficulty to ventilate.
- Cardiovascular deterioration with mediastinal shift (tension).

Diagnosis

Chest X-ray—most easily seen on erect views with absent lung markings lateral to a well-defined lung border (Figure 22.1). Tension pneumothorax results in a contralateral mediastinal shift. Distinguish from bullae, especially with severe emphysema, as inadvertent bulla drainage may cause a bronchopleural fistula.

A pneumothorax may be missed on a supine chest X-ray as this may sit anterior to normal lung giving lung markings on the radiograph. A lateral chest X-ray may help. Consider supine pneumothorax with (i) hyperlucent lung field compared to contralateral lung, (ii) poorly visualized diaphragm outline, (iii) 'deep sulcus' sign (looks like an inverted diaphragm), and (iv) particularly clear part of the cardiac contour.

Ultrasonography—'stratosphere sign' (absent lung sliding and the sand-like appearance beneath the pleural line is replaced by parallel lines), absence of lung pulsing (transmission of cardiac pulse to the pleural line), absence of B lines, and presence of a lung point.

CT scan—very sensitive and may be useful in difficult situations, e.g. ARDS, and to direct drainage of a localized pneumothorax.

Management

1. Increase FiO_2 if hypoxaemic.
2. If life-threatening with circulatory collapse, aspirate air on affected side with a needle, followed by formal drain insertion.
3. Repeated needle aspiration may be sufficient in spontaneously breathing patients without respiratory failure; this is not generally recommended if the patient is ventilated.
4. Chest drain insertion. The usual site is in the mid-axillary line in the fifth intercostal space with local anaesthetic infiltration prior. Ultrasound or CT guidance may facilitate placement if localized due to surrounding lung fibrosis. Thoracostomy, e.g. Seldinger, tubes are often inserted; however, 14 Fr pigtail catheters (or smaller) can be used for simple pneumothorax. The drain tip should be directed apically.
5. Once inserted, attach drain to an underwater seal (or Heimlich valve). Ensure air-tight connections and tube well secured to the chest wall.
6. If the lung does not fully re-expand then apply low pressure suction (<2 kPa) to the drain. Resolution will be quicker if the patient can be extubated.

7. Drains may be sequentially removed if not swinging/bubbling for ≥1 days. They should not be clamped beforehand. Ensure after removal the entry site is well covered and no air leak is present.

A small pneumothorax (<2 cm width on chest X-ray for spontaneous pneumothorax, <1 cm for secondary pneumothorax) may be left undrained but drain promptly if cardiorespiratory deterioration occurs. Consider need for drainage if transferring patients between hospitals, especially by air.

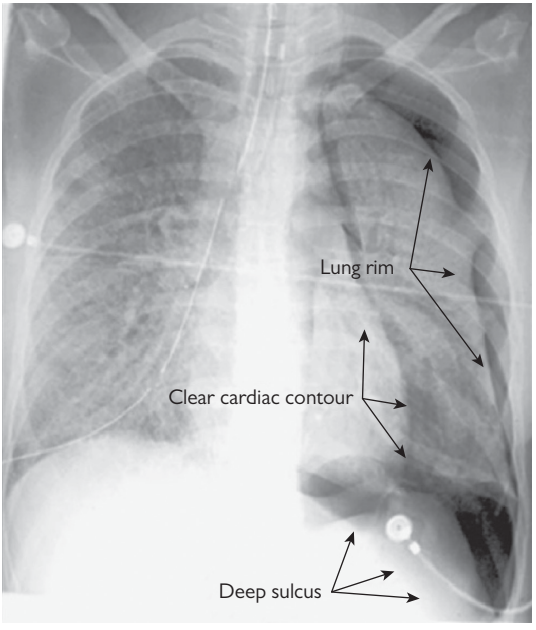

Fig. 22.1 Chest X-ray appearance of pneumothorax.

Bronchopleural fistula

Denoted by continual drainage of air. Usually responds to conservative treatment with continual application of 2–5 kPa negative pressure. It may take weeks to resolve. For severe leak and/or compromised ventilation, high-frequency jet ventilation and/or a double-lumen endobronchial tube may be considered. Surgical intervention is occasionally necessary.

Further reading

Kulvatunyou N, Erickson L, Vijayasekaran A, et al. 2014. 'Randomized clinical trial of pigtail catheter versus chest tube in injured patients with uncomplicated traumatic pneumothorax'. *Br J Surg* 101: pp17–22. doi: 10.1002/bjs.9377

➔ See Chest drain insertion, p92; Respiratory imaging, p178; Dyspnoea, p366; Respiratory failure, p370.

Haemothorax

Usually secondary to chest trauma or following a procedure, e.g. cardiac surgery, chest drain insertion, central venous catheter insertion. Spontaneous haemothorax is rare, even in patients with clotting disorders.

Clinical features

- Stony dullness.
- Decreased breath sounds.
- Hypovolaemia and deterioration in gas exchange (if large).

Diagnosis

- Erect chest X-ray—blunting of hemidiaphragm and progressive loss of basal lung field.
- Supine chest X-ray—increased opacity of affected hemithorax plus decreased clarity of cardiac contour on that side.
- Large-bore needle aspiration to confirm presence of blood. A small-bore needle may be unable to aspirate a haemothorax if it has clotted.

Management

1. If small, observe with serial X-rays and monitor for signs of cardiorespiratory deterioration.
2. Correct coagulopathy with fresh frozen plasma, platelets or other blood products as indicated.
3. Ensure cross-matched blood is available for urgent transfusion if necessary.
4. If significant in size or patient becomes symptomatic, insert large-bore chest drain, e.g. size 28 Fr, ideally with ultrasound guidance. The drain should be directed posteroinferiorly towards the dependent area of lung and placed on 5 kPa suction.
5. Contact thoracic surgery for possible operative repair if drainage exceeds 1 L or >200 mL/h for 3–4 h despite correcting any coagulopathy.
6. Drains inserted for a haemothorax may be removed after 1–2 days if no further bleeding occurs.

Perforation of an intercostal vessel during chest drain insertion may cause considerable bleeding into the pleura. If deep tension sutures around the chest drain fail to stem blood loss, remove the chest drain and insert a Foley urethral catheter through the hole. Inflate the balloon and apply traction on the catheter to tamponade the bleeding vessel. If these measures fail, contact a thoracic surgeon.

Further reading

➔ See Chest drain insertion, p92; Coagulants & antifibrinolytics, p340; Bleeding disorders—causes & diagnosis, p494; Multiple trauma—initial management, p628.

Haemoptysis

May be a presenting feature of a patient admitted to critical care, or may result from critical illness and its treatment. Likely to disrupt gas exchange before hypovolaemia is life-threatening.

Causes

Massive haemoptysis

- Disruption of a bronchial artery by acute inflammation or invasion (e.g. neoplasm, trauma, cavitating TB, bronchiectasis, lung abscess and aspergilloma).
- Rupture of arteriovenous malformations and bronchovascular fistulae.
- Pulmonary infarction secondary to prolonged pulmonary artery catheter wedging or pulmonary artery rupture.

Minor haemoptysis

- Intrapulmonary inflammation (e.g. anti-glomerular basement membrane disease) or infarction (e.g. PE).
- ET tube trauma (e.g. mucosal erosion, balloon necrosis, trauma from the tube tip, trauma to a tracheostomy stoma, trauma from suction catheters).
- Tissue breakdown in critically ill patients (e.g. tissue hypoperfusion, coagulopathy, poor nutritional state, sepsis, and hypoxaemia).

Investigation and assessment

- Assess cardiorespiratory function and monitor closely. Massive haemoptysis will require resuscitation and urgent intubation.
- Chest X-ray may identify a cavitating lesion. Lower lobe shadowing on a chest X-ray may be the result of overspill of blood from elsewhere in the bronchial tree. CT angiography can identify location and underlying cause, and a bleeding point while bleeding is active.
- Early bronchoscopy may identify the source of haemoptysis, although only while bleeding is active. Blood in multiple bronchial orifices may be confusing but saline lavage may make the source visible.
- Rigid bronchoscopy is useful in massive haemoptysis allowing oxygenation and wide-bore suctioning.

Management

- Basic resuscitation (high FiO_2 to maintain adequate oxygenation, ET intubation, and blood transfusion) is needed for cardiorespiratory compromise.
- Correction of coagulopathy is a priority.
- Bronchoscopy allows direct instillation of 1 in 200,000 epinephrine (or iced saline) if the source of haemorrhage can be identified. Specialist techniques include topical haemostatic tamponade using oxidized regenerated cellulose (ORC), injecting fibrin-thrombin solutions, tranexamic acid, or (sub-)segmental endobronchial tamponade with a balloon catheter.

- In severe haemorrhage from one lung, a double-lumen ET tube or bronchial blocker may prevent overspill while definitive treatment is organized. Such tubes, however, carry risks and may be difficult to place.
- Definitive treatment may include bronchial artery embolization by interventional radiology or surgical resection.

Further reading

➔ See Positive end-expiratory pressure—principles, p70; Continuous positive airway pressure (CPAP), p76; Fibreoptic bronchoscopy, p96; Coagulation monitoring, p252.

Inhalation injury

Causes include smoke, steam, noxious gases, and aspiration of gastric contents.

Clinical features

- Dyspnoea, coughing.
- Stridor (if upper airway obstruction).
- Bronchospasm.
- Signs of lung/lobar collapse (especially with aspiration).
- Signs of respiratory failure.
- Cherry-red skin colour (carbon monoxide).
- Agitation, coma.
- ARDS (late).

General principles of management

1. High-flow, high-concentration O_2, targeting SaO_2 of 92–98%.
2. Early intubation if upper airway is compromised or threatened.
3. Early bronchoscopy if inhalation of soot, debris, vomit suspected.

Specific conditions

Smoke inhalation

- Smoke rarely causes thermal injury beyond the major bronchi as it has a low specific heat content. However, soot is a major irritant to the upper airways and can produce very rapid and marked inflammation.
- Urgent laryngoscopy should be performed if soot is present in the nares, mouth, or pharynx.
- If soot is seen or the larynx appears inflamed, perform early ET intubation. As the upper airway can obstruct quickly, early intubation should be performed rather than as an emergency procedure where it may prove impossible. Intubation should be performed if any concern, before intra- or inter-hospital transfer.
- After intubation, perform urgent bronchoscopy with bronchial toilet using warmed 0.9% saline to remove as much soot as possible.
- Commence benzylpenicillin 1.2 g qds IV.
- Specific treatment for poisons contained within smoke (e.g. carbon monoxide, cyanide).

Steam inhalation

- Consider early/prophylactic intubation.
- Steam has a much higher heat content than smoke and can cause injury to the whole respiratory tract.
- Consider early bronchoscopy and lavage with cool 0.9% saline.

Aspiration of gastric contents

- Early bronchoscopy and physiotherapy to remove as much particulate and liquid matter as possible.
- Antibiotics are not generally indicated. If concerns about secondary infection, treat with either cefuroxime/cefotaxime plus metronidazole, or clindamycin for 3–5 days.
- Corticosteroid therapy has no proven benefit.

Further reading

See Fibreoptic bronchoscopy, p96; Antibacterials, p344; Basic resuscitation, p358; Inhaled poisons, p570; Burns—airway & circulatory management, p638; Burns—general management, p640.

Chapter 23

Cardiovascular disorders

Hypotension

Blood pressure (BP) is the product of blood flow (cardiac output (CO)) and vascular resistance. An adequate perfusion pressure is needed for normal organ functioning. 'Normal' BP varies between patients so individual titration is necessary. 'Normal' does not, however, guarantee adequate organ perfusion. Circulatory support should aim to achieve both adequate blood flow and pressure. Prolonged hypotension should be avoided to decrease the risk of organ dysfunction, e.g. acute kidney injury (AKI).

Assessment of hypotension

Determine the cause, e.g. hypovolaemia, haemorrhage, sepsis, myocardial infarction, arrhythmias, pulmonary embolus, tension pneumothorax, poisoning. Sedative agents are commonly responsible in patients in the intensive care unit (ICU). Hypotension requires correction if there are signs of poor tissue perfusion (e.g. oliguria, confusion, altered consciousness, cool peripheries, metabolic acidosis). This will usually be at mean arterial pressure (MAP) values <60 mmHg (or higher if a history of chronic hypertension). MAP is generally targeted in patients with invasive arterial line monitoring, and systolic BP with non-invasive techniques as this is more reliably measured.

Initial treatment of hypotension

Treat the cause as appropriate. Most cases require fluid as first-line management to restore an adequate circulating volume. For massive haemorrhage use local protocols to replace blood and blood products and intervention(s) to stop the losses. Exceptions include acute heart failure, arrhythmias, tamponade, and pneumothorax, though fluid may still be indicated if hypovolaemia coexists. This may be suggested by assessing BP, heart rate ± stroke volume response to a straight leg raise.

For patients in extremis (e.g. cardiac arrest, profound hypotension) institute advanced life support (ALS) to restore pressure and output promptly.

For low BP states refractory to fluid bolus(es) or straight leg raise, commence a vasopressor, either by low-dose bolus (repeated as needed) and/or continuous infusion, to obtain an adequate perfusion pressure. Do not elevate BP excessively as this may compromise CO and thus tissue perfusion. α-adrenergic agonists (e.g. norepinephrine, metaraminol, ephedrine, phenylephrine) can be given peripherally by small, repeated boluses or continuous infusion in the short term. If a longer-term infusion is required, a central venous catheter should ideally be inserted for administration.

Vasopressors should not, however, be viewed as a panacea if the patient remains hypovolaemic. Conversely, fluid overload should be avoided. Such patients need CO monitoring or imaging to assess volaemic status.

Mild hypotension in the absence of organ compromise may be left untreated but closely monitored.

Pharmacological treatment

If hypotension persists after restoring an adequate circulating volume and correcting other causes (e.g. hypoxaemia, pneumothorax, arrhythmia), use:

- An inotropic agent if low CO, e.g. heart failure.
- A vasopressor if peripherally vasodilated and stroke volume adequate.

See Table 23.1 for drug dosages. Ideally, such patients should have CO monitored as titrating therapy against BP alone may cause inappropriate

vasoconstriction and reduced CO. Titrate drugs against stroke volume as tachycardia may maintain a seemingly adequate CO. Inotropes such as dobutamine, phosphodiesterase (PDE) inhibitors (e.g. milrinone), and levosimendan (especially with a loading dose) can cause excessive vasodilatation and hypotension.

Once stroke volume has been corrected, vasoactive agents should be titrated against MAP. In many patients, a MAP of 60–65 mmHg is adequate. However, the target MAP may need to be adjusted; younger patients may tolerate lower levels, though chronic hypertensives may require a higher MAP target. Titrate to end-organ function (urine output, cerebral function). Vasopressors may reduce CO if given in excess or to patients with poor ventricular function. This effect should be monitored and corrected by adjustment of dose. Non-adrenergic agents such as vasopressin, its synthetic analogue, terlipressin, or angiotensin may also be used for high-output, catecholamine-resistant, vasodilatory shock. Care should be taken to avoid hypovolaemia, excessive peripheral constriction, or impairment of organ perfusion with all vasopressor agents.

Table 23.1 Drug dosages in hypotension

Epinephrine	Infusion starting from 0.05 μg/kg/min
Dobutamine	Infusion from 2.5–25 μg/kg/min
Ephedrine	3–6 mg IV bolus, repeat as required
Levosimendan	Loading 6–12 μg/kg over 10 min, followed by infusion 0.05–0.2 μg/kg/min
Metaraminol	0.5–1 mg IV bolus, infusion 0.5–10 mg/h
Norepinephrine	Infusion starting from 0.05 μg/kg/min
Phenylephrine	100–500 μg slow IV, infusion up to 180 μg/min
Vasopressin	0.01–0.04 U/min
Terlipressin	0.25–0.5 mg bolus, repeated at 30 min intervals as necessary to maximum 2 mg

Further reading

Annane D, Vignon P, Renault A, et al. for the CATS Study Group. 2007. 'Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial'. *Lancet* 370: pp676–84. doi: 10.1016/S0140-6736(07)61344-0

Myburgh J, Higgins A, Jovanovska A, et al. for the CAT Study investigators. 2008. 'A comparison of epinephrine and norepinephrine in critically ill patients'. *Intensive Care Med* 34: pp2226–34. doi: 10.1007/s00134-008-1219-0

Asfar P, Meziani F, Harnel J-F, et al. for the SEPSISPAM Investigators. 2014. 'High versus low blood-pressure target in patients with septic shock'. *N Engl J Med* 370: pp1583–93. doi: 10.1056/NEJMoa1312173

See Intra-aortic balloon pump, p108; Blood pressure monitoring, p186; Arterial cannulation, p188; Inotropes, p286; Vasopressors, p290; Basic resuscitation, p358; Cardiac arrest, p360; Fluid challenge, p362.

Hypertension

Often defined as diastolic BP ≥80 or systolic BP ≥130 mmHg.

Causes of acute hypertension in the ICU

- Idiopathic/essential.
- Agitation/pain.
- Excessive vasoconstriction, e.g. cold, vasopressor drugs.
- Head injury, cerebrovascular accident, raised intracranial pressure.
- Drug related, e.g. serotonin syndrome, drug withdrawal.
- Dissecting aneurysm.
- Vasculitis, thrombotic thrombocytopenic purpura.
- (Pre-)eclampsia.
- Endocrine, e.g. thyroid crisis, pheochromocytoma (rare).
- Renal failure, renal artery stenosis (rare).
- Spurious—underdamped transducer; transducer below level of heart.

Urgencies and emergencies

- Hypertensive urgencies are situations with marked elevations in BP but without progressive organ dysfunction. Patients often present with headache, epistaxis, and/or faintness.
- Hypertensive emergencies are situations with severe elevations in BP (>180/120 mmHg) in patients with impending or progressive organ dysfunction, e.g. affecting brain, heart.

Principles of management

1. Adequate monitoring, e.g. invasive (or frequent non-invasive) BP, electrocardiogram (ECG), urine output, neuromonitoring, ± CO.
2. Treat pain, hypovolaemia, hypothermia, and agitation.
3. Consider specific treatments, e.g. for pheochromocytoma, thyroid crisis, aortic dissection, inflammatory vasculitis.
4. For urgencies, aim to reduce BP to target levels over 24 h.
5. Avoid excessive sudden drop in BP to reduce risk of renal, cerebral, or coronary ischaemia.
6. For emergencies, consider initial target of <25% reduction in MAP within 1 h, then reduction to ~160/100 mmHg over 4–6 h, with stabilization over the next 24–48 h. Exceptions include:
   - specific conditions such as acute aortic dissection, severe pre-eclampsia/eclampsia, and pheochromocytoma crisis. Aim for systolic BP <140 mmHg during first hour (<120 mmHg for aortic dissection)
   - acute pulmonary oedema where heart function may improve with further BP reduction
   - for intracerebral haemorrhage only reduce systolic BP if >220 mmHg within 6 h of symptom onset
   - for ischaemic stroke aim <185/110 mmHg pre-thrombolysis.
7. For emergencies, consider initially an IV infusion of glyceryl trinitrate (GTN), short-acting β-blocker (e.g. esmolol), or combined α/β-blocker (labetalol) titrated to effect. Other options include nitroprusside, hydralazine (IV or IM). See Table 23.2 for drug dosages.
8. Longer-term oral treatment (e.g. β-blocker, calcium channel blocker, angiotensin-converting enzyme (ACE) inhibitor) should be instituted once stabilized.

Table 23.2 Drug dosages in hypertension

GTN	0.5–20 mg/h
Sodium nitroprusside	0.5–1.5 µg/kg/min, increased to max 8 µg/kg/min
Labetalol	50 mg IV over 1 min repeated every 5 min to maximum 200 mg
Metoprolol	1.25–5 mg slow IV or infused to max 0.1 mg/kg/h
Esmolol	50–300 µg/kg/min (can give 0.5–1 mg/kg bolus prior)
Hydralazine	5–10 mg slow IV followed by 50–150 µg/min

Indications for acute treatment

- For emergencies, controlled reduction of BP as indicated above. A staged approach is advised as rapid reductions in BP may adversely affect organ perfusion, leading to further deterioration.
- Hypertension after a cerebrovascular event is common, but should not be treated rapidly unless very high, e.g. systolic BP >220 mmHg.
- For conditions with raised intracranial pressure, a cerebral perfusion pressure >60–70 mmHg is usually targeted.

Hypertensive crisis

The patient is symptomatic (e.g. increasing drowsiness, seizures, acute retinopathy, hypertensive encephalopathy, cerebrovascular event, myocardial infarction, pulmonary oedema) in the presence of an elevated BP. Diastolic BP usually exceeds 120–130 mmHg and mean BP >140–150 mmHg, although encephalopathy can occur at lower pressures.

Further reading

Anderson C, Heeley E, Huang Y, et al. for the INTERACT2 Investigators. 2013. 'Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage'. *N Engl J Med* 368: pp2355–65. doi: 10.1056/NEJMoa1214609

He J, Zhang Y, Xu T, et al. for the CATIS investigators. 2014. 'Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial'. *JAMA* 311: pp479–89. doi: 10.1001/jama.2013.282543

See Blood pressure monitoring, p186; Intracranial pressure monitoring, p224; Vasodilators & antihypertensives, p288; Intracranial haemorrhage, p478; Subarachnoid haemorrhage, p480; Stroke, p482; Pre-eclampsia & eclampsia, p686.

Tachyarrhythmias

If pulseless and signs of life are absent, follow ALS guidelines. If BP is very low with poor perfusion, consider urgent direct current (DC) cardioversion (synchronized if QRS complex visible). Otherwise, initial management includes correction of hypoxaemia, potassium (to ensure levels of 4.5–5.5 mmol/L) and magnesium (targeting plasma levels of 1.5–2 mmol/L).

Causes of tachyarrhythmias

Where possible, treat the cause, e.g. hypovolaemia, hypotension (may be due to the arrhythmia), hypoxaemia, myocardial infarction, pain, anaemia, hypercapnia, anxiety, thyrotoxicosis, drug toxicity.

Diagnosis

Broad complex tachycardia

Assume ventricular tachycardia (VT) until proved otherwise. Regular complexes with atrioventricular (AV) dissociation (fusion beats, concordance, QRS >140 ms, axis <−30°, capture beats) suggest VT. If no AV dissociation, then arrhythmia is probably supraventricular tachycardia (SVT) with aberrant conduction; adenosine may be used for diagnosis since SVT may respond but VT will not. Irregular broad complexes are probably AF with aberration. Torsades de pointes is a form of VT with a variable axis.

Narrow complex tachycardia

An irregularly irregular rhythm with absence of P waves suggests atrial fibrillation. A regular P-wave rate >150/min often suggests SVT, whereas slower rates may represent sinus tachycardia or atrial flutter with block. P waves are abnormal (flutter waves) in atrial flutter and QRS complexes may be irregular in variable block. Extremely fast SVT may be due to a re-entry pathway with retrograde conduction. In Wolff–Parkinson–White syndrome the re-entry pathway inserts below the bundle of His allowing rapid AV conduction and re-entry tachyarrhythmias. Pre-arrhythmia there may be a short PR interval and delta wave (pre-excitation) on the ECG.

Treatment

Ventricular tachycardia

DC cardioversion is needed if VT results in significant haemodynamic compromise or is refractory to drug treatment. Drug options (Table 23.3) include amiodarone, magnesium, a β-blocker (e.g. metoprolol or esmolol), or flecainide. Overdrive pacing may be used if a pacing wire is *in situ*, pacing the ventricle faster than the arrhythmia and gradually reducing the pacing rate. Torsades de pointes may be exacerbated by antiarrhythmics so magnesium or overdrive pacing are safest. Isoprenaline may also be used.

Supraventricular tachycardia and atrial flutter

Consider carotid sinus massage in patients with low risk of calcified atheromatous carotid deposits. Consider adenosine, amiodarone, magnesium or β-blockers. Verapamil may be used if complexes are narrow (no risk of misdiagnosed VT) although this drug and other AV node blockers should be avoided in re-entry tachycardias. See Table 23.3 for drug dosages.

Atrial fibrillation

Consider cardioversion if onset <48 h, especially if haemodynamic compromise. Drug therapies include β-blockers, amiodarone, calcium channel blockers, and, occasionally, digoxin (Table 23.3).

Table 23.3 Drug dosages and cautions for tachyarrhythmias

Adenosine	3 mg IV as rapid bolus (2 s). If no response in 1–2 min give 6 mg then (if needed) 12 mg
Amiodarone	Loading dose of 300mg over 20–30 min via large-bore peripheral venous cannula or centrally, then continuous infusion up to 15mg/kg/24h in 5% glucose via a central vein. Can be given peripherally over 3–5 min in an emergency. Avoid with other class III agents (e.g. sotalol) since QT interval may be severely prolonged
Metoprolol	Up to 5 mg given at a rate of 1–2 mg/min. Infusion rate of 0.04–0.1 mg/kg/h
Esmolol	Loading dose (if needed) of 500 μg/kg given over 1 min then 50 μg/kg/min for 4 min. If inadequate response after 5 min, reload with 500 μg/kg over 1 min then infuse 100 μg/kg/min for 4 min. Repeat as needed until maximum rate of 300 μg/kg/min
Magnesium	20 mmol $MgSO_4$ over 1–2 h. Can give over 5 min in an emergency
Verapamil	2.5 mg IV slowly. If no response repeat to maximum of 20 mg. An IV infusion of 1–10 mg may be used. Consider pre-treatment with 5–10 mL 10% $CaCl_2$ to prevent hypotension. Avoid verapamil in re-entry tachyarrhythmias since ventricular response may increase. Life-threatening hypotension may occur in misdiagnosed VT. Severe bradycardia with hypotension may occur if the patient has been previously β-blocked
Digoxin	0.5 mg given PO or IV over 10–20 min. Repeat at 4–8 h intervals until loading achieved (assessed by clinical response). Maintenance dose thereafter is 0.0625–0.25 mg/day depending on plasma levels and clinical response

Further reading

➔ See Electrical cardioversion, p102; ECG monitoring, p184; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Antiarrhythmics, p294; Basic resuscitation, p358.

Bradyarrhythmias

Critically ill patients may develop sick sinus syndrome or complete heart block. This may result in transient and often spontaneously reversible bradycardia or be more prolonged and life-threatening. Depending on severity the patient may require close monitoring only, drug therapy, or temporary pacing.

If peripheral pulses are impalpable and signs of life absent, follow ALS guidelines. For asymptomatic bradycardia, treatment may not be required other than close monitoring and correction of any identifiable cause. The exception is higher degrees of heart block occurring after myocardial infarction where pacing may be required.

Causes

Treat the cause where possible, e.g. hypovolaemia, hyperkalaemia, hypotension (may also be due to bradycardia), myocardial infarction, drug toxicity, hypothyroidism, hypopituitarism, and raised intracranial pressure.

Diagnosis

Sinus bradycardia

Slow ventricular rate with normal P waves, normal PR interval and 1:1 AV conduction.

- Heart block.
- Normal P waves, a prolonged PR interval and 1:1 AV conduction suggest first-degree (1°) heart block.
- In second-degree (2°) heart block the ventricles fail to respond to atrial contraction intermittently. This may be associated with regular P waves and an increasing PR interval until ventricular depolarization fails (Mobitz I or Wenckebach) or a normal, non-elongating PR interval with regular failed ventricular depolarization (Mobitz II). In the latter case the AV conduction ratio may be 2:1 or more or variable.
- In third-degree (3°) heart block there is complete AV dissociation with a slow, idioventricular rate.

Absent P-wave bradycardia

Absent P waves may represent slow atrial fibrillation or sinoatrial dysfunction where there will be a slow, idioventricular rate.

Treatment

Hypoxaemia must be corrected in all symptomatic bradycardias. First-line drug treatment is usually atropine 0.3 mg or glycopyrronium bromide (glycopyrrolate) 200 µg IV, repeat as required. Failure to respond to drug treatment requires temporary pacing. This may be accomplished rapidly with an external system if there is haemodynamic compromise, or by transvenous placement. Higher degrees of heart block after myocardial infarction will usually require permanent pacing.

Indications for temporary pacing

- Persistent symptomatic bradycardia.
- Blackouts associated with:
  - 3° heart block
  - 2° heart block (Mobitz II)

  - right bundle branch block (RBBB) and left posterior hemiblock.
- Cardiovascular collapse.
- Inferior myocardial infarction with symptomatic 3° heart block.
- Anterior myocardial infarction with:
  - 3° heart block
  - RBBB and left posterior hemiblock
  - alternating RBBB and left bundle branch block (LBBB).

Further reading

See Temporary pacing, p104; ECG monitoring, p184; Chronotropes, p296; Basic resuscitation, p358.

Acute coronary syndrome—diagnosis

Symptoms

Ischaemic occlusion of coronary arteries can result in precordial pressing or crushing pain, ± radiation to jaw, neck, or arms. The sedated, ventilated patient will not usually complain of pain, but may show discomfort, e.g. tachycardia, sweating, hypertension, pallor. Regularly scrutinize the ECG for ST-segment and/or T-wave changes.

A spectrum of severity is present, ranging from stable angina to myocardial infarction. Anginal attacks may have recently increased in frequency and/or severity, persist longer, respond less well to nitrates, and occur at rest or after minimal exertion.

Pathophysiology

- Myocardial oxygen supply–demand imbalance due to either:
  - occlusive coronary artery atheroma ± disruption of plaque (type I)
  - a non-atheromatous pathophysiological mechanism (type II), e.g. induced by tachyarrhythmia, sepsis, trauma, surgery, drugs. Coronary flow to the left ventricle only occurs during diastole. As heart rate increases, coronary flow falls as the diastole shortens, potentially triggering type II ischaemia. Non-occlusive coronary atheroma may also limit maximal coronary flow
- Rarely, coronary artery vasospasm (Prinzmetal angina) or dissection.
- Vasopressor drugs may compromise myocardial perfusion by further constricting already stenosed coronary arteries or microcirculation.
- Vasodilator drugs may compromise myocardial perfusion by 'coronary steal' where blood flow is re-distributed away from stenosed vessels.

Diagnosis

Myocardial ischaemia

- Symptoms, especially chest pain, but may be non-specific, e.g. sweating, nausea, faintness.
- Dynamic ECG changes: raised/depressed ST segment, inverted T wave.
- Rise in high-sensitivity troponin above the myocardial infarct threshold at presentation (repeated 30–180 min later, if the first is equivocal).
- Regional wall motion abnormalities may be seen on echocardiography.

Type I myocardial infarction

- Rise and/or fall of high-sensitivity cardiac-specific troponin (I or T) measured at presentation and (if needed) 30–180 min later, with at least one value >99th centile of the assay's upper reference limit plus evidence of myocardial ischaemia with one or more of:
  - symptoms of myocardial ischaemia
  - new ST–T changes or LBBB on ECG
  - pathological Q waves on ECG
  - new loss of myocardium or new regional wall motion abnormality
  - intracoronary atherothrombotic occlusion seen at angiography or autopsy.

Type II myocardial injury

- An elevated troponin is commonplace in ICU patients (e.g. sepsis, pulmonary embolus, myocarditis, severe hypotension). It is indicative of

myocardial injury and prognosticates for poor outcomes. Troponin may also be elevated with renal dysfunction due to failure to excrete.

- Subarachnoid haemorrhage and emotional stress can lead to Takotsubo cardiomyopathy with troponin elevation and severe, acute left ventricular dysfunction.

Further reading

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See ECG monitoring, p184; Echocardiography—use & indications, p214; Cardiac function & injury, p242.

Acute coronary syndrome—management

A different strategy may be needed if the acute coronary syndrome is the primary cause for ICU admission or complicates a pre-existing acute illness or elective surgery. Discuss an individualized treatment plan with cardiology, including suitability for angioplasty, thrombolysis, or anticoagulation, and insertion of mechanical support devices taking into account potential risks and benefits.

General management

- Ensure adequate oxygenation (SaO_2 94–98%).
- Monitor ECG, vital signs, blood gases; consider early echocardiography and advanced haemodynamic monitoring.
- Correct hypo- and hypertension, arrhythmias, tissue hypoperfusion, electrolyte and glucose abnormalities.
- An opiate ± antiemetic may be needed if pain persists.
- If symptoms are severe and/or persisting, consider bed rest and postponing any ventilator weaning.
- Do not delay arterial or central venous cannulation if clinically indicated. An experienced operator should perform procedures to minimize the risk of bleeding.

Directed treatment in consultation with cardiology

- See Table 23.4 for drug dosages. Unless contraindicated, give:
  - prompt aspirin
  - nitrate (as sublingual spray or continuous infusion)
  - β-blocker, e.g. metoprolol, bisoprolol or a calcium channel blocker, e.g. diltiazem.
- Desirability/timing of percutaneous intervention (PCI) if symptomatic <12 h (or >12 h and symptoms/ST elevation persists).
- Low-molecular-weight heparin (e.g. enoxaparin) while hospitalized or until PCI.
- Use of platelet $P2Y_{12}$ inhibitor (e.g. prasugrel, ticagrelor, clopidogrel) or factor Xa neutralization (fondaparinux) balanced against bleeding risk.
- A glycoprotein IIb/IIIa inhibitor, e.g. eptifibatide, tirofiban, in addition to a platelet $P2Y_{12}$ inhibitor, may be suggested if at intermediate-to high risk of myocardial infarction or death, and angioplasty is likely within 96 h.
- Utility of urgent intervention if symptoms or ST-segment changes persist despite optimal medical intervention.
- Use of IV thrombolytic agent for ST-segment elevation myocardial infarction (STEMI) or high-risk non-STEMI (NSTEMI) if interventional procedure unavailable or significantly delayed.
- Other medication, e.g. high-intensity statin, ACE inhibitor/A2R blocker.

Table 23.4 Drug dosages in acute coronary syndrome

Alteplase	15 mg IV bolus, then 0.75 mg/kg over 30 min, then 0.5 mg/kg over 1 h to maximal dose of 100 mg, followed by heparin for 24–48 h
Aspirin	300 mg PO stat
Clopidogrel	300–600 mg PO loading then 75 mg PO od
Ticagrelor	180 mg PO loading then 90 mg bd
Prasugrel	60 mg PO loading then 10 mg daily
Bivalirudin	0.75 mg/kg bolus then 1.75 mg/kg/h
Enoxaparin	0.5 mg/kg IV bolus
GTN	10–200 μg/min IV or 0.5–1 mg SL
GTN spray	0.4–0.8 mg SL
β-blocker, e.g. bisoprolol	5 mg PO od, increasing to 10–20 mg od
Diltiazem	60 mg PO tds

Identification and management of complications

- Cardiopulmonary arrest—cardiopulmonary resuscitation.
- Pericarditis—consider non-steroidal anti-inflammatory.
- Heart failure and/or cardiogenic shock—directed medical management with consideration of PCI or invasive support devices (e.g. intra-aortic balloon counterpulsation, venoarterial extracorporeal membrane oxygenation (ECMO)).
- For hypotension, consider hypovolaemia, especially after diuretics.
- Tachyarrhythmia—antiarrhythmics; synchronized DC cardioversion, maintain plasma K^+ >4.5 mmol/L and Mg^{2+} >0.8 mmol/L.
- Bradyarrhythmia—chronotrope; ± temporary (or permanent) pacing.
- Valve dysfunction (usually mitral)—heart failure management; surgery.
- Pericardial tamponade (rare)—pericardial aspiration, consider surgery.
- Ventricular septal defect (unusual, often presents 2–5 days later)—heart failure management; consider surgery.
- Manage complications of therapy, e.g. arrhythmias, bleeding, hypotension, anaphylactoid reaction.

Further reading

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➲ See Coronary revascularization techniques, p112; Vasodilators & antihypertensives, p288; Anticoagulants—parenteral, p334; Thrombolytics, p338; Basic resuscitation, p358; Cardiac arrest, p360; Hypotension, p408; Tachyarrhythmias, p412; Bradyarrhythmias, p414; Acute coronary syndrome—diagnosis, p416; Heart failure—assessment, p420; Decompensated heart failure—management, p422.

Heart failure—assessment

Impaired ability of the heart to supply adequate oxygen and nutrients to meet the demands of the body's metabolizing tissues, in the presence of an adequate circulating volume.

Major causes

- Myocardial infarction/ischaemia.
- Pulmonary embolus.
- Drugs, e.g. β-blockers, cytotoxics, cocaine.
- Tachy- or bradyarrhythmias.
- Hypertensive crisis.
- Sepsis.
- Anatomical, e.g. valve dysfunction/stenosis, septal defect.
- Cardiomyopathy/myocarditis/stress-induced (Takotsubo).
- Pericardial tamponade.

Clinical features

Decreased forward flow leading to poor tissue perfusion

- Muscle fatigue leading ultimately to hypercapnia and collapse.
- Confusion, agitation, drowsiness, coma.
- Oliguria.
- Increasing metabolic acidosis, arterial hypoxaemia, and dyspnoea.

Increased venous congestion secondary to right heart failure

- Peripheral oedema.
- Hepatic congestion.
- Increased renal vein pressure compromising renal function.
- Splanchnic ischaemia.
- Raised intracranial pressure.
- Peripheral oedema implies total body salt and water retention but not necessarily intravascular fluid overload.

Increased pulmonary hydrostatic pressure from left heart failure

- Pulmonary oedema, dyspnoea.
- Hypoxaemia.

Investigations

Table 23.5 lists common investigations in the assessment of heart failure.

Table 23.5 Investigations to consider in heart failure

Test	Diagnosis
ECG	Myocardial ischaemia/infarction, arrhythmias
Chest X-ray	With left heart failure: pulmonary oedema (interstitial perihilar ('bat's wing') shadowing, upper lobe blood diversion, Kerley B lines, pleural effusion) ± cardiomegaly
Flow monitoring	Low CO and stroke volume, raised PAWP (with left heart failure), raised right atrial pressure (with right heart failure), V waves on central venous pressure trace with tricuspid regurgitation
Blood tests	Hypoxaemia, hypercapnia, metabolic acidosis, hyperlactataemia, low (mixed or central venous) O_2 saturation, raised cardiac enzymes, high-sensitivity troponin (marker of cardiac injury), B-type natriuretic peptide (marker of ventricular stretch and dysfunction), glucose; (if indicated) thyroid function, toxicology
Echocardiography	Impaired systolic and/or diastolic dysfunction, ventricular wall motion abnormalities, pericardial effusion, valve stenosis or incompetence, intracardiac shunts
Chest ultrasound	Pulmonary oedema, pleural effusion
Angiography	Coronary vessel patency, intracardiac shunts, valve stenosis or incompetence

Further reading

See Respiratory imaging, p178; ECG monitoring, p184; Blood pressure monitoring, p186; Central venous catheter—use, p192; Cardiac output—central thermodilution, p200; Cardiac output—peripheral thermodilution, p202; Cardiac output—indicator dilution, p204; Cardiac output—Doppler ultrasound, p206; Cardiac output—pulse contour analysis, p208; Cardiac output—other techniques, p210; Echocardiography—use & indications, p214; Tissue perfusion monitoring, p220; Cardiac function & injury, p242; Dyspnoea, p366; Hypotension, p408; Tachyarrhythmias, p412; Bradyarrhythmias, p414; Acute coronary syndrome—diagnosis, p416; Acute coronary syndrome—management, p418; Decompensated heart failure—management, p422.

Decompensated heart failure—management

Basic measures

- Determine and treat underlying cause, e.g. antiarrhythmic.
- Oxygen to maintain pulse oximetry oxygen saturation (SpO_2) at 94–98%.
- GTN spray, then IV nitrate infusion titrated rapidly until good clinical effect. Hypotension at low dosage suggests ventricular underfilling, e.g. hypovolaemia, tamponade, mitral stenosis, pulmonary embolus.
- If patient agitated or in pain, give (dia)morphine 2.5 mg IV prn.
- Consider early non-invasive ventilation (NIV) to reduce work of breathing and to improve oxygenation, left ventricular work, and wall tension. CO often improves. However, do not delay intubation, if appropriate, if patient is in extremis or failing to improve with NIV support.
- Furosemide is often not needed initially unless intravascular fluid overload is present. Initial symptomatic relief is provided by its prompt vasodilating action. The subsequent diuresis may result in marked hypovolaemia leading to compensatory vasoconstriction, increased cardiac work, and worsening myocardial function. Diuretics may be indicated for acute-on-chronic failure, especially if the patient is on long-term diuretics, but should not be used if hypovolaemic. If furosemide is needed, start at low dose (e.g. 10–20 mg) then reassess.

Directed management

- Adequate monitoring and investigation (echo ± computed tomography ± angiography).
- Avoid hypovolaemia. Cautious fluid challenge as needed.
- If vasoconstriction persists (high BP, low CO), titrate nitrate infusion to optimize stroke volume. Accept lower BP provided end organs remain perfused. If hypovolaemia suspected (i.e. stroke volume falls), give fluid challenges to re-optimize stroke volume.
- Within 24 h of nitrate infusion consider ACE inhibition, initially at a low dose, but rapidly increase to appropriate long-term doses.
- Give inotropes (e.g. epinephrine, dobutamine, milrinone) if tissue hypoperfusion persists despite optimal fluid loading and nitrate dosing, or severe hypotension is present. Epinephrine may sometimes cause excessive constriction, dobutamine and milrinone may excessively vasodilate. The calcium sensitizer levosimendan increases CO by improving contractile efficiency but, especially if a bolus loading dose is given, can cause hypotension.
- High-dose glucose–insulin–potassium (GIK) is recommended for drug overdose but may also have utility in failure due to other causes.
- Intra-aortic balloon counterpulsation augments CO, reduces cardiac work, and improves coronary artery perfusion. May be used as a bridge to coronary revascularization.
- Ventricular assist devices (VADs) or venoarterial ECMO may be considered in some cases.
- Angioplasty or surgical revascularization are beneficial if performed early after myocardial infarct. Surgery may be necessary for mechanical defects, e.g. acute mitral regurgitation.

Table 23.6 Drug dosages in heart failure

GTN	2–20 mg/h IV or 0.4–0.8 mg by SL spray
Isosorbide dinitrate	2–20 mg/h IV
Sodium nitroprusside	20–400 µg/min IV
Ramipril	1.25 mg PO test dose rising to 10 mg od
Enalapril	2.5 mg PO test dose rising to 40 mg od
Epinephrine	Infusion starting from 0.05 µg/kg/min
Dobutamine	2.5–25 µg/kg/min IV
Milrinone	50 µg/kg IV loading dose over 10 min then infusion from 0.375–0.75 µg/kg/min
Enoximone	0.5–1 mg/kg IV loading dose over 10 min then infusion from 5–20 µg/kg/min
Levosimendan	12–24 µg/kg over 10 min (if rapid effect needed) followed by 0.1 µg/kg/min for 24 h
Diamorphine	2.5 mg IV. Repeat every 5 min as necessary
Furosemide	10–20 mg IV bolus. Repeat as needed

Treatment end-points

- Symptomatic relief.
- Adequate but not excessive BP and CO to maintain organ perfusion (e.g. no oliguria, confusion, dyspnoea, or metabolic acidosis). Avoid elevating BP if organs are adequately perfused.
- Mixed (or central) venous oxygen saturation ≥60%. Avoid excessive inotrope as myocardial O_2 demand will be increased.
- B-type natriuretic peptide levels may be targeted for longer-term control.

Further reading

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See Oxygen therapy, p40; Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Positive end-expiratory pressure- principles, p70; Positive end expiratory pressure—management, p72; Continuous positive airway pressure (CPAP), p76; Intra-aortic balloon pump, p108; Ventricular assist device, p110; Inotropes, p286; Vasodilators & antihypertensives, p288; Diuretics, p292; Heart failure—assessment, p420.

Chapter 24

Renal disorders

Oliguria

Defined as a urine output <0.5 mL/kg/h and caused by:

- Pre-renal (renal hypoperfusion): hypovolaemia, low cardiac output, hypotension, inadequate renal blood flow.
- Intrinsic renal failure, e.g. acute tubular necrosis (ATN) (ischaemia, drugs, or toxins), glomerulonephritis, tubulointerstitial nephritis.
- Post-renal: urinary tract obstruction, e.g. blocked catheter, ureteric trauma, prostatism, raised intra-abdominal pressure, blood clot, bladder tumour, stone disease, pelvic pathology/malignancy compressing ureters.

Postoperative oliguria (likely due to excess antidiuretic hormone) may persist despite adequate fluid loading, cardiac output, and blood pressure (BP). This usually self-corrects with time. Monitor fluid balance carefully to avoid overload.

Hypovolaemia

Correct hypovolaemia by fluid challenge(s). Oliguria in hypovolaemic patients may be in part physiological (appropriate conservation of fluid) and in part due to reduced renal perfusion.

Inadequate renal blood flow and/or pressure

If cardiac output remains low, despite correcting hypovolaemia, and oliguria persists, vasodilators and/or inotropes may be needed.

If BP remains low despite an adequate cardiac output, vasopressors may be needed to achieve an adequate renal perfusion pressure aiming for a mean BP ≥60 mmHg. In those with pre-existing chronic hypertension, a higher BP target may be necessary. This target should be achieved promptly to avoid established ATN with oligo-anuric renal failure.

Urinary tract obstruction

Exclude a full bladder by palpation or bedside ultrasound scan. Ensure a patent catheter is present. If obstruction is due to blood clot the bladder should be irrigated. A urological opinion should be sought for hydronephrosis, strictures, or complex catheterization. If obstruction is suspected more proximally in the renal tract, perform renal imaging to diagnose hydronephrosis and/or hydroureter and guide optimal intervention (e.g. nephrostomies, stents). This will be urgent with an obstructed, infected system. Raised intra-abdominal pressure may cause oliguria by impeding renal venous drainage (particularly if >20 mmHg). Relief of the high pressure often promotes a diuresis.

Biochemical assessment

Typical biochemical values in oliguria are shown in Table 24.1. These are not applicable if diuretics have been given previously.

Table 24.1 Biochemical values in pre-renal and renal oliguria

	Pre-renal cause	Renal cause
Urine osmolality (mOsm/kg)	>500	<400
Urine Na (mmol/L)	<20	>40
Urine:plasma creatinine	>40	<20
Fractional Na excretion (FE_{Na})	<1	>2

$$FE_{Na} = 100 \times \frac{\text{urine:plasma}\left[Na^{+}\right]}{\text{urine:plasma}\left[\text{Creatinine}\right]}$$

Further reading

See Renal function, p234; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Urinalysis, p236; Basic resuscitation, p358; Fluid challenge, p362; Acute kidney injury—diagnosis, p428.

Acute kidney injury—diagnosis

The incidence of acute kidney injury (AKI) is 10–15% of hospitalized patients, but >50% in intensive care. The majority of patients have sub-clinical disease.

Severity staging of acute kidney injury

The KDIGO organization's severity staging criteria (Table 24.2) supersede the earlier RIFLE (risk, injury, failure, loss, and end-stage renal disease) and Acute Kidney Injury Network (AKIN) criteria.

Presentation

Renal failure occurs when renal function is inadequate to clear waste products of metabolism despite absence or correction of circulatory or mechanical causes. Renal failure is suggested by:

- Uraemic symptoms (drowsiness, nausea, hiccough, twitching).
- Raised plasma creatinine.
- Hyperkalaemia.
- Hyponatraemia.
- Metabolic acidosis.
- Fluid overload.

Oligo-anuria is often present, but there may be non-oliguric AKI with 2–3 L of poor-quality urine per day.

History and clinical features may suggest the cause of AKI and direct further investigation. ATN may occur following rapid loss of perfusion, e.g. major haemorrhage. However, minimal cell death is seen in sepsis.

Causes

The main causes of AKI are prolonged hypovolaemia, shock, sepsis, drug toxicity, decompensated heart failure, AKI on known chronic kidney disease (CKD), intrinsic kidney disease, and/or postoperative (e.g. urinary tract damage, obstructive nephropathy, renal arterial disruption).

Other causes

- Nephrotoxins (including drugs)—may cause ATN, interstitial nephritis, or renal tubular obstruction.
- Rhabdomyolysis—suggested by myoglobinuria and raised creatine kinase. Causes include hyperpyrexia, crush injury, pressure necrosis, extreme exertion, seizures.
- Glomerular disease—suggested by red cell casts with microscopic haematuria, proteinuria with AKI, and systemic features (e.g. hypertension, rash, arthralgia, pulmonary haemorrhage). Specific blood tests ± renal biopsy are used to confirm diagnosis and urgent treatment, (e.g. antinuclear cytoplasmic antibody-associated vasculitis, anti-glomerular basement membrane disease, systemic lupus erythematosus (SLE)).
- Haemolytic uraemic syndrome (HUS)—suggested by haemolysis, uraemia, thrombocytopenia, diarrhoea in D+ (*Escherichia coli*) HUS.
- Crystal nephropathy (e.g. urate, oxalate)—seek crystals in the urinary sediment, and appropriate blood tests. Release of purines and urate are responsible for AKI in tumour lysis syndrome.
- Renovascular disorders—loss of vascular supply may be diagnosed by computed tomography angiography. Loss of arterial supply may occur

in abdominal trauma or aortic disease (particularly dissection). More commonly, arterial supply is partially compromised (e.g. renal artery stenosis) and blood flow further reduced by haemodynamic instability or locally via drug therapy (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors). Renal vein obstruction may be due to thrombosis or compression (e.g. raised intra-abdominal pressure).

- Hepatorenal syndrome.

Table 24.2 KDIGO severity staging criteria

Stage	Serum creatinine	Urine output
1	1.5–1.9 × baseline or ≥26.5 μmol/L rise in 48 h	<0.5 mL/kg/h for 6–12 h
2	2–2.9 × baseline	<0.5 mL/kg/h for ≥12 h
3	3 × baseline or increase ≥353.6 μmol/L or initiation of renal replacement therapy	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

Renal biomarkers

Creatinine (and creatinine clearance) are traditionally used though 50–75% of renal function must be lost before serum creatinine rises. Creatinine is produced (via creatine) mainly from muscle and liver. Production may fall with severe illness, liver disease, and muscle wasting so the rise in creatinine may not be so marked.

Many new biomarkers of AKI (measured in urine and/or blood) have been launched, including NGAL, cystatin C, cell cycle arrest biomarkers (IGFBP7, TIMP-2). Although more sensitive than creatinine, no outcome studies have yet been performed to show particular utility.

Nephrotoxins

- Drugs, e.g. antibiotics (including aminoglycosides, sulphonamides, penicillins, cephalosporins, amphotericin), chemotherapy, NSAIDs.
- Radiographic contrast.
- Ingestion of some herbal medicines, heavy metals, paraquat, organic solvents, e.g. ethylene glycol, aspirin overdose.

Further reading

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Ronco C, Bellomo R, Kellum J. 2019. 'Acute kidney injury'. *Lancet* 394: pp1949–64. doi: 10.1016/S0140-6736(19)32563-2

➔ See Renal Function, p234; Biomarkers, p248; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Abdominal sepsis, p446; Pancreatitis, p462; Postoperative complications, p668.

Acute kidney injury—management

- Identify and correct reversible causes, e.g. hypovolaemia.
- Seek specialist advice for managing intrinsic kidney disease, e.g. SLE.
- Carefully attend to fluid management and nutritional support.
- Renal replacement techniques (RRTs) can create space for fluid and nutritional support. No evidence exists for outcome benefit from the timing or type of RRT, although continuous techniques generally cause less cardiovascular disturbance.

The presence of AKI is associated with worse outcomes, but direct cause and effect has not been demonstrated. In survivors, end-stage renal failure requiring dialysis is rare in pre-renal/sepsis-associated AKI. Recovery of adequate renal function usually occurs in 1–6 weeks. There is, however, an increased risk of long-term CKD.

Urinary tract obstruction

- Decompress lower urinary tract obstruction with a bladder catheter (suprapubic if there is urethral disruption) ± irrigation (for clots).
- Decompress ureteric obstruction by nephrostomy or stent.
- Massive diuresis is common after urinary tract decompression so ensure adequate circulating volume to prevent secondary pre-renal AKI.

Haemodynamic management

- Correct the circulating volume first.
- Prompt restoration of circulating volume and any necessary inotrope or vasopressor support may reverse pre-renal failure.

Persistent oliguria

If the above measures fail and the patient remains fluid overloaded, diuretics may be trialled. Give boluses of furosemide (e.g. 10 mg IV) with further incremental doses if no adequate response. A low-dose infusion (1–10 mg/h IV) can also be considered. Patients on long-term diuretic therapy, may require regular dosing to pass urine. Failure to re-establish urine output may require RRT.

Discontinue diuretic therapy if the patient remains anuric; loop diuretics may be nephrotoxic in the context of volume depletion so fluid balance assessment is essential. Indications for RRT include fluid overload, hyperkalaemia that is non-responsive to medical treatment, metabolic acidosis, creation of space for nutrition or drugs, and significantly abnormal renal biochemistry.

Metabolic management

Urgent treatment of hyperkalaemia

- 10–20 mL 10% calcium chloride by slow IV injection.
- 100 mL 8.4% sodium bicarbonate IV (centrally).
- Glucose (50 g) and insulin (10–20 IU) IV with careful monitoring.
- Consider urgent renal replacement therapy.

Other metabolic management

- Treat hypocalcaemia with calcium supplementation and correction of hypomagnesaemia.
- Hyponatraemia is usually due to water excess.

- Hyperphosphataemia may be treated with RRT or in CKD with phosphate binders.
- Metabolic acidosis (not due to tissue hypoperfusion) may be corrected with RRT, dialysis, or a sodium bicarbonate infusion (e.g. 1.26%) if the patient is still diuresing. Of note, a recent multi-centre study found improved outcomes in patients with metabolic acidosis (pH ≤7.2) randomized to receive bicarbonate.

Nephrotoxins and crystal nephropathies

Avoid nephrotoxic agents if possible and modify drug dosing according to the glomerular filtration rate. In some cases, urinary excretion of nephrotoxins (e.g. salicylates) may be encouraged by urinary alkalinization.

Glomerular disease

Start immunosuppressive therapy following nephrologist input. RRT is often required for more severe forms despite immunosuppression. Plasma exchange may also be indicated.

Renal replacement therapy

Continuous haemo(dia)filtration forms the mainstay of RRT in critically ill patients who may not tolerate dialysis.

Indications to consider renal replacement therapy

- Fluid excess, especially in the context of anuria (e.g. pulmonary oedema).
- Hyperkalaemia (>6.5 mmol/L).
- Metabolic acidosis (pH <7.2).
- Clearance of dialysable nephrotoxins and other drugs.
- Uraemic complications (pericarditis, pericardial effusion, encephalopathy).
- To create space for nutrition or drugs.

Further reading

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➲ See Continuous renal replacement therapy—techniques & indications, p116; Haemo(dia)filtration, p118; Peritoneal dialysis, p120; Acute kidney injury—diagnosis, p428; Hyperkalaemia, p518.

Chapter 25

Gastrointestinal disorders

Vomiting/gastric stasis

While vomiting per se is uncommon in patients in the intensive care unit (ICU), large-volume gastric aspirates are commonplace and likely represent the major reason for failure of enteral nutrition.

General principles

- Seek underlying cause.
- Ensure circulating and total body fluid status is adequate, especially as aspirates/vomit can exceed several litres/day.
- Monitor and correct electrolyte abnormalities, e.g. metabolic alkalosis, hypokalaemia.
- Consider oesophageal rupture (Boerhaave's syndrome) if forceful vomiting is followed by severe retrosternal pain.

Ileus

Ileus affects the stomach more frequently than the rest of the gastrointestinal (GI) tract. Abdominal surgery, drugs (particularly opiates), gut dysfunction as part of multiorgan dysfunction, hypoperfusion, and prolonged starvation are risk factors. Early and continued use of the bowel for feeding may maintain forward propulsive action.

Treat the cause where possible. Motility stimulants (e.g. metoclopramide, erythromycin) have poor evidence of efficacy and a risk of complications (e.g. extrapyramidal side effects with metoclopramide). In resistant cases, consider bypassing the stomach with a nasoduodenal or nasojejunal tube, a percutaneous endoscopic or radiologically placed gastrojejunostomy, or open jejunostomy.

Exercise caution when establishing enteral feeding if the patient has increasing abdominal distension and/or pain, or unexplained and increasing metabolic acidosis. Consider possible bowel ischaemia. Large-bore nasogastric tube insertion, bowel rest ± total parenteral nutrition (TPN) may be needed if symptoms fail to settle.

Upper bowel obstruction

This is relatively uncommon. Consider primary surgical causes such as neoplasm or adhesions, or gastric outlet obstruction related to long-standing peptic ulcer disease, or pyloric and/or duodenal swelling consequent to gastro-duodenitis. Diagnosis is usually made endoscopically and treated as appropriate.

Gastric irritation

Drugs or chemicals ingested either accidentally or intentionally (e.g. aspirin, alcohol, bleach) or therapeutically (e.g. corticosteroids), may result in irritation and potentially lead to vomiting. Treatments include (as appropriate) (i) removal of the cause, (ii) dilution with copious amounts of fluid (iii) neutralization with alkali and/or gastric protectant, and (iv) administration of an antiemetic.

Neurological

Stimulation of the emetic centre may follow any neurological event (e.g. trauma, CVA), drug therapy (e.g. chemotherapy), pain and metabolic disturbances. Treat the cause where possible and consider judicious use of

antiemetics such as metoclopramide, prochlorperazine, ondansetron, or cyclizine. Levomepromazine can be considered for resistant cases though its side effect profile is higher.

Further reading

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➔ See Nasogastric & nasojejunal tubes, p128; Upper gastrointestinal endoscopy, p134; Enteral nutrition, p142; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Antiemetics & gut motility agents, p308; Upper gastrointestinal haemorrhage, p438; Bowel perforation & obstruction, p444; Intracranial haemorrhage, p478; Stroke, p482; Raised intracranial pressure, p484; Hypokalaemia, p520; Pain, p660; Effects of chemo- & radiotherapy, p676.

Diarrhoea & constipation

Diarrhoea

Defining diarrhoea in the ICU patient is problematic as the amount of stool passed daily is difficult to measure. Frequency and consistency may also vary significantly. Loose/watery and frequent (≥4× day) stool often requires investigation and/or treatment.

Common ICU causes

- Infection—gastroenteritis maybe viral (e.g. noro-, rota-, adeno-virus) or bacterial (e.g. *Campylobacter*, *Escherichia coli*, *Salmonella* spp., *Shigella* spp.), *Clostridioides difficile* (formerly *Clostridium difficile*), rarer tropical causes (e.g. cholera, dysentery, giardiasis), parasitic infections.
- Drugs, e.g. antibiotics, laxatives, chemotherapy.
- GI—feed (e.g. lactose intolerance), coeliac disease, other malabsorption syndromes, inflammatory bowel disease, diverticulitis, pelvic abscess, bowel obstruction with overflow, graft-versus-host disease.
- Enteral feed is often implicated but rarely causative.
- For bloody diarrhoea consider infection, gut ischaemia, vasculitis, or inflammatory bowel disease.

Diagnosis

- Examine abdomen and perform rectal examination to exclude impaction with overflow. Sigmoidoscopy may reveal a colitis. A colonoscopy is less commonly required to make a diagnosis and incurs increased patient morbidity. *C. difficile* infection is suggested by a pseudomembrane.
- Send stool to laboratory for microscopy, culture, and sensitivity, and toxins and antigens including *C. difficile* (if indicated). Molecular diagnostic panels covering the commonest viruses, bacteria, and parasites are now available. Discuss need with microbiology.
- Fat estimation (malabsorption) is rarely needed in ICU patients.
- If suspecting ischaemic or inflammatory bowel disease, a computed tomography (CT) or supine abdominal X-ray may reveal dilated loops of bowel (NB: toxic megacolon), thickened walls (increased separation between loops), intramural bowel gas (pneumatosis intestinalis), and 'thumb-printing' (suggestive of mucosal oedema). Fluid levels seen on erect or lateral abdominal X-ray may be seen in diarrhoea or paralytic ileus and do not necessarily indicate obstruction. Diarrhoea is often, but not always, bloody.
- If abscess suspected, perform ultrasonography or CT scan.

Management

- Treat cause where possible. For *C. difficile*, current recommendation for first line is vancomycin (125 mg orally (PO) qds for 10 days) and second line (for vancomycin failure) is fidaxomicin (200 mg PO bd for 10 days). Metronidazole is no longer recommended. Colestyramine may reduce diarrhoea by binding the toxin. Faecal microbiota transplants can be considered for recurrent or ongoing *C. difficile* infection not responding to drug treatments.
- Stop antibiotics and other potential causative agents if possible.

- Consider temporary (e.g. 12–24 h) cessation of enteral feed if severe. Change feed if appropriate, e.g. coeliac disease, lactose intolerance.
- Consider anti-diarrhoeal (e.g. loperamide) if infection excluded.
- Careful attention to fluid and electrolyte balance, in particular Na^+, Cl^-, K^+ and Mg^{2+}.
- Request surgical opinion, e.g. for bowel infarction, non-resolving inflammation, toxic dilatation or abscess.

Constipation

Common ICU causes

- Prolonged ileus/decreased gut motility (e.g. opiates, post-abdominal surgery, especially with major handling of bowel).
- Immobility, insufficient fluids and enteral fibre.
- Bowel obstruction—occasionally due to a tumour, but mainly seen in the ICU in postoperative patients, either after curative procedure or following development of adhesions.
- Colonic pseudo-obstruction (Ogilvie's syndrome)—presents with obstruction, often massive caecal and/or colonic dilatation, but no mechanical cause, may develop after surgery or critical illness.

Management

- Clinically exclude obstruction and confirm presence of stool per rectum.
- Ensure adequate hydration.
- Consider anti-constipation therapy, usually starting with laxatives, e.g. lactulose, sodium docusate, senna or, for more urgent response, magnesium sulfate. If this fails, proceed to glycerol suppositories and/or enemata.
- Consider reducing/stopping dose of opiate if possible.
- For paralytic ileus or colonic pseudo-obstruction consider 2 mg intravenous (IV) neostigmine. A total of three further doses can be given at 6-hrly intervals as necessary. This is often effective but may cause cramps, vomiting, bradycardia, and, very occasionally, bowel perforation. Endoscopic decompression may be necessary.

Further reading

Ponec R, Saunders M, Kimmey M. 1999. 'Neostigmine for the treatment of acute colonic pseudo-obstruction'. *N Engl J Med* 341: pp137–41. doi: 10.1056/NEJM199907153410301

➔ See Enteral nutrition, p142; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Bacteriology, p256; Virology, p258; Antidiarrhoeals, p310; Anti-constipation agents, p312; Lower intestinal bleeding & colitis, p442; Bowel perforation & obstruction, p444; Abdominal sepsis, p446; Pancreatitis, p462.

Upper gastrointestinal haemorrhage

Clinical presentation

Coffee-ground or fresh bleeding from vomit or nasogastric aspirate and/or melaena. Brisk bleeding may present as red bloody colour in stool (haematochezia). The patient may present in shock and/or with a falling haemoglobin before bleeding becomes apparent.

Common causes of upper gastrointestinal haemorrhage

- Peptic ulceration.
- Oesophagitis/gastritis/duodenitis.
- Varices.
- Mallory–Weiss lower oesophageal tear.
- Angiodysplasia.
- Neoplasms.
- Trauma.

Peptic/stress ulceration

Peptic ulceration is related to protective barrier loss leading to gastric or bile acid damage of the underlying mucosa and submucosa. Barrier loss occurs secondary to *Helicobacter pylori*, critical illness, alcohol, drugs (e.g. non-steroidals), and poisons including corrosives. Feeding tubes may cause an inflammatory reaction in the lower oesophagus. Mucosal damage ('stress ulcers') may occur as a result of tissue hypoperfusion. Gastric hypersecretion is uncommon in critically ill patients; indeed, gastric acid secretion is often reduced.

Prophylaxis

- Small-bore feeding tubes.
- Nasogastric enteral nutrition (even nasojejunal or parenteral feeding reduces the incidence of stress ulcer bleeding).
- Adequate tissue perfusion (flow and pressure).
- Prophylactic drug therapy (e.g. proton pump inhibitor) decreases the incidence of stress ulceration though this is largely based on historic data when gut hypoperfusion was more prevalent. Patients at highest risk for stress ulcer bleeding are those with shock, requiring prolonged mechanical ventilation, or with a concurrent coagulopathy. Routine use of gastric protectants is not necessary in most ICU patients and may induce harm, e.g. bacterial overgrowth.

Treatment of major haemorrhage

- Secure ≥2 large-bore vascular access cannulae.
- Initiate hospital major haemorrhage protocol.
- Start fluid resuscitation using clear fluid (preferably warmed) until blood available to restore volaemic status and raise haemoglobin (Hb). O-negative or group-specific blood may be needed if bleeding is very severe and the patient is critically anaemic. Maintain Hb >70–100 g/L and have cross-matched blood available for further haemorrhage.
- Correct coagulopathy with blood products as appropriate (e.g. platelets, fresh frozen plasma, cryoprecipitate, human prothrombin complex (Octaplex®)) as guided by haematology.

- If possible, discontinue/reduce ongoing anticoagulation and consider reversal agents. Consider restarting once patient has stabilized.
- Consider urgent fibreoptic endoscopy or angiography as appropriate, to diagnose the cause and possibly treat. Endoscopic options include local injection of epinephrine or sclerosants, banding, glue, clips, and thermal sealing. Banding or sclerosant injection may arrest bleeding varices. Elective intubation is generally advisable in such cases to protect the airway.
- Angiographic embolization may be offered by interventional radiology.
- If oesophageal varices are suspected, consider vasopressin or terlipressin ± a Sengstaken-type tube for severe haemorrhage, either as a bridge to endoscopy or if banding/injection is unsuccessful. Sources other than varices may also be present, e.g. peptic ulcer.
- For peptic ulceration and generalized inflammation, commence a proton pump inhibitor, initially by IV infusion. Enteral antacid may also be beneficial. If a *H. pylori* test is positive, commence triple therapy for 10–14 days, e.g. lansoprazole, amoxicillin, and clarithromycin.
- Surgery is now rarely necessary but should be considered if bleeding continues, e.g. >6–10 unit transfusion need, and/or if repeated endoscopy or embolization is not available or fails. Inform surgeons of the patient and the need for possible surgical intervention.
- Tranexamic acid did not reduce mortality from GI bleeding in a 12,000-patient study (HALT-IT), but doubled the rate of venous thromboembolic events.

Further reading

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HALT-IT Trial Collaborators. 2020. 'Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial'. *Lancet* 395: pp1927–36. doi: 10.1016/S0140-6736(20)30848-5

See Sengstaken-type or Minnesota tube, p132; Full blood count, p250; Coagulation monitoring, p252; Colloids, p270; Blood transfusion, p272; Blood products, p274; H_2 blockers & proton pump inhibitors, p304; Antacids, p306; Basic resuscitation, p358; Bleeding varices, p440.

Bleeding varices

Varices develop following prolonged portal hypertension, usually related to liver cirrhosis. Approximately one-third bleed. They are commonly found in the lower oesophagus and sometimes in the stomach or duodenum. Torrential haemorrhage may occur. The 6-week mortality is ~20%. If bleeding is left untreated, the rebleed rate is 60% within 1–2 years, with 33% mortality.

Management

1. Intubate and mechanically ventilate for airway and/or breathing compromise. Elective intubation is advisable to protect the airway during endoscopy, and to facilitate control of agitation and possible Sengstaken-type tube placement. Ideally, ensure adequate intravascular filling before intubation.
2. Fluid resuscitate with clear fluid and blood. Use blood products as appropriate to correct any coagulopathy. Ensure good venous access (at least two 14 G cannulae). Group-specific or O-negative blood may be needed for emergency use. Maintain Hb >70–100 g/L and have at least 4 units of cross-matched blood available for urgent transfusion. Cardiac output monitoring should be considered if the patient remains haemodynamically unstable or there is a history of heart disease.
3. If bleeding is torrential, insert a Sengstaken-type tube and commence administration of IV terlipressin.
4. Perform urgent fibreoptic endoscopy to enable variceal banding or local injection of a sclerosing agent. This can also exclude other sources of upper GI bleeding. Bleeding is arrested in ~90% of cases. Endoscopy may be impossible if bleeding is too severe and may have to be delayed for 6–24 h until a period of tamponade by the Sengstaken-type tube ± terlipressin has enabled control.
5. Give IV terlipressin or octreotide for severe bleeding, or as prophylaxis against fresh bleeding (Table 25.1). Terlipressin controls bleeding in ~60% of cases and its efficacy and safety appears to be enhanced by concurrent glyceryl trinitrate. The side effect profile of terlipressin is lower as it does not appear to precipitate as much mesenteric, cardiac or digital ischaemia. Octreotide, a long-acting somatostatin analogue, is as effective as terlipressin but with fewer side effects.
6. Gentle placement of a large-bore nasogastric tube is reasonably safe and facilitates drainage of blood, lessens the risk of aspiration, and can be used to assess continuing blood loss.
7. Consider transjugular intrahepatic portosystemic stented shunt (TIPSS) for ongoing bleeding after prolonged tamponade (2–3 days) and repeated endoscopy. Mortality is lower compared to surgery although the risk of encephalopathy is increased.
8. Relatively small trials have suggested that antibiotics (e.g. norfloxacin, ciprofloxacin, ceftazidime), decrease the rate of bacterial infection, incidence of early rebleeding, and reduce mortality.

Table 25.1 Drug dosages for variceal bleeding

Octreotide	50 µg bolus then 50 µg/h infusion
Terlipressin	2 mg IV followed by 1–2 mg IV 4–6-hrly until bleeding controlled for up to 72 h
Vasopressin	20 U over 20 min then 0.4 U/min infusion Consider glyceryl trinitrate 2–20 mg/h to counteract myocardial and mesenteric ischaemia

Further reading

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See Sengstaken-type or Minnesota tube, p132; Upper gastrointestinal endoscopy, p134; Full blood count, p250; Coagulation monitoring, p252; Colloids, p270; Blood transfusion, p272; Blood products, p274; H_2 blockers & proton pump inhibitors, p304; Basic resuscitation, p358; Upper gastrointestinal haemorrhage, p438; Acute liver failure, p454; Hepatic encephalopathy, p456.

Lower intestinal bleeding & colitis

Main causes of lower gastrointestinal bleeding

- Bowel ischaemia/infarction.
- Inflammatory bowel disease (ulcerative colitis, Crohn's disease).
- Infection, e.g. *Shigella* spp., *Campylobacter* spp., amoebic dysentery.
- Upper GI source, e.g. peptic ulceration.
- Angiodysplasia.
- Neoplasm.
- Diverticulitis.

Although relatively rare, massive lower GI haemorrhage can be life-threatening.

Ischaemic/infarcted bowel

Can occur following:

- Prolonged hypoperfusion ± hypotension (non-occlusive mesenteric ischaemia).
- Mechanical obstruction (e.g. strangulated hernia, adhesions).
- Mesenteric embolus, arterial thrombosis, venous thrombosis (especially in patients with malignancy, liver disease, intra-abdominal infection, or a prothrombotic tendency).
- Trauma.

Usually presents with severe abdominal pain, bloody diarrhoea, and systemic toxicity, including a rapidly increasing metabolic acidosis. CT or X-ray may show thickened, oedematous bowel loops ('thumb-printing') with an increased distance between bowel loops.

Treatment is by restoration of tissue perfusion, blood transfusion to maintain Hb >70–100 g/L, and, as indicated, embolectomy, endovascular stenting, vascular reconstruction, and/or bowel resection (especially if deteriorating).

Inflammatory bowel disease

Presents with weight loss, abdominal pain, and diarrhoea that usually contains blood. Complications of ulcerative colitis include perforation and toxic megacolon while complications of Crohn's disease include fistulae, abscesses, and perforations.

Management involves:

1. Fluid and electrolyte replacement.
2. Blood transfusion to maintain Hb >70–100 g/L.
3. High-dose corticosteroids IV under the guidance of gastroenterology and once infective causes and/or collections/abscesses excluded. If distal bowel involvement can be administered by enema.
4. Nutrition (often parenteral).
5. Regular surgical review. Surgery may be indicated if symptoms fail to settle after 5–7 days, or for toxic megacolon, perforation, abscesses, or obstruction.
6. Antidiarrhoeal drugs should be avoided.
7. Discuss with gastroenterology the need for escalation of medical care including use of anti-tumour necrosis factor (TNF) antibodies, e.g. infliximab.

Angiodysplasia

- An arteriovenous malformation, more common in the elderly.
- Presents as fresh bleeding per rectum.
- Endoscopy may be useful in identifying location and offering first-line treatment through ablative therapy.
- Localization and embolization by angiography may be curative during active bleeding.
- Surgery may be required if bleeding fails to settle on conservative management and, occasionally, 'blind' laparoscopic embolization of a mesenteric vessel.
- Localization of the lesion may be difficult at laparotomy, and may necessitate extensive bowel resection.

Further reading

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See Blood transfusion, p272; Blood products, p274; Basic resuscitation, p358; Diarrhoea & constipation, p436; Abdominal sepsis, p446.

Bowel perforation & obstruction

Patients with bowel perforation or obstruction may come to ICU post-surgery, for preoperative resuscitation and optimization, or for conservative management. Though rarely occurring *de novo* in the ICU patient (other than anastomotic leak), diagnosis may be difficult because of sedation ± muscle relaxation. Consider when there is:

- Abdominal pain, tenderness, peritonism, or distension.
- Agitation.
- Increased nasogastric aspirates, vomiting.
- Faeculent abdominal drain output.
- Increasing metabolic acidosis ± hyperlactataemia.
- Signs of hypovolaemia or sepsis.

A firm diagnosis may not be made until laparotomy though abdominal X-ray may reveal free peritoneal gas (perforation) or dilated bowel loops with fluid levels (obstruction). Ultrasound and percutaneous sampling may identify intraperitoneal faecal fluid following perforation. CT scan may identify the site of perforation or obstruction (transition point of dilated proximal bowel with distal collapsed bowel).

It may be difficult to distinguish bowel obstruction from a paralytic ileus clinically and radiologically.

Management

1. Correct fluid and electrolyte abnormalities. Resuscitation should be prompt and usually consists of clear fluid and blood (as needed) to maintain Hb >70 g/L. Inotropes or vasopressors may be needed to restore an adequate circulation, particularly after perforation. Consider cardiac output monitoring if circulatory status remains unstable or vasoactive drugs are required.
2. Inform surgical team. A conservative strategy may be adopted with upper small bowel perforation, though surgery is usually required for large bowel perforation. Small or large bowel obstruction may be managed conservatively if spontaneous resolution may occur, e.g. adhesions. Surgical exploration is needed if there are signs of systemic toxicity and clinical deterioration.
3. Conservative and postoperative management of perforation and obstruction usually require continuous nasogastric drainage to decompress the stomach, nil by mouth, and (usually) TPN.
4. Pain relief should not be withheld.
5. Start broad-spectrum antibiotic therapy promptly. Therapy usually comprises Gram-negative and anaerobic cover (e.g. second/third-generation cephalosporin + metronidazole, or piperacillin–tazobactam or carbapenem). An aminoglycoside may be added though outcome benefit is unproved. With adequate source control, 4 days' antibiotic treatment produced similar outcomes to 8 days' treatment.
6. Postoperative management of bowel perforation may involve repeated imaging and/or laparotomies to exclude pus collection or bowel ischaemia; surgery should be expedited if the patient's condition deteriorates. Delayed wound closure ± negative-pressure wound therapy may be needed.

Oesophageal perforation

Causes

- Iatrogenic—typically as a complication of endoscopy, placement of a feeding tube, or surgery. This accounts for 85–90% of cases.
- Boerhaave's syndrome—oesophageal rupture related to forceful vomiting or, rarely, forceful coughing or obstruction by food.
- External trauma (usually penetrating injuries).
- Corrosive liquids.

Diagnosis

- Patient usually complains of acute onset and very severe chest and/or epigastric pain.
- The Mackler triad (vomiting, chest pain, subcutaneous emphysema) is associated with spontaneous oesophageal rupture, though is only present in 50% of cases.
- Chest X-ray—mediastinal and/or subcutaneous emphysema, mediastinal widening (due to oedema and air-fluid levels).
- Oesophagogram with Gastrografin® swallow.
- CT scan with oral contrast.
- Endoscopy (performed by experienced endoscopist/surgeon).

Complications

- Pneumomediastinum.
- Mediastinitis.
- Sepsis.
- High mortality (30%), especially with late diagnosis.

Management

- Early broad-spectrum antibiotic therapy, particularly covering Gram-negative and anaerobic organisms.
- Intravascular volume replacement.
- Pain relief.
- Consider surgery with placement of mediastinal drains, repair of the perforation (if performed within 24 h before tissues become too friable), ± oesophageal exclusion and cervical oesophagostomy.
- In selected cases, patients may be managed conservatively ± stenting.
- Nil by mouth and parenteral nutrition for several weeks. Jejunostomy feeding may also be considered.

Further reading

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Sawyer R, Claridge J, Nathens A, et al. 2015. 'Trial of short-course antimicrobial therapy for intraabdominal infection'. *N Engl J Med* 372: pp1996–2005. doi: 10.1056/NEJMoa1411162

Markar S, Mackenzie H, Wiggins T, et al. 2015. 'Management and outcomes of esophageal perforation: a national study of 2,564 patients in England'. Am J Gastroenterol 110: pp1559–66. doi: 10.1038/ajg.2015.304

➔ See Nasogastric & nasojejunal tubes, p128; Upper gastrointestinal endoscopy, p134; Parenteral nutrition, p144; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Antibacterials, p344; Basic resuscitation, p358; Fluid challenge, p362; Abdominal sepsis, p446; Raised intra-abdominal pressure, p448; Metabolic acidosis, p534; Sepsis—definitions & pathophysiology, p592; Postoperative complications, p668.

Abdominal sepsis

This is common but often difficult to diagnose in the ICU patient. Some are admitted post-surgical repair while others develop abdominal sepsis *de novo* or as a secondary postoperative complication, e.g. anastomotic leak. Sepsis may be localized to an organ (e.g. cholecystitis), an intraperitoneal collection (abscess), or there may be a generalized peritonitis. Non-bowel infection or inflammation can present similarly, e.g. pancreatitis, cholecystitis.

Clinical features

- Non-specific signs, e.g. pyrexia (especially swinging), neutrophilia or neutropenia, falling platelets, increasing metabolic acidosis, circulatory instability.
- Abdominal distension ± localized discomfort, peritonism.
- Abdominal mass, e.g. gall bladder, pseudocyst, abscess.
- Failure to tolerate enteral feed/large nasogastric aspirates.
- Pleural effusion (if subdiaphragmatic sepsis).
- Diarrhoea (if pelvic sepsis).

Diagnosis

- Radiological imaging (e.g. ultrasound, CT, or magnetic resonance imaging scan).
- Laparotomy.
- Appropriate samples should be taken for urgent microbiological analyses (e.g. blood, urine, drain fluid, vaginal discharge). A sample of pus is strongly preferred to a swab.

Treatment

- Broad-spectrum antibiotic therapy to provide broad Gram-negative and anaerobic cover (e.g. second/third-generation cephalosporin plus metronidazole, or piperacillin–tazobactam or carbapenem).
- Aminoglycosides can be added if severely ill though outcome benefit is unproved. Consider an antifungal in appropriate patients (e.g. immunosuppressed). An appropriate Gram-positive-active antibiotic may be needed if enterococcal infection is suspected.
- Ultrasonic or CT-guided drainage of abscess.
- Laparotomy with removal of pus, peritoneal lavage, etc.
- With adequate source control, 4 days' antibiotic treatment gives similar outcomes to an 8-day course. Treatment can be modified depending on culture results and patient response.
- A negative laparotomy should be viewed as a useful means of excluding intra-abdominal sepsis rather than an unnecessary procedure. Laparotomy should be encouraged if the patient deteriorates and a high suspicion of abdominal pathology persists.
- Cholecystitis, with or without (acalculous) the presence of gallstones, may present with signs of infection. There is a characteristic ultrasound and CT appearance of an enlarged organ with a thickened, oedematous wall surrounded by fluid. Treatment is initially conservative with antibiotics as above. Percutaneous, ultrasound- or CT-guided drainage may be achieved via a pigtail catheter.

- Cholangitis management depends on severity. For mild acute cholangitis, antibiotics will generally suffice. Consider biliary drainage in non-responders. For moderate cholangitis, treatment consists of early biliary drainage and antibiotics. For severe cholangitis, appropriate organ support and haemodynamic stabilization is required with urgent endoscopic or percutaneous transhepatic biliary drainage. When the patient's condition improves, the underlying cause should be definitively treated.

Further reading

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➔ See Nasogastric & nasojejunal tubes, p128; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Full blood count, p250; Bacteriology, p256; Virology, p258; Antibacterials, p344; Basic resuscitation, p358; Fluid challenge, p362; Vomiting/gastric stasis, p434; Bowel perforation & obstruction, p444; Cholecystitis & cholangitis, p460; Pancreatitis, p462; Sepsis—definitions & pathophysiology, p592; Postoperative complications, p668.

Raised intra-abdominal pressure

Intra-abdominal pressure (IAP) is normally <6 mmHg at rest. A healthy individual may increase IAP to 25 mmHg with defecation, 45 mmHg with vomiting, and 60 mmHg with coughing.

Raised IAP is defined when pressures remain >12 mmHg (Table 25.2). A sustained increase >20 mmHg affects organs both within and outside the abdomen. Transmission of pressure to the pleural space reduces lung compliance, increasing ventilation/perfusion mismatch with resulting hypoxaemia and hypercapnia. Higher inspiratory pressures are required during mechanical ventilation. The increase in abdominal and intrathoracic pressures reduces venous return, leading to a fall in cardiac output and rise in intracranial pressure.

Despite the fall in venous return, a raised IAP increases measured central venous pressure. Due to the fall in cardiac output and venous congestion reducing capillary blood flow, intra-abdominal organ perfusion may be compromised. Acute kidney injury, splanchnic hypoperfusion, decreased liver metabolism, and metabolic acidosis may follow (abdominal compartment syndrome).

Main causes

- Trauma.
- Bowel or abdominal wall oedema, e.g. large-volume resuscitation.
- Intestinal obstruction.
- Intra- and retroperitoneal haemorrhage, e.g. ruptured aneurysm.
- Ascites.
- Pancreatitis.

Measuring intra-abdominal pressure

The classical technique is to measure pressure in the relaxed bladder via a Foley catheter. With the patient supine, the catheter tubing is clamped distal to the sampling bung. A pressure manometer is connected to a three-way tap and needle inserted into the sampling bung. The bladder is partially filled via the three-way tap with 50 mL 0.9% saline. The transducer is zeroed at the level of the symphysis pubis. Bladder pressure measurement is assumed to be equivalent to IAP. Manometers for measuring bladder pressure are now available.

Table 25.2 Grading of IAP

Grade I	12–15 mmHg
Grade II	16–20 mmHg
Grade III	21–25 mmHg
Grade IV	>25 mmHg

Management

- Remove cause if possible.
- Restore cardiac output with fluid resuscitation. Avoid overfilling.
- Improve abdominal wall compliance (sedation, analgesia, consider neuromuscular blockade, avoid head of bed >30°).
- Evacuate bowel contents (nasogastric decompression, rectal decompression, pro-kinetic agents).
- Evacuate intra-abdominal fluid collections (paracentesis, percutaneous drainage).
- Consider surgical decompression (laparostomy), or tube decompression for pseudo-obstruction, if IAP >25 mmHg. However, no clear evidence base exists to support this approach.

Further reading

Kirkpatrick A, Roberts D, De Waele J, et al. for the World Society of the Abdominal Compartment Syndrome. 2013. 'Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome'. *Intensive Care Med* 39: pp1190–206. doi: 10.1007/s00134-013-2906-z

Rogers W, Garcia L. 2018. 'Intraabdominal hypertension, abdominal compartment syndrome, and the open abdomen'. *Chest* 153: pp238–50. doi: 10.1016/j.chest.2017.07.023

See Invasive ventilation—failure to deliver ventilation, p58; Respiratory failure, p370; Oliguria, p426; Acute kidney injury—diagnosis, p428; Bowel perforation & obstruction, p444; Abdominal sepsis, p446; Pancreatitis, p462; Rhabdomyolysis, p648.

Chapter 26

Hepatopancreatobiliary disorders

Jaundice

Jaundice is a clinical diagnosis of yellow pigmentation of sclera and skin resulting from a raised plasma bilirubin. It is usually visible when the plasma bilirubin exceeds 40–50 μmol/L.

Common causes seen in the intensive care unit (ICU)

- Pre-hepatic—intravascular haemolysis (e.g. drugs, malaria, haemolytic uraemic syndrome), Gilbert's syndrome.
- Hepatocellular—critical illness, ischaemia (highest risk with combination of hypoxia, hypotension and right heart failure), hepatic vascular thrombosis, viral (hepatitis A, B, C, Epstein–Barr virus, cytomegalovirus (CMV)), alcohol, drugs (e.g. paracetamol, halothane), leptospirosis, etc.
- Post-hepatic—cholestatic (e.g. drugs), biliary obstruction (e.g. gallstones, neoplasm, pancreatitis).

Diagnosis

- Measurement of conjugated and unconjugated bilirubin—conjugated bilirubin predominates in cholestatic jaundice, unconjugated in pre-hepatic jaundice; a mixed picture is often seen in hepatocellular jaundice.
- Plasma alkaline phosphatase is usually elevated in obstructive jaundice while prothrombin times, aspartate transaminase, and alanine aminotransferase predominate in hepatocellular jaundice.
- Ultrasound or computed tomography (CT) scan will diagnose extrahepatic biliary obstruction.

Management

1. Identify and treat cause. Where possible, discontinue any drug that could be implicated. If obstruction, consider percutaneous transhepatic drainage (under radiology guidance), endoscopic retrograde cholangiopancreatography (ERCP) ± bile duct stenting or, rarely, surgery.
2. Liver biopsy is rarely necessary in a jaundiced ICU patient unless the diagnosis is unknown and the possibility exists of liver involvement in the underlying pathology, e.g. malignancy.
3. Non-obstructive jaundice usually settles with conservative management as the patient recovers.
4. Topical oily calamine may provide symptomatic relief for pruritus if troublesome. Colestyramine (4 g tds orally (PO)) may be helpful in obstructive jaundice.

Further reading

➔ See Liver function tests, p244; Coagulation monitoring, p252; Acute liver failure, p454; Decompensated chronic liver failure, p458; Haemolysis, p504.

Acute liver failure

Massive damage to liver cells leading to severe liver dysfunction with jaundice, coagulopathy, and encephalopathy. Survival rates for liver failure with grade 3 or 4 hepatic encephalopathy range from 10% to 40% on medical therapy alone, to >70% with liver transplantation.

Causes

- Alcohol.
- Drugs, especially paracetamol overdose; idiosyncratic reactions.
- Viral hepatitis, particularly hepatitis A, B, and E.
- Poisons, toxins, e.g. carbon tetrachloride, *Amanita phalloides* mushrooms.
- Acute fatty liver of pregnancy.
- Rarer causes include Wilson's disease, autoimmune hepatitis, vascular (e.g. portal vein thrombosis, Budd–Chiari, ischaemic).
- Ischaemic liver injury.

Diagnosis

- Consider liver failure in any patient presenting with jaundice, generalized bleeding, encephalopathy, or marked hypoglycaemia. Ascites is unusual in the early phase.
- Blood tests show prolonged prothrombin time or international normalized ratio (INR), hyperbilirubinaemia, hyperammonaemia, hypoglycaemia, hyperlactataemia, and elevated liver enzymes. In later stages of severe failure, enzyme levels may not be elevated.
- Ultrasound, CT, or magnetic resonance imaging (MRI), liver biopsy, as indicated to seek cause.

Management

- Acetylcysteine (*N*- acetylcysteine, NAC) should be given for paracetamol overdose, regardless of timing of ingestion (Table 26.1).
- See following section for management of encephalopathy.
- General measures include fluid resuscitation. Transfuse blood to keep haemoglobin (Hb) 70–100 g/L. Use vasopressors if hypotensive despite adequate fluid.
- Only give fresh frozen plasma (FFP) in patients who are bleeding, requiring invasive procedures, or if INR >7. Otherwise, withhold as this provides a good guide to recovery or the need for transplantation.
- Institute adequate monitoring for cardiorespiratory instability.
- Mechanical ventilation may be necessary for airway protection (e.g. encephalopathy, variceal bleed) or respiratory failure (e.g. lung shunts, hepatopulmonary syndrome). Use lowest sedative doses (e.g. fentanyl, propofol) compatible with patient comfort.
- Infection is common and may be Gram-positive, Gram-negative, or fungal. Clinical signs are often lacking. Send appropriate samples (e.g. blood, urine, sputum, ascites) for microbiology testing. Ascitic white cell count >250 per high power field suggests spontaneous bacterial peritonitis. No strong evidence exists for antibiotic prophylaxis.
- Monitor closely for hypoglycaemia. Treat with enteral nutrition, or 10–50% glucose infusion.
- Nutrition is important and protein should not be withheld.

- Renal failure occurs in 30–70% of cases. Hypovolaemia should be avoided and renal replacement therapy (RRT) may be needed.
- Gastrointestinal (GI) bleeding is common (coagulopathy and infection). Consider prophylactic proton pump inhibitors.
- Corticosteroid therapy is used in selected cases, e.g. alcoholic hepatitis.
- Extracorporeal systems bind and scavenge circulating toxins via albumin dialysis. Outcome benefit has not been shown though these may be a useful bridge to transplantation.
- Criteria for liver transplantation are shown in Table 26.2. Contact specialist liver centre to discuss transfer ± transplantation.

Table 26.1 Acetylcysteine (*N*-acetylcysteine, NAC) dosage regimen in paracetamol overdose

Loading dose	150 mg/kg IV infused over 1 h diluted in 250 mL 5% glucose
First maintenance dose	50 mg/kg IV infused over 4 h diluted in 500 mL 5% glucose
Second maintenance dose	100 mg/kg IV infused over 16 h dilute in 1000 mL 5% glucose
Continuing treatment	150 mg/kg over 24 h until liver failure improves or transplant

Each infusion immediately follows the previous; total treatment time 21 h.

Table 26.2 UK clinical guidelines (2020) for liver transplantation

Paracetamol related	Either arterial pH <7.3 or HCO_3 <18 (irrespective of GCS) INR >3 on day 2 or >4 thereafter, creatinine >300 μmol/L, anuria + grade 3–4 encephalopathy Oliguria and/or AKI Altered level of consciousness Hypoglycaemia Arterial lactate >4 unresponsive to fluid resuscitation
Non-paracetamol related	Either arterial pH <7.3 or HCO_3 <18 (irrespective of GCS) INR >1.8 Oliguria and/or AKI or Na <130 mmol/L Encephalopathy, hypoglycaemia, or metabolic acidosis Bilirubin >300 μmol/L

AKI = acute kidney injury; GCS = Glasgow Coma Scale.

Further reading

Stravitz RT, Lee WM. 2019. 'Acute liver failure'. *Lancet* 39: pp869–81. doi: 10.1016/S0140-6736(19)31894-X

Millson C, Considine A, Cramp M, et al. 2020. 'Adult liver transplantation: a UK clinical guideline—part 1: pre-operation'. *Frontline Gastroenterol* 11: pp375–84. doi: 10.1136/flgastro-2019-101215

See Other blood purification techniques, p124; Extracorporeal liver support, p136; Liver function tests, p244; Lactate, p246; Coagulation monitoring, p252; Acute kidney injury—management, p430; Upper gastrointestinal haemorrhage, p438; Bleeding varices, p440; Hepatic encephalopathy, p456; Decompensated chronic liver failure, p458; Paracetamol poisoning, p558.

Hepatic encephalopathy

The risk of cerebral oedema (at intracranial pressure (ICP) >30 mmHg) is much higher (50–85%) at grades 3 and 4 encephalopathy (Table 26.3). Suggestive signs include hypertension, bradycardia, and increasing muscle rigidity. Hepatic encephalopathy is unlikely if blood ammonia levels are normal. Ammonia levels can be used to assess response to therapy.

Management

- Monitor neurological status closely.
- Minimize external stimuli.
- Correct/avoid aggravating factors, e.g. gut haemorrhage, oversedation, hypoxia, hypoglycaemia, infection, fluid and electrolyte imbalance (hypokalaemia enhances renal ammonia production).
- Maintain patient in head-up position (30°).
- Lactulose 15–30 mL 12-hrly PO to achieve 2–3 motions/day. Give in combination with rifaximin (550 mg bd PO).
- Commence nutrition early, ideally enterally, provided airway is protected. Do not restrict protein intake as this promotes endogenous protein utilization but avoid excess protein intake.
- Consider intubation and ventilation if airway unprotected or GCS ≤8.
- For raised ICP use mannitol (0.5–1 g/kg intravenously (IV)) or hypertonic saline infusion to maintain Na^+ 145–155 mmol/L. For emergencies, use short-term hyperventilation to achieve a $PaCO_2$ of 3.5–4 kPa.
- Measure serum ammonia level. Consider RRT or sodium benzoate (2 g tds PO) if the patient is severely hyperammonaemic.
- ICP monitoring may be useful in specialist centres as brain CT and clinical features correlate poorly with ICP.
- Consider early RRT if AKI develops.
- Exercise caution with concomitant drug usage, e.g. benzodiazepines.
- Consider embolizing any large portosystemic shunt.
- Discuss possibility of liver transplantation with regional centre.

Table 26.3 Grading of hepatic encephalopathy

Grade	
1	Mild lack of awareness; euphoria or anxiety; decreased attention span; impaired performance
2	Lethargy; mild; personality change; odd behaviour
3	Somnolent but responsive to verbal stimuli; confused; grossly disorientated
4	Coma (unresponsive to verbal or noxious stimuli)

Further reading

Bernal W, Jalan R, Quaglia A, et al. 2015. 'Acute-on-chronic liver failure'. *Lancet* 386: pp1576–87. doi: 10.1016/S0140-6736(15)00309-8

Rose CF, Amodio P, Bajaj JS et al. 2020. 'Hepatic encephalopathy: novel insights into classification, pathophysiology and therapy'. *J Hepatol* 73: pp1526–47. doi: 10.1016/j.jhep.2020.07.013

See Decompensated chronic liver failure, p458.

Decompensated chronic liver failure

Tailor management to the individual considering underlying aetiology, comorbidities, and patient preferences. Invasive and prolonged organ support will not benefit some patients while few would be eligible for liver transplantation. Table 26.4 shows the Child–Pugh scoring system for prognosis. Discuss management plan early with a hepatologist.

Table 26.4 Child–Pugh scoring system

Measure	1 point	2 points	3 points
Bilirubin (μmol/L)	<34	34–50	>50
Serum albumin (g/L)	>35	28–35	<28
Prothrombin time (s)	<4.0	4.0–6.0	>6.0
Ascites	None	Mild	Moderate/severe
Hepatic encephalopathy	None	Grade I–II (or drug controlled)	Grade III–IV (or refractory)

Class	Points	1-year survival	2-year survival
A	5–6	100%	85%
B	7–9	81%	57%
C	10–15	45%	35%

Specific associated problems

- Acute decompensation—consider infection, sedation, hypovolaemia, hypotension, diuretics, GI haemorrhage, electrolyte imbalance.
- Infection—the patient may transmit infection, e.g. hepatitis A, B or C and, by being immunosuppressed, is also more prone to acquiring or activating dormant infections (e.g. tuberculosis (TB), CMV, and fungi).
- Drug metabolism—many drugs are metabolized in whole or part by the liver and/or excreted into the bile duct. Drug actions may be prolonged. Drug excess can lead to organ toxicity and delayed waking (sedation) so dosing should be adjusted as necessary.
- Portal hypertension results in ascites, varices, and splenomegaly. Ascites may splint the diaphragm and may become infected. Drainage may incur protein loss but aid impaired ventilation. Varices may bleed while splenomegaly may result in thrombocytopenia.
- Encephalopathy with hyperammonaemia.
- Renal failure may occur from high intra-abdominal pressure or hepatorenal syndrome (HRS).
- Bleeding—increased risk due to reduced production of clotting factors (II, VII, IX, X), varices, and thrombocytopenia.
- Alcohol—acute withdrawal may lead to delirium tremens with severe agitation, hallucinations, seizures, and cardiovascular disturbances.
- Secondary hyperaldosteronism—oliguria, salt and water retention.
- Increased tendency to jaundice, especially during critical illness.

Hepatorenal syndrome

- HRS is characterized by normal kidney histology. Recovery often occurs post-liver transplantation.
- HRS relates to arteriolar vasodilatation and renal vasoconstriction.

- Diagnosis is after exclusion of other aetiologies. The incidence in hospitalized patients with cirrhosis is ~10%:
  - type I HRS is rapid and progressive, often related to spontaneous bacterial peritonitis. Hypotension and hyponatraemia are risk factors. Mortality is very high without treatment
  - type II HRS causes moderate, more stable dysfunction.

Management

General

- Identify and treat precipitating causes of acute decompensation.
- Monitor and treat abnormal glucose; hypoglycaemia is common. 10–20% glucose infusion may be required until feed is established.
- Review drugs and dose regularly. Use proton pump inhibitor cautiously.

Infection

- Perform thorough infection screen including fungal markers.
- Consider early empiric antibiotic therapy.

Ascites

- Sample fluid for microbiological analysis (including fungi, TB), protein, and cytology. If white cells >250 per high power field give antibiotics (including Gram-negative coverage). Consider antifungal therapy.
- If present in large quantity: (i) decrease sodium and water intake; (ii) start spironolactone PO (or potassium canrenoate IV) ± furosemide; (iii) perform paracentesis, or ascitic reinfusion if non-infected.
- Urinary sodium level may help guide diuretic dosing.

Coagulopathy

- Establish and manage cause, e.g. portal hypertension.
- Vitamin K 10 mg/day slow IV bolus for 2–3 days.
- Use FFP, platelets, or prothrombin complex concentrate for bleeding or invasive procedures. Routine prophylactic use is discouraged.
- Consider thrombopoietin receptor agonists (TPO-RAs) in thrombocytopenic patients undergoing a major procedure.
- Continue low-molecular-weight heparin thromboprophylaxis unless contraindicated.

Nutrition

- Give adequate nutrition, preferably by enteral route. Nasogastric tube placement is not contraindicated with non-bleeding varices.
- Aim for 20–30 kcal/kg/day and protein of at least 1.2–1.5 g/kg/day.
- Vitamin supplementation; patients often malnourished and at risk of beriberi. Initially IV Pabrinex® then switch to PO thiamine.

Renal dysfunction

- Treat underlying cause. Paracentese if abdominal pressures are high.
- Give terlipressin 0.5 mg IV 6-hrly and albumin for HRS-AKI.
- Those with non-HRS-AKI can benefit from RRT. RRT delays time to death for type I HRS unless transplantation can be offered.
- Consider transjugular intrahepatic portosystemic stented shunt (TIPSS) to reduce portal hypertension.

Further reading

See Liver function tests, p244; Coagulation monitoring, p252; Hepatic encephalopathy, p456; Hypoglycaemia, p540.

Cholecystitis & cholangitis

Cholecystitis

Causes

- Bile duct obstruction from gallstones, sludge (90% of cases).
- Acalculous cholecystitis—seen in critical illness, postoperatively.

Diagnosis

- Right upper quadrant pain (colicky or constant), fever, nausea, vomiting, local rebound tenderness.
- Blood tests may show a (usually mild) obstructive jaundice pattern and markers of inflammation. Cultures may be positive.
- Imaging studies—ultrasound most commonly used and may reveal gallstones, gall bladder wall thickening, pericholecystitic fluid, bile duct dilatation. CT scan may be useful to diagnose perforation or gangrene.
- Table 26.5 shows the classification of severity.

Complications

- Shock and multiorgan failure.
- Peritonitis from perforation.
- Empyema.
- Fistula formation and gallstone ileus.

Management

- General measures including fluid resuscitation, nil-by-mouth, analgesia, respiratory support, and, if indicated, vasopressors.
- Give broad-spectrum antibiotics to cover Gram-negative aerobic and anaerobic bacteria as the gallbladder often becomes secondarily infected.
- Urgent cholecystectomy may be needed if patient is deteriorating or not settling with conservative management.
- If the patient is not deemed fit for surgery and deteriorating, consider percutaneous cholecystotomy or endoscopic ultrasound-guided cholecystoduodenostomy stent drainage to decompress the gall bladder and drain infected fluid.

Table 26.5 Classification of severity

Severity	Finding
Grade III (severe)	Multiorgan dysfunction
Grade II (moderate)	WBC >18 × 10^9/L, palpable, tender right upper quadrant mass, duration >72 h, marked local inflammation (e.g. gangrenous cholecystitis)
Grade I (mild)	Cases not meeting grade II or III criteria

Cholangitis

This life-threatening condition is related to infection usually related to bile duct obstruction. The need for urgent intervention to enable biliary drainage is often not appreciated.

Causes

- Bile duct obstruction from gallstones, sludge.
- Postoperative or post-procedural (e.g. after ERCP).
- Biliary stricture, neoplasm, parasitic infection.

Diagnosis

- Charcot's triad (right upper quadrant pain, jaundice, fever) and Reynolds' pentad (right upper quadrant pain, jaundice, fever, shock, altered mental status) have low sensitivity (<20%) but high specificity.
- Blood tests usually show an obstructive jaundice pattern. Blood cultures may be positive.
- Imaging studies—bile duct obstruction by ultrasound, CT scan, magnetic resonance cholangiopancreatography (MRCP), or ERCP.

Management

- General measures including fluid resuscitation, analgesia, respiratory support, and, if indicated, vasopressors.
- Broad-spectrum antibiotics; Gram-negative aerobic and anaerobic bacteria predominate; enterococcus may cause up to 20% of cases.
- Definitive treatment is to relieve any underlying obstruction. This should be performed promptly, especially if the patient continues to deteriorate. While usually achieved by ERCP, a percutaneous transhepatic approach may be needed to decompress the biliary system and drain infected bile. Dilated bile ducts may not necessarily be present.
- Cholecystectomy is usually performed as a delayed elective procedure for gallstone disease once the patient has improved as this reduces the risk of recurrence.

Further reading

Kiriyama S, Takada T, Strasberg S, et al. 2013. 'TG13 guidelines for diagnosis and severity grading of acute cholangitis (with videos)'. *J Hepatobiliary Pancreat Sci* 20: pp24–34. doi:10.1007/s00534-012-0561-3

Miura F, Takada T, Strasberg S, et al. 2013. 'TG13 flowchart for the management of acute cholangitis and cholecystitis'. *J Hepatobiliary Pancreat Sci* 20: pp47–54. doi:10.1007/s00534-012-0563-1

See Antibacterials, p344; Abdominal sepsis, p446; Jaundice, p452; Sepsis—definitions & pathophysiology, p592.

Pancreatitis

The inflamed pancreas and surrounding retroperitoneal tissues may be mildly oedematous or haemorrhagic and necrotic. Walled-off necrosis (pseudocyst) may develop which can become infected, and the bile duct may be obstructed causing jaundice. Overall mortality is quoted at 5–10%, but much higher (~40%) in those with severe pancreatitis requiring ICU admission. Prolonged critical care admission is often required.

Causes

- Gallstones and alcohol abuse are the main causes worldwide.
- Other causes include ischaemia, trauma, viral, hypertriglyceridaemia, hypercalcaemia, drugs, and after procedures (e.g. ERCP).

Diagnosis and severity assessment

- Non-specific features, e.g. central, severe abdominal pain, pyrexia, haemodynamic instability, vomiting, ileus. Peri-umbilical discolouration (Cullen's sign) or flanks (Grey Turner's sign) are rare.
- Plasma levels of amylase or lipase >3× upper limit of normal. Relatively sensitive, but non-specific and do not relate to severity.
- C-reactive protein >100 mg/L suggests pancreatic necrosis.
- Alanine aminotransferase >100 IU/L at presentation strongly predicts biliary cause (usually gallstones).
- Contrast-enhanced CT, ultrasound, MRI.
- Pancreatitis is severe if APACHE II score >8. Tables 26.6 and 26.7 detail methods to classify severity.

Complications

- Multiorgan dysfunction syndrome.
- Infection/abscess formation.
- Bleeding from erosion of local artery or vein, or pseudoaneurysm.
- Hypocalcaemia.
- Diabetes mellitus.

Table 26.6 Ranson severity score

On hospital admission	At 48 h after admission
Age >55 years old	Haematocrit fall >10%
Blood glucose >11 mmol/L	Blood urea rise >1 mmol/L
Serum LDH >300 U/L	Serum calcium <2 mmol/L
Serum AST >250 U/L	PaO_2 <8 kPa
White blood count >16 × 10^9/L	Arterial base deficit >4 mmol/L
	Estimated fluid sequestration > 6 L

Pancreatitis severe if ≥2 criteria met within 48 h of admission.

AST = aspartate aminotransferase; LDH = lactate dehydrogenase; PaO_2 = arterial partial pressure of oxygen.

Table 26.7 Revised Atlanta Classification of Acute Pancreatitis 2012

Severity	Finding
Mild	No organ failure and no local or systemic complications
Moderate	Transient organ failure (<48 h) and/or local or systemic complications without persistent organ failure (>48 h)
Severe	Persistent organ failure (>48 h)

Management

- General measures (e.g. fluid resuscitation, transfusion to maintain Hb >70 g/L, respiratory support, analgesia, antiemetics).
- Routine antibiotic prophylaxis is not recommended.
- Studies show safety and efficacy of enteral feeding started within 1–3 days, even if pain has not resolved. Distal feeding tubes may be placed if there are large gastric aspirates. Total parenteral nutrition may be needed if enteral feeding fails.
- Relieve gallstone obstruction by ERCP if cholangitis is present.
- Treat hypocalcaemia by slow IV 10% calcium chloride.
- Control hyperglycaemia by continuous IV insulin infusion.
- A conservative approach ± percutaneous drainage of infected and/or necrotic debris is generally adopted.
- Specialist centres may offer endoscopic ultrasound-guided trans-gastric necrosectomy, with placement of a stent to enable continuing drainage of walled-off necrosis.
- Open (surgical) necrosectomy may be performed if endoscopic or radiological drainage are not possible. However, this is now rarely done due to the risk of local complications.
- Severe bleeding may arise from visceral pseudoaneurysms, e.g. cystic or gastroduodenal artery. Consider transcatheter embolization.
- Probiotic therapy is associated with poorer outcomes.

Further reading

Lankisch P, Apte M, Banks P. 2015. 'Acute pancreatitis'. *Lancet* 386: pp85–96. doi: 10.1016/S0140-6736(14)60649-8

Mederos MA, Reber HA, Girgis MD. 2021. 'Acute pancreatitis: a review.' *JAMA* 325: pp382–90. doi: 10.1001/jama.2020.20317

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See APACHE scoring, p30; Hypocalcaemia, p528; Hyperglycaemia, p538; Sepsis—definitions & pathophysiology, p592.

Chapter 27

Neurological disorders

Coma

Causes

- Brain injury, e.g. trauma, acute stroke, meningoencephalitis, vasculitis, malaria, (post-)ictal, space-occupying lesion, ventriculoperitoneal shunt blockage.
- Metabolic, e.g. hypo- or hyperglycaemia, severe electrolyte disturbance (e.g. Na^+), renal failure, liver failure, beriberi.
- Septic encephalopathy.
- Autoimmune-mediated encephalopathy.
- Drug-related or poisoning, e.g. opiates, benzodiazepines, carbon monoxide poisoning, recreational drugs, alcohol.
- Haemodynamic—poor cerebral perfusion (cardiac arrest, severe heart failure, arrhythmia, hypotension).
- Respiratory, low arterial partial pressure of oxygen (PaO_2) and/or high arterial partial pressure of carbon dioxide ($PaCO_2$).
- Endocrine, e.g. myxoedema, Addison's disease.
- Temperature disturbance (hyperpyrexia, hypothermia).

Investigation

Dictated by presenting history and examination findings:

- Urgent blood sugar testing (at the bedside).
- Urea and electrolytes, glucose (laboratory-measured), calcium, liver function tests plus ammonia.
- Full blood count and clotting screen to exclude coagulopathy.
- Urgent blood gas analysis (including carboxyhaemoglobin if indicated).
- Blood and urine poison/drug screen; alcohol level.
- Plasma creatine kinase; test urine for 'positivity' for blood if rhabdomyolysis possible (immobility, recreational drugs, hyperpyrexia).
- Metabolic screen (e.g. thyroid function, cortisol).
- Septic screen ± malaria screen.
- Lumbar puncture (LP) (after computed tomography (CT) scan if concerned about raised intracranial pressure (ICP)) with appropriate cerebrospinal fluid (CSF) microbiological and metabolic tests.
- CT scan.
- Other neurological tests, e.g. electroencephalogram (EEG), magnetic resonance imaging (MRI), antibodies for B- or T-cell-mediated autoimmune encephalitis (e.g. anti-*N*-methyl-D-aspartate (anti-NMDA) receptor antibody).

Management

- ABC—ensure adequate (protected) airway, breathing, circulation.
- Correct remediable causes promptly, e.g. hypoglycaemia, seizures, specific drug/poison antidote, or treatment.
- If meningitis suspected, give prompt antibiotics (e.g. ceftriaxone) ± antivirals (aciclovir) ± corticosteroids.
- Prioritize investigations based on likely diagnosis; treat accordingly.
- Institute measures to lower ICP if concerns of herniation (coning).
- Urgent referral to neurosurgeon if CT demonstrates space-occupying lesion (e.g. haematoma) or for brain decompression (craniectomy, clot evacuation).

- Urgent investigation and consideration of thrombolysis, embolectomy, or angioplasty as appropriate for embolic stroke.
- Consider duration of coma when treating metabolic abnormality. Correction of abnormal Na^+ and high glucose may need to be more gradual, if present for several days.
- Unconscious patients involved in trauma have an unstable spine until specifically excluded and managed accordingly.
- Consider active warming (for hypothermia) or, if pyrexial, cooling to achieve normothermia (but not hypothermia) for prolonged cardiac arrest, severe head injury, malignant hyperpyrexia.
- If rhabdomyolysis present, ensure adequate circulating volume, good urine output ± urinary alkalinization. Relieve compartment syndrome.
- Deep vein thrombosis (DVT) prophylaxis, nutrition, and pressure sore prevention.

Further reading

Uy C, Binks S, Irani S. 2021. 'Autoimmune encephalitis: clinical spectrum and management.' *Pract Neurol* 21: pp412–23. doi: 10.1136/practneurol-2020-002567

See Airway maintenance, p42; Endotracheal intubation—indications & equipment, p44; Targeted temperature management, p106; Blood gas analysis, p174; Intracranial pressure monitoring, p224; Electroencephalogram (EEG), p228; Renal function, p234; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Liver function tests, p244; Full blood count, p250; Coagulation monitoring, p252; Toxicology, p262; Acute kidney injury—diagnosis, p428; Acute liver failure, p454; Delirium, p470; Meningitis, p474; Encephalitis, p476; Intracranial haemorrhage, p478; Subarachnoid haemorrhage, p480; Stroke, p482; Raised intracranial pressure, p484; Hypernatraemia, p514; Hyponatraemia, p516; Hypocalcaemia, p528; Hyperglycaemia, p538; Hypoglycaemia, p540; Poisoning—general principles, p554; Sedative poisoning, p560; Infection—diagnosis, p588; Head injury—management of complications, p634.

Acute weakness

Causes

Acute weakness has many causes, some of which are more specific to a patient in the intensive care unit (ICU) such as critical illness neuromyopathy (Box 27.1). Acute weakness may be due to an exacerbation of an existing muscle disorder.

- Critical illness neuromyopathy presents with generalized weakness ± loss of sensation, and usually becomes apparent on reducing sedation.
- New-onset stroke—usually unilateral weakness. Risk of stroke rises in ICU patients with cerebral hypoperfusion and/or coagulopathy.
- Metabolic myopathies—correct low K^+, Mg^{2+}, Ca^{2+}, uraemia, etc.
- Prolonged effects of muscle relaxants—consider low pseudocholinesterase activity or myasthenia gravis if occurs after suxamethonium. Prolonged effects of non-depolarizing muscle relaxants suggested by response to an anticholinesterase (neostigmine 2.5 mg slow intravenous (IV) bolus with an anticholinergic). Patients with myasthenia gravis also respond.
- Cord compression, e.g. tumour, trauma, epidural haematoma.
- Guillain–Barré syndrome—LP usually shows raised CSF protein with normal cell counts. If LP findings are not typical but suspicion remains strong, repeat LP several days later or perform nerve conduction studies which may demonstrate segmental demyelination with slow conduction velocities.
- Myasthenia gravis—fatigable weakness or ptosis suggests myasthenia gravis; response to IV edrophonium, a strongly positive acetylcholine or muscle-specific kinase (anti-MuSK) receptor antibody titre, and single-fibre electromyography (EMG), are confirmatory tests. Malignancy-associated myasthenic syndrome (Eaton–Lambert syndrome) usually involves pelvic and thigh muscles, and tends to spare ocular muscles.
- Other diagnoses are made largely on the basis of history, examination, and specialized tests.

Box 27.1 Causes of acute weakness in the ICU

- Acute stroke.
- Cord compression.
- Adverse drug reaction, substance abuse, or poisoning.
- Metabolic, e.g. electrolyte disturbances, hypocalcaemia, renal failure.
- Guillain–Barré syndrome.
- Myositis.
- Myasthenia gravis.
- Chronic disorders (e.g. multiple sclerosis, motor neurone disease).
- Critical illness neuromyopathy.
- Prolonged effects of muscle relaxants ± immobilization.
- Excessive neuraxial blockade (epidural or spinal).
- Uncommon causes, e.g. botulism, diphtheria.

Management

- May require urgent (or pre-emptive) intubation and mechanical ventilation if the patient is tiring, or if gas exchange is deteriorating.
- Correct electrolyte and metabolic abnormalities; remove (if possible) potential contributory factors such as corticosteroids.
- For Guillain–Barré syndrome, monitor gas exchange 2–4-hrly; intubate and mechanically ventilate if tiring or $PaCO_2$ rising. Although forced vital capacity (FVC) is traditionally used, in practice the clinical picture and blood gases are better guides. Give intravenous immunoglobulin (IVIg) daily for 5–7 days; consider plasmapheresis.
- Weak respiratory muscles can lead to progressive basal atelectasis and secretion retention. Chest infection is a significant risk; regular chest physiotherapy with intermittent positive pressure breathing is required for prophylaxis in spontaneously breathing patients.
- Give DVT prophylaxis to immobile patients. Pay attention to posture to prevent pressure sores and contractures.
- Long-term bladder catheterization (with a silastic catheter) and assistance with bowel movements (e.g. lactulose, suppositories, manual evacuation) may be needed for long-term paresis/paralysis.
- Weak bulbar muscles may compromise swallowing with consequent malnutrition or pulmonary aspiration. Give enteral nutritional support via a nasogastric tube (or percutaneous endoscopic gastrostomy/jejunostomy (PEG/PEJ) if long-term feeding likely).
- Spinal cord compression is a surgical emergency. Prompt imaging and referral to neurosurgeons are necessary.
- Closely monitor patients with neuraxial blockade (spinal or epidural) for uni/bilateral leg weakness or paralysis. If reducing or stopping the epidural infusion rate does not lead to rapid improvement, consider urgent imaging to exclude haematoma or abscess with nerve compression. Discuss with neurosurgical team if indicated.
- Enteral nutrition may not be possible in patients with autonomic neuropathy, necessitating parenteral nutrition. Such patients may also suffer arrhythmias and hypotension requiring appropriate support.

Further reading

➔ See Airway maintenance, p42; Endotracheal intubation—indications & equipment, p44; Guillain–Barré syndrome, p486; Myasthenia gravis, p488; Critical care neuromyopathies, p490; Tetanus, p492; Botulism, p494.

Delirium

ICU agitation and/or confusion are often related to loss of day–night rhythm, poor sleep pattern, sepsis, cerebral hypoperfusion, and/or drugs (or their withdrawal). Delirium is associated with increased mortality. 'ICU psychosis' is a common occurrence in the patient recovering from severe illness. Silent ('hypoactive') delirium, usually presenting as a withdrawn, non-communicative patient, is often under-recognized.

Common ICU causes

- Infection—including chest, urinary tract, catheter-related. Consider cerebral infection such as meningitis, encephalitis, and malaria.
- Drug-related: (i) adverse reaction (particularly in the elderly), e.g. sedatives, analgesics, diuretics; (ii) withdrawal, e.g. sedatives, analgesics, ethanol; (iii) abuse, e.g. opiates, amphetamines, alcohol, hallucinogens; (iv) consider drug interactions.
- Metabolic, e.g. low/high glucose or Na^+, high Ca^{2+}, uraemia, hepatic encephalopathy, hypo- or hyperthermia, dehydration.
- Respiratory—hypoxaemia, hypercapnia.
- Neurological—infection, post-head injury/seizure/cardiac arrest, space-occupying lesion (e.g. haematoma), encephalitis.
- Haemodynamic—low-output state, hypotension, endocarditis.
- Pain—full bladder (blocked Foley catheter), abdominal pain.
- Psychosis—'ICU psychosis', post-ictal psychosis, other psychiatric conditions, pre-morbid mental health illness.

Diagnosing delirium

Confusion Assessment Method for the ICU (CAM-ICU) is a validated monitoring tool (Table 27.1). Concurrent sedation can be confounding.

Table 27.1 The Confusion Assessment Method for the ICU (CAM-ICU)

Feature 1: Acute onset or fluctuating course Different to baseline mental status or any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (e.g. RASS), GCS, or previous delirium assessment
Feature 2: Inattention Positive if cannot provide correct answers to number or picture tests
Feature 3: Disorganized thinking Positive if fails to answer logical statements correctly (e.g. can you use a hammer to cut wood?) or to perform simple repetitive commands
Feature 4: Altered level of consciousness Positive if RASS or other sedation score is anything other than normal

Overall CAM-ICU score: Presence of features 1 and 2 and either feature 3 or 4 = delirium

GCS = Glasgow Coma Scale; RASS = Richmond Agitation Sedation Scale.

Prevention

Primary prevention is preferred and can be achieved with various methods:

- Good sleep, minimize noise, light control.
- Regular reorientation of patient, glasses, hearing aids as required.
- Early mobilization and cognitively stimulating activities.
- Adequate analgesia and prevention of oversedation.

Principles of management

1. Reassure and calm the patient.
2. Consider (i) infection; (ii) cardiovascular instability; (iii) covert pain, e.g. full bladder; (iv) metabolic or blood gas derangement; (v) neurological causes, e.g. hypoperfusion, hypoxia; (vi) adverse drug reaction.
3. Treat as appropriate. Do not label as ICU delirium or psychosis until treatable causes are excluded.
4. Maintain quiet atmosphere and reduce noise. Try to restore day–night rhythm, change ambient lighting, use of oral hypnotics, e.g. melatonin.
5. Consider dose and type of sedative or tranquillizer. Sedatives (e.g. propofol) calm and sedate, while tranquillizers (e.g. haloperidol) may calm without excess sedation. α_2 agonists (e.g. clonidine) are intermediate. Consider opiates if pain or opiate withdrawal are factors.
6. If the patient is highly agitated and likely to self-harm, rapid short-term control can be achieved by a small IV bolus of sedative, repeated as necessary (Table 27.2). Consider propofol, midazolam, or haloperidol at low dose to achieve the desired effect; observe for hypotension, respiratory depression, arrhythmias, and extrapyramidal effects.
7. If delirium continues, consider regular dosing with an appropriate agent, either enteral, intermittent injection, or continuous IV infusion, with additional boluses as required. Do not stop medication abruptly once the patient is calm as there may be rebound worsening.
8. Evidence for the use of antidepressants in ICU patients is weak.

Table 27.2 Drug dosages for severe agitation

Haloperidol	2.5 mg by slow IV bolus. Repeat after 10–15 min if needed. For regular prescription, give 2.5–5 mg qds
Midazolam/diazepam	2.5 mg by slow IV bolus. Repeat prn
Propofol	20 mg by slow IV bolus. Repeat prn
Clonidine	50–150 μg tds IV or 100–150 μg/h by infusion
Dexmedetomidine	1 μg/kg over 10 min, then 0.2–0.7 μg/kg/h by infusion
Chlordiazepoxide	For alcohol withdrawal: 10–30 mg qds (increase to 50 mg qds if severe) + 10–40 mg prn, max to 250 mg/day
Oxazepam	For alcohol withdrawal: 20 mg qds (high-dose regimen 30 mg qds) + 10–20 mg prn to max dose 200 mg on day 1. Reduce dose after 2 days

NB: beware excessive central and respiratory depression.

Further reading

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See Toxicology, p262; Sedatives, p322; Tranquillizers, p324; Meningitis, p474; Encephalitis, p476; Infection—diagnosis, p588; Malaria, p614; Pain, p660.

Generalized seizures

Control seizures to prevent ischaemic brain damage, reduce cerebral O_2 requirements and lower ICP. Where possible, correct the cause and give specific treatment. Consider urgent CT scan to identify structural causes. Common causes include:

- Hypoxaemia/anoxia (e.g. post-cardiac arrest).
- Stroke.
- Abnormal plasma glucose, Ca^{2+}, Na^+, and Mg^{2+} levels.
- Space-occupying lesions, e.g. blood clot, tumour, abscess.
- Metabolic and toxic disorders, e.g. liver failure, renal failure.
- Drug toxicity or withdrawal, e.g. alcohol, benzodiazepines.
- Infection, especially meningoencephalitis.
- Trauma.
- Autoimmune-mediated.
- Idiopathic.

Prolonged seizures may be related to autoimmune causes such as NMDA receptor antibody encephalitis.

Most seizures are self-limiting, so simply protect the patient from injury (left lateral position, protect head). Do not force anything into the mouth. Seek and treat reversible causes, e.g. low glucose.

Specific treatment

- Correct hypoxaemia with O_2, aiming to achieve 94–98% saturation.
- Intubate and ventilate if the airway is unprotected or the patient remains hypercapnic and/or hypoxaemic (despite a high fraction of inspired O_2).
- Urgently measure blood glucose and treat hypoglycaemia (25–50 mL 50% glucose IV; repeat as necessary).
- Correct electrolyte disorders, e.g. low Mg^{2+}, low Na^+.
- Measure and correct blood anticonvulsant levels in patients with known epilepsy.
- Manage cerebral oedema acutely with sedation, ± induced hypothermia, controlled hyperventilation, and osmotic diuresis.
- In patients with a known tumour, arteritis, or parasitic infection, consider high-dose dexamethasone.
- Give thiamine 100 mg IV to alcoholic or malnourished patients.
- Consider surgery for space-occupying lesions.
- Consider steroids, IVIg, plasmapheresis, and/or specific treatments for autoimmune cases.

Anticonvulsants

Many seizures are short-lived and self-terminating. If prolonged, frequent, and/or central cyanosis occurs then active treatment is indicated.

- Give benzodiazepines (e.g. lorazepam IV) for rapid control and repeat after 5–10 min if seizures continue. If no IV access available, rectal diazepam or buccal midazolam are alternatives.
- Levetiracetam is preferred as an initial second-line agent over phenytoin as it is quicker to administer and has fewer adverse effects.
- Phenytoin—needs an IV loading dose with electrocardiogram (ECG) and blood pressure (BP) monitoring. Adjust dose if taking regular phenytoin or compliance concerns.

- If seizures continue, other appropriate anticonvulsants include:
  - sodium valproate (avoid if possibility of pregnancy)
  - magnesium sulfate IV (recommended first line for (pre)eclampsia)
  - clonazepam (particularly useful for myoclonic seizures)
  - propofol
  - thiopental, phenobarbital, or valproate if severe/intractable.
- For drug dosages see Table 27.3, With all anticonvulsants, care should be taken to avoid hypoventilation and respiratory failure.

Table 27.3 Drug dosages for generalized seizures

Lorazepam	4 mg IV over 2–4 min. Repeat, if needed, after 10–20 min
Diazepam	Initially 2.5–5 mg IV or PR. Further increments as necessary to 20 mg
Midazolam	Initially 2.5–5 mg IV or PR. Further increments as necessary to 20 mg then consider infusion
Levetiracetam	60 mg/kg IV (max 4500 mg), rate of 6 mg/kg/min
Phenytoin	Loading dose 18 mg/kg IV at a rate <50 mg/min with continuous ECG monitoring. Maintenance at 300–400 mg/day IV, IM, or PO adjusted according to levels
Fosphenytoin	15–20 mg phenytoin equivalents/kg IV at rate of 50–100 mg phenytoin equivalents/min
Sodium valproate	40 mg/kg IV (max 3000 mg) at a rate of 10 mg/kg/min
Propofol	0.5–2 mg/kg IV followed by 1–5 mg/kg/h
Magnesium sulfate	20 mmol over 3–5 min, then 5–10 mmol/h infusion if needed
Clonazepam	1 mg/h IV
Thiopental	3–5 mg/kg IV, followed by infusion (usually 3–5 mg/kg/h)
Phenobarbital	5 mg/kg IV given at rate of 100 mg/min

Other supportive treatment

Muscle relaxants prevent muscular contraction during seizures but will not prevent continued seizures. They may be necessary to facilitate mechanical ventilation but continuous (or repeated) EEG monitoring must be used to judge seizure control. Correction of circulatory disturbance is required to maintain adequate cerebral blood flow. Prevent or treat pyrexia.

Further reading

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➔ See Airway maintenance, p42; Endotracheal intubation—indications & equipment, p44; Anticonvulsants, p328; Acute kidney injury—diagnosis, p428; Acute liver failure, p454; Hepatic encephalopathy, p456; Meningitis, p474; Encephalitis, p476; Intracranial haemorrhage, p478; Stroke, p482; Raised intracranial pressure, p484; Hyponatraemia, p516; Hypomagnesaemia, p524; Hypocalcaemia, p528; Hypoglycaemia, p540; Head injury—management of complications, p634.

Meningitis

A life-threatening condition requiring prompt treatment. Meningism may be absent so suspect in those presenting with obtundation, agitation, seizures, or focal neurology. A rash is only present in 30% of meningococcaemia. Signs may be subtle and present insidiously in immunosuppressed patients and the elderly; in these patients *Listeria monocytogenes* may cause early seizures and focal neurology. Meningitis is a notifiable disease in the UK.

Diagnosis

- Bacterial meningitis is primarily diagnosed by CSF examination (Table 27.4). Send CSF for urgent microscopy and culture, polymerase chain reaction (PCR), rapid antigen tests, virology, protein, and glucose. Multiplex PCR panels for common pathogens have excellent specificity and high sensitivity, providing results within 1–2 h. Normal or lymphocytic CSF may be found in early meningitis, especially with *Listeria* spp. Send cytology if concerned about intracerebral neoplasm.
- Take concurrent blood cultures, plus plasma and urine for PCR and/or antigen.
- Ideally perform the LP before antibiotics are given. Cultures are positive in 50% with prior antibiotics and 60–90% if untreated. However, start antibiotics beforehand if LP is delayed or contraindicated (e.g. coagulopathy, patient agitation, raised ICP).
- Perform a CT scan before LP if focal neurology, continuous seizures, papilloedema, or other concerns of significantly raised ICP. A normal CT scan does not totally exclude raised ICP.

Table 27.4 Typical CSF values in meningitis

	Pyogenic	Viral	Tuberculosis
Classical appearance	Turbid	Clear	Fibrin web
Predominant cell type	Polymorphs	Lymphocytes	Lymphocytes
Cell count/mm^3	>1000	<500	50–1500
Protein (g/L)	>1	0.5–1	1–5
CSF: blood glucose	<60%	>60%	<60%

Management

1. Begin antibiotic therapy with corticosteroids promptly. For antibiotic selection, consider patient age and relevant factors, e.g. travel, splenectomy, immunosuppression, shunt.
2. Guidelines suggest antibiotic duration should be ≥10 days (Table 27.5); recent studies, however, suggest equal efficacy for common pathogens with shorter courses (5 days).
3. Start dexamethasone (10 mg qds for 4 days) before, or up to 12 h after antibiotics have started. Outcome benefit has only been proven for pneumococcal meningitis. Discontinue steroids if meningitis is subsequently excluded or another pathogen is isolated.
4. Manage raised ICP, if present.

5. Give oral ciprofloxacin (adults only) or rifampicin to family and close social contacts of meningococcal and *Haemophilus influenzae* meningitis. Also treat the index case prior to discharge.

Table 27.5 Organisms and empirical starting antibiotic therapy

Organism	Patients mainly affected	Antibiotic & dosage regimen (alternatives in brackets)
Neisseria meningitidis (meningococcus)	Young adults	Ceftriaxone 2–4 g IV od (cefotaxime 50 mg/kg IV 8-hrly) (benzylpenicillin 1.2g IV 2–4-hrly) (chloramphenicol 12.5 mg/kg IV 6-hrly)
Streptococcus pneumoniae (pneumococcus)	Older adults	Ceftriaxone 2–4 g IV od (cefotaxime 50 mg/kg IV 8-hrly) (chloramphenicol 12.5 mg/kg IV 6-hrly)
Haemophilus influenzae	Children	Ceftriaxone 20–50 mg/kg IV od (cefotaxime 50 mg/kg IV 8-hrly) (chloramphenicol 12.5 mg/kg IV 6-hrly)
Listeria monocytogenes	Elderly, immunocompromised	Ampicillin 1 g IV 4–6-hrly plus gentamicin 120 mg IV stat, then 80 mg 8–12-hrly (adjust by plasma levels)
Mycobacterium tuberculosis	Social deprivation, immunocompromised	Rifampicin/isoniazid/ethambutol/pyrazinamide
Cryptococcus neoformans	Immunocompromised	Amphotericin B 250 µg/kg IV od + flucytosine 50 mg/kg IV 6-hrly
Staphylococcus aureus	Recent invasive procedure	Flucloxacillin 2 g IV 6-hrly (vancomycin, teicoplanin, or linezolid + rifampicin if meticillin-resistant *Staph aureus*)

Aseptic meningitis

No organisms are identified by routine CSF analysis despite a high neutrophil and/or lymphocyte count. Causes include prior antibiotics, viruses (e.g. herpes simplex virus, mumps, measles), fungi, leptospirosis, listeriosis, brucellosis, atypical tuberculosis, systemic lupus erythematosus (SLE). Identification may be made by rising titres, antigen or PCR testing.

Further reading

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See Bacteriology, p256; Virology, p258; Antibacterials, p344; Corticosteroids, p352; Basic resuscitation, p358; Raised intracranial pressure, p484.

Encephalitis

This is an acute inflammation of the brain. Presenting features include drowsiness, headache, coma, agitation, confusion, hallucinations, pyrexia, seizures, and focal signs; meningism need not necessarily be present.

Causes

- Infectious—the commonest cause of encephalitis, especially viral:
  - viruses—e.g. herpes simplex, varicella zoster, human papillomavirus, measles, mumps, West Nile, St Louis, rabies
  - bacterial (as for meningitis)
  - other infections, e.g. malaria, leptospirosis, toxoplasmosis, disease. CSF contains no organisms but high lymphocytes
  - sepsis can cause an encephalopathy, however classical changes are not seen on MRI and organisms are not found on LP.
- Autoimmune—a heterogeneous group of inflammatory disorders:
  - anti-NMDA receptor encephalitis—presents with psychosis, seizures, catatonia, abnormal movements, and autonomic dysfunction. Often associated with an underlying germ cell tumour (usually ovarian or testicular teratoma)
  - other including, e.g. (i) glycine receptor (GlyR) antibodies associated with progressive encephalomyelitis, rigidity, and myoclonus (PERM) ± autonomic disturbance and respiratory failure; (ii) leucine-rich glioma-inactivated 1 (LGI-1) antibodies with dystonic seizures, hyponatraemia, limbic encephalitis; (iii) contactin-associated protein-like 2 (CASPR-2) antibodies with limbic encephalitis, seizures, cognitive and memory impairment, disordered mood and sleep
  - paraneoplastic—manifests as a syndrome of remote neurological consequences (e.g. decreased consciousness, opsoclonus-myoclonus). The neoplasm may be overt or covert cancer
  - acute disseminated encephalomyelitis (ADEM)—a post-infectious syndrome characterized by demyelination in the brain and spinal cord. The preceding infection is usually viral (cytomegalovirus, Epstein–Barr virus, herpes zoster virus, influenza, human herpesvirus-6, hepatitis A, HIV) but can follow other infections (e.g. *Mycoplasma pneumoniae*, β-haemolytic streptococci) or immunization (e.g. rabies, tetanus, influenza, hepatitis B).
- Posterior reversible encephalopathy syndrome (PRES)—mainly affects posterior occipital and parietal lobes and presents with headache, seizures, altered mental status, and visual loss. Causes include severe hypertension, renal failure, drugs, and pre-eclampsia. Despite its name, impairment may be permanent.
- Immune effector cell-associated neurotoxicity syndrome (ICANS)—a complication of chimeric antigen receptor T-cell (CAR-T) therapy used for haematological malignancy. It presents days to weeks after treatment and manifests with neuropsychiatric syndrome (confusion, delirium), headaches, seizures, aphasia, or tremors.
- Encephalitis lethargica—fever, headache, lethargy of unknown origin.
- Stroke, trauma, tumours, and acute confusional states related to drugs, toxins, or acute psychoses may result in similar features.

Diagnosis

Signs of meningism suggest the patient has meningoencephalitis. Herpes simplex classically affects the temporal lobe.

- CT—with and without contrast agent.
- MRI—with/without gadolinium. This test is more sensitive than CT in detecting early changes.
- EEG.
- LP with cultures (to include viral cultures), PCR, antigens, biochemical analysis, antibody screen, electron microscopy.
- Blood tests (e.g. cultures, PCR, serology, malaria, antibody screen).
- Brain biopsy—96% sensitive, 100% specific.

Management

- Aciclovir (10 mg/kg 8-hrly IV) is given for 14 days for herpes simplex virus or varicella zoster virus. Other antiviral therapy may be indicated for specific viruses. In HIV, consider foscarnet due to an increased risk of aciclovir resistance.
- Appropriate antibacterials if bacterial cause suspected.
- Steroids (dexamethasone 8 mg IV 6-hrly) to reduce oedema.
- For PRES, remove any causative drug agent, actively control BP, treat seizures and renal impairment as needed. Autoimmune causes may respond to steroids and cyclophosphamide.
- Symptomatic and supportive management, e.g. sedation. Treat seizures and/or raised ICP as per standard protocols.

Further reading

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See Bacteriology, p256; Virology, p258; Antibacterials, p344; Corticosteroids, p352; Basic resuscitation, p358; Raised intracranial pressure, p484; Chimeric antigen receptor T-cell (CAR-T) therapy, p680.

Intracranial haemorrhage

Causes

Extradural haemorrhage

Usually presents acutely after head injury. Characterized by falling GCS progressing to coma, focal signs (lateralizing weakness or decreased sensation, pupillary signs), visual disturbances, and seizures. Treatment by random burr holes has been supplanted by directed drainage after CT scan localization.

A conservative approach may be adopted for small haematomas but an increase in size (assessed by regular CT scans) or clinical deterioration are indications for prompt surgical referral and intervention.

Subdural haemorrhage

Classically presents days to weeks following head trauma with a fluctuating level of consciousness (35%), agitation, confusion, seizures, and signs of raised ICP, localizing signs, or a slowly evolving stroke. Diagnosis is made by CT scan. Consult with local neurosurgeons.

Intracerebral haemorrhage

Causes include hypertension, neoplasm, vasculitis, coagulopathy, mycotic aneurysms associated with bacterial endocarditis.

Clinical features include sudden-onset coma, drowsiness, and/or neurological deficit. Headache usually occurs only with cortical and intraventricular haemorrhage. Rate of evolution depends on size and site of the bleed.

Diagnosis

- CT angiography is the initial test of choice. This may proceed to interventional radiology or neurosurgical intervention.
- Coagulation and vasculitis blood screens, as indicated.
- Consider an underlying diagnosis of cerebral amyloid angiopathy (CAA) in the event of a lobar bleed.

Treatment

- Bed rest.
- Supportive (e.g. hydration, nutrition, analgesia, ventilatory support).
- BP control—initially maintain systolic BP 150–220 mmHg and avoid both hypo- and hypertension.
- Correct coagulopathy.
- Control raised ICP.
- Interventional radiology: embolization of bleeding vessel or aneurysm.
- Surgery—contact regional centre, e.g. for consideration of haematoma evacuation, repair/clipping of aneurysm, cranial decompression.
- Corticosteroid therapy is ineffective.

Further reading

See Vasodilators & antihypertensives, p288; Neuroprotective agents, p330; Coagulants & antifibrinolytics, p340; Raised intracranial pressure, p484.

Subarachnoid haemorrhage

Pathology

- In 15% no cause is found; of the remainder, 80% are due to a ruptured aneurysm, 5% to arteriovenous malformations, and 15% trauma.
- The anterior circle of Willis is affected in 90–95% of cases while 10–15% affect the vertebrobasilar system.
- Risk of rebleeding is 30%, for which mortality is 40%. The greatest risk is within the first day. After a month, 90% survive 1 year.
- Cerebral vasospasm occurs in 30–40% at 4–12 days post-bleed. This is the most important cause of morbidity and mortality.
- Complications include hydrocephalus, rebleed, vasospasm, seizures, hyponatraemia, inappropriate antidiuretic hormone secretion, cardiac dysfunction.

Clinical features

- Subarachnoid haemorrhage may be preceded by a prodrome of headache (48%), dizziness (10%), orbital pain (7%), and visual disturbances (4%).
- Onset often rapid (minutes to hours). May have collapse, severe headache, nausea/vomiting, meningism, loss of consciousness, seizure.
- Cranial nerve palsies, drowsiness, and hemiplegia may occur.

Diagnosis

- Diagnosis usually made by CT scan without contrast.
- If no evidence of raised ICP, a LP may be performed revealing blood-stained CSF with xanthochromia. Other causes should be sought in the CSF fluid.
- Angiography (CT or magnetic resonance) should follow to identify the source of the bleed.
- Cardiac troponin levels are often raised and indicate poor prognosis.

Clinical severity scales

Various scales are in use to describe severity. Table 27.6 shows the World Federation of Neurological Surgeons grading scale.

Table 27.6 The World Federation of Neurosurgeons severity scale for subarachnoid haemorrhage

Grade 1	Glasgow Coma Scale (GCS) 15, motor deficit absent
Grade 2	GCS of 13–14, motor deficit absent
Grade 3	GCS of 13–14, motor deficit present
Grade 4	GCS of 7–12, motor deficit absent or present
Grade 5	GCS of 3–6, motor deficit absent or present

Complications

- Hydrocephalus.
- Rebleeding.
- Vasospasm.
- Seizure.
- Hyponatraemia.
- Cardiac dysfunction and arrhythmias—troponin levels are often raised and a sign of poor prognosis.

Management

- Maintain adequate, but not excessive, hydration, nutrition, analgesia, and sedation.
- Elevate bed to 30° head-up tilt.
- Minimize noise and other stimuli.
- Intubate and mechanically ventilate if GCS low or signs of herniation.
- Vasospasm is prevented by nimodipine 60 mg qds for 21 days. Switch to an infusion if an ischaemic neurological deficit is present.
- Use antihypertensives if mean arterial pressure (MAP) >130 mmHg, e.g. short-acting β-blockers. NB: nitroprusside and glyceryl trinitrate may increase ICP.
- Treat raised ICP as per standard protocols.
- Monitor for, and treat, heart failure. ECG abnormalities are common but generally benign.
- Consider endovascular coiling, embolization of the aneurysm, or neurosurgery to clip the aneurysm. Timing remains controversial with either early (<72 h) or delayed (7–10 days) intervention advocated. Early coiling or surgery is increasingly recommended for straightforward aneurysms of favourable clinical grade, whereas delayed intervention is recommended for very large or complicated aneurysms.
- Antifibrinolytic therapy (e.g. tranexamic acid) reduces the incidence of rebleeding but has no beneficial effect on outcome.

Further reading

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➔ See Vasodilators & antihypertensives, p288; Neuroprotective agents, p330; Coagulants & antifibrinolytics, p340; Intracranial haemorrhage, p478; Stroke, p482; Raised intracranial pressure, p484.

Stroke

A stroke is a neurological deficit secondary to an acute focal injury of the central nervous system, leading to significant longterm morbidity and may be fatal. May be referred to as a cerebrovascular accident.

Causes

- Thrombotic, embolic, or haemorrhagic.
- 'Secondary' stroke may occur with meningitis, bacterial endocarditis, subarachnoid haemorrhage, and vasculitis.
- Suspect dissection in younger patients who may present with severe headache, neck pain, Horner's syndrome, and/or seizures after trauma or neck manipulation.
- Cerebral venous thrombosis may mimic stroke, tumour, subarachnoid haemorrhage, or meningoencephalitis and may present with severe headache, seizures, focal signs, or coma.

Investigations

- Perform non-enhanced CT scan as early as possible. If thrombectomy possibly indicated, perform CT contrast angiography thereafter (if beyond 6 h of symptom onset add CT/magnetic resonance perfusion imaging). Directed and effective treatment depends on an accurate and prompt diagnosis of the underlying aetiology ('time costs brain').
- Echocardiography or neck vessel ultrasound for sources of emboli.
- Blood tests to investigate hyperlipidaemia, diabetes mellitus.
- Other tests as indicated, e.g. for vasculitis, hypercoagulability, thrombotic thrombocytopenic purpura.

Revascularization therapy

- Early revascularization is key for acute ischaemic stroke.
- After excluding intracranial haemorrhage, administer IV thrombolytic therapy with alteplase 0.9 mg/kg to patients with moderate-to-severe deficits presenting within 4.5 h from onset of symptoms. Door-to-needle time should be <60 min. The risk of bleeding increases in the elderly (especially >80 years) and if hypertensive.
- In addition, consider mechanical thrombectomy if available and:
  - patient presents after 4.5 h but before 8 h
  - IV alteplase is contraindicated; e.g. BP >185/110 mmHg or platelets $<30 \times 10^9$/L
  - no major bleeding elsewhere
  - the cause is a proximal (middle cerebral and internal carotid) artery occlusion (30% of strokes); these are more severe clinically, and relatively resistant to alteplase alone
  - if CT/MRI perfusion scan suggests limited core volume, thrombectomy can be undertaken 6–24 h after onset of symptoms
  - pre-stroke functional status is good, e.g. modified Rankin scale <3.
- Intra-arterial alteplase can be used within 6 h of symptom onset if IV alteplase is contraindicated.
- Thrombolysis/thrombectomy is contraindicated if haemorrhage seen on CT, or if >30% middle cerebral artery territory affected.

Other management

- Give aspirin (300 mg PO) as soon as possible, and anticoagulate unless a large established infarct is seen (increased risk of bleeding) and intracerebral haemorrhage has been excluded.
- To protect the ischaemic penumbra carefully manage oxygenation, hydration, glycaemia, pyrexia, and hyper- and hypocapnia.
- If suitable, consider intubation and ventilation for unprotected airway and/or poor gas exchange. Tracheostomy may later be needed. Life support withdrawal or non-escalation may be appropriate.
- BP control with acute haemorrhage should aim to lower systolic BP <140 mmHg, but do not exceed >60 mmHg fall in first hour.
- Do not rapidly drop BP if underlying structural cause, GCS <6, need for early neurosurgery or poor prognosis.
- For non-haemorrhagic ischaemic stroke, reduce BP slowly (aim 15% reduction in first 24 h). However, reduce below 185/110 mmHg if significant hypertensive emergency (e.g. encephalopathy, heart failure, aortic dissection) or thrombolysis considered. Monitor closely.
- Avoid sublingual nifedipine.
- Treat hypotension aggressively with fluids, inotropes, or vasopressors, as indicated.
- Consider early decompressive craniectomy for cerebellar haematoma, cerebellar infarction, and the 'malignant middle cerebral artery syndrome' (for massive infarction on the non-dominant side).
- Maintain normothermia and avoid hypo- and hyperthermia.
- Prophylactic antibiotics have no benefit.
- Mobilize early; give low-molecular-weight heparin prophylaxis.
- Ensure adequate nutrition, and perform swallow assessment.
- Repeat CT if subsequent deterioration and treat as indicated.
- If patient does not require critical care, manage on a hyperacute stroke unit (HASU) if available.

Further reading

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See Oxygen therapy, p40; Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Targeted temperature management, p106; Vasodilators & antihypertensives, p288; Neuroprotective agents, p330; Thrombolytics, p338; Intracranial haemorrhage, p478; Subarachnoid haemorrhage, p480; Raised intracranial pressure, p484.

Raised intracranial pressure

Causes of raised intracranial pressure

- Space-occupying lesion (e.g. neoplasm, blood clot, abscess).
- Increased capillary permeability (e.g. trauma, infection, hepatic encephalopathy).
- Cell death (e.g. post-arrest hypoxia).
- Obstruction (e.g. hydrocephalus).
- Idiopathic.

Clinical features

- Headache (often postural, worse sitting up), vomiting, dizziness, visual disturbance.
- Seizures, focal neurology, papilloedema.
- Increasing BP, bradycardia (late responses).
- Agitation, increasing drowsiness, coma.
- Slow deep breaths, Cheyne–Stokes breathing, apnoea.
- Ipsilateral progressing to bilateral pupillary dilatation.
- Decorticate progressing to decerebrate posturing.

Diagnosis

- CT scan or MRI.
- ICP measurement >20 mmHg.
- Avoid LP because of the risk of herniation. Neither CT scan nor the absence of papilloedema definitively excludes raised ICP.

Management

1. Bed rest, 20–30° head-up tilt, sedation, quiet environment, minimal suction and noise. Sedation and β-blockade are often needed to overcome a hyperadrenergic state, though avoid sedative-induced hypotension.
2. Intubate and ventilate if low GCS airway unprotected, or very agitated. Ensure endotracheal tube ties do not impede jugular venous drainage.
3. Maintain PaO_2 >10 kPa and $PaCO_2$ at 4.5–5 kPa; avoid rapid changes. CSF bicarbonate re-equilibrates in 4–6 h, negating longer-term benefit.
4. If available and not contraindicated, monitor ICP. Aim to maintain ICP <20 mmHg and cerebral perfusion pressure (CPP = MAP − ICP) >60–70 mmHg. Vasopressor therapy may be needed. Do not treat systemic hypertension unless very high (e.g. systolic BP >220 mmHg).
5. Consider mannitol 0.5–1.0 mg/kg IV over 15 min. Repeat at 4-hrly intervals depending on CPP measurements and/or clinical signs of deterioration. Stop when plasma osmolality reaches 320 mOsm/kg.
6. Hypertonic saline is an alternative to mannitol though evidence of superiority is weak. Give 100 mL bolus of 7% saline followed by a continuous IV infusion of 3% saline. Maintain serum Na^+ between 145 and 149 mmol/L. Beware fluid overload.
7. Avoid alkalosis as it increases cerebral vascular resistance.
8. Avoid hypo- or hyperthermia.

9. Consider specific treatment, e.g. for meningitis, malaria, hepatic encephalopathy, surgery. Discuss decompressive craniectomy with neurosurgeons for generalized oedema. Dexamethasone (4–16 mg qds IV) is beneficial for oedema surrounding a tumour or abscess, and may be used with aciclovir for herpes simplex encephalitis.
10. Give anticonvulsant therapy as indicated.

Acute deterioration/risk of imminent herniation (coning)

1. Mechanically ventilate to $PaCO_2$ 4.0–4.5 kPa for 10–20 min.
2. Give hypertonic saline (e.g. 100 mL 7% saline) or mannitol (0.5 g/kg IV) over 10–15 min. Repeat as needed (see above).
3. If no response in ICP, CPP and/or clinical features, give thiopentone (successful in 50% of resistant cases).
4. Refer for surgical opinion if a space-occupying lesion is diagnosed.

Further reading

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➔ See Intracranial pressure monitoring, p224; Jugular venous bulb saturation, p226; Neuroprotective agents, p330; Acute liver failure, p454; Hepatic encephalopathy, p456; Coma, p466; Intracranial haemorrhage, p478; Subarachnoid haemorrhage, p480; Stroke, p482; Generalized seizures, p472; Meningitis, p474; Malaria, p614; Head injury—management of complications, p634.

Guillain–Barré syndrome

- This is an immune-mediated acute demyelinating polyradiculopathy.
- May be triggered by *Campylobacter* gastroenteritis, viral infections, and immunizations.
- Often presents as areflexic motor weakness (often symmetrical, ascending, and involving cranial nerves including facial, bulbar, and extraocular weakness) with progression over days to weeks.
- Minor sensory disturbances (e.g. paraesthesiae) may be present.
- Autonomic dysfunction is often seen.
- There is no increase in cell count on CSF examination but protein levels usually rise progressively (>0.4 g/L).
- Nerve conduction shows slow velocities with prolonged F waves.
- Other features include muscle tenderness and back pain.
- Major contributors to morbidity and mortality are respiratory muscle weakness and autonomic dysfunction (hypo- or hypertension, arrhythmias, ileus, urinary retention).

Specific treatment

- IVIg (0.4 g/kg/day for 5 days) or plasma exchange (five 50 mL/kg exchanges over 8–13 days) is effective if started within 14 days of onset of symptoms.
- Corticosteroids are not beneficial.

Supportive treatment

Respiratory care

Regular chest physiotherapy is required. Consider mechanical ventilation if the patient is tiring, or $PaCO_2$ is rising. FVC <15 mL/kg body weight indicates likely need. Consider early tracheostomy if mechanical ventilation is likely to continue for several weeks to months. Patients with bulbar involvement or inadequate cough should have a tracheostomy even if breathing spontaneously.

Cardiovascular care

Continuous monitoring is required due to the effects of autonomic involvement. Arrhythmias are particularly likely with anaesthesia (especially with suxamethonium). Treat as indicated but be aware that hypertensive and hypotensive responses may be exaggerated with vasoactive drugs.

Nutritional support

Enteral nutrition via a PEG tube is usually required for long-term cases. Give parenteral nutrition if ileus persists.

Analgesia and anxiolysis

Analgesia is required for muscle, abdominal, and neuropathic pain. Although non-steroidal anti-inflammatory drugs (NSAIDs) may be useful, opiates are often required. Benzodiazepines may be needed for anxiety and lability. Monitor mood for depression.

Other support

Multidisciplinary input is needed from physiotherapy, dieticians, speech and language, psychologists, etc. Rehabilitation is likely to improve longer-term outcomes. Particular attention is required to pressure areas and DVT prophylaxis.

Further reading

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➲ See Airway maintenance, p42; Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Plasma exchange, p122; Respiratory failure, p370; Acute weakness, p468.

Myasthenia gravis

- An autoimmune disease associated with acetylcholine receptor and, rarely, anti-striated muscle antibodies. It is associated with autoimmune thyroid disease, SLE, and rheumatoid arthritis.
- Painless weakness with normal tendon reflexes, deteriorating after exertion and recovering after rest. Weakness deteriorates during stress, infection, trauma or some drug treatments (Box 27.2).
- Younger, predominantly female patients may have a thymoma.

Box 27.2 Drugs causing deterioration in myasthenia gravis

- Aminoglycosides
- Streptomycin
- Tetracyclines
- Local anaesthetics
- Muscle relaxants
- Opiates

Diagnosis of myasthenia

- Edrophonium (short-acting anticholinesterase) is used for diagnosis. For myasthenic patients with acute deterioration, a response to this test may distinguish myasthenic from cholinergic crisis.
- A positive test is judged by improvement of weakness within 3 min compared to no improvement with saline injection.
- In cholinergic crisis, edrophonium may, however, cause further deterioration so atropine and facilities for urgent intubation and ventilation should be available. To minimize the risk, administer a test dose of 1 mg. If no adverse events are noted after 1 min, give an additional 4 mg. If no change is apparent after 1 min, give a further 5 mg.
- The test may be combined with objective assessment of respiratory function by measuring the FVC response or by assessing the response to repetitive single-fibre stimulation with an EMG.

Treatment

Maintenance treatment

Anticholinesterase drugs provide the mainstay of symptomatic treatment. Corticosteroids, immunosuppressives, and plasma exchange may provide pharmacological remission. Anticholinesterases may produce improvement in some muscle groups and cholinergic deterioration in others due to differential sensitivity. Anticholinesterases can cause diarrhoea, abdominal cramps, and/or excessive saliva. Anti-muscarinic agents such as propantheline bromide or atropine may be used to suppress these symptoms. Maintenance drug dosages are shown in Table 27.7.

Myasthenic crisis

- Presents with dyspnoea and respiratory failure ± bulbar weakness (dysphagia, upper airway obstruction).
- Provide ventilatory support (invasive or non-invasive) if patient tiring or $PaCO_2$ is rising.
- If life-threatening signs, commence pyridostigmine, corticosteroids, and IVIg or plasma exchange.
- If steroids contraindicated, use immunosuppressants, e.g. azathioprine, mycophenolate mofetil.
- Newer treatment options approved for refractory acetylcholine receptor-positive myasthenia gravis include efgartigimod alfa, an IgG1 antibody that reduces circulating levels of IgG autoantibodies.

Cholinergic crisis

- Now rare.
- Cholinergic symptoms (e.g. sweating, salivation, lacrimation, colic, ataxia, fasciculation, confusion, small pupils, bradycardia, hypertension, seizures) are usually most severe 2 h after the last anticholinesterase.
- Ventilatory support if patient tiring, or $PaCO_2$ is raised. An FVC falling <15 mL/kg body weight suggests that support many be needed.
- Atropine given prophylactically may mask cholinergic symptoms.
- If edrophonium test is negative, stop all drugs and give atropine.
- Reintroduce anticholinesterases when edrophonium test is positive.

Table 27.7 Drug dosages

Prednisolone	80 mg/day orally
Azathioprine	2.5 mg/kg/day orally
Pyridostigmine	60–180 mg 6-hrly orally
Neostigmine	1–2.5 mg 2–4-hrly IV
Propantheline bromide	15 mg 8-hrly orally, max daily dose 120 mg/24 h
Atropine	1 mg 6-hrly IV repeated every 30 min to max 8 mg

Further reading

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➔ See Airway maintenance, p42; Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Plasma exchange, p122; Corticosteroids, p352.

Critical care neuromyopathies

Consider if patients fail to wean from mechanical ventilation or limb weakness is noted on stopping sedation. This may be profound and can persist for weeks to months, or even permanently. Variable degrees of neuropathy and myopathy are found on EMG, nerve conduction studies, and biopsy. Corticosteroids and prolonged use of paralysing agents are implicated but causation remains unproven. Disuse atrophy, catabolic states, and drug therapy (e.g. high-dose corticosteroids) may be contributory. A neuromyopathic component of multiorgan failure is likely to be particularly relevant.

Critical illness neuropathy

- Patients have flaccid, symmetrical, predominantly distal weakness and/or sensory loss following a prolonged period of intensive care. There may be respiratory muscle involvement but facial and extraocular muscles are generally spared. Neurophysiological studies demonstrate an acute, idiopathic axonal degeneration.
- Sensation may be affected, alone or in combination with motor fibres. Reflexes may be preserved in the early stages but diminish and may be abolished over time.
- Nerve conduction velocities are normal, indicating no demyelination. CSF is normal unlike Guillain–Barré syndrome.
- The neuropathy is self-limiting but prolongs the recovery phase of critical illness. Recovery may take weeks to years or be permanent.
- There is no specific treatment. Recovery requires multidisciplinary input for rehabilitation and management of neuropathic pain.

Critical illness myopathy

- Causes a proximal symmetrical weakness. It is twice as common as other forms of ICU-acquired weakness but carries a better prognosis.
- Disuse atrophy and drug-induced myopathy are common causes in ICU patients.
- Respiratory muscles may also be involved but facial and ocular muscles are typically spared. Deep tendon reflexes are reduced/absent.
- Muscle histology shows abnormalities (fibre atrophy, mitochondrial defects, myopathy, and necrosis) that are not associated with corticosteroid or muscle relaxant therapy.
- Critical illness myopathy is associated with various forms of muscle degeneration but is usually self-limiting. Recovery may take weeks to years. Residual deficit occasionally remains.
- There is no specific treatment. Recovery requires multidisciplinary input for rehabilitation.

Further reading

See Acute weakness, p468.

Chapter 28

Haematological disorders

Bleeding disorders—causes & diagnosis

Bleeding may be:

- Large vessel bleeding—usually traumatic (including 'surgical'), aneurysmal, or following a procedure (e.g. chest drain, tracheostomy, accidental arterial puncture, removal of intravenous (IV) or intra-arterial catheter); peptic ulcer bleeding is now relatively uncommon due to improved attention to perfusion and nutrition.
- Around vascular catheter sites or from intubated/instrumented lumens and orifices—usually related to severe multisystem illness or excess anticoagulant therapy, including thrombolytics.
- Small vessel bleeding, e.g. skin petechiae, gastric erosions—usually related to anticoagulation or severe generalized illness including vasculitis or disseminated intravascular coagulation (DIC) triggered by release of tissue factor (or other thromboplastic substances) into the circulation, and by widespread endothelial injury/activation.

In general, platelet deficiencies result in petechiae or purpura while clotting factor deficiencies cause ecchymoses, haematomas, or prolonged bleeding after a laceration, procedure or surgery.

Thrombocytopenia often occurs with critical illness including sepsis. Recovery of the count usually coincides with overall patient recovery.

Common intensive care unit (ICU) causes

- Post surgery and haemodilution are the most common ICU causes.
- Decreased platelet production, e.g. post-surgery, haemodilution, sepsis, drug-induced (e.g. chemotherapy, antibiotics), marrow infiltration.
- Decreased production of coagulation factors, e.g. liver failure, haemophilia, von Willebrand disease.
- Increased consumption of platelets and/or clotting factors, e.g. trauma, sepsis, bleeding, microangiopathic haemolytic anaemias (e.g. DIC), thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS), extracorporeal circuits.
- Increased platelet sequestration (e.g. hypersplenism).
- Impaired or deranged platelet function, especially following drugs such as aspirin, clopidogrel, and epoprostenol or with uraemia.
- Other drug effects, e.g. heparin-induced thrombocytopenia (HIT; type I commencing soon after therapy or the more severe type II that usually occurs 5–14 days post-therapy), warfarin (inhibits vitamin K-dependent synthesis of clotting factors), fondaparinux (indirect factor Xa inhibitor).
- Decreased platelet survival, e.g. autoimmune causes with antiplatelet antibodies, e.g. systemic lupus erythematosus (SLE), post-transfusion, human immunodeficiency virus (HIV), haemophagocytic syndrome—haemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome.
- Decreased protease inhibitors, e.g. antithrombin, protein S and protein C deficiency. This may be congenital or following sepsis.

Diagnostic tests

- Imaging (e.g. computed tomography scan ± angiography), endoscopy, occasional nuclear scans to identify any bleeding site, underlying neoplasm, etc.

- 'Routine' tests of clotting function, e.g. platelets, APTT, prothrombin time (PT), international normalized ratio (INR).
- Specialized tests (as indicated), e.g. fibrinogen, D-dimers (for DIC), protein S and C levels, clotting factors, e.g. factor VIII, IX, vWF, anti-Xa activity (heparin excess), ADAMTS13 activity (TTP), Shiga toxin in stool (HUS), bone marrow (haemophagocytic syndrome, aplastic anaemia), ferritin ≥500 ng/mL (haemophagocytic syndrome).
- Thromboelastography.

Further reading

➔ See Full blood count, p250; Coagulation monitoring, p252; Thromboelastography & rotational thromboelastometry, p254; Clotting disorders, p498; Thrombotic microangiopathies, p506; Platelet disorders, p508.

Bleeding disorders—management

Principles of management

- Identify and treat the underlying cause, e.g. infection, haemorrhage.
- Diagnostic laboratory tests to determine if clotting defects exist (platelets and/or factors); treat as appropriate.
- Thromboelastography may also be used to guide treatment.
- For major haemorrhage, commence treatment using an emergency pack before laboratory results become available (see below). Ensure adequate coagulation factor replacement (fresh frozen plasma (FFP)) to avoid dilutional coagulopathy.
- Transfuse platelets promptly on receipt (> 30 min per pool). See Table 28.1 for indications; keep at room temperature.
- Antiplatelet medication (e.g. aspirin, clopidogrel) taken within the last few weeks may affect platelet function, resulting in bleeding despite a normal platelet count; platelet transfusion may be indicated.
- Abnormalities in PT may be due to liver impairment, drugs, or poor nutrition. Vitamin K, orally (PO) or IV, is indicated. FFP is not needed unless significant bleeding.
- In patients on warfarin, urgent reversal of INR may be indicated:
  - 1 mg vitamin K will reverse warfarin within 4–6 h
  - 10 mg saturates liver stores, preventing warfarin activity for >1 week. Prothrombin complex concentrate (PCC) (e.g. Octaplex®, Beriplex®) will correct the INR within 20–30 min
- For a life-threatening bleed, 5 mg vitamin K and 15–50 U/kg of PCC are given. Check PT/INR after PCC dosing and at 6 h.
- For bleeding related to thrombolysis, stop the drug infusion, give tranexamic acid (10 mg/kg 6–8-hrly), FFP (10–15 mL/kg), and fibrinogen replacement (cryoprecipitate or fibrinogen concentrate).
- Cryoprecipitate or fibrinogen concentrate may be required with a reduction in fibrinogen levels, e.g. with DIC. Standard FFP contains fibrinogen and may be satisfactory. However, with fibrinogen levels <1.0 g/L and, especially <0.5 g/L, may require replacement. The aim is to increase fibrinogen levels >1.5 g/L. Cryoprecipitate is not indicated in patients with von Willebrand's disease or haemophilia.
- Factor VIIa should not be used for bleeding.
- Do not give platelet transfusions in TTP or HIT unless advised by haematology.

Management of vascular catheter or percutaneous drain site bleeding

1. Direct pressure/occlusive dressing or device, e.g. Femostop™.
2. Correct coagulopathy; consider use of tranexamic acid.
3. Surgical/radiological intervention is rarely necessary although perforation/laceration of local artery/vein should be considered if bleeding fails to stop or becomes significant.

Management of major bleeding.

1. If external, direct occlusion/deep suture.
2. Urgent expert opinion, e.g. for surgery, endoscopy + injection, interventional radiography + embolization, etc.

3. Transfuse red blood cells (RBCs) and clear fluids to maintain adequate perfusion and pressure.
4. Give FFP and platelets. Trauma guidelines recommend a 1:1:1 ratio for RBC:FFP:platelets; others suggest a plasma:RBC ratio of at least 1:2 and 1 pool platelets or 1 apheresis pack.
5. Give tranexamic acid 1 g over 10 min, then 1 g infused over 8 h.
6. Monitor (and treat, if necessary) ionized calcium levels.
7. Consider fibrinogen concentrate (3–4 g) or cryoprecipitate (50 mg/kg); repeat according to fibrinogen levels or thromboelastography.
8. Consider PCC if bleeding very severe and persisting, if on warfarin, fondaparinux, or oral anti-Xa agents (e.g. rivaroxaban) but not direct thrombin inhibitors, e.g. dabigatran, desmopressin.
9. Specific antidotes include andexanet alfa—neutralizes the anticoagulant effect of oral anti Xa inhibitors (e.g. apixaban or rivaroxaban), and idarucizumab—reverses dabigatran.

Table 28.1 Relative indications for platelet transfusion

Count × 10^9/L	Situation
<10	Usually given to reduce risk of spontaneous bleeding. One pool is often adequate
<20	Acute bleeding, sepsis, or other abnormalities of haemostasis. Before (semi-)elective insertion of central venous catheter
<50	Invasive procedures, e.g. lumbar puncture, transbronchial biopsy, laparotomy. Recent intracerebral bleed or other major bleeding
<80	Epidural or spinal anaesthetic
<100	Procedures involving closed sites such as surgery to the eyes or brain. Patients with ongoing bleeding and/or brain trauma
Any	Patients receiving dual antiplatelet therapy who suffer an intracranial haemorrhage

Further reading

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➔ See Blood transfusion, p272; Blood products, p274; Thromboelastography & rotational thromboelastometry, p254; Coagulants & antifibrinolytics, p340.

Clotting disorders

Critically ill patients tend to be auto-anticoagulated. However, the risk of major venous thrombosis increases with long-term immobility and paralysis and in specific prothrombotic conditions such as pregnancy, TTP, SLE (lupus anticoagulant), sickle cell crisis, hyperosmolar diabetic coma, HIT, and congenital or acquired protein C or protein S deficiency.

DIC is associated with microvascular clotting, consumption coagulopathy, and increased fibrinolysis.

Clotting of extracorporeal circuits, e.g. for renal replacement therapy may be due to:

- Mechanical obstruction to flow, e.g. kinked catheter.
- Inadequate anticoagulation.
- Severe illness due to a decrease in endogenous anticoagulants (e.g. antithrombin); this may result in circuit blockage despite a coexisting thrombocytopenia and/or coagulopathy.

Axillary vein or subclavian vein thrombosis may result from indwelling IV catheters.

Management

- Use thromboembolic deterrent (TED) stockings (grade II), preferably above the knee. Exceptions are patients with arterial vascular disease, peripheral oedema, or those in whom the stockings do not fit.
- Consider intermittent pneumatic compression, especially if the patient is at high risk and cannot be anticoagulated.
- If no contraindications, give prophylactic low-molecular-weight heparin (LMWH) with higher doses used in high-risk patients (e.g. previous deep vein thrombosis, femoral fractures).
- For treatment of pulmonary embolism or deep vein thrombosis, give treatment dose LMWH.
- Check APTT regularly if giving unfractionated heparin and maintain at 2–3 times normal. Monitoring is considered not necessary for LMWH, though an anti-factor Xa activity assay can be used.
- Intra-arterial clot can be treated by heparinization ± local infusion of thrombolytics. Alternatives include embolectomy or epoprostenol. Seek senior vascular surgical advice.
- Axillary or subclavian vein thrombosis should be managed by elevating the arm (e.g. in a Bradford sling), and heparinization.
- Some conditions require specific therapies, e.g. plasma exchange for SLE and TTP, whole blood exchange for sickle cell crisis.
- If HIT is suspected, stop all heparin infusions (including arterial catheter flush). Alternative non-heparin treatments include danaparoid, argatroban, fondaparinux or direct oral anticoagulant (DOAC). Confirm with a HIT antibody test (anti-PF4).
- Avoid warfarinization until the platelet count is within the normal range, as it may exacerbate the prothrombotic risk.

Further reading

See Thrombotic microangiopathies, p506.

Anaemia

Sub-normal haemoglobin (Hb) due to a decreased red cell mass. It may also be 'physiological' due to dilution from an increased plasma volume, e.g. pregnancy, vasodilated states. Although anaemia is often diagnosed at <130 g/L for men and <120 g/L for women, much lower levels are tolerated in intensive care practice, as multiple randomized controlled trials show no impact on outcomes using transfusion thresholds of 70 g/L for most patients (and 80 g/L for specific groups, e.g. active ischaemic heart disease) versus high higher thresholds.

Major causes in the ICU patient

- Blood loss, e.g. haemorrhage, regular blood sampling.
- Severe illness—analogous to 'anaemia of chronic disease', there is decreased marrow production and, possibly, a decreased lifespan.

Rarer causes include

- Microcytic anaemia—predominantly iron deficiency.
- Normocytic—chronic disease.
- Bone marrow failure (idiopathic, drugs, neoplasm, radiation).
- Haemolysis.
- Renal failure.
- Macrocytic—vitamin B_{12} and folate deficiency, alcoholism, cirrhosis, sideroblastic anaemia, hypothyroidism.
- Congenital diseases—sickle cell, thalassaemia.

Management

- Treatment of the cause where possible, e.g. iron replacement in iron deficiency anaemia.
- Blood transfusion—the ideal Hb level for optimal O_2 carriage and viscosity remains contentious. Improved outcomes were seen with a trigger of 70 g/L, though this was with non-leukodepleted blood that is now rarely used. A higher transfusion threshold, e.g. 90–100 g/L or higher, may potentially benefit those with cardiorespiratory disease although prospective trial data are lacking.
- Transfusion is usually given as packed red cells (PRC). Administer rapidly during active blood loss, or slowly (over 4 h) for correction of a gradually falling Hb.
- In patients needing massive blood transfusion, prevent dilutional coagulopathy. For each 6–8 units of PRC give FFP 10–15 mL/kg (~3 bags for a 70 kg person), a pool of platelets, and 1 unit of cryoprecipitate.
- Patients with chronically low Hb, i.e. <40–50 g/L, secondary to malnutrition or vitamin deficiency, need a slower elevation in Hb level to avoid precipitating acute heart failure. Thiamine should be co-administered to prevent beriberi. An initial target of 70–80 g/L is often acceptable. In patients with vitamin B_{12} deficiency, blood transfusion should be avoided; treat with vitamin B_{12}.
- Erythropoietin reduces the need for transfusion in long-term ICU patients and may be useful in those with multiple antibodies or declining transfusion for religious reasons. Prospective studies found no mortality benefit except in the subgroup admitted following trauma. There was a significant increase in thrombotic events.

Further reading

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➔ See Full blood count, p250; Blood transfusion, p272.

Sickle cell disease

A chronic, hereditary disease where HbS constitutes >50% of the Hb. The commonest and most severe form is HbSS (sickle cell anaemia) which predominantly affects people of African descent, but also others, e.g. Asian, Middle Eastern, and Hispanic. As the RBCs lack HbA, when deprived of oxygen these cells assume sickle shapes resulting in erythrostasis, occlusion of blood vessels, thrombosis, and infarction. After stasis, cells released are fragile and prone to haemolysis. Occasionally, there may be bone marrow failure.

Other sickle genotypes exist including HbSC (usually moderate clinical severity), HbS + β thalassaemia. A carrier of one HbS alone results in sickle cell trait which is usually asymptomatic, but RBCs may sickle under extreme conditions, e.g. low arterial partial pressure of oxygen (PaO_2), hypothermia.

Chronic features

Patients with sickle cell disease are usually anaemic (70–80 g/L) with a hyperdynamic circulation. Splenomegaly is common in youth but, with progressive episodes of infarction, splenic atrophy occurs with increased risk of infection, particularly pneumococcal. Chronic features include skin ulcers, renal failure, avascular bone necrosis (± supervening osteomyelitis, especially *Salmonella* spp.), hepatomegaly, jaundice, and cardiomyopathy. Sudden cardiac death is not uncommon before the age of 30.

Sickle cell crises

Crises are precipitated by various triggers, e.g. hypoxaemia (air travel, anaesthesia, etc.), infection, cold, dehydration, stress.

Thrombotic crisis

Seen mainly in bones and joints but also affects chest and abdomen giving rise to severe pain. Neurological symptoms (e.g. seizures, focal signs), haematuria, or priapism may occur. Pulmonary crises are the commonest reason for ICU admission; secondary chest infection or acute respiratory distress syndrome may supervene, worsening the crisis.

Haemolytic crisis

Haemolysis with haemoglobinuria, jaundice, and renal failure.

Aplastic crisis

Related to parvovirus B19 infection, consider if worsening anaemia and a reduction in the normally elevated reticulocyte count (10–20%).

Sequestration crisis

Rapid hepatic and splenic enlargement due to red cell trapping with severe anaemia. This condition is particularly serious.

Management

Prophylaxis against crises includes avoidance of hypoxaemia and other known precipitating factors, prophylactic penicillin and pneumococcal vaccine, and exchange transfusions.

1. Painful crises usually require prompt opiate infusions. Although psychological dependence is a risk in some patients, analgesia should not be withheld. Consider patient-controlled analgesia. Non-opiate

analgesics, e.g. paracetamol, non-steroidal anti-inflammatory drugs, can be given.
2. Give oxygen to maintain arterial oxygen saturation (SaO_2) at 95–98%. Avoid hyperoxia. Use bronchodilators if bronchospastic.
3. Rehydrate with IV fluids and keep warm. Avoid overhydration.
4. If bacterial infection is suspected, give appropriate antibiotics. Consider cover for pneumococcus, and perhaps a macrolide to cover atypical infections ± antiviral if viral infection suspected.
5. Transfuse blood if Hb falls significantly, but keep haematocrit <36%. For central nervous or chest crises perform a red cell exchange transfusion (manual or apheresis), aiming to lower the proportion of sickle cells to <30%. Note that cross-matching may be problematic.
6. Non-invasive or invasive mechanical ventilation may be necessary for chest crises.
7. Such patients may have iron overload from chronic transfusion, with possible heart and liver failure. Patients may be on oral chelator drugs.

Further reading

Howard J, Hart N, Roberts-Harewood M, et al. 2015. 'Guideline on the management of acute chest syndrome in sickle cell disease'. *Br J Haematol* 169: pp492–505. doi: 10.1111/bjh.13348

See Oxygen therapy, p40; Blood transfusion, p272; Non-opioid analgesics, p316; Opioid analgesics, p318; Antibacterials, p344.

Haemolysis

Shortening of erythrocyte lifespan below the expected 120 days. Marked intravascular haemolysis may lead to jaundice and haemoglobinuria.

Causes

- Blood transfusion reactions.
- Malaria.
- Sickle cell haemolytic crisis.
- Drugs, e.g. high-dose penicillin, methyldopa.
- Autoimmune (cold or warm antibody-mediated)—may be idiopathic or secondary, e.g. lymphoma, SLE, mycoplasma.
- HUS/TTP (microangiopathic haemolytic anaemia (MAHA)).
- Trauma (cardiac valve prosthesis).
- Glucose-6-phosphate dehydrogenase deficiency—oxidative crises occur following ingestion of fava beans or administration of drugs (e.g. primaquine, sulphonamides) leading to rapid-onset anaemia and jaundice.
- Paroxysmal nocturnal haemoglobinuria.

Diagnosis

- Unconjugated hyperbilirubinaemia, increased lactate dehydrogenase and urinary urobilinogen—increased RBC breakdown.
- Reticulocytosis—increased RBC production.
- Splenic hypertrophy—extravascular haemolysis.
- Methaemoglobinaemia, haemoglobinuria, free plasma Hb (intravascular haemolysis), reduced serum haptoglobins.
- RBC fragmentation (MAHA).
- Coombs' test (immune-mediated haemolysis).
- Other (including Hb electrophoresis, bone marrow biopsy).

Management

1. Identification and specific treatment of the cause where possible.
2. Blood transfusion to maintain Hb >70 g/L.
3. Massive intravascular haemolysis may lead to acute kidney injury. Maintain a good diuresis and haemo(dia)filter if necessary.

Further reading

See Blood transfusion, p272; Sickle cell disease, p502; Thrombotic microangiopathies, p506; Malaria, p614.

Thrombotic microangiopathies

Conditions such as TTP, HUS, and DIC cause endothelial cell injury/activation and microvascular thrombi resulting in haemolytic anaemia, non-immune thrombocytopenia, and organ failure.

Associated disorders include infection, cancer, pregnancy disorders (e.g. pre-eclampsia, HELLP), severe hypertension, autoimmune disorders such as SLE, and after stem cell or organ transplantation.

TTP

TTP is a medical emergency associated with severe deficiency of the ADAMTS13 metalloproteinase, with a resulting inability to cleave ultra-large von Willebrand factor multimers.

Classically associated with microangiopathic haemolytic anaemia, thrombocytopenic purpura (rarely severe bleeding), neurological abnormalities (e.g. altered mentation, seizures, hemiplegia that often fluctuates), pyrexia, and (generally mild) acute kidney injury.

Patients may die rapidly from heart dysfunction and dysrhythmias—perform echocardiogram, monitor troponin, and electrocardiogram.

Platelet count is usually 20–50 × 10^9/L and Hb 80–90 g/L with moderate-to-severe schistocytosis and raised lactate dehydrogenase and bilirubin (haemolysis). Avoid platelet transfusion unless directed by haematology.

ADAMTS13 activity is very low in TTP (<10%) but moderately reduced in HUS, sepsis, liver disease, pregnancy. ADAMTS13 activity and platelet count indicate treatment response.

Initial treatment may include caplacizumab, plasma exchange, steroids (12-hrly in severe, resistant cases) and rituximab.

HUS

Typical HUS is associated with Shiga-toxin producing (enterohaemorrhagic) *Escherichia coli*, especially the O157:H7 serotype.

Atypical, complement-mediated HUS (CM-HUS) describes all non-*E. coli* causes—may be sporadic or familial; up to 25% die during the acute phase and up to half may get end-stage renal disease or brain damage. Up to half of atypical HUS cases recur.

HUS is characterized by renal failure, thrombocytopenia, microangiopathic haemolytic anaemia. Brain, heart, gut, and other organs may also be involved. RBC fragmentation is seen on a blood film. The pathophysiology relates to an underlying complement dysregulation.

For Shiga-toxin HUS, antibiotics have not been shown to be effective. Treatment is supportive, e.g. renal replacement, blood pressure control.

For CM-HUS, treat initially and promptly with plasma exchange and complement inhibitor therapy, e.g. C5 inhibitor, eculizumab.

DIC

Causes of DIC include:

- Infection (e.g. Gram-negative sepsis including meningococcaemia, malaria, haemorrhagic fevers, e.g. Ebola).
- Obstetric complications (e.g. placental abruption, amniotic fluid embolism, pre-eclampsia).
- Neoplasms.

- Massive tissue injury (e.g. trauma, burns, major surgery).
- Miscellaneous (e.g. heatstroke, vasculitis, toxins, drugs snakebite, transfusion incompatibility).

The pathophysiology involves tissue factor-mediated thrombin generation leading to extensive formation of fibrin clots, mainly in small and mid-sized vessels, with depletion of coagulation proteases and platelets that may lead to bleeding.

Platelet count and protease inhibitors (e.g. protein C, antithrombin) are depleted, PT and aPTT are prolonged, and fibrin degradation products are increased.

Clinical presentation is bleeding from unrelated sites with organ dysfunction, often kidney or liver.

Treatment consists of removing the underlying cause (if possible) plus supportive care. Platelets and clotting factors should only be used for significant bleeding or to aid procedures/interventions. Heparin ± antithrombin can be considered for those with major thromboembolic disease but without evidence of significant haemorrhage.

Further reading

See Plasma exchange, p122; Blood transfusion, p272; Blood products, p274; Haemolysis, p504; Infection—diagnosis, p588; Pre-eclampsia & eclampsia, p686; HELLP syndrome, p688.

Platelet disorders

Thrombocytopenia

This is rarely symptomatic until the platelet count is $<50 \times 10^9$/L; spontaneous bleeding is much more likely with counts $<20 \times 10^9$/L. Bleeding is often minor, e.g. skin petechiae, oozing at intravascular catheter sites, but may be life-threatening, e.g. haemoptysis, intracranial haemorrhage.

Causes

- Sepsis—a common cause of a low platelet count in the critically ill; it is often a barometer of deterioration.
- DIC.
- Bone marrow suppression, e.g. chemotherapy agents.
- Related to antiplatelet antibodies, e.g. HIT, sulphonamides, quinine. See Table 28.2 for a risk scoring system for HIT.
- Other drugs, e.g. aspirin, chlorpromazine, digoxin.
- Following massive bleeding and multiple blood transfusions.
- Bone marrow failure, e.g. tumour infiltration, drugs.
- Splenomegaly.
- TTP, HUS.
- Idiopathic thrombocytopenic purpura (ITP).
- Specific infections, e.g. measles, infectious mononucleosis, typhus.
- Collagen vascular diseases, e.g. SLE.

Management

1. Treat cause, e.g. antibiotics (sepsis), stopping offending drugs, plasma exchange (TTP), splenectomy and corticosteroids (ITP).
2. Unless significant bleeding and otherwise well, platelets can be withheld while the count $>10 \times 10^9$/L.
3. If bleeding, septic or having an invasive procedure give 1–2 pools of platelets if count $<50 \times 10^9$/L.
4. Platelet transfusion is generally contraindicated in TTP, HUS, and HIT.

Deranged platelet function

Function may be deranged albeit with normal counts, e.g. following aspirin within past 1–2 weeks, epoprostenol, uraemia. Fresh platelets may be required if the patient is symptomatic. In uraemia, one dose of 0.3 μg/kg desmopressin given over 30 min may be useful before surgery.

Thrombocythaemia

Rare in ICU patients; platelet counts may exceed 800×10^9/L.

Causes

Prolonged low-level bleeding, post-splenectomy, myeloproliferative disorders. Essential (idiopathic) thrombocythaemia is unusual.

Management

As the major risk is thrombosis, management is based upon mobilizing the patient and administration of prophylactic aspirin (150 mg bd PO), dipyridamole (300–600 mg tds PO) or LMWH (5000 IU od subcutaneously).

Table 28.2 The 4Ts scoring system for pre-test clinical diagnosis of HIT

Score	2	1	0
Thrombocytopenia	>50% platelet fall to nadir ≥20	30–50% platelet fall, or nadir 10–19	<30% platelet fall, or nadir <10
Timing of onset of platelet fall after first heparin exposure	Days 5–10, or ≤day 1 with previous heparin in past 30 days	>Day 10 or timing unclear; or <day 1 with previous heparin in past 31–100 days	<Day 4 with no previous recent heparin
Thrombosis or other sequelae	New thrombosis; skin necrosis; or acute systemic reaction after IV heparin bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis	None
Other cause(s) of platelet fall	None	Possible	Definite

The 4Ts score is the sum of scores for all categories. Risk of HIT is low for scores 1–3, intermediate for scores 4–5, and high for scores 6–8.

Further reading

Lo G, Juhl D, Warkentin T, et al. 2006. 'Evaluation of pretest clinical score (4Ts) for the diagnosis of heparin induced thrombocytopenia in two clinical settings'. *J Thromb Haemost* 4: pp759–65. doi: 10.1111/j.1538-7836.2006.01787.x

➔ See Blood transfusion, p272; Antibacterials, p344; Thrombotic microangiopathies, p506; Infection—diagnosis, p588.

Chapter 29

Metabolic & endocrine disorders

Electrolyte management

A balance must be achieved between electrolyte intake and output. With electrolyte disturbances consider:

- Altered intake.
- Impaired renal excretion.
- Increased body losses (Table 29.1).
- Body compartment redistribution (e.g. increased capillary leak, secondary hyperaldosteronism, syndrome of inappropriate antidiuretic hormone secretion (SIADH)).

Plasma electrolyte values poorly reflect whole-body stores for predominantly intracellular ions (Table 29.2). However, excessively high or low plasma levels may induce symptoms and deleterious sequelae.

Water balance must also be taken into account; intravascular depletion or excess may respectively concentrate or dilute electrolyte levels.

Gravitational peripheral oedema implies increased total body Na^+ and water though intravascular salt and water depletion may still coexist.

The usual daily requirements of Na^+ and K^+ are ~1 mmol/kg/day assuming normal losses (e.g. sweat, urine, stool).

Table 29.1 Electrolyte losses

Large nasogastric aspirate, vomiting	Na^+, Cl^-, K^+
Sweating	Na^+, Cl^-
Polyuria	Na^+, Cl^-, K^+, Mg^{2+}
Diarrhoea	Na^+, Cl^-, K^+, Mg^{2+}
Ascitic drainage	Na^+, Cl^-, K^+

Table 29.2 Normal ranges and predominant location

Electrolyte	Predominant location	Normal plasma range
Na^+	Extracellular	135–145 mmol/L
Cl^-	Extracellular	95–105 mmol/L
K^+	Intracellular	3.5–5.0 mmol/L
Mg^{2+}	Intracellular	0.7–1.0 mmol/L
Ca^{2+}	Intracellular	2.2–2.6 mmol/L
PO_4^{3-}	Intracellular	0.8–1.5 mmol/L

Principles of management

1. Establish source and degree of fluid and electrolyte losses.
2. Assess patient for signs of:
   - intravascular fluid depletion
   - total body NaCl and water overload; i.e. gravitational oedema.
3. Measure serum urea, creatinine, and electrolytes, and if needed, osmolality plus, urine urea, electrolytes and osmolality.
4. As appropriate, either replace estimated fluid and electrolyte deficit or increase excretion (with diuretics, haemofiltration).

Further reading

➔ See Renal function, p234; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Hypernatraemia, p514; Hyponatraemia, p516; Hyperkalaemia, p518; Hypokalaemia, p520; Hypomagnesaemia, p524; Hypercalcaemia, p526; Hypocalcaemia, p528; Hypophosphataemia, p530.

Hypernatraemia

Causes

Hypernatraemia may occur with low, normal, or high total body Na^+. Table 29.3 lists causes and biochemical features.

Diabetes insipidus may be due to antidiuretic hormone (ADH) deficiency (cranial) or insensitivity of the nephron to ADH (nephrogenic). See Table 29.4 for differences.

Clinical features

Thirst, lethargy, coma, seizures, muscular tremor and rigidity, and an increased risk of intracranial haemorrhage. Thirst usually occurs when the plasma sodium rises 3–4 mmol/L above normal. Lack of thirst is associated with central nervous system disease.

Table 29.3 Causes and biochemical features of hypernatraemia

Type	Aetiology	Urine features
Low total body Na^+	Renal losses: diuretic excess, osmotic diuresis (glucose, urea, mannitol)	$[Na^+]$ >20 mmol/L Iso- or hypotonic
	Extrarenal losses: excess sweating	$[Na^+]$ <10 mmol/L Hypertonic
Normal total body Na^+	Renal losses: diabetes insipidus	$[Na^+]$ variable Hypo-, iso-, or hypertonic
	Extrarenal losses: respiratory and renal insensible losses	$[Na^+]$ variable Hypertonic
Increased total body Na^+	Conn's syndrome, Cushing's syndrome, excess NaCl, hypertonic $NaHCO_3$	$[Na^+]$ >20 mmol/L Iso- or hypertonic

Table 29.4 Features of diabetes insipidus

Feature	Cranial	Nephrogenic
Urine output	>3 L/day	>3 L/day
Plasma osmolality	>300 mOsm/kg	>300 mOsm/kg
Urine osmolality	<300 mOsm/kg	<300 mOsm/kg
Urine specific gravity	<1.005	<1.005
Plasma ADH	Low	High
Urine osmolality post-ADH administration	>750 mOsm/kg	<300 mOsm/kg

Management

Depends upon the cause and whether total body sodium stores are normal, low, or elevated and body water is normal or low. In all cases monitor Na^+ regularly during treatment.

Rate of correction

- If hyperacute (<24 h), correction can be rapid.
- Traditional management suggests gradual correction of plasma sodium levels over 1–3 days (<0.5 mmol/L/h or 10–12 mmol/L/24 h), particularly in chronic cases (>2 days' duration), to avoid cerebral oedema through sudden lowering of osmolality and rapid fluid shifts. However, the evidence base for this recommendation is negligible. Indeed, one recent observational study of 449 adult cases with Na^+ levels >155 mmol/L reported no cases of cerebral oedema despite correction rates of ≥1 mmol/L/h.
- If hypovolaemia is accompanied by haemodynamic alterations, restore the circulation with a balanced salt solution (e.g. Hartmann's). If serum Cl^- is high or rising, switch to hypotonic saline or 5%.

Normal total body Na^+ (water loss)

- Water replacement, either added to enteral feed or as 5% glucose intravenously (IV). Up to 5 L/day may be necessary.
- For cranial diabetes insipidus (CDI) restrict salt. CDI may be complete or partial. Complete CDI will require desmopressin (10 µg bd intranasal or 1–2 µg IV bd) whereas partial CDI may require desmopressin but often responds to drugs that increase ADH secretion or end-organ responsiveness to ADH, e.g. chlorpropamide, carbamazepine.
- Nephrogenic diabetes insipidus is managed by a low-salt diet and thiazides. High-dose desmopressin may be effective. Stop causative agents such as lithium.

Low total body Na^+ (Na^+ loss and proportionally greater water loss)

- Treat hyperosmolar hyperglycaemic state or uraemia as appropriate.
- Otherwise consider 0.9% saline or hypotonic (0.45%) saline. Up to 6 L/day may be needed.

Increased total body Na^+ (Na^+ excess)

- Water replacement, either added to enteral feed or as 5% glucose IV. Up to 5 L/day may be necessary.
- Add furosemide (10–20 mg IV as required (prn)).

Further reading

Chauhan K, Pattharanitima P, Patel N, et al. 2019. 'Rate of correction of hypernatremia and health outcomes in critically ill patients'. *Clin J Am Soc Nephrol* 14: pp656–63. doi: 10.2215/CJN.10640918

See Urinalysis, p236; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Coma, p466; Generalized seizures, p472; Intracranial haemorrhage, p478; Hyperosmolar diabetic emergencies, p544.

Hyponatraemia

Causes

See Table 29.5.

Causes of inappropriate ADH secretion

- Neoplasm, e.g. lung, pancreas, lymphoma.
- Most pulmonary lesions.
- Most central nervous system lesions.
- Surgical and emotional stress.
- Glucocorticoid and thyroid deficiency.
- Idiopathic.
- Drugs, e.g. carbamazepine, narcotics.

Table 29.5 Causes and biochemical features of hyponatraemia

Type	Aetiology	Urine [Na^+]
ECF volume depletion	Renal losses: diuretic excess, osmotic diuresis (glucose, urea, mannitol), renal tubular acidosis, salt-losing nephritis, mineralocorticoid deficiency, cerebral salt wasting	>20 mmol/L
	Extrarenal losses: vomiting, diarrhoea, burns, pancreatitis	<10 mmol/L
Modest ECF volume excess (no oedema)	Water intoxication: (NB: postoperative, transurethral resection syndrome), inappropriate ADH secretion, hypothyroidism, drugs (e.g. carbamazepine), glucocorticoid deficiency, pain, emotion	>20 mmol/L
	Acute and chronic renal failure	>20 mmol/L
ECF volume excess (oedema)	Nephrotic syndrome, cirrhosis, heart failure	<10 mmol/L

ECF = extracellular fluid.

Clinical features

Nausea, vomiting, headache, fatigue, weakness, muscular twitching, obtundation, psychosis, seizures, and coma. Symptoms depend on the rate as well as the magnitude of fall in plasma [Na^+].

- Severe hyponatraemia describes values <120 mmol/L.
- When duration exceeds 48 h it is deemed chronic.

Management

Rate and degree of correction

- Acute hyponatraemia can be corrected quickly, usually aiming to raise levels to >120 mmol/L in the first instance.

- For chronic hyponatraemia, more cautious correction is advised though there is no clear consensus on the optimal rate. The major risk of over-rapid correction, albeit rare, is the development of osmotic demyelination syndrome (ODS), which presents with brainstem pathologies beginning 48–72 h later. Key features of ODS include confusion, horizontal gaze paralysis, spastic quadriplegia.
- ODS can occur with normal Na^+ levels and with slow correction rates. Risk factors include alcoholism and malnutrition.
- With severe features such as seizures, aggressively elevate Na^+ by 5 mmol/L. Use small boluses/low infusion rates of hypertonic (3%) saline. Monitor Na^+ level regularly, hourly if necessary.
- The lack of randomized controlled trial data has generated inconsistent guidelines for rate of correction of chronic hyponatraemia ranging from 3 to 12 mmol/L per day. The evidence base suggests that risk is not increased with rates <18 mmol/L in the first 24 h.
- If Na^+ rise is too fast, consider diluting with 5% glucose, and/or desmopressin.

Extracellular fluid (ECF) volume excess

- If symptomatic and oedematous, consider furosemide (10–20 mg IV bolus prn) and replacement of urinary sodium losses with aliquots of hypertonic saline.
- If not symptomatic, restrict water to 1–1.5 L/day. If hyponatraemia persists, consider inappropriate ADH (SIADH) secretion.
- Vaptans, e.g. tolvaptan can be used for euvolaemic or hypervolaemic hyponatraemia including SIADH. These drugs should not be used if the patient is hypovolaemic or acutely symptomatic.
- For SIADH, give 0.9% saline; consider tolvaptan or demeclocycline.
- If SIADH unlikely, consider furosemide (10–20 mg IV bolus prn) and hypertonic saline.
- Renal replacement therapy may be needed.

General points

- Equations that calculate excess water are unreliable. It is safer to perform frequent estimations of plasma sodium levels.
- Use hypertonic saline cautiously in the elderly and those with poor cardiac function.
- Many patients achieve normonatraemia by spontaneous diuresis.
- True hyponatraemia may occur with a normal measured osmolality in the presence of abnormal solutes, e.g. ethanol, ethylene glycol, glucose.

Further reading

Nagler E, Vanmassenhove J, van der Veer S, et al. 2014. 'Diagnosis and treatment of hyponatremia: a systematic review of clinical practice guidelines and consensus statements'. *BMC Med* 12:1. doi: 10.1186/s12916-014-0231-1

Hofmaenner D, Singer M. 2022. 'Challenging management dogma where evidence is non-existent, weak or outdated'. *Intensive Care Med* 48: pp548–58. doi: 10.1007/s00134-022-06659-4

MacMillan T, Shin S, Topf J, et al. 2023. 'Osmotic demyelination syndrome in patients hospitalized with hyponatremia'. *NEJM Evid* 2: pp1–9. doi: 10.1056/evidoa2200215

Seethapathy H, Zhao S, Ouyang T, et al. 2023. 'Severe hyponatremia correction, mortality, and central pontine myelinolysis'. *NEJM Evid* 2: EVIDoa2300107. doi: 10.1056/EVIDoa2300107

See Urinalysis, p236; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Coma, p466; Acute weakness, p468; Generalized seizures, p472.

Hyperkalaemia

Plasma potassium depends on the balance between intake, excretion, and the distribution of potassium across cell membranes. Excretion is normally controlled by the kidneys.

Causes

- Reduced renal excretion (e.g. acute kidney injury, chronic renal failure, adrenal insufficiency, diabetes, potassium-sparing diuretics).
- Intracellular K^+ release (e.g. acidosis, rapid transfusion of old blood), cell lysis (including rhabdomyolysis, haemolysis, tumour lysis), K^+ channel openers (nicorandil, isoflurane, ciclosporin).
- Potassium poisoning and iatrogenic overload. A rapid rate of rise of K^+ is more dangerous than a chronically elevated level. Cardiac arrest can potentially occur following 40 mmol KCl infused over 1 h.

Clinical features

Hyperkalaemia may cause dangerous arrhythmias including severe bradycardia and cardiac arrest. Arrhythmias are more related to the rate of rise of K^+ than the absolute level.

Clinical features such as paraesthesiae and areflexic weakness are not closely related to the degree of hyperkalaemia but usually occur after electrocardiogram (ECG) changes (tall 'T' waves, flat 'P' waves, prolonged PR interval, and wide QRS).

Hypotension resistant to high doses of catecholamines may occur with hyperkalaemia related to excess K^+ channel activation.

Management

- Restrict K^+, stop K^+-containing or -sparing drugs (e.g. spironolactone).
- Look for 12-lead ECG features of hyperkalaemia.
- In hyperglycaemic emergencies, potassium levels will fall rapidly after the first few hours of insulin and fluid treatment; replacement will then be needed.

Cardiac arrest associated with hyperkalaemia

Give 8.4% sodium bicarbonate (50–100 mL) in addition to standard cardiopulmonary resuscitation and other treatments as detailed below.

Acute rise to plasma potassium >7 mmol/L or >6 with ECG changes

Give 10% calcium chloride 10 mL urgently. Although $CaCl_2$ does not reduce plasma K^+ levels, it stabilizes the myocardium against arrhythmias.

Give 50% glucose (50 mL) and soluble insulin (10 IU IV over 20 min). Monitor blood glucose every 15 min, and give more glucose if necessary.

K^+ >6 mmol/L

Consider glucose and insulin as above. Salbutamol will reduce K^+ by 0.7 mmol/L (peak effect 30 min IV vs 90 min if nebulized).

Give oral potassium binders such as sodium zirconium cyclosilicate (10 g tds up to 48 h) or calcium polystyrene sulfonate (15 g qds orally (PO) or 30 g bd rectally (PR)).

If resistant to medical treatment, use haemodialysis or haemodiafiltration (more effective than haemofiltration).

Hyperkalaemia related to K^+ channel opening drug

In addition to glucose and insulin for severe hyperkalaemia, consider glibenclamide (glyburide) 5–10 mg via the nasogastric tube. An effect is often seen within 30 min.

Further reading

Singer M, Coluzzi F, O'Brien A, et al. 2005. 'Reversal of life-threatening, drug-related potassium-channel syndrome by glibenclamide'. *Lancet* 365: pp1873–5. doi: 10.1016/S0140-6736(05)66619-6

➲ See Haemo(dia)filtration, p118; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Cardiac arrest, p360; Bradyarrhythmias, p414; Acute kidney injury—diagnosis, p428; Acute kidney injury—management, p430; Rhabdomyolysis, p648.

Hypokalaemia

Plasma potassium depends on the balance between intake, excretion, and the distribution of potassium across cell membranes. Excretion is normally controlled by the kidneys.

Causes

- Inadequate intake or replacement.
- Gastrointestinal losses (e.g. vomiting, diarrhoea, fistula, ileostomy).
- Renal losses (e.g. diabetic ketoacidosis, hyperaldosteronism, Cushing's syndrome, renal tubular acidosis types 1 and 2, metabolic alkalosis, hypomagnesaemia, drugs (e.g. diuretics, corticosteroids, theophyllines)).
- Haemofiltration losses.
- Potassium transfer into cells (e.g. acute alkalosis, glucose infusion, insulin treatment, salbutamol, familial periodic paralysis).

Clinical features

- Arrhythmias (supraventricular tachycardia, ventricular tachycardia, and torsades de pointes).
- ECG changes (ST depression, 'T'-wave flattening, 'U' waves).
- Metabolic alkalosis.
- Constipation.
- Ileus.
- Weakness.

Management

1. Treat any cause of potassium loss, e.g. loperamide for diarrhoea.
2. If K^+ <2.5 mmol/L or the patient is symptomatic give K^+ IV with ECG monitoring. Give up to 20 mmol via a central vein over 30–60 min, then repeat depending on serum levels. In an emergency, up to 40 mmol can be given over an hour via central venous catheter.
3. Slower IV replacement (20 mmol over 1–2 h) can be used otherwise.
4. Replace magnesium if low.
5. Give oral/nasogastric K^+ supplements (to a total intake of 80–120 mmol/day, including nutritional input) when hypokalaemia is mild (>2.5 mmol/L) with no clinical features and enteral absorption is satisfactory.
6. Consider the degree of ongoing fluid and potassium losses.

Further reading

See Diuretics, p292; Metabolic alkalosis, p536.

Hypermagnesaemia

Causes

- Renal failure.
- Excessive intake, e.g. magnesium-containing medications.
- Lithium therapy.
- Hypothyroidism, adrenal insufficiency.

Clinical features

Magnesium is involved in production and utilization of energy stores and in the mediation of nerve transmission. Symptoms do not usually occur until plasma levels are >2.0 mmol/L. Symptoms are exaggerated by concomitant hypocalcaemia, hyperkalaemia, or uraemia:

- Attenuation of deep tendon reflexes.
- Paraesthesiae, especially affecting the face.
- Muscle weakness progressing to apnoea.
- Hypotension.
- Bradyarrhythmias and heart block.
- Paralytic ileus.
- Coagulation disturbance due to reduced platelet adhesiveness.

Management

- Where possible, identify and treat the cause.
- In patients with severe hypermagnesaemia infuse calcium gluconate 10% (10–20 mL IV).
- If renal function is adequate consider furosemide (20–40 mg IV 3–4-hrly).

Further reading

See Calcium, magnesium, & phosphate, p240; Diuretics, p292.

Hypomagnesaemia

Causes

- Excess loss, e.g. diuretics, other causes of polyuria (including poorly controlled diabetes mellitus), severe diarrhoea, prolonged vomiting, large nasogastric aspirates, ileostomy.
- Inadequate intake, e.g. starvation, parenteral nutrition, alcoholism, malabsorption syndromes.

Clinical features

Magnesium is involved in production and utilization of energy stores and in the mediation of nerve transmission. Severe symptoms do not usually occur until levels drop below 0.5 mmol/L. Low plasma levels, which do not necessarily reflect either intracellular or whole-body stores, may thus be associated with features related to these functions:

- Confusion, irritability.
- Seizures.
- Muscle weakness, lethargy.
- Arrhythmias.
- Symptoms related to hypocalcaemia and hypokalaemia which are resistant to calcium and potassium supplementation, respectively.

Management

- Where possible, identify and treat the cause.
- For severe, symptomatic hypomagnesaemia, give $MgSO_4$ (10 mmol IV over 3–5 min). Repeat as needed.
- In less acute situations, or for asymptomatic hypomagnesaemia, give $MgSO_4$ (10–20 mmol IV over 1–2 h). Repeat as necessary, or according to repeat plasma levels.
- Continuous IV infusion (e.g. 3–5 mmol $MgSO_4$ solution/h) can be given with blood pressure (BP) monitoring. This is usually reserved for therapeutic indications aiming for supranormal plasma Mg^{2+} levels (1.5–2 mmol/L), e.g. treatment of supraventricular and ventricular arrhythmias, pre-eclampsia and eclampsia, bronchospasm.
- Oral magnesium sulfate has a laxative effect and may cause severe diarrhoea. Magnesium glycerophosphate may be better tolerated.
- Hypermagnesaemia may develop in renal failure; caution should be applied when administering IV magnesium.

Further reading

See Calcium, magnesium, & phosphate, p240; Diuretics, p292.

Hypercalcaemia

Serum calcium is bound to albumin, and values should be adjusted for serum albumin. Alternatively, use ionized calcium.

Causes

- Malignancy (e.g. myeloma, bony metastases, hypernephroma).
- Primary or tertiary hyperparathyroidism.
- Drugs, e.g. thiazides, lithium, theophylline toxicity.
- Sarcoidosis, tuberculosis.
- Excess intake of calcium, vitamin A or D.
- Immobilization, rhabdomyolysis.
- Rarely, thyrotoxicosis, adrenal insufficiency.
- Reversal of citrate anticoagulation for renal replacement therapy.

Clinical features

Usually become apparent when total (ionized and unionized) plasma levels >3.5 mmol/L, or the ionized fraction >1.7 mmol/L (normal range 1.05–1.25). Symptoms depend on age, duration and rate of increase of plasma calcium, and concurrent medical conditions. Features include:

- Nausea, vomiting, weight loss, pruritus.
- Polyuria, renal calculi, renal failure.
- Shortened QTc, arrhythmias, hypertension, cardiomyopathy.
- Depression, mania, psychosis, confusion, drowsiness, coma.
- Abdominal pain, constipation.
- Acute pancreatitis, peptic ulceration.
- Muscle weakness, fatigue, lethargy.

Severity

- <3 mmol/L: often asymptomatic, no urgent treatment indicated.
- 3.0–3.5 mmol/L: may be symptomatic depending on rate of elevation. Requires prompt correction.
- >3.5 mmol/L: risk of arrhythmias and coma. Requires urgent treatment.

Management

1. Identify and treat cause where possible.
2. Monitor haemodynamics, urine output, and ECG morphology with frequent measures of plasma Ca^{2+}, PO_4^{3-}, Mg^{2+}, Na^+, and K^+.
3. Volume repletion with 0.9% saline (4–6 L per 24 h) which inhibits tubular reabsorption of calcium and lowers plasma Ca^{2+} by 0.4–0.6 mmol/L. This intervention should precede other therapy.
4. After fluids, consider IV bisphosphonates (e.g. pamidronate, zoledronic acid) infusion. May require repeat dosing after 7 days. See Table 29.6 for drug dosages.
5. Mobilization should be encouraged, where possible.
6. Calciuresis—after adequate volume repletion, consider a forced diuresis with furosemide plus 0.9% saline to maintain normovolaemia. An effect is usually seen <12 h. Loop diuretics inhibit calcium reabsorption. Thiazide diuretics reduce tubular reabsorption and may worsen hypercalcaemia.

7. Dialysis/haemofiltration—may be indicated early if patient is in established oligo-anuric renal failure ± fluid overloaded. Note that citrate anticoagulation for renal replacement therapy may be a cause if too much calcium reversal is given.
8. Corticosteroids can be effective for hypercalcaemia related to haematological cancers, vitamin D overdose, and sarcoidosis.
9. Calcitonin has a rapid onset of action with a nadir often reached within 12–24 h. Rebound hypercalcaemia may occur. It generally does not drop plasma Ca^{2+} by more than 0.5 mmol/L.

Table 29.6 Drug dosages for treating hypercalcaemia

Diuretics	Furosemide 10–40 mg IV 2–4 h or equivalent by infusion (may be increased, if necessary)
Pamidronate	60–90 mg IV infusion over 2–24 h at 20 mg/h
Zoledronic acid	4 mg over 15 min
Corticosteroids	Hydrocortisone 100 mg qds IV or prednisolone 40–60 mg PO for 3–5 days
Calcitonin	3–4 U/kg IV followed by 4 U/kg SC bd

Further reading

Walsh J, Gittoes N, Selby P, for the Society for Endocrinology Clinical Committee. 2016. 'Society for Endocrinology endocrine emergency guidance: emergency management of acute hypercalcaemia in adult patients. *Endocr Connect* 5: ppG9–G11. doi: 10.1530/EC-16-0055

➔ See Calcium, magnesium, & phosphate, p240; Diuretics, p292; Corticosteroids, p352; Acute kidney injury—diagnosis, p428; Pancreatitis, p462; Thyroid emergencies, p546; Hypoadrenal crisis, p548.

Hypocalcaemia

Acute reduction may be an emergency. Establish cause to optimize treatment.

Causes

- Associated with hyperphosphataemia:
  - renal failure
  - severe vitamin D deficiency (common but often unrecognized in critical illness)
  - rhabdomyolysis
  - hypoparathyroidism (including parathyroidectomy)
  - pseudohypoparathyroidism
- Associated with low/normal phosphate:
  - critical illness including sepsis, burns
  - hypomagnesaemia
  - pancreatitis, rhabdomyolysis
  - osteomalacia
  - over-hydration
  - massive blood transfusion (citrate-binding)
  - citrate anticoagulation
  - hyperventilation and resulting respiratory alkalosis may reduce ionized plasma Ca^{2+} and induce clinical features

Clinical features

Usually appear when total plasma Ca^{2+} <2 mmol/L and the ionized fraction is <0.8 mmol/L:

- Perioral and peripheral paraesthesiae.
- Tetany (including carpopedal spasm).
- Laryngospasm.
- Muscular weakness.
- Chvostek and Trousseau's signs.
- Prolonged QT interval, arrhythmias, and hypotension.
- Seizures.

Management

Mild: asymptomatic, serum Ca^{2+} >1.9 mmol/L

- PO calcium supplements.
- Correct vitamin D if deficient.
- Correct serum magnesium if Mg^{2+} low.

Severe: symptomatic and/or serum Ca^{2+} <1.9 mmol/L

- Give 5–10 mL 10% calcium chloride solution as a slow IV bolus over 2–5 min. Repeat as necessary.
- ECG monitoring during IV calcium infusion.
- Treat underlying cause:
  - postoperatively, may require vitamin D correction, e.g. with alfacalcidol
  - correct hypomagnesaemia and/or hypokalaemia if present
  - if respiratory alkalosis is present, adjust ventilator settings or, if spontaneously hyperventilating and agitated, calm ± sedate.

Further reading

Amrein K, Schnedl C, Holl A, et al. 2014. 'Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial'. *JAMA* 312: pp1520–30. doi: 10.1001/jama.2014.13204

Turner J, Gittoes N, Selby P, for the Society for Endocrinology Clinical Committee. 2016. 'Society for Endocrinology endocrine emergency guidance: emergency management of acute hypocalcaemia in adult patients. *Endocr Connect* 5: ppG7–G8. doi: 10.1530/EC-16-0056

➔ See Calcium, magnesium, & phosphate, p240; Pancreatitis, p462; Hypomagnesaemia, p524; Hypophosphataemia, p530.

Hypophosphataemia

Causes

- Critical illness.
- Inadequate intake.
- Loop diuretic therapy.
- Renal replacement therapy.
- Parenteral nutrition—levels may fall rapidly during high-dose IV glucose therapy, especially if insulin is given.
- Alcoholism.
- Hyperparathyroidism.
- Refeeding syndrome—occurs when patients with prolonged starvation or malnutrition are given high carbohydrate loads, with rapidly falling phosphate, magnesium, and potassium, and fluid retention. This can precipitate arrhythmias. Acute heart failure can be triggered by a sudden increase in insulin release resulting in increased anabolism. Evidence that refeeding syndrome occurs after short periods of starvation (e.g. <10 days) is weak.

Clinical effects

Plasma phosphate represents <1% of total body stores. Plasma levels fall rapidly with acute illness, renal replacement, or insulin therapy but the patient usually remains asymptomatic, even with very low levels (<0.3 mmol/L). Features rarely associated with hypophosphataemia include muscle weakness, rhabdomyolysis, paraesthesiae, haemolysis, platelet dysfunction, cardiac failure. However, such features may be driven by the underlying cause of the critical illness rather than the low phosphate itself.

Management

Unless chronically depleted, hypophosphataemia may be left untreated as levels usually normalize spontaneously within a few days.

Correction of established hypophosphataemia, if needed, should be guided by aetiology, symptomatology, severity, and duration:

- Give phosphate supplements (5–10 mmol) by IV infusion over 6 h, and repeat as needed.
- To prevent refeeding syndrome, recognize the possibility in malnourished or long-term starved patients. Start feed slowly (50–70% of normal for 3–5 days) with close monitoring of electrolytes (K^+, Mg^{2+}, phosphate) to direct supplementation as needed. Add thiamine and other vitamin supplements.

Further reading

Rio A, Whelan K, Goff L, et al. 2013. 'Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study'. *BMJ Open* 3:e002173. doi: 10.1136/bmjopen-2012-002173

See Enteral nutrition, p142; Parenteral nutrition, p144; Calcium, magnesium, & phosphate, p240; Diuretics, p292.

General acid–base principles

In health, acid–base balance is tightly regulated by the lungs (blowing off CO_2), kidney (removing H^+ and generating HCO_3^-), and by intracellular (e.g. proteins, phosphate) and extracellular (e.g. bicarbonate) buffering agents. Arterial blood is usually maintained within a pH range of 7.38 and 7.42.

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

Changes in pH may be due to either metabolic or respiratory causes. A decrease in pH leads to acidaemia and an increased pH leads to alkalaemia.

Respiratory causes relate to increased or decreased exhalation of CO_2. Metabolic causes include excess ingestion or production, loss or failure of excretion, of acid or base.

By the Stewart theory, blood pH is determined by arterial partial pressure of carbon dioxide ($PaCO_2$), the strong ion difference (SID), and the concentration of non-volatile weak acids. Weak acids dissociate to produce weak anions (predominantly albumin, phosphate). Bicarbonate is also a weak anion but is not a dependent pH determinant. Strong ions are completely ionized. Normally, there is an excess of strong cations. The strong ion difference balances weak anions to maintain electrical equilibrium.

$$SID = \left(Na^+ + K^+ + Mg^{2+} + Ca^{2+}\right) - \left(Cl^- + \text{lactate} + \text{other strong anions}\right)$$

This can be estimated by the Na^+ to Cl^- gap (normally 35–40 mmol/L). A smaller gap indicates a lower SID. A change in charge equilibrium (by altering SID or weak anion concentration) is compensated by a change in H^+ ion concentration with a resulting acid–base disturbance.

Over time, respiratory and renal adjustments correct pH towards normal by altering $PaCO_2$ and SID.

Principles of management

1. Correct (where possible) the underlying cause, e.g. hypoperfusion.
2. Avoid large volume saline-based fluids. Consider balanced electrolyte solutions such as Hartmann's or Ringer's lactate, or glucose solutions if hyperchloraemic acidosis develops.
3. NaCl infusion for vomiting-induced alkalosis; insulin, Na^+, and K^+ for diabetic ketoacidosis.
4. $NaHCO_3$ (iso- or hypertonic depending on fluid status) can be used when appropriate, e.g. renal failure with metabolic acidaemia or hyponatraemia with concurrent hyperchloraemia.

Factors altering pH

In addition to changes in $PaCO_2$, the following will affect pH:

Increased strong ion difference (alkalosis)

- Cl^- loss, e.g. vomiting, large gastric aspirates, diuretics, hyperaldosteronism, corticosteroids.
- K^+ retention, e.g. renal failure, renal tubular acidosis type 4.
- Na^+ load.

Decreased strong ion difference (acidosis)

- Cl^- increase, e.g. excessive 0.9% saline, acetazolamide.

- Hyperlactataemia.
- Na^+ or K^+ loss, e.g. diarrhoea, small bowel fistula, uretero-enterostomy, renal tubular acidosis types 1 and 2.
- Unmeasured anions, e.g. ketosis, salicylate, methanol, ethanol, ethylene glycol poisoning.

Decreased weak acids (alkalosis)

- Hypoalbuminaemia.

Further reading

See Sodium bicarbonate, p268.

Metabolic acidosis

A subnormal arterial blood pH with a base deficit >2 mmol/L, reduced strong ion difference, and/or an increase in weak acids. Outcome is associated with the severity and duration of metabolic acidosis.

Causes

- Associated with hyperlactataemia, e.g.:
  - tissue hypoperfusion/ischaemia
  - other causes of increased anaerobic respiration (glycolysis), e.g. lymphoma
  - excess lactate administration, e.g. buffered lactate fluids
  - decreased utilization/metabolism, e.g. liver failure
  - inhibition of mitochondrial aerobic respiration, e.g. sepsis, drugs (e.g. metformin) or carbon monoxide poisoning
  - high endogenous stress driven by a hyperadrenergic state, or a catecholamine infusion can cause accelerated aerobic glycolysis in the absence of tissue hypoxia. This drives increased activity of muscle Na^+ pumps, releasing lactate to be utilized by vital organs (e.g. brain, heart) as a fuel source
  - increased muscle activity (e.g. post-seizure).
- Hyperchloraemia, e.g. excessive 0.9% saline infusion.
- Ketoacidosis—high levels of ketones (β-hydroxybutyrate, acetoacetate), e.g. uncontrolled diabetes, starvation alcoholism.
- Renal failure—accumulation of organic acids.
- Drugs, e.g. salicylate overdose (causing uncoupling), acetazolamide (carbonic anhydrase inhibition), ammonium chloride, drugs inhibiting mitochondria (e.g. highly active antiretroviral therapy), vasopressor agents inducing regional ischaemia, or accelerated aerobic glycolysis.
- Ingestion of poisons, e.g. paraldehyde, ethylene glycol, methanol.
- Cation loss, e.g. severe diarrhoea, small bowel fistulae, ileostomy.
- Glucose-6-phosphatase deficiency.
- Thiamine deficiency (affects glycolysis and the Krebs cycle).
- Prolonged seizures or excessive muscular activity.

Clinical features

- Dyspnoea including Kussmaul breathing.
- Haemodynamic instability, especially where there is tissue hypoxia.
- A rapidly increasing metabolic acidosis (over minutes to hours) is not due to renal failure alone. Suspect other causes (e.g. tissue hypoperfusion, sepsis, tissue necrosis) if systemic deterioration.

Management

1. Identify and treat the underlying cause where possible rather than simply administering alkali to normalize the arterial pH.
2. Urgent haemo(dia)filtration may be necessary if oligo-anuria persists.
3. Reversal of the metabolic acidosis is generally an indication of successful therapy. An increasing base deficit suggests ongoing therapeutic manoeuvres are either inadequate or wrong.

4. Bicarbonate therapy may be appropriate when tissue hypoperfusion has been corrected/excluded. This is particularly the case for ongoing loss of alkali (e.g. biliary fistula, diarrhoea) or inability to acidify urine.

Further reading

Levy B, Gibot S, Franck P, et al. 2005. 'Relation between muscle Na^+K^+ATPase activity and raised lactate concentrations in septic shock: a prospective study'. *Lancet* 365: pp871–5. doi: 10.1016/S0140-6736(05)71045-X

Adeva-Andany M, López-Ojén M, Funcasta-Calderón R, et al. 2014. 'Comprehensive review on lactate metabolism in human health'. *Mitochondrion* 17: pp76–100. doi: 10.1016/j.mito.2014.05.007

Kraut J, Madias N. 2014. 'Lactic acidosis'. *N Engl J Med* 371: pp2309–19. doi: 10.1056/NEJMra1309483

Kimmoun A, Novy E, Auchet T, et al. 2015. Hemodynamic consequences of severe lactic acidosis in shock states: from bench to bedside. *Crit Care* 19:175. doi: 10.1186/s13054-015-0896-7

➔ See Blood gas analysis, p174; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Lactate, p246; Crystalloids, p266; Sodium bicarbonate, p268; Acute kidney injury—diagnosis, p428; General acid–base principles, p532; Diabetic ketoacidosis, p542; Sepsis—definitions & pathophysiology, p592.

Metabolic alkalosis

Elevated arterial blood pH with a base excess >2 mmol/L and increased strong ion difference due to loss of (non-carbonic) acid and/or gain of base.

The kidney is efficient at excreting large quantities of bicarbonate. Persistence of a metabolic alkalosis is often a result of chronic renal failure or a diminished ECF volume with severe depletion of K^+ resulting in an inability to reabsorb Cl^- in excess of Na^+.

- The patient is usually asymptomatic though, if spontaneously breathing, will generally hypoventilate.
- A metabolic alkalosis will cause a left shift of the oxyhaemoglobin curve, reducing oxygen availability to the tissues.
- If severe (pH >7.6) metabolic alkalosis may result in encephalopathy, seizures, decreased coronary blood flow, and cardiac contractility.

Causes

- Diuretics.
- Large nasogastric aspirates, vomiting.
- Secondary hyperaldosteronism with potassium depletion.
- Use of renal replacement fluid containing excess buffer (e.g. lactate).
- Renal compensation for chronic hypercapnia, developing within a week. Though more apparent when the patient hyperventilates, or is hyperventilated to normocapnia, an overcompensated metabolic alkalosis can occasionally be seen in the chronic state (i.e. a raised pH in an otherwise stable long-term hypercapnic patient).
- Excess administration of bicarbonate.
- Excess administration of citrate (e.g. large blood transfusion, renal replacement therapy).
- Drugs, including laxative abuse, corticosteroids.
- Rarely, Cushing's, Conn's, or Bartter's syndromes.

Management

1. Replacement of fluid, Na^+, Cl^- (i.e. give 0.9% saline), and K^+ is often sufficient to restore acid–base balance.
2. With distal renal causes related to hyperaldosteronism, consider spironolactone (or IV potassium canrenoate).
3. Active treatment is rarely necessary. If so, give ammonium chloride (5 g tds PO). Hydrochloric acid can be used for severe metabolic alkalosis (pH >7.7), via a central vein in a concentration of 1 mmol HCl/mL H_2O at a rate <1 mmol/kg/h. Renal replacement therapy is another option.
4. Compensation of long-standing respiratory acidosis, followed by correction of that acidosis, e.g. with mechanical ventilation, will lead to an uncompensated metabolic alkalosis. This usually corrects with time though acetazolamide (or, rarely, mechanical 'hypoventilation', i.e. maintaining hypercapnia) can be considered.

Further reading

See Blood gas analysis, p174; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Sodium bicarbonate, p268; Blood transfusion, p272; Diuretics, p292; Sepsis—definitions & pathophysiology, p592; Sepsis—management, p594.

Hyperglycaemia

Causes

- A common occurrence in critically ill patients. Hyperglycaemia is often due to a combination of impaired glucose tolerance, insulin resistance, high circulating levels of endogenous catecholamines and corticosteroids, and drugs that antagonize insulin.
- Pancreatitis resulting in islet cell damage.
- Pancreatectomy.

Clinical features

None in the short term, other than polyuria from the osmotic diuresis. The patient may complain of thirst or show signs of hypovolaemia if fluid balance is allowed to become too negative.

Metabolic effects

A relative lack of insulin prevents cellular glucose uptake and utilization resulting in:

- Altered cellular metabolism with increased lipolysis, ketone body production, and acidaemia.
- Increased oxidative damage.
- Increased risk of infection (decreased neutrophil activity).

Treatment goal

Carefully titrate insulin to avoid hyperglycaemia and hypoglycaemia as both are associated with an increased rate of adverse outcomes. Guidelines recommend blood sugar levels be maintained between 5 and 10 mmol/L.

Management

- Treat if blood glucose persists >10 mmol/L.
- Use a short-acting insulin infusion (e.g. Actrapid®) and titrate to maintain normoglycaemia (4–10 mmol/L). Usually 1–4 U/h are required though this may need to be increased, especially in diabetics who become critically ill. Regular bedside monitoring of blood sugar should be performed, up to hourly if unstable.
- Unless the patient is stable, oral hypoglycaemic agents are generally avoided in the ICU because of their prolonged duration of action and possibly unpredictable absorption.

Further reading

Van den Berghe G, Wouters P, Weekers F, et al. 2001. 'Intensive insulin therapy in critically ill patients'. *N Engl J Med* 345: pp1359–67. doi:10.1056/NEJMoa011300

Van den Berghe G, Wilmer A, Hermans G, et al. 2006. 'Intensive insulin therapy in the medical ICU'. *N Engl J Med* 354: pp449–61. doi:10.1056/NEJMoa052521

Brunkhorst F, Engel C, Bloos F, et al. 2008. 'Intensive insulin therapy and pentastarch resuscitation in severe sepsis'. *N Engl J Med* 358: pp125–39. doi: 10.1056/NEJMoa070716

NICE-SUGAR Study Investigators. 2009. 'Intensive versus conventional glucose control in critically ill patients'. *N Engl J Med* 360: pp1346–9. doi:10.1056/NEJMoa0810625

See Pancreatitis, p462; Diabetic ketoacidosis, p542; Hyperosmolar diabetic emergencies, p544.

Hypoglycaemia

Causes

- Excess insulin or sulfonylurea.
- Liver failure with depletion of glycogen stores.
- Alcohol.
- Hypoadrenalism (including Addison's disease), hypopituitarism.
- Other drugs, e.g. quinine, aspirin.
- Inadequate intake of carbohydrate.

Clinical features

- Nausea, vomiting.
- Increased sympathetic activity, e.g. sweating, tachycardia.
- Altered behaviour and conscious level.
- Seizures, focal neurological signs.

Management

1. Monitor carefully and increase monitoring frequency in high-risk conditions for hypoglycaemia, e.g. insulin infusion, liver failure, quinine treatment of malaria.
2. Administer 50–100 mL 20% glucose solution IV (or 25–50 mL of 50% glucose via a central venous line) if the blood glucose is:
   - ≤3 mmol/L or
   - ≤4 mmol/L and the patient is symptomatic or
   - within the normal range but the patient is symptomatic (usually long-standing poorly controlled diabetics).
3. Repeat as necessary every few minutes until symptoms abate and the blood glucose level has normalized.
4. If blood glucose is 3–4 mmol/L and the patient is non-symptomatic, reduce the rate of insulin infusion (if present) and/or increase calorie intake (enterally or parenterally). In type 1 diabetes mellitus, continue insulin with adequate glucose intake.
5. A continuous parenteral infusion of 10%, 20%, or 50% glucose solution varying from 10 to 100 mL/h may be needed. This depends on persisting hypoglycaemia plus fluid balance/urine output. Liver failure may result in persisting hypoglycaemia. 5% glucose solution only contains 20 Cal/100 mL and is not useful to prevent or treat hypoglycaemia.
6. In the rare instance of no venous access, hypoglycaemia may be temporarily reversed by glucagon 1 mg given either intramuscularly or SC.
7. Continuing hypoglycaemia in the face of adequate treatment and lack of symptoms should be confirmed with formal laboratory blood sugar estimation to exclude malfunctioning of the bedside testing equipment.

Further reading

See Acute liver failure, p454; Hypoadrenal crisis, p548.

Diabetic ketoacidosis

May occur *de novo* in a previously undiagnosed diabetic, or after an acute insult (e.g. infection) or inadequate insulin in known diabetics.

Clinical features

- Hyperglycaemia (NB: ~10–15% may have mild hyperglycaemia). Consider euglycaemic ketoacidosis if the patient is fasting with recent use of sodium–glucose cotransporter 2 (SGLT2) inhibitors. Glycosuria results in euglycaemia despite ketoacidosis.
- Excess fat metabolism, with increased generation of fatty acids and ketones leading to ketoacidosis.
- Osmotic diuresis with large losses of fluid (up to 6–10 L), sodium (400–800 mmol), potassium (250–800 mmol), and magnesium.

Symptoms arise from hypovolaemia, metabolic acidosis, and electrolyte imbalance with polyuria. Hyperventilation is prominent. Coma need not necessarily be present for the condition to be life-threatening. Plasma amylase is often >1000 U/L but does not necessarily indicate pancreatitis.

Causes

- Precipitating causes include sepsis, myocardial infarction, stroke, gastroenteritis.
- Abdominal pain should not be dismissed as part of the syndrome and may be a feature of an underlying cause.

Fluid and electrolyte management

- Monitor and titrate fluid and electrolyte repletion to individual needs. Traditional regimens (e.g. 3–4 L within the first 3–4 h) increase the risk of cerebral oedema, cardiac and renal failure, and are usually unnecessary.
- Give 200–250 mL fluid challenges initially to restore an adequate circulating blood volume and correct tissue hypoperfusion.
- Thereafter, replace fluid with a Na^+ containing fluid at a rate of 100–200 mL/h until the salt and water debt has been replenished. While 0.9% saline is traditionally recommended, this can cause significant hyperchloraemia and a persisting metabolic acidosis. The unwary may respond by giving further saline, inducing further acidaemia. Lactate-based solutions (e.g. Hartmann's) are more appropriate from the acid–base balance perspective.
- Hypotonic (0.45%) saline resuscitation may be appropriate in the non-shocked patient if the plasma sodium is rising rapidly (shift of water and potassium into cells and sodium out).
- Substitute 5–10% glucose (100–200 mL/h) after replacing sodium. This is usually begun after achieving normoglycaemia.
- Check levels frequently to confirm normokalaemia. Both acidosis and excessive K^+ administration can cause hyperkalaemia while fluid and insulin may produce hypokalaemia. Infusion of KCl (10–40 mmol/h) may be needed. Carefully monitor K^+ replacement.
- Replace magnesium (3–5 mmol/h $MgSO_4$ usually suffices).

Hyperglycaemia

- Correct blood glucose slowly (by 2–4 mmol/h) by adjusting the rate of a short-acting insulin infusion (usually 1–5 U/h).
- Avoid rapid blood sugar reduction to reduce the risk of cerebral oedema.
- Monitor blood glucose hourly in the first instance, until a stable rate of decline is seen.
- Continue IV insulin (with IV glucose, enteral feed, or diet) after achieving normoglycaemia.
- Check for reduction and then disappearance of blood or urine ketones, and normalization of the base deficit.

Other aspects of managing ketoacidosis

- Only give antibiotics for proved or highly suspected infection.
- If obtunded, insert a nasogastric tube, if possible, as gastric emptying is often delayed and acute gastric dilatation is common.
- Generally avoid bicarbonate, even for severe acidosis (pH <7.0). Rapid infusion of bicarbonate may increase intracellular acidosis and depress respiration due to a cerebrospinal fluid alkalosis.
- Low-molecular-weight heparin thromboprophylaxis is indicated due to an increased risk of thromboembolism.
- While blood ketone monitoring has been advocated, no evidence base supports the superiority of insulin dose titration by ketone levels rather than glucose levels. Indeed, this approach may result in excessive falls in blood glucose. However, in managing euglycaemic ketoacidosis (more common due to increasing SGLT2-inhibitor use) regular monitoring may be useful to guide therapy.

Further reading

Besen B, Ranzani O, Singer M. 2023. 'Management of diabetic ketoacidosis'. *Intensive Care Medi* 49: pp95–8. doi: 10.1007/s00134-022-06894-9

See Vomiting/gastric stasis, p434; Metabolic acidosis, p534; Hyperglycaemia, p538.

Hyperosmolar diabetic emergencies

Though more common in elderly, type 2 diabetes can present *de novo* in young adults. Precipitating factors are similar to ketoacidosis, e.g. sepsis, myocardial infarction.

Clinical features

- Fluid depletion is greater, blood glucose levels often higher, coma more common, and mortality higher than ketoacidosis.
- Confusion, agitation, and drowsiness may persist for 1–2 weeks.
- A metabolic acidosis may be present but is not usually profound; ketoacidosis is not a major feature.
- Hyperosmolality may predispose to thrombotic events; this is the major cause of mortality in this condition. Hyperosmolality may not be severe.
- Focal neurological signs are occasionally recognized.

Management

As for diabetic ketoacidosis; however:

- Unless the patient shows signs of hypovolaemia and tissue hypoperfusion, in which case fluid challenges should be given for prompt resuscitation, fluid replacement should be more gradual as the risk of cerebral oedema is higher. This can be with either 0.9% saline (or Hartmann's solution to avoid hyperchloraemia) or, if the plasma sodium is high, 0.45% saline at a rate of 100–200 mL/h.
- Plasma sodium rises with treatment, even with 0.45% saline, and can often increase in the first few days to 160–170 mmol/L before gradually declining thereafter. Aim to correct slowly.
- Serum magnesium levels can fall rapidly; replacement may be considered, as guided by plasma levels. Phosphate levels also decrease as the insulin encourages phosphate movement into the cell.
- Patients may be hypersensitive to insulin and require lower doses.
- Unless otherwise contraindicated, and in view of the high risk of thromboembolism, heparinize the patient (i.e. therapeutic dosing) until full recovery (which may take ≥5 days).

Further reading

➔ See Hypernatraemia, p514; Hypomagnesaemia, p524; Hypophosphataemia, p530; Hyperglycaemia, p538.

Thyroid emergencies

Thyrotoxic crisis

Presents as exaggerated features of hyperthyroidism (e.g. pyrexia, hyperdynamic circulation, heart failure, confusion). There is usually a precipitating factor such as infection, surgery, ketoacidosis, myocardial infarction. It may present with exhaustion in the elderly with few features of hyperthyroidism. Diagnosis is confirmed by standard laboratory tests.

Management

- Careful fluid and electrolyte management.
- Control pyrexia by surface cooling (avoid aspirin which displaces thyroxine (T_4) from plasma proteins).
- Reduce catecholamine effects by β-blockade (may need IV esmolol or metoprolol). Use with caution in acute heart failure. If contraindicated, use a calcium channel blocker (e.g. diltiazem).
- Blockade of T_4 synthesis by potassium iodide (200–600 mg IV over 2 h then 2 g/day PO) and carbimazole (60–120 mg/day PO).
- Block peripheral T_4 to triiodothyronine (T_3) conversion with dexamethasone (2 mg IV qds).

Myxoedema coma

Presents as exaggerated features of hypothyroidism (e.g. hypothermia, coma, bradycardia, acidosis, anaemia). Precipitating factors include cold, infection, surgery, myocardial infarction, CVA, central nervous system depressant drugs. Diagnosis is confirmed by thyroid function tests.

Management

- Treat complications of severe hypothyroidism (e.g. hypotension, heart failure, hypothermia, bradycardia, seizures); this is more important than thyroid hormone replacement.
- T_4 replacement should initially be with low doses (0.1–0.2 mg PO or PR, or lower if ischaemic heart disease is present).
- There are no definite advantages of liothyronine (T_3 replacement), high dose replacement regimens or IV treatment. IV liothyronine can be considered if there are gut absorption issues.
- Corticosteroids (hydrocortisone 100 mg qds IV) should be given before thyroid treatment is commenced for myxoedema.

Sick euthyroid/low T_3 syndrome

This is a frequent complication of critical illness with low T_3 and T_4 and high reverse T_3 (rT_3) levels. These correlate with the severity of disease and poor outcomes. TSH secretion is often reduced and there may be altered peripheral thyroid metabolism. Optimal treatment remains unknown. One study giving T_4 to patients with multi-organ failure significantly worsened outcomes though thyroid tests were not measured.

Further reading

Acker C, Singh A, Flick R, et al. 2000. 'A trial of thyroxine in acute renal failure'. *Kidney Int* 57: pp293–8. doi: 10.1046/j.1523-1755.2000.00827.x

Roberts C, Ladenson P. 2004. 'Hypothyroidism'. *Lancet* 363: pp793–803. doi: 10.1016/S0140-6736(04)15696-1

Hypoadrenal crisis

Acute adrenal crisis or adrenal insufficiency is a life-threatening emergency requiring prompt identification and management.

Clinical features

- Glucocorticoid deficiency, e.g. fatigue, weakness, vomiting, diarrhoea, abdominal pain, hypoglycaemia, confusion, delirium or coma, shock.
- Mineralocorticoid deficiency, e.g. dehydration, hyponatraemia, weight loss, postural hypotension (>20 mmHg supine to standing), hyperkalaemia.

Primary hypoadrenalism

- Skin pigmentation mainly palmar creases, scars, oral mucosa due to ACTH excess.

Secondary hypoadrenalism

- May be due to critical illness, corticosteroid withdrawal after 2 weeks' treatment, hypopituitarism, or etomidate use.
- No skin pigmentation.
- Features of mineralocorticoid deficiency may be absent.

Investigation findings

- Hyponatraemia.
- Hyperkalaemia.
- Acute kidney injury.
- Normochromic anaemia.
- Serum cortisol and ACTH levels.
- Short Synacthen® (ACTH analogue) test: baseline cortisol and 30 min after IV injection 250 µg ACTH. ACTH should produce a >200 nmol/L rise in plasma cortisol. In primary hypoadrenalism, levels remain <600 nmol/L. However, baseline levels may be normal or elevated in relative adrenal deficiency (critical illness-related corticosteroid insufficiency (CIRCI)), sepsis, and other critical illnesses.

Management

If patient severely unwell, treatment should begin on clinical suspicion.

- IV hydrocortisone 100 mg bolus followed by either a 200 mg infusion over 24 h, or 50 mg 6-hrly on day 1, then reduced to 20–50 mg tds when clinically improved. Hydrocortisone may be changed to equivalent doses of dexamethasone (4–6 mg od) when a Synacthen test is performed.
- Correct salt and water deficiency. In general, 4–5 L/day of 0.9% saline will be needed for several days.
- Carefully monitor fluid management to ensure adequate replacement without fluid overload.
- The relative hypoadrenalism related to sepsis and other critical illness (CIRCI) can be treated with hydrocortisone 50 mg qds for 5–7 days, and then a reducing dose over the next 5–7 days.
- Consider fludrocortisone 50–300 µg if more mineralocorticoid activity is required, e.g. for hyperkalaemia.

Further reading

Marik P, Pastores S, Annana D, et al. 2008. 'Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force'. *Crit Care Med* 36: pp1937–49. doi: 10.1097/CCM.0b013e31817603ba

Arlt W; Society for Endocrinology Clinical Committee. 2016. 'Society for Endocrinology endocrine emergency guidance: emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients.' *Endocr Connect* 5: ppG1–G3. doi: 10.1530/EC-16-0054

Rushworth R, Torpy D, Falhammar H. 2019. Adrenal crisis. *N Engl J Med* 381: pp852–61. doi: 10.1056/NEJMra1807486

See Corticosteroids, p352; Hyponatraemia, p516; Hyperkalaemia, p518; Hypoglycaemia, p540.

Neuroendocrine tumours

Carcinoid

Rare neuroendocrine tumour that secretes multiple amines. Most are asymptomatic. Carcinoid syndrome occurs in 20–30%, especially with metastatic disease.

Carcinoid syndrome

Facial and upper chest flushing provoked by eating, stress, alcohol, or defecation. Also provoked by catecholamines, general anaesthesia, or cardiopulmonary bypass. Severe vasodilatation causes hypotension and tachycardia. Other features include diarrhoea, cough, wheezing, dyspnoea, nausea, vomiting, and abdominal pain. Cardiac manifestations also possible.

Management

Diagnosis is confirmed by raised urinary 5-hydroxyindoleacetic acid (5-HIAA, end-product of serotonin metabolism) or raised chromogranin A (glycoprotein from neuroendocrine secretory granules). Treatment of choice is surgery to remove/debulk the tumour. Chemotherapy is used in metastatic disease. Symptom control and prevention of surgical carcinoid crisis can be managed with octreotide, a somatostatin analogue. If crisis does occur, fluid resuscitation and vasopressin are required. Catecholamines are contraindicated.

Pheochromocytoma

Rare catecholamine-secreting tumour most commonly located in the adrenal medulla. About 10% are malignant and 10% are multiple.

Features include paroxysmal sweating, palpitations, headaches, abdominal pain, and dyspnoea. Hypertension may be sustained or paroxysmal. Symptoms may be precipitated by stress, pain, tyramine-containing foods, or anaesthesia. Drugs such as metoclopramide, phenothiazines, droperidol, amitriptyline, adrenocorticotropic hormone, glucagon, histamine, and cocaine may precipitate symptoms. 20–25% present with severe hypotension and may be mistaken for septic shock.

Diagnosis

Laboratory testing may show hyperglycaemia, hyperlactatemia with acidosis (epinephrine secretion), or raised haematocrit (hypovolaemia or erythropoietin secretion). Diagnostic tests include plasma free- or 24 h-urine fractionated metanephrines. Catecholamines are often raised in critical illness. Tumour location requires computed tomography, magnetic resonance imaging, metaiodobenzylguanidine (MIBG), or positron emission tomography scanning.

Management

Use α-adrenergic blockade (phentolamine, phenoxybenzamine) to control BP and allow volume re-expansion. Use β-blockade (esmolol) or $MgSO_4$ for tachycardia control. Labetalol, a mixed α- and β-blocker, can be given but may cause increased hypertension due to inadequate α-blockade. Encourage liberal fluid and salt intake. Postoperative intensive care monitoring and management may be required for shock. After fluid resuscitation and normalization of stroke volume, vasopressin may be considered. Epinephrine may be required in low stroke volume states.

Insulinoma

Usually benign and presents with severe hypoglycaemia. Clinical symptoms include sweating, confusion, palpitations, and tremor. Diagnosis is confirmed by high serum insulin levels during hypoglycaemia. Diazoxide or octreotide may control insulin secretion prior to surgical resection of the tumour (Table 29.7). These drugs are effective in 50% of patients.

Table 29.7 Drug dosages for neuroendocrine tumours

Octreotide (carcinoid crisis)	25–500 μg IV bolus or hourly infusion. Extremely high doses have been used in severe crisis
Phenoxybenzamine	10–20 mg/day PO, increased by 10 mg every 3–4 days. High doses may be needed over several weeks to gain systolic BP <140 mmHg
Phentolamine	5 mg bolus for preoperative BP control or 1 mg/h infusion titrated to BP control
Labetalol	2 mg/min IV and titrate to response then discontinue. Usual dose 50–200 mg
Diazoxide	150–600 mg/day PO in divided doses to control hypoglycaemia
Octreotide (insulinoma)	50–200 μg SC daily titrated to control hypoglycaemia. Severe hypoglycaemia may require continuous SC infusion at higher doses

Further reading

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Platts J, Drew P, Harvey J. 1995. 'Death from phaeochromocytoma: lessons from a post-mortem survey'. *J R Coll Physicians Lond* 29: pp299–306. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5401324/pdf/jrcollphyslond90372-0039.pdf

See Hypertension, p410.

Chapter 30

Poisoning

Poisoning—general principles

Consider poisoning in patients presenting with altered consciousness, respiratory or cardiovascular depression, vomiting, hypothermia, or seizures. Diagnosis is often obvious though obtunded or truly suicidal patients may prevent an accurate history being taken. Clinical signs may be confused due to ingestion of multiple poisons, or absent if effects are delayed. Poisons may also enter the body via routes other than ingestion, e.g. inhalation or transdermal. Salicylate and paracetamol poisoning are common and patients often present without alteration in conscious level.

Investigation

Patients requiring intensive care unit (ICU) admission should have measurements made of urea and electrolytes, baseline liver function, coagulation studies, blood glucose, and blood gas analysis. Consider the need for urine and blood samples ± gastric aspirate for toxicology analysis. If concerned, obtain salicylate and paracetamol levels urgently to direct specific early treatment. Other drug levels may be sought, as indicated by history, examination, and/or initial lab tests. Treatment is often supportive but specific antidotes may be available; seek early support from the local Poisons Information Service.

Supportive treatment

Treat cardiovascular and respiratory compromise and neurological disturbance as per standard ICU practice. On occasion, consider temporarily reversing opiates and benzodiazepines in the unconscious patient to assess underlying neurology; caution in epileptics.

Gastric emptying

Despite previous widespread use, there is little supportive evidence and significant complication risks with gastric emptying. It is thus not indicated except in rare occasions. Forced emesis (ipecacuanha) is no longer recommended as vomiting may be delayed for 30 min and may be intractable. Aspiration is a serious risk with either form of gastric emptying therapy; if used, consider intubation for airway protection if agitated or consciousness is significantly impaired (e.g. Glasgow Coma Scale score <8).

Prevention of absorption

Useful for certain drugs and plant toxins, but ineffective for alcohol, acids, bases, organic solvents, inorganic salts, cyanide, or metals. Single-dose activated charcoal is more effective than gastric emptying in preventing drug absorption. A single dose of activated charcoal (50 g) can be given orally (if patient is able to swallow safely), or via a nasogastric (NG) tube, to adsorb poison remaining in the gut. A cathartic agent may be added. Give as soon as possible, ideally within 1 h of ingestion. An additional dose of activated charcoal may be indicated for sustained/modified-release preparations, drugs which delay gastric emptying, and/or where the dose ingested exceeds the adsorption capacity of the initial dose.

Enhanced elimination

Laxatives and cathartics

Agents such as sorbitol and sodium sulfate are no longer recommended because of doubtful efficacy and significant risks of volume depletion and electrolyte abnormalities.

Urinary alkalinization

This acts as an 'ion trap' preventing reabsorption from renal tubules. This is useful for toxins that are weak acids, e.g. salicylates, barbiturates, methotrexate. Sodium bicarbonate is infused intravenously (IV) to generate an alkaline urine (pH >7.5). Regimens include 225 mL of 8.4% $NaHCO_3$ given over 1 h or 1.5 L of 1.26% $NaHCO_3$ over 2 h. Hypokalaemia should be sought and corrected as necessary. Theoretically, for each unit change in urine pH there is a 10-fold increase in renal clearance.

Multi-dose activated charcoal (MDAC)

Typically, 2–6 smaller doses of activated charcoal are given to enhance gut clearance of a small number of agents, e.g. carbamazepine, phenobarbitone, quinine, methylxanthines (e.g. theophylline). Maintaining a concentration gradient across the gut encourages movement of agent from blood to gut lumen ('gut dialysis'). MDAC also disrupts the enterohepatic circulation of drugs that undergo biliary elimination. MDAC has been used to decrease absorption of ingested salicylates. It can also be considered for removal of sustained-release drugs.

Haemo(dia)filtration and/or haemodialysis

Consider a 4 h dialysis for life-threatening toxicity from molecules with a low distribution volume, low protein binding, and low molecular weight (< dialysis membrane cut-off). Examples include ethylene glycol, methanol, oxalic acid, valproate, formic acid, salicylates, lithium, and theophylline. It can be used to reverse lactic acidosis related to metformin toxicity.

Haemofiltration and haemodiafiltration act in a similar manner to haemodialysis. While clearance rates are lower than dialysis, they are better tolerated in patients with haemodynamic instability. As membranes used for these continuous techniques have a higher molecular weight cut-off level compared to dialysis membranes, substances such as heparin, myoglobin, and vancomycin are better removed as are agents that redistribute back from tissue to blood, e.g. lithium, valproate, theophylline.

Further reading

Juurlink D. 2015. 'Activated charcoal for acute overdose: a reappraisal'. *Br J Clin Pharmacol* 81: pp482–7. doi: 10.1111/bcp.12793

Lu J-D, Xue J. 2019. 'Poisoning: kinetics to therapeutics.' In: Ronco C, Bellomo R, Kellum J, et al. (Eds) *Critical Care Nephrology*, 3rd ed, pp600–29. Philadelphia: Elsevier.

➔ See Airway maintenance, p42; Endotracheal intubation—indications & equipment, p44; Renal function, p234; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Liver function tests, p244; Toxicology, p262; Salicylate (aspirin) poisoning, p556; Paracetamol poisoning, p558; Sedative poisoning, p560; Antidepressant poisoning, p562; Amphetamines & Ecstasy, p564; Cocaine poisoning, p566; Inhaled poisons, p570; Methanol & ethylene glycol, p574; Organophosphate poisoning, p576.

Salicylate (aspirin) poisoning

Serious, life-threatening toxicity is likely after ingesting >7.5 g salicylate. Loss of consciousness is rare but metabolic derangements are complex. These include respiratory alkalosis due to respiratory centre stimulation, excess salt and water loss, renal bicarbonate excretion, hypokalaemia, metabolic acidosis due to interference with carbohydrate, lipid, and amino acid metabolism, and hyperthermia due to uncoupling of oxidative phosphorylation and increased metabolism. Bleeding may occur due to reduced prothrombin levels. Although gastric erosions are common with aspirin treatment, bleeding from this source is rare in acute poisoning.

A reported complication of intubation and mechanical ventilation is rapid reversal of the respiratory alkalosis leading to metabolic acidosis, increased salicylate transfer into the brain, with increased toxicity and risk of death.

Management

Prevention of absorption

If patient presents within 1 h of ingestion, give activated charcoal (50–100 g NG) to adsorb salicylate remaining in the gut.

Salicylate levels

As salicylate levels may continue to rise while absorption continues, repeat blood levels 2-hrly if levels >1.4 mmol/L (200 mg/L) or patient is symptomatic. Continue until levels fall and/or symptom improvement.

For patients with salicylate levels <3.1 mmol/L (425 mg/L) after 1 h of ingestion and with no metabolic derangement, observation, fluids and repeat levels is indicated. Alkalinize the urine if [salicylate] >3.6 mmol/L (500 mg/L) or there is metabolic derangement but no renal failure. Consider haemodialysis if levels >5.1 mmol/L (700 mg/L) (or >3.6 mmol/L (500 mg/L) with renal failure).

Urine alkalinization

Alkalinization rather than forced diuresis is more important for salicylate excretion. Target a urinary pH >7.5–8.5 without arterial alkalosis (pH <7.5). Potassium loss occurs with bicarbonate infusion due to the diuresis and as a toxic effect of the salicylate, so alkalinizing should start once potassium levels are normal/high–normal. The bicarbonate infusion may induce hypernatraemia or hypercapnia (related to a compensatory respiratory acidosis). Monitor K^+, Na^+, and blood gases and correct abnormal values as necessary. Alkalinization, if successful, should continue until salicylate levels fall <3.6 mmol/L (500 mg/L). Calcium levels may drop with prolonged alkalinization.

Haemodialysis

Extracorporeal therapy removal (ECTR) is recommended in any of the following situations:

- [Salicylate] >7.2 mmol/L (1000 mg/L).
- [Salicylate] >6.5 mmol/L (900 mg/L) with renal dysfunction.
- Mental status is altered.
- New hypoxaemia requiring supplemental oxygen.
- Failure of standard therapy (supportive measures, bicarbonate, etc.) and:
  - [salicylate] >6.5 mmol/L (900 mg/L) or

- [salicylate] >5.8 mmol/L (800 mg/L) with renal dysfunction or
- blood pH ≤7.20.

Multi-dose activated charcoal (MDAC)

Repeated doses of activated charcoal given orally/NG may decrease absorption of aspirin from the gut.

Further reading

Juurlink D, Gosselin S, Kielstein J, et al. for the EXTRIP Workgroup. 2015. 'Extracorporeal treatment for salicylate poisoning: systematic review and recommendations from the EXTRIP Workgroup'. *Ann Emerg Med* 66: pp165–81. doi: 10.1016/j.annemergmed.2015.03.031.

➔ See Blood gas analysis, p174; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Calcium, magnesium & phosphate, p240; Toxicology, p262; Poisoning—general principles, p554.

Paracetamol poisoning

Serious, life-threatening toxicity is unlikely if <75 mg/kg has been taken. Of note, the patient may not provide a history, may not reliably inform the time of ingestion, or may have taken a staggered intentional or accidental supratherapeutic overdose. Presentation may be delayed beyond 24 h.

Paracetamol is rapidly absorbed from the stomach and upper small bowel and is metabolized by conjugation in the liver. Hepatic necrosis occurs due to toxicity of an alkylating metabolite normally removed by conjugation with glutathione; glutathione is rapidly depleted with overdose.

Clinical features

Symptomatology depends on time after ingestion:

- Phase 1 (0.5–24 h): asymptomatic or non-specific malaise and nausea.
- Phase 2 (18–72 h): right upper quadrant abdominal pain, anorexia, nausea and vomiting ± tachycardia and hypotension.
- Phase 3 (72–96 h): ongoing nausea and vomiting, abdominal pain.

If hepatic failure develops there may be jaundice, coagulopathy, hypoglycaemia, and encephalopathy.

Management

If ingestion >150 mg/kg has occurred in the previous hour, give activated charcoal (50–100 g NG) to adsorb paracetamol remaining in the gut. Blood levels should not be interpreted for toxicity unless taken >4 h post-ingestion. The mainstay of treatment is acetylcysteine (*N*-acetylcysteine, NAC) IV to restore hepatic glutathione levels by increasing intracellular cysteine levels.

Acetylcysteine (N-acetylcysteine, NAC)

Treatment is most effective if started within 8 h of ingestion but is currently advised for up to 24 h post ingestion. It can also be given if presenting >24 h after ingestion with evidence of liver dysfunction (raised enzymes, international normalized ratio (INR)) or clinical symptoms. Start acetylcysteine in single time-point paracetamol overdoses if the level is about the nomogram line (Figure 30.1) or >150 mg/kg paracetamol has likely been ingested. Seek advice from a poisons centre for staggered intentional or supratherapeutic accidental overdose. Continue acetylcysteine until paracetamol <10 mg/L. It is given by continuous IV infusion (100 mg/kg over 2 h then 200 mg/kg over 10 h).

Guidelines for referral to a specialist liver centre

- Arterial pH <7.3.
- INR >3 on day 2, or >4 thereafter.
- Oliguria and/or rising creatinine.
- Altered conscious level.
- Hypoglycaemia.

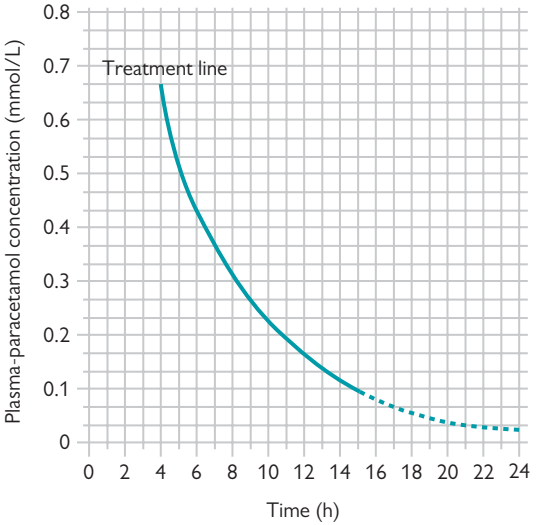

Fig. 30.1 Nomogram for predicting treatment requirement.

Guidelines for liver transplantation

- Arterial pH <7.3 or all the following:
  - PT >100 s (INR >6.5)
  - creatinine >300 μmol/L
  - grade 3–4 encephalopathy

High lactate levels (>3.5 mmol/L at 4 h and 12 h) and low factor V levels are also associated with a poor outcome if not transplanted.

Further reading

'Treating paracetamol overdose with intravenous acetylcysteine: new guidance'. UK government. September 2012. Accessed June 2023. https//:www.gov.uk/drug-safety-update/treating-paracetamol-overdose-with-intravenous-acetylcysteine-new-guidance

Pettie J, Caparrotta T, Hunter R, et al. 2019. 'Safety and efficacy of the SNAP 12-hour acetylcysteine regimen for the treatment of paracetamol overdose'. *EClinicalMedicine* 11: pp11–7. doi: 10.1016/j.eclinm.2019.04.005

➔See Liver function tests, p244; Coagulation monitoring, p252; Toxicology, p262; Acute liver failure, p454; Poisoning—general principles, p554.

Sedative poisoning

Patients can present with reduced conscious level, respiratory failure, and/or cardiovascular disturbance. Treatment is usually supportive and may require mechanical ventilation. Consider the possibility of rhabdomyolysis after prolonged immobility.

Benzodiazepine poisoning

- Benzodiazepines are commonly used for self-poisoning but severe features are uncommon, except at extremes of age.
- Flumazenil (0.2–1.0 mg IV given in 0.1 mg increments) is now not generally recommended (i) for use as a diagnostic test; (ii) at more than the minimum dose needed to reverse respiratory impairment (full reversal of central nervous system (CNS) depression is not desirable); (iii) if convulsion risk is high, e.g. mixed poisoning with tricyclic antidepressant; and (iv) concern about possible Na^+ channel blocker or stimulant poisoning (e.g. wide QRS interval, tachycardia, mydriasis).
- Flumazenil is short-acting so may require repeat doses.
- Rapid benzodiazepine reversal may induce anxiety attacks or seizures.

Opioid poisoning

- Treatment is supportive with attention particularly to respiratory depression and cardiovascular disturbance.
- Naloxone may be used as an antidote for severe respiratory depression or inadequate airway protection. Give an initial dose of 0.4 mg IV; if no response after 1 min give a further 0.8 mg, and a repeat 0.8 mg if still no response after a further min. If no response is seen after a total of 2 mg, give a further 2 mg. Larger doses may be needed in those exposed to highly potent opioids or who are severely poisoned. Aim to reverse respiratory depression and restore airway protective reflexes rather than full reversal of the abnormal conscious level.
- Give naloxone in lower doses (0.1–0.2 mg) and then 0.1 mg increments if needed in chronic opioid users at risk of acute withdrawal or if needed to reverse postoperative respiratory depression.
- As naloxone is short-acting, reversal may be temporary.
- For iatrogenic overdose, naloxone will also reverse the pain relief.

Barbiturates

Treatment is supportive with particular attention to respiratory and cardiovascular depression. Vasodilatation may be extreme requiring fluid and, in some cases, inotropic support. Phenobarbitone may be eliminated by extracorporeal removal or MDAC.

Antipsychotics

Complications of phenothiazine overdose include hypotension, tachycardia, arrhythmias, and hypothermia. Dystonic reactions or convulsions may occur. Treatment is supportive. Dystonic reactions usually respond to procyclidine or diazepam.

Further reading

➔ See Airway maintenance, p42; Respiratory stimulants, p280; Coma, p466; Poisoning—general principles, p554.

Antidepressant poisoning

Tricyclic antidepressants

Tricyclic antidepressants are rapidly absorbed from the gastrointestinal (GI) tract, although gastric emptying is delayed.

Clinical features

- Anticholinergic effects (dilated pupils, dry mouth, ileus, urine retention).
- Arrhythmias (often associated with prolonged QT interval and broad QRS complex).
- Hypotension related to arrhythmias and/or cardiac depression through Na^+ channel blockade.
- Hyperreflexia with extensor plantar reflex, visual hallucinations, coma, and seizures. Drug levels do not correlate with severity.
- Metabolic acidosis.

Examples of tricyclic antidepressants

Amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine.

Management

- No specific antidote exists for tricyclic antidepressant poisoning. Metabolism is usually rapid and improvement usually occurs <24 h.
- If symptomatic, patients require electrocardiogram (ECG) monitoring during the first 24 h and until ECG changes have disappeared for 12 h. If asymptomatic they can be discharged after 6 h.
- Activated charcoal (50 g NG) will adsorb tricyclics remaining in the bowel, ideally within 1 h of ingestion. It may be used later as gastric emptying may be slowed through anticholinergic activity.
- Cardiac arrhythmias are more common if there is an acidosis. Risk increases if QRS >100 ms. Give bicarbonate to achieve arterial pH of 7.50–7.55. If arrhythmias occur with no acidosis and fail to respond to treatment with amiodarone or phenytoin, sodium bicarbonate (25–50 mL 8.4% IV) may be useful. Bradyarrhythmias may require a chronotropic agent or temporary pacing.
- Seizures are best managed with IV benzodiazepines. Greatest risk of seizures are at 6–8 h post-ingestion.
- When above therapies have failed, consider 20% Intralipid® (1.5 mL/kg over 1 min IV then 0.25 mL/kg/h to a maximum of 500 mL). For severe cardiac depression consider high-dose insulin, glucagon, or ECMO.

Selective serotonin reuptake inhibitors (SSRIs)

Clinical features

Severe toxicity in overdose is uncommon. Symptoms include nausea and vomiting, agitation, drowsiness, and tachycardia. Convulsions may occur. Serotonin syndrome can occur with severe poisoning, resulting in hypertension, hyperthermia (>40°C), hyperactive reflexes, insomnia, severe agitation/aggression, metabolic acidosis, rhabdomyolysis, acute kidney injury, and disseminated intravascular coagulation (DIC).

Example SSRIs

Citalopram, escitalopram, fluoxetine, sertraline.

Management

- Supportive.
- Activated charcoal if ingested <1 h.
- Treat agitation and convulsions with benzodiazepines.
- Hyperthermia—fluid replacement, active cooling (cooled IV fluids and packing the patient in ice/ice pack; endovascular temperature management system can also be used).

If benzodiazepines or supportive care do not improve hyperthermia consider cyproheptadine (12 mg PO/NG followed by 4–8 mg qds PO) until improvement.

Further reading

See Airway maintenance, p42; Sodium bicarbonate, p268; Tachyarrhythmias, p412; Coma, p466; Generalized seizures, p472; Poisoning—general principles, p554; Hyperpyrexia, p656.

Amphetamines & Ecstasy

Amphetamines, e.g. 3,4 methylenedioxymethamphetamine (MDMA, 'Ecstasy') and 3,4 methylenedioxymethamphetamine ('Eve'), are stimulants taken predominantly for recreational use or as appetite suppressants. They are hallucinogenic at higher doses. MDMA cause rapid decreases in CNS 5-hydroxytryptamine and 5-hydroxyindole-3-acetic acid levels, and increased dopamine release.

Clinical features of overdose

- Agitation, hyperactivity, hypertension, hallucinations, paranoia followed by exhaustion, coma, convulsions, and hyperthermia.
- Risk of toxicity from amphetamine-type stimulants is related to the dose ingested, ambient air temperature, other co-used recreational drugs, and regular prescribed medicines.
- Features include profound hyperthermia (>40°C), agitation, seizures, muscle rigidity, hypertension, tachycardia, sweating, coma, DIC, and rhabdomyolysis.
- These complications lead to hypovolaemia, electrolyte imbalance (particularly hyperkalaemia), and a metabolic acidosis.
- Acute hyponatraemia can occur; this relates to ingestion of large volumes of water or syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Management

- Activated charcoal if within 1 h of ingestion.
- Oral sedation (e.g. benzodiazepines) and reassurance can be used for mild agitation (Richmond Agitation Sedation Scale (RASS) +1 to + 2). Intramuscular or IV sedation are needed for moderate to severe agitation (RASS +3 to +4). If appropriate, physical restraint may be needed to protect patient and/or staff. If unsuccessful, sedation, intubation, and ventilation may be required. Avoid fentanyl due to a greater risk of serotonin toxicity.
- Fluid resuscitation and electrolyte correction are often needed. Requirements may be high with severe hyperthermia.
- Early stages of amphetamine poisoning can often be controlled with tepid sponging. A forced acid diuresis to increase urinary excretion is rarely needed and can increase seizure risk, unopposed α-stimulation, and worsening hypertension.
- Manage severe complications as they arise:
  - hyperpyrexia (>38.5°C): temperatures >39.5°C are life-threatening. Hyperpyrexia requires rapid cooling with cooled IV fluids and packing the patient with ice/ice packs; other options include active cooling (e.g. temperature management system), sedation ± paralysis. Consider dantrolene
  - hypertension—if benzodiazepines are unsuccessful, consider combined α- ± β-blockade, nitrates.
  - tachyarrhythmias—short-acting β-blockade, amiodarone
  - seizures—anticonvulsants
  - rhabdomyolysis—urine alkalinization ± fasciotomies
  - coagulopathy—platelet and fresh frozen plasma infusions

Further reading

See Airway maintenance, p42; Hypertension, p410; Coma, p466; Delirium, p470; Generalized seizures, p472; Hyperkalaemia, p518; Metabolic acidosis, p534; Poisoning—general principles, p554; Rhabdomyolysis, p648; Hyperpyrexia, p656.

Cocaine poisoning

Clinical presentation may be within minutes to hours of use. Cocaine and crack cocaine can be snorted, smoked, or injected. Life-threatening features include neurological events (agitation, seizures, psychosis), cardiovascular events (arrhythmias, myocardial infarction, hypertension), and hyperthermia.

Modes of action

- Blocks reuptake of dopamine (causing euphoria, hyperactivity) and norepinephrine (causing vasoconstriction and hypertension).
- Blocks Na^+ channels, resulting in a local anaesthetic action and myocardial depression.
- Platelet activation.
- Mitochondrial dysfunction leading to myocardial depression.

Complications

- Hyperthermia-induced rhabdomyolysis, cerebral oedema, acute kidney injury.
- Heart failure.
- Carotid or aortic dissection.
- Cerebrovascular accidents (subarachnoid haemorrhage or infarction).
- Pneumothorax ± pneumomediastinum.
- Premature labour—placental abruption.

Management

- Local chest pain/acute coronary syndrome guidelines should be followed. ECG abnormalities often resolve within 12 h. Measure troponin at 12 h.
- Give benzodiazepine for agitation, delirium, chest pain. Give aspirin and nitrates (buccal, sublingual, and/or IV) for chest pain.
- Consider low-molecular-weight heparin and/or clopidogrel provided the patient is not actively bleeding or coagulopathic and there is no significant hypertension.
- Angioplasty may be necessary for patients not responding to medical treatment.
- Arrhythmias should be treated with benzodiazepines alongside antiarrhythmics; avoid β-blockers because of an unopposed α action.
- Verapamil or phentolamine may be useful for treating hypertension.

Further reading

➔ See Pneumothorax, p398; Hypertension, p410; Acute coronary syndrome—diagnosis, p416; Acute coronary syndrome—management, p418; Heart failure—assessment, p420; Decompensated heart failure: management, p422; Delirium, p470; Generalized seizures, p472; Stroke, p482; Poisoning—general principles, p554; Rhabdomyolysis, p648; Hyperpyrexia, p656.

Gamma-hydroxybutyric acid toxicity

Gamma hydroxybutyric acid (GHB) and the related analogues gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD) are predominately CNS depressants in overdose. Patients may present highly agitated, discoordinate, with seizures or (more likely) myoclonic jerks, or in a comatose state. There may be respiratory compromise.

Treatment is supportive. Patients may require short-term intubation and mechanical ventilation but often wake abruptly. Beware of attempted self-extubation. ICU admission may also be needed for IV sedation and close monitoring.

In patients who are regular users (usually multiple times per day on a daily basis), physical dependency with associated withdrawal can occur. Withdrawal symptoms include tremors, anxiety/agitation, and psychosis. Withdrawal can occur due to cessation of use and may also complicate recovery following an acute overdose. Initial treatment includes benzodiazepines, as required. There are some reports that baclofen may be useful.

Further reading

See Poisoning—general principles, p554; Sedative poisoning, p560.

Inhaled poisons

Carbon monoxide (CO)

Consider CO poisoning in anyone found in a smoke-filled enclosed space. CO displaces oxygen from haemoglobin, to which it has 200 times greater affinity, thus preventing oxygen carriage. There is direct inhibition of mitochondrial oxidative phosphorylation as CO competes with oxygen for the same binding site on mitochondrial cytochrome oxidase (complex IV).

Clinical features

- Fatigue, headache, vomiting, dizziness, confusion, dyspnoea, cerebral oedema in severe poisoning. Late neurological sequelae can occur.
- Cherry-red appearance of the skin and mucosae.
- Arterial partial pressure of oxygen (PaO_2) is normal unless there is respiratory depression; standard pulse oximetry (SpO_2) is misleading as carboxyhaemoglobin (COHb) is misread as O_2Hb.
- The half-life of COHb is 4–6 h when breathing room air and 90 min when breathing 100% oxygen.

Management

- Measure COHb levels with a bench co-oximeter. Start treatment immediately with oxygen at the maximum concentration that can be delivered (ideally fraction of inspired oxygen (FiO_2) 1.0).
- Hyperbaric oxygen is no longer recommended in the UK.
- Death is likely with COHb levels >60%.
- High-concentration oxygen should continue until COHb falls <10%.

Cyanide

Severe cyanide poisoning has an extremely rapid onset and occurs in some cases of smoke inhalation. Survival may be associated with anoxic brain damage. Diagnosis must be made clinically; blood cyanide levels take >3 h to perform in specialist centres only.

Clinical features

Anxiety, agitation, hyperventilation, headache, loss of consciousness, dyspnoea, weakness, dizziness, and vomiting. The skin remains pink. Hypotension may be severe. An unexplained elevated anion gap metabolic acidosis, lactate >7 mmol/L, or high central venous oxygen saturation are suggestive:

- Mild poisoning: nausea, dizziness, drowsiness, hyperventilation, anxiety, lactate <10 mmol/L.
- Moderate poisoning: reduced conscious level, vomiting, seizures, hypotension, lactate 10–15 mmol/L.
- Severe poisoning: coma, fixed dilated pupils, cardiovascular collapse, respiratory failure, cyanosis, lactate >15 mmol/L.

Late neurological complications include a Parkinson-like syndrome and neuropsychiatric sequelae.

Management

- Give high-concentration oxygen.
- Decontaminate the patient with removal of clothing/skin flushing.
- Give general supportive care as indicated, including mechanical ventilation, fluid, and vasopressor therapy.

- In mild cases rapid natural detoxification reduces cyanide levels by ~50% within 1 h, thus only supportive therapy is indicated.
- For more severe cases, options include hydroxocobalamin, sodium thiosulfate, and sodium nitrite.
- Hydroxocobalamin works rapidly, combining with cyanide to form vitamin B_{12} (cyanocobalamin) which is renally excreted. It may dissociate slowly from cyanide, allowing detoxification by the mitochondrial enzyme, rhodanese. Hydroxocobalamin carries less toxicity compared to other agents. Because of its bright red colour, it may interfere with laboratory chemistry tests and co-oximetry.
- Sodium thiosulfate converts cyanide to thiocyanate but is slow-acting. The dosing regimen is 150 mg/kg IV followed by 30–60 mg/kg/h. It can be given alone or in combination with other antidotes, but should be infused through a separate line.
- Sodium nitrite is rapid in onset but may produce significant methaemoglobinaemia and life-threatening toxicity. Caution should be applied in patients with concurrent smoke inhalation where COHb levels may be high as well.

Further reading

See Oxygen therapy, p40; Blood gas analysis, p174; Poisoning—general principles, p554.

Household chemical poisoning

Corrosives

Ingestion may be accidental or intentional. Common agents include sodium hydroxide (caustic soda), sodium hypochlorite (bleach), and sulphuric acid. Ingestion of strong acids and alkalis may lead to shock and upper GI tract perforation. Airway damage can also occur. Ingestion of alkali leads to liquefaction necrosis of oesophagus and/or stomach and thus may cause damage to the surrounding mediastinum. As ingestion of acid is very painful, smaller volumes are consumed; this leads to superficial coagulation necrosis usually beyond the oesophagus though deep injuries are uncommon.

Management

Assess airway and intubate if necessary. A tracheostomy may be required if oral intubation is problematic. Perform early endoscopy and/or computed tomography imaging to assess the degree of injury unless the patient is asymptomatic. Local or encircling deep ulceration (or worse) is an indication for ICU admission. Keep nil by mouth unless asymptomatic. Avoid blind NG tube insertion. Proton pump inhibitors and analgesia should be given as required. Prophylactic broad-spectrum antibiotics should be given for severe injury. Perforation, mediastinitis, and peritonitis are indications for emergency surgical intervention. Laryngo-bronchoscopy should be performed if the airway is potentially injured.

Avoid gastric elimination techniques as aspiration of corrosives may cause severe lung damage and heat generated from neutralizers may worsen tissue injury. Corticosteroid use to prevent stricture formation is controversial.

Petrols and hydrocarbons

Examples include petrol, kerosene, solvents, white spirit, and turpentine. These may cause early CNS depression, seizures, chemical pneumonitis from volatile hydrocarbons, or dysrhythmias. Inhalation injury can manifest up to 6 h post-exposure. Surface exposure to hydrocarbons can lead to skin necrosis, burns, and ocular damage.

Management

For ingestion avoid gastric elimination techniques since a few drops of petroleum spilling into the lungs can lead to a severe pneumonitis. The low surface tension and vapour pressure allows rapid spread in the lungs. NG aspiration via a NG tube may be considered if performed with 60 min of ingestion. Intubate early if severe CNS depression and/or difficult to manage seizures; avoid phenytoin. Chemical pneumonitis is managed supportively, neither corticosteroids nor prophylactic antibiotics are indicated.

For surface exposure, remove contaminated clothing and irrigate affected areas with copious water. Give analgesia as required. Healthcare givers should don appropriate personal protective equipment (PPE) to reduce risk of contamination.

Paraquat

Paraquat is a selective weedkiller and common worldwide agent in suicide, with a 50% fatality rate. A 2–3 g dose is usually fatal (equivalent to 80–120 g

of granules or 10–15 mL of industrial liquid concentrate). Paraquat inhibits mitochondria and generates superoxide, leading to multiorgan failure.

Clinical features

- Ingested paraquat is rapidly but incompletely absorbed from the gut. It reaches maximal tissue levels after 6 h especially in lung, kidney, liver, and muscle. A large dose leads rapidly to shock with widespread tissue necrosis.
- Burning sensation in the mouth and abdomen, development of painful mouth ulcers, and, after several days, a relentless, proliferative alveolitis leading to acute respiratory distress syndrome and death from pulmonary fibrosis. Death may be slow.

Management

- Remove patient from ongoing contact, remove clothing and decontaminate exposed skin as soon as possible. Staff should take care not to contaminate themselves and don PPE.
- Treatment should begin on clinical grounds in view of the severity of toxicity and the time taken for laboratory confirmation. Serum paraquat predicts the risk of death using the Severity Index of Paraquat Poisoning (SIPP) score. This may help establish if active treatment or palliative care is more appropriate.
- Initial resuscitation may require several litres of IV fluid.
- Pulmonary fibrosis is more severe when breathing high FiO_2. Supplemental oxygen should be avoided but, in severe hypoxaemia, give the lowest concentration possible, accepting a low PaO_2.
- GI decontamination with 50 g activated charcoal, even up to 12 h after ingestion, may be beneficial. NG aspiration can be performed prior in cases that present early.
- Severe diarrhoea may ensue requiring careful fluid management.
- Consider haemoperfusion or renal replacement therapy within 4 h of ingestion.
- Antioxidant, anti-inflammatory, and immunosuppressive therapies have been given but none have shown outcome benefit in prospective randomized controlled trials.

Further reading

Sawada Y, Yamamoto I, Hirokane T, et al. 1988. 'Severity index of paraquat poisoning'. *Lancet* 1: p1333. doi: 10.1016/s0140-6736(88)92143-5

See Other blood purification techniques, p124; Toxicology, p262; Poisoning—general principles, p554.

Methanol & ethylene glycol

The parent alcohols are relatively non-toxic; toxicity mainly arises from metabolites produced by alcohol and aldehyde dehydrogenases. Even a small (50–100 mL) ingestion may produce significant toxicity. Suspect in patients with severe metabolic acidaemia. Abnormalities in anion and osmolal gaps fluctuate. The osmolal gap is initially elevated due to the presence of the parent alcohol, but decreases after 12–24 h. The anion gap is elevated with metabolic acidaemia at 12–24 h. After 24 h, anion and osmolar gaps may be normal. The gold standard diagnostic test is a serum methanol and/or ethylene glycol level; often this is not readily available and therefore a presumptive diagnosis is made on the basis of history of ingestion and/or abnormal anion gap and/or osmolal gap.

Methanol

Toxicity from oxidation to formic acid and formaldehyde. This pathway proceeds at 20% of the rate of ethanol oxidation.

Clinical features

Clinical features of poisoning include visual disturbances (due to concentration in the vitreous humour), severe metabolic acidosis, headache, nausea, vomiting, and abdominal pain.

Management

- Metabolism of methanol is slow so treatment will be prolonged.
- If ingestion suspected, treat by early administration of fomepizole (15 mg/kg loading dose, then 10 mg/kg 12-hrly IV increasing to 15 mg/kg 12-hrly after 4 doses) to inhibit alcohol dehydrogenase. Though more expensive than alcohol, it is effective, well tolerated, and has no need for therapeutic monitoring.
- If fomepizole is unavailable, infuse 10% ethanol (10 mL/kg over 30 min followed by 1.0 mL/kg/h). Titrate to blood ethanol levels of 100–150 mg/dL. Ethanol levels need to be repeated every 1–2 h and the infusion adjusted to maintain a blood ethanol level of 100–150 mg/dL.
- If arterial pH <7.3, consider sodium bicarbonate infusion.
- Consider haemodialysis if evidence of end-organ injury, or if blood methanol level >50 mg/dL; continue treatment until <25 mg/dL.
- Folinic acid 30 mg IV 6-hrly for 48 h.

Ethylene glycol

Ethylene glycol is metabolized by alcohol dehydrogenase to glycolate and oxalate leading to severe metabolic acidosis, flank pain, and oliguria. The patient may develop renal failure, hypocalcaemia, hypotension, cardiogenic shock, cerebral oedema, or seizures.

Clinical features

Inebriation, ataxia, slurred speech, drowsiness, agitation, nausea, and vomiting. There may be tetany secondary to hypocalcaemia. Lactate levels may be spuriously high due to cross reaction of L-lactate oxidase with glycolate or glyoxylate. Variable lactate levels measured by different blood gas analysers should raise suspicion of poisoning.

Formal diagnosis is made by serum ethylene glycol levels (significant toxicity >25 mg/dL), serum glycolic acid levels (better correlate of toxicity), and calcium oxalate crystals in urine; absence does not exclude poisoning.

Management

Treatment as for methanol. Fomepizole or ethanol alone may be insufficient if acidosis or acute kidney injury are established; in these situations haemodialysis/haemofiltration should be commenced to remove oxalate and other metabolites. Suggested indications for dialysis include:

- pH <7.25.
- Acute kidney injury.
- Serum [ethylene glycol] >50 mg/dL
- Serum glycolic acid >8 mmol/L.

Further reading

See Blood gas analysis, p174; Metabolic acidosis, p534; Poisoning—general principles, p554.

Organophosphate poisoning

Can occur by deliberate ingestion, particularly in low–middle-income countries, with occupational or accidental exposure, and exposure to nerve agents (e.g. sarin). Can be absorbed through intact skin, gut, or inhaled. Mode of toxicity is cholinesterase inhibition. Presentation varies by predominance of muscarinic vs nicotinic effects. Diagnosis often requires history of exposure. The precise agent should be identified as the rate and duration of toxicity vary. An atropine trial (1 mg) can be utilized; no anticholinergic response suggests poisoning. Though raised plasma cholinesterase activity is easier to measure, it is not as reliable or useful as red blood cell acetylcholinesterase activity.

Muscarinic effects

- SLUDGE (Salivation, Lacrimation, Urination, Diarrhoea, GI upset, Emesis).
- Bronchospasm and respiratory failure.
- Bradycardia and hypotension.
- Miosis and blurred vision.

Nicotinic effects

- Muscle weakness and fasciculation with paralysis.
- Diaphragmatic failure.
- Tachycardia and hypertension.
- Mydriasis.

Central nervous system effects

- Anxiety, confusion, agitation, and ataxia.
- May lead to respiratory paralysis.
- Seizures and tremors.
- Coma.
- Intermediate neurological syndrome presents in 10–40% of patients at 1–4 days post-exposure with loss of reflexes, cranial nerve abnormalities, proximal weakness, and respiratory failure.

Management

- Early skin decontamination is crucial. The patient's clothes should be removed and their body thoroughly washed with soap and water to prevent further absorption. Staff should wear appropriate PPE.
- Early intubation often required and oxygen given to avoid hypoxaemia (ventricular fibrillation more common with atropine in hypoxaemia).
- Adequate volume resuscitation to replace fluid losses.
- Cholinergic toxicity is treated with atropine and pralidoxime.
- Give atropine 3 mg; double dose every 3–5 min if no effect seen until muscarinic signs improve (respiratory secretions and bronchoconstriction). Severe poisoning may require >100 mg atropine by bolus ± infusion over days. Non-responders may require epinephrine.
- Pralidoxime treats both muscarinic and nicotinic syndromes and neuromuscular dysfunction. It must be given concurrently with atropine.

Give a loading dose of 30 mg/kg over 20 min, followed by an infusion of 8 mg/kg/h to a maximum dose of 12 g in 24 h.

- Benzodiazepines can be used both prophylactically and for treatment.

Further reading

➔ See Bronchodilators, p278; Chronotropes, p296; Bradyarrhythmias, p414; Poisoning—general principles, p554.

Chapter 31

Infection, sepsis, & inflammation

Infection control—general principles

Nosocomial infection is a major cause of mortality, morbidity, and increased length of stay. Marked variations in infection control policies for isolation, microbiological surveillance, hand-washing, glove and gown use, impregnated vascular catheter use, duration of indwelling catheters, and frequency of change of disposables reflect the weak evidence base. Hand-washing before and after patient contact, and strict aseptic technique when performing invasive procedures, should be mandatory.

Staff measures

- Remove watches and jewellery. Arms below the elbow should be bare.
- Clean hands and forearms before and after touching patient. Use alcohol-based gel after skin or local environment contact, and soap and water for body fluid contact or if the patient has diarrhoea or known *Clostridioides* (formerly *Clostridium*) *difficile* (alcohol does not eradicate spores).
- Wear gloves and aprons when handling any body fluid, and eye protection if any risk of fluid or droplet splash.
- Cover open cuts and raw dermatitis/eczema areas.
- Wear full-face protection if patient is at risk of having an infectious disease such as tuberculosis (TB), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19), H1N1 influenza.
- Wear full face and body protection and appropriate protective face mask if a highly contagious disease is suspected, e.g. Ebola.
- Use strict aseptic technique for invasive procedures (e.g. central venous catheter insertion) and clean technique for basic procedures, e.g. endotracheal suction, changing ventilator circuits, or drug infusions.
- Immunize against hepatitis B, TB, influenza, SARS-CoV-2.
- Clean equipment after patient use.
- Take adequate precautions with disposal of body fluids, sharps.

Visitors

- Non-intensive care unit (ICU) medical and paramedical staff, relatives, and friends should adhere to local ICU infection control policies.

Transmission of infection

- Bedside equipment (e.g. computer keyboards, infusion and syringe pumps, ventilators, bed rails) should be cleaned regularly.
- Clearly signpost precautions on access doors.
- Inform the infection control team should transmission arise. The microorganism should be typed to confirm an outbreak as different strains may cause concurrent infection. Review procedures to see if lapses in infection control have occurred.
- Source isolate patients who carry multi-resistant or virulent organisms (or who are at high risk of carriage).
- If cross-infection persists/spreads, seek potential sources, e.g. taps, sinks, reusable equipment (e.g. ventilators).
- Deep clean cubicles/bays as per infection risk.

Isolation

- Source isolation—for patients carrying potentially contagious, virulent, or multi-resistant organisms. Ideally isolate in a negative pressure environment.
- Protective isolation—for immunosuppressed patients at risk of acquiring infection, e.g. neutropenic patients post-chemotherapy. Ideally isolate in a positive pressure environment relative to the rest of the clinical area.

Microbiological surveillance

Policies vary between ICUs; some routinely screen sputum, bronchoalveolar lavage, blood, urine, and drain fluid on admission or every 2–4 days while others screen only on clinical indication. Some perform routine meticillin-resistant *Staphylococcus aureus* (MRSA) surveillance, e.g. nasal and perineal swabs.

Further reading

➲ See Infection control—blood-borne viruses, p582; Infection control—dangerous pathogens, p584; Routine changes of disposables, p586.

Infection control—blood-borne viruses

Protection of staff from transmission of blood-borne viruses follows standard universal precautions:

- Do not handle body fluids without gloves.
- Protect face and eyes if any risk of splash contamination.
- Discard needles in appropriate burn bins without re-sheathing.
- Clean up any fluid spillages immediately.

Robust procedures are usually adhered to when a patient is known to be infected or carrying a particular virus, e.g. HIV, hepatitis B, hepatitis C. The greater risk is when viral status is unknown, and particularly when patients present with non-related acute illnesses. Sensible precautions should therefore be adopted for all patients.

Staff exposure

Needlestick injury, eye or skin-cut contact with body fluids should be prevented by strict infection control procedures. Should exposure happen:

- Wash the area thoroughly with running water and plenty of soap. The wound should not be scrubbed or sucked.
- Contact the designated person within the hospital promptly (e.g. virologist, microbiologist, HIV specialist) who can advise on risk and the desirability of taking post-exposure prophylaxis against HIV or hepatitis B.

The risk of infection from a needlestick injury is 0.23% for HIV, 6–30% for hepatitis B, and 1.8% for hepatitis C.

Patient testing

Policies differ between countries with regard to testing viral status on incapacitated patients. Current UK guidance is based on the likelihood of temporary or permanent incapacity.

Temporary incapacity

Defer testing until the patient regains capacity, unless testing is immediately necessary to save the patient's life or prevent a serious deterioration of their condition.

Permanent incapacity

If lack of capacity is, or is likely to be, permanent, seek a decision from a person with relevant power of attorney, or follow any valid advance directives. If neither are available, HIV testing may be undertaken if in the best interests of the patient. Should consciousness be regained, the patient should be told of the test result as soon as practicable. If the patient dies, a decision on disclosure should be made according to specific circumstances (e.g. others at risk, previously disclosed wishes).

When a healthcare worker has been exposed to blood or other bodily fluid, ask the patient's consent to test (if competent). If the patient lacks capacity, use local/national guidelines.

Further reading

Palfreeman A, Sullivan A, Rayment M, et al. 2020. 'British HIV Association/British Association for Sexual Health and HIV/British Infection Association. Adult HIV testing guidelines 2020'. *HIV Med* 21 Suppl 6: pp1–26. doi: 10.1111/hiv.13015

See Critical care unit layout, p2; Patient safety, p14; Infection control—general principles, p580; Infection control—dangerous pathogens, p584; Multi-resistant infections, p600; Viral critical illness, p612.

Infection control—dangerous pathogens

Risk assessment

Before exposing staff to patients with dangerous pathogens there should be a full risk assessment. Seek advice from communicable disease and infection control experts. This must include likely pathogens in endemic areas visited or, if locally acquired, local infection surveillance data. A risk assessment should ideally be performed in advance of the ICU referral and should include:

- Which pathogen(s) may be present (hazard identification).
- The likelihood of infection.
- The severity of infection, if it occurs.
- Where the pathogen is likely to be present, e.g. in airway secretions, blood (samples or spillages), on contaminated instruments and equipment, in waste, or contaminated clothing.
- Risk to other patients, e.g. is pathogen transmitted by airborne spread or contact?
- Ways in which staff may be exposed, e.g. through direct personal exposure to blood in invasive procedures, accidental exposure, handling contaminated items for cleaning or disposal.
- Estimate of exposure, i.e. number and range of sources and frequency of contact, taking account of systems of work and protective measures.

Control measures

- Standard precautions as a minimum.
- Consider isolation in single room/cubicle depending on pathogen and route of transmission. If available, use negative pressure isolation when airborne precautions are indicated.
- If airborne spread, use appropriate masks depending on risk (Table 31.1). All tight-fitting masks should be pre-tested for fit to ensure no leaks.
- Contact precautions (long sleeved, fluid-repellent gown giving total body coverage and (double) protective gloves with tight-fitting cuffs. There should be eye protection for organisms that can infect via eye splash).
- For highly contagious pathogens (e.g. Ebola), follow hospital protocols regarding time spent with patient, colleague to assist gowning/degowning and disinfecting.
- Clinical waste precautions. in addition to universal precautions for handling waste, leak-proof biohazard bags must be used for safe disposal and incineration.

Table 31.1 Types of face mask

Surgical	Loose-fitting mask. Does not protect the healthcare worker but protects the patient from droplets expelled by the wearer
FFP-1	Filters ≥80% of airborne particles. Not generally used in hospital settings
FFP-2 (N95)	Filters ≥94% of airborne particles. Does offer protection to the wearer
FFP-3	Filters ≥99% of airborne particles. Should be used for highly pathogenic organisms
Respirator	Full-head mask with FFP-2 or FFP-3 rating for those unable to wear standard masks

FFP = filtering face piece.

Further reading

See Patient safety, p14; Infection control—general principles, p580; Infection control—blood-borne viruses, p582; HIV-related disease, p610.

Routine changes of disposables

A scheme for routine changes of respiratory, intravascular, and urinary catheters appears in Table 31.2.

Care of intravascular catheters

- Sites should be covered with transparent semi-permeable dressings to allow observation and prevent secretions from accumulating.
- Intravascular catheters should be removed as soon as clinically feasible. The risk of infection increases after 2–3 days for a peripheral venous cannula and 5 days for a central venous catheter. Infection risk from arterial cannulae and tunnelled central venous catheters (e.g. percutaneous intravenous central catheter (PICC) or Hickman catheters) is much lower. Such lines can stay in for far longer periods but strict infection control must be observed during handling. If catheters need replacing, a risk–benefit assessment should be made balancing the risk of catheter-related infection versus other risks, e.g. if new access is problematic.
- Catheters should be changed to a fresh site if:
  - the old site appears infected
  - the patient shows signs of severe infection
  - a positive growth is obtained from a blood culture drawn through the catheter.
- Catheter changes over a guidewire are no longer recommended as sterility cannot be assured. This can be considered if new central venous access if very difficult or the risk of complications from insertion is high (e.g. marked coagulopathy).

Table 31.2 Routine changes of disposables

Disposable	Change frequency
Ventilator circuit with bacterial filters	Between patients unless soiled
Ventilator circuit with water bath humidifier	Daily
Endotracheal tube catheter mount and bacterial filter	Between patients unless soiled
Oxygen masks	Between patients unless soiled
Continuous positive airway pressure (CPAP) circuits	Between patients unless soiled
Rebreathing bags and masks	Between patients unless soiled
Intravenous infusion giving sets	48 h
Parenteral nutrition giving sets	Daily
Enteral feeding giving sets	Daily
Arterial/venous pressure transducer sets	48 h
Urinary catheter bags	Weekly

Infection—diagnosis

Infection is a common cause of ICU admission and a major secondary complication (Table 31.3). Critically ill patients are predisposed to new infection as many of their natural barriers and defence mechanisms are lost, altered, or penetrated. They are often heavily instrumented, sedated, and immobile. They are often immunosuppressed as part of their critical illness, underlying comorbidities, and/or treatment. High antibiotic loads encourage colonization by pathogenic organisms and subsequent multi-drug-resistant infection by bacteria and/or other organisms (e.g. fungi, viruses), or reactivation of viruses (e.g. cytomegalovirus (CMV)).

Table 31.3 Sites of infection pre- and post-ICU admission

Organ	Infection site prompting critical care admission	Infection site acquired while in critical care
Brain	+	+
Sinuses	+/−	+/−
Cannula/wound sites	+	+++
Other skin and soft tissue	++	+
Chest	+++	+++
Urogenital tract	+++	+
Abdomen	+++	++
Bone	+/−	+/−
Heart valves	+/−	+/−

Diagnosis

- Often problematic in the critically ill patient as focal signs may be lacking and/or camouflaged by concurrent disease, e.g. ventilator-associated pneumonia on top of pre-existing acute respiratory distress syndrome (ARDS). Symptoms are often not forthcoming from the patient due to lack of competency (e.g. agitation, sedation).
- Traditional clinical and biochemical markers of infection (e.g. pyrexia, neutrophilia, altered sputum colour/consistency) are non-specific. The frequent presence of colonizing organisms, e.g. MRSA (skin), *Pseudomonas aeruginosa* (respiratory tract), does not necessarily indicate concomitant infection.
- Molecular pathogen diagnostics (e.g. multiplex polymerase chain reaction (PCR)), or chromatographic techniques (e.g. matrix-assisted laser desorption ionization–time of flight (MALDI-TOF)) can identify organisms and antimicrobial resistance patterns far quicker (often within hours) than standard culture and speciation. Some pathogens can be identified by antigen testing, e.g. *Pneumococcus* spp., *Legionella* spp.
- The value of routine screening (microbiological surveillance) is unproved, though may help to identify possible infecting organisms earlier (e.g. colonized with *Candida* spp.).

- If a bacterial, viral, or fungal infection is suspected, take appropriate samples (e.g. blood, sputum, wound swabs, drainage fluid, aspirated pus, catheter tips, cerebrospinal fluid) for analysis before commencing new antimicrobials.
- Consider less common causes of infection such as endocarditis or osteomyelitis, particularly if the patient fails to settle after a standard course of therapy.
- Standard host response markers of inflammation (e.g. C-reactive protein (CRP, procalcitonin, neutrophilia) may assist but should not be used in isolation to diagnose infection. Studies show conflicting results regarding specificity/sensitivity of these markers in diagnosing infection or sepsis. Such biomarkers are often raised for several days after any inflammatory insult (e.g. surgery, trauma), or may sometimes not increase (e.g. with chronic liver disease, immunosuppression).
- Many novel host response biomarkers are available, though the evidence for specificity/sensitivity in identifying infection remains weak or inconclusive.

Differential diagnosis of pyrexia

- Infection.
- Non-infective causes of inflammation, e.g. trauma, surgery, burns, myocardial infarction, vasculitis, hepatitis, cholecystitis, pancreatitis.
- Adverse drug reactions.
- Transfusion of blood and blood products.
- Excessive ambient heating.
- Miscellaneous causes, e.g. neoplasm.

Definitions of terms used

Infection

Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

Bacteraemia

The presence of viable bacteria in the blood.

Systemic inflammatory response syndrome (SIRS)

Two or more of:

- Temperature >38°C or <36°C.
- Heart rate >90 bpm.
- Respiratory rate >20 breaths/min or arterial partial pressure of carbon dioxide ($PaCO_2$) <4.3 kPa (32 mmHg).
- White blood cell count 12 x 10^9/L, <4 x 10^9/L, or >10% immature forms.

SIRS represents a host systemic inflammatory response that is usually appropriate to any significant insult. It is no longer used to define sepsis. SIRS is a non-specific response but may assist in the clinical identification of infection.

Further reading

See Bacteriology, p256; Virology, p258; Mycology, p260; Infection control—general principles, p580.

Infection—treatment

Principles

- Take laboratory specimens before starting antibiotic(s). Antibiotics may not be needed for mild infections with source control, e.g. removal of an infected catheter.
- Remove any catheters/cannulae suspected to be the infection source.
- Perform radiological and/or surgical interventions as needed, e.g. drainage of pus, repair/isolation of perforations, opening or proximal drainage of obstructed tract, e.g. stenting of biliary duct or ureter, percutaneous cholecystotomy.

Antibiotic stewardship

- Start antibiotics empirically if suspected infection contributes to significant clinical deterioration (Table 31.4).
- Follow local guidelines in selecting appropriate empiric therapy. This depends on the likely site of infection, likely infecting organism(s), whether community-acquired or nosocomial (including ICU-acquired), immunosuppression status, and known local antibiotic resistance patterns.
- Consult microbiology or infectious diseases if uncertain. Over-treatment with antibiotics enhances the risk of overgrowth of resistant/atypical organisms.
- Review antibiotic use daily and stop early once infection is excluded.
- Broad-spectrum therapy may be initially needed, with refinement, cessation, or change after 2–3 days depending on clinical response and sensitivity patterns of organisms subsequently isolated. This may include de-escalation or change to a narrow-spectrum antibiotic.
- Fixed treatment duration remains contentious and makes little biological sense in ICU medicine. Certain conditions (e.g. endocarditis, osteomyelitis) require prolonged therapy. Otherwise, it may be sufficient to stop within 5 days, if not earlier, provided the patient shows adequate signs of recovery.

Antibiotic dosing

Generally, give parenterally as gut absorption may be unreliable in critical illness. Nonetheless, blood levels are still highly variable across individual patients depending on hepatic metabolism and/or excretion, renal clearance (augmented or reduced), volumes of distribution, protein binding, and use of renal replacement therapy. Thus, patients are often under- or overdosed. While continuous infusions of some antibiotics are promoted to increase the time above minimum inhibitory concentration (MIC), outcome benefit has yet to be clearly shown.

Consider patients not responding or deteriorating as either treatment failures or inappropriately treated (i.e. no infection was present in the first place). Markers of infection are not specific in the critically ill. Pyrexia may even settle on stopping antibiotic treatment. Consider stopping or changing the antibiotic regimen according to the patient's condition and available laboratory results. An advantage of stopping therapy is the ability to take further specimens for culture in an antibiotic-free environment.

Other measures

It may be necessary to remove tunnelled vascular catheters, prosthetic joints, plates, pacemakers, implants, grafts, and stents if these are the suspected cause of infection. This should be done in consultation with microbiologists and the appropriate specialist as individual risks and benefits need to be carefully weighed up.

Table 31.4 Specimen antibiotic regimens (organism unknown)

Sepsis of unknown origin	Cephalosporin OR quinolone OR carbapenem OR piptazobactam ± aminoglycoside (if Gram-negative suspected) ± metronidazole (as anaerobic cover if cephalosporin used) ± glycopeptide or linezolid (if MRSA suspected)
Pneumonia—community acquired	Cephalosporin ± macrolide
Pneumonia—nosocomial	Third-generation cephalosporin OR quinolone OR carbapenem OR piptazobactam (if Gram-negative suspected)+ teicoplanin, vancomycin. Linezolid if MRSA likely
Skin & soft tissue	Flucloxacillin (if MSSA likely)Glycopeptide or linezolid (if MRSA likely) Benzylpenicillin (if *Streptococcus* suspected) Consider clindamycin if non-resistant group A *Streptococcus* isolated
Abdominal	Cephalosporin (unless long-term hospitalization) OR quinolone OR carbapenem OR piptazobactam± aminoglycoside ± metronidazole (if using cephalosporin or quinolone)
Gynaecological	Cephalosporin OR quinolone OR carbapenem OR piptazobactam± aminoglycoside + metronidazole (if using cephalosporin or quinolone) NB: different therapy may be needed for sexually transmitted pelvic inflammatory diseases
Nephro-urological	Cephalosporin OR quinolone and aminoglycoside, OR carbapenem OR piptazobactam

NB: local resistance patterns should be borne in mind when prescribing.

MSSA = meticillin-sensitive *Staphylococcus aureus*; piptazobactam = piperacillin–tazobactam.

Further reading

See Antibacterials, p344; Pneumonia—diagnosis, p374; Abdominal sepsis, p446; Meningitis, p474; Tetanus, p492; Botulism, p494; Sepsis—management, p594; Multi-resistant infections, p600; HIV-related disease, p610; Viral critical illness, p612; Malaria, p614.

Sepsis—definitions & pathophysiology

Definitions

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is represented by an increase in Sequential Organ Failure Assessment (SOFA) score ≥2 points above the patient's baseline. Sepsis is associated with an in-hospital mortality >10%.

Septic shock is defined as a subset where profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality. Such patients are identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) ≥65 mmHg and serum lactate >2 mmol/L despite adequate volume resuscitation. Hospital mortality in this subset is >40%.

The new 'Sepsis-3' definitions supersede and simplify the previous classification of sepsis that used SIRS criteria. SIRS criteria are not necessarily present, and may also indicate an appropriate host response to an infection, or a response to a non-infectious inflammatory insult.

Pathophysiology

The microorganism or its constituents, e.g. Gram-negative bacterial endotoxins, are termed 'pathogen-associated molecular patterns' (PAMPs). PAMPs trigger an exaggerated host inflammatory response detected through pattern recognition receptors (PRRs) such as Toll-like receptors. A similar response is elicited by injured host tissue releasing damage-associated molecular patterns (DAMPs) into the circulation, e.g. heat shock proteins (HSP), high motility group box 1 (HMGB1), DNA, histones, mitochondria. Activation of PRRs triggers a downstream cascade with activation of innate immunity including neutrophils, macrophages, and endothelium with release of inflammatory mediators and effectors (e.g., cytokines, eicosanoids, proteases, reactive oxygen species, nitric oxide, endothelin). This results in microvascular abnormalities, blood flow redistribution, endothelial swelling, loss of tight junctions between cells, interstitial oedema, and later fibrosis.

Other pathways including coagulation, metabolic, hormonal, and bioenergetic are either activated or depressed. Consequent myocardial depression occurs in ~40% of cases, albeit to variable degrees. A net result is mitochondrial dysfunction and a metabolic shutdown leading to organ dysfunction. Of note, the histology of failed organs often shows inflammatory infiltrate, variable degrees of fibrosis, but minimal to no cell death.

Further reading

Singer M, Deutschman C, Seymour C, et al. for the Sepsis Definitions Task Force. 2016. 'The third international consensus definitions for sepsis and septic shock (Sepsis-3)'. *JAMA* 315: pp801–10. doi: 10.1001/jama.2016.0287

Arina P, Singer M. 2021. 'Pathophysiology of sepsis'. *Curr Opin Anaesthesiol* 34: pp77–84. doi: 10.1097/ACO.0000000000000963

Hollenberg S, Singer M. 2021. 'Pathophysiology of sepsis-induced cardiomyopathy'. *Nat Rev Cardiol* 18: pp424–34. doi: 10.1038/s41569-020-00492-2

See Organ failure scoring, p34; Sepsis—management, p594; Multiorgan dysfunction—causes & definitions, p596; Multiorgan dysfunction—management, p598.

Sepsis—management

Guidelines produced by the Surviving Sepsis Campaign (SSC) are updated every 4 years. The evidence base is, however, weak for most recommendations due to lack of definitive outcome studies. There is consensus on the need for prompt recognition, intervention with antibiotics and source control, and resuscitation to correct organ hypoperfusion. At present, no recommendations are offered for adjunctive therapies such as monoclonal antibodies, antioxidants, extracorporeal blood purification, and immunoglobulin.

Sepsis management bundles

These are promoted by the SSC but have changed frequently over the last 25 years as individual components have not been shown to produce outcome benefit. The 1 h bundle currently promoted by SSC for initial resuscitation recommends:

1. Measure serum lactate.
2. Obtain blood cultures prior to antibiotic administration.
3. Give broad-spectrum antibiotic(s) within 1 h for septic shock or definite/probable sepsis, or 3 h if shock absent and diagnosis is uncertain.
4. Begin administering 30 mL/kg crystalloid if hypotensive or lactate ≥4 mmol/L.
5. Commence vasopressor if hypotensive during or after resuscitation to maintain MAP ≥65 mmHg.

These guidelines are somewhat didactic. Patients may not need as much as 30 mL/kg fluid and MAP values <65 mmHg may be adequate for some patients. Our personal preference is for an individualized approach, regularly assessing and titrating treatments and targets according to response. For antibiotic timing and therapy, the UK Academy of Medical Royal Colleges produced a consensus statement in 2022 that was endorsed by NICE in 2024. Diagnostic tests and antibiotic administration should be completed within 6, 3, or 1 h after recording a NEWS-2 of 1–4, 5–6, or ≥7, respectively; Table 31.5). These are maximum periods, not targets, and high-risk patients (e.g. immunosuppressed) may go into higher bands.

Specific treatments for sepsis

Low-dose hydrocortisone (50 mg 6-hrly) for ongoing vasopressor requirement. This reduces time on vasopressor therapy, but has not been shown to improve survival.

Further reading

Evans L, Rhodes A, Alhazzani W, et al. 2021. 'Executive summary: Surviving Sepsis Campaign: international guidelines for the management of sepsis and septic shock 2021'. *Crit Care Med* 49: pp1974–82. doi: 10.1097/CCM.0000000000005357

'Statement on the initial antimicrobial treatment of sepsis'. Academy of Medical Royal Colleges. October 2022, V2.0. Accessed July 2023. https://www.aomrc.org.uk/reports-guidance/statement-on-the-initial-antimicrobial-treatment-of-sepsis-v2-0/

Suspected sepsis: Recognition, diagnosis and early management. NICE guideline. Last updated: 31 January 2024 www.nice.org.uk/guidance/ng51

See Lactate, p246; Bacteriology, p256; Antibacterials, p344; Sepsis—definitions & pathophysiology, p592; Multiorgan dysfunction—causes & definitions, p596; Multiorgan dysfunction—management, p598.

Table 31.5 Academy of Medical Royal Colleges antibiotic guideline

Vital signs	Vital signs: NEWS-2: 'Physiology first'	0	1–4	5–6	≥7
Initial assessment	**History, examination, lab results**	***If clinical or carer concern, continuing deterioration, surgically remediable sepsis, neutropaenia, or blood gas/lab evidence of organ dysfunction, including elevated serum lactate, update actions at least to next NEWS2 level →***			
	Comorbid disease, frailty, patient preferences?	*Consider influence of comorbid disease, frailty and ethnicity on NEWS-2, and patient preferences for treatment intensity, limits, end-of-life care*			
Initial (generic) actions	**Monitoring and escalation plan**	Standard observations	• Registered nurse review <1 h • Obs 4–6-hrly if stable • Escalate if no improvement	• Obs hrly • Review <1 h by clinician competent in acute illness assessment • Escalate if no improvement	• Obs every 30 min • Review <30 min by clinician competent in acute illness assessment • Senior doctor review <1 h if no improvement: refer to Outreach or ICU
	Initial treatment of precipitating condition	Standard care	<6 h	<3 h	<1 h
Likelihood of infection & specific actions	Unlikely	Standard care	Review daily and reconsider infection if diagnosis remains uncertain		
	Possible	Review at least daily	**<6 h** • Source identification & control plan documented.	**<3 h** • Microbiology tests • Antimicrobials: administer or revise • Source identification & control plan documented **<6 h** • Source control initiated **48–72 h** • Review antimicrobials with ID/micro/ senior clinician	**<1 h** • Microbiology tests • Antimicrobials: administer or revise (broad-spectrum if causative organism uncertain) **<3 h** • Source identification **3–6 h** • Source control initiated according to clinical urgency **48–72h** • Review antimicrobials with ID/micro/ senor clinician
	Probable or definite	**<6 h** • Diagnostic tests & treatment plan	**<6 h** • Microbiology tests • Anti-microbials: administer or revise • Source identification & control plan • D/w ID/ micro if uncertain, & review		

D/w = discuss with; ID = infectious diseases; micro = microbiology.

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Multiorgan dysfunction—causes & classification

The dysregulated host response to an inflammatory insult results in organ dysfunction. Organ dysfunction may vary from mild to severe, and can affect single or multiple organs resulting in combinations of cardiovascular collapse, gastrointestinal failure, renal failure (acute kidney injury), hepatic failure, encephalopathy, neuropathy, myopathy, and/or disseminated intravascular coagulation. ARDS and its milder variant, acute lung injury (ALI), are the respiratory components of this pathophysiological response. There are changes in both innate and adaptive immunity, with early excessive activation, followed by an overall suppression of function, thereby predisposing the immobile, intubated, multiply cannulated patient to secondary infection. Immunosuppression is often present as early as ICU admission and can persist for months.

There are broad clinical and biological similarities across different triggering insults such as infection, trauma, and pancreatitis. However, within patient subgroups there are also fairly distinct biological signatures—clinical, transcriptomic, proteomic, metabolomic. These are termed subphenotypes or endotypes and carry different mortality risks. Retrospective analyses of trial data suggest specific treatments (e.g. immunomodulatory agents) may benefit particular subphenotypes only.

Causes

- Infection.
- Trauma, burns.
- Pancreatitis.
- Inhalation injuries.
- Massive blood loss/transfusion.
- Miscellaneous including drug-related, myocardial infarction, drowning, hyperthermia, pulmonary embolus.

Classification

The SOFA score is used to classify organ dysfunction of six organ systems (cardiovascular, respiratory, renal, coagulation, neurological, hepatic) with a point score, depending on severity, from 1 to 4. An increasing score correlates with mortality risk and is designed to be simple to perform, repeatable, and available in most hospitals worldwide. It is intentionally rudimentary (e.g. only bilirubin is measured for hepatic dysfunction) and may be confounded by concurrent treatment (e.g. sedation affecting GCS). There are no agreed criteria for other organ systems such as gastrointestinal and immune dysfunction. As a result, clinical or laboratory markers such as large nasogastric aspirates, ileus, and lymphopenia are used variably.

Outcomes

Single organ failure carries a 15–20% risk of mortality, rising to over 60% when 5+ organs are involved. Long-term physical, cognitive, and psychological sequelae affect many survivors.

Further reading

Shankar-Hari M, Harrison DA, Rowan KM. 2016. 'Differences in impact of definitional elements on mortality precludes international comparisons of sepsis epidemiology'. *Crit Care Med* 44: pp2223–30. doi: 10.1097/CCM.0000000000001876

Prescott H, Angus D. 2018. 'Enhancing recovery from sepsis: a review'. *JAMA* 319: pp62–75. doi: 10.1001/jama.2017.17687

Maslove D, Tang B, Shankar-Hari M, et al. 2022. 'Redefining critical illness'. *Nat Med* 28: pp1141–8. doi: 10.1038/s41591-022-01843-x

See Organ failure scoring, p34; Sepsis—management, p594; Multiorgan dysfunction—management, p598.

Multiorgan dysfunction—management

1. Actively seek to identify and treat the underlying cause, e.g. collections, drainage of pus, closure of perforation, stenting of obstructed lumen, debridement/excision of necrotic tissue.
2. Support dysfunctional organ systems until recovery takes place with, e.g. vasopressor support, mechanical ventilation, renal replacement therapy. An important facet of organ support is to minimize iatrogenic trauma and prevent secondary complications such as avoidable line-related infection, venous thromboembolism, stress ulceration, pulmonary barotrauma, and pressure sores.
3. Provide passive and active exercises to prevent contractures, foot drop, etc. Mobilize in/out of bed according to clinical status and stability. Aggressive early mobilization offers no outcome benefits, but a greater risk of complications.

Principles of management

See Table 31.6.

Table 31.6 Principles of management of multiorgan dysfunction

Respiratory	Adequate oxygenation Avoid ventilator-induced lung injury Tolerate permissive hypercapnia if airway pressures high
Cardiovascular	Maintain adequate cardiac output/oxygen delivery and blood pressure compatible with adequate organ perfusion. Avoid both hypovolaemia and fluid overload
Sedation	Titrate drugs to achieve desired target
Renal	Maintain adequate metabolic and fluid homeostasis by intravascular filling, diuretics, vasoactive agents, and/or renal replacement therapy
Haematological	Maintain adequate haemoglobin and platelets levels, correct coagulopathy if severe or undergoing invasive procedures
Gastrointestinal	Stress ulcer prophylaxis, especially if history of peptic ulcer disease or other upper gastrointestinal tract bleeding and/or significant hypoperfusion. Stop once enteral nutrition is established
Infection	Appropriate, timely empiric and subsequently targeted antibiotics, pus drainage, good infection control
Nutrition	Enteral route by preference. Trophic feeding may protect the gut. Supplement vitamins and trace elements
Deep vein thrombisis prophylaxis	Low-molecular-weight heparin and/or intermittent pneumatic devices
Pressure area/ mouth/joint care	Frequent turns, low-pressure support surfaces, nursing care and physiotherapy
Psychological	Support to both patient and family

Further reading

TEAM Study Investigators and the ANZICS Clinical Trials Group. 2022. 'Early active mobilization during mechanical ventilation in the ICU'. *N Engl J Med* 387: pp1747–58. doi: 10.1056/NEJMoa2209083

See Ventilatory support—indications, p48; Continuous renal replacement therapy—techniques & indications, p116; Enteral nutrition, p142; Wound management principles, p152; Special support surfaces, p156; Vasopressors, p290; Sedatives, p322; Antibacterials, p344; Infection control—general principles, p580; Multiorgan dysfunction—causes & definitions, p596.

Multi-resistant infections

Background

Antimicrobial resistance is an increasing problem worldwide, in particular from organisms resistant to multiple antibiotic classes, e.g.:

- Gram-positive organisms, notably MRSA and vancomycin-resistant *Enterococcus* (VRE)
- Gram-negative bacteria, e.g. carbapenem-resistant organisms (CROs), extended spectrum β-lactamase (ESBL) and New Delhi metallo-beta-lactamase 1 (NDM-1) organisms. Common pathogens include *Acinetobacter*, *Pseudomonas*, and *Klebsiella* spp.
- Fungi, e.g. fluconazole resistance varies between *Candida* subtypes, whose prevalence varies by country.
- Other organisms including multi-resistant *Mycobacterium tuberculosis*.

Stewardship

Concerted efforts must be made to minimize antibiotic use:

- Is infection likely and due to a treatable organism? If not, do not give antibiotics or stop promptly once alternative diagnosis confirmed.
- Is antibiotic prophylaxis needed? Surgery can often be performed without, or with only 1–3 doses. Avoid prolonged courses.
- If antibiotics are required, re-evaluate daily the need for continuation or possible de-escalation/discontinuation.
- Antibiotics can generally be stopped 1–2 days after resolution of clinical symptoms and 3–5 days' treatment may be sufficient for 'uncomplicated' infection (e.g. without bone or heart valve involvement).
- If an organism is isolated and sensitivities known, consider changing from broad-spectrum to targeted monotherapy. There is no strong evidence that combinations are superior to monotherapy.

Management

When prescribing antibiotics consider the likelihood of multi-resistance in the following patients:

- In-patient for ≥3 days.
- Recently hospitalized.
- Recently in an area with known high resistance rates, e.g. penicillin-resistant meningococcus from Spain, multi-resistant Gram-negative organisms from southern and eastern Europe, southeast Asia.

Patients colonized/infected with multi-resistant organisms should ideally be placed in source isolation to protect other patients. Source isolation is probably more relevant for airborne (aerosolized) organisms spread by coughing, and organisms producing diarrhoeal illnesses. Strict hand hygiene, glove and gown wearing, and other local infection control policies should be observed.

Decolonization regimens may be considered for MRSA, e.g. chlorhexidine bodywashes and topical antibiotics (e.g. mupirocin) nasally and/or orally (PO). Again, the evidence base remains weak.

Further reading

See Bacteriology, p256; Virology, p258; Antibacterials, p344; Infection control—general principles, p580.

Necrotizing fasciitis

A rapidly spreading and often lethal soft tissue infection. It can be monomicrobial (predominantly group A β-haemolytic streptococci) or polymicrobial including Gram-negative, other Gram-positive, and anaerobic organisms (Table 31.7). Two-thirds are polymicrobial.

It can involve any layer within the soft tissue compartment (dermis, subcutaneous tissue, superficial or deep fascia, muscle) and is associated with tissue necrosis. It is not usually associated with abscess formation, but can originate from untreated/inadequately drained abscesses.

Fournier's gangrene is a polymicrobial necrotizing fasciitis affecting the perineal–perianal area.

Table 31.7 Types of necrotizing fasciitis

Type	Mono- or polymicrobial	Common organisms
1	Polymicrobial (aerobic & anaerobic)	*Escherichia coli, Bacteroides* spp., *Clostridium* spp., among others
2	Monomicrobial	Group A *Streptococcus*
3	Monomicrobial	*Staph. aureus*, including MRSA
4	Gram-negative polymicrobial	*Vibrio vulnificus*
5	Fournier's gangrene: specific to perineal area	Similar to type 1 but may involve specific genital flora

Risk factors

- Comorbidities, e.g. diabetes, immunosuppression, obesity.
- Recent surgery.
- Intramuscular/subcutaneous drug injection (including recreational drugs).

Diagnosis

- Have a high index of suspicion as diagnosis may be difficult initially. Patient may be symptomatic with severe pain disproportionate to clinical appearance. Signs of local infection may be absent.
- Classic features are swelling, erythema, and pain over affected area. With progression, tense oedema appears with skin discoloration, subcutaneous bruising, blisters/bullae, necrosis, crepitus and/or subcutaneous gas.
- Fever, tachycardia, hypotension, shock.
- Elevated creatine kinase, markers of inflammation (CRP, procalcitonin), neutrophilia.
- Computed tomography (CT)/magnetic resonance imaging (subcutaneous gas and inflamed fascia) or X-ray (subcutaneous gas) have high sensitivity but low specificity.
- If in doubt, diagnostic surgical exploration may be needed and should not be delayed.

Treatment

- Source control—urgent and complete debridement by an experienced surgeon to remove all infected tissue. After surgery, clinical deterioration is often seen. Frequent (24–48-hrly) repeat examinations under anaesthesia ± debridement are needed until the fasciitis stops spreading and no further dead tissue is seen.
- Antibiotics: high-dose clindamycin, a potent protein synthesis inhibitor, inhibits toxin production, particularly in *Streptococcus* and *Clostridium* infection. Give in combination with high-dose carbapenem ± an aminoglycoside. Continue until no further debridement needed. Consult microbiology for advice.
- Patients often require multiple organ support, fluid resuscitation, correction of coagulopathy, blood transfusion.
- Intravenous immunoglobulin (IVIg) can be considered for toxin-related infection due to group A *Streptococcus* or *Clostridium*. UK guidance supports use in those not responding to initial therapy.
- Hyperbaric oxygen may improve outcomes, but randomized trials are lacking. This must not delay or prevent surgical debridement.

Further reading

Stevens D, Bryant A. 2017. 'Necrotizing soft-tissue infections'. *N Engl J Med* 377 pp2253–65. doi: 10.1056/NEJMra1600673

Madsen M, Skrede S, Perner A, et al. 2019. 'Patient's characteristics and outcomes in necrotising soft-tissue infections: results from a Scandinavian, multicentre, prospective cohort study'. *Intensive Care Med* 45: pp1241–51. doi: 10.1007/s00134-019-05730-x

See Bacteriology, p256; Antibacterials, p344; Infection—diagnosis, p588; Infection—treatment, p590; Sepsis—management, p594.

Toxic shock syndrome

Toxic shock syndrome (TSS) is a specific infection syndrome related to the immune response to exotoxin release usually from *Staph. aureus* or Group A *Streptococcus*.

Clinical features

Often a non-specific prodrome including malaise, fever, diarrhoea and vomiting, headache, and/or myalgia. The acute severe illness is characterized by significant pyrexia, confusion, an erythematous sunburn-like rash (often first appearing on the chest) followed by desquamation, classically of palms and soles, and hypotension. This may evolve into shock as quickly as 12 h in some cases. Of note, despite marked hypotension and often significant renal and other organ dysfunction, the patient may be remarkably lucid. These toxin-producing organisms do not generate pus, so a visible source of infection, e.g. a cut, surgical wound or insect bite, may just show surrounding erythema and serous fluid ooze. Mortality is high (30–70%), with significant morbidity in survivors, e.g. amputation, hysterectomy, surgical debridement.

Causes

- Wounds—surgical, postpartum, burns, other, e.g. cuts.
- Retained tampon—prolonged use of single tampon.
- Deeper infections—pharyngitis, sinusitis, pneumonia, empyema, osteomyelitis, and arthritis.

Management

- Empiric antibiotic therapy should be started promptly and should include clindamycin which decreases toxin synthesis and release (or linezolid if local high resistance to clindamycin), vancomycin or teicoplanin (especially if *Staph. aureus* is suspected), and either meropenem or piperacillin–tazobactam ± an aminoglycoside. The regimen can be rationalized once organism and sensitivities are known.
- Search for infection site and perform early source control if identified by an experienced surgeon. This may require extensive debridement and regular re-exploration, drainage and removal of infected tampon or catheters. Send tissue or fluid samples for microbiological analysis.
- Supportive therapy including fluid to correct hypovolaemia, vasopressors, and mechanical organ support. Often hypotension is refractory to fluids. Fluid overload should be avoided as this can precipitate or worsen acute lung injury. Coagulopathy should be corrected as appropriate.
- IVIg is often given though no randomized trials have been performed due to the relative rarity of the condition. Other possible, but unproven, therapies include corticosteroids, plasmapheresis, and hyperbaric oxygen.

Further reading

Hua C, Urbina T, Bosc R, et al. 2023. 'Necrotising soft-tissue infections'. *Lancet Infect Dis* 23: ppe81–94. doi: 10.1016/S1473-3099(22)00583-7

See Plasma exchange, p122; Bacteriology, p256; Antibacterials, p344; Immunomodulatory therapies, p354; Infection—diagnosis, p588; Infection—treatment, p590; Sepsis—management, p594.

Tetanus

The clinical syndrome caused by the exotoxin tetanospasmin from the anaerobe *Clostridium tetani* in contaminated or devitalized wounds. Tetanospasmin ascends intra-axonally in motor and autonomic nerves blocking the release of inhibitory neurotransmitters. The disease may be modified by previous immunization such that milder or localized symptoms may occur with heavier toxin loads.

Clinical features

- Gradual onset of stiffness, dysphagia, muscle pain, hypertonia and rigidity, and muscle spasm; >80% present with trismus (lockjaw).
- Laryngospasm often follows dysphagia.
- Widespread autonomic instability.
- Muscle spasm is often provoked by minor disturbance, e.g. laryngospasm may be provoked by swallowing.
- Onset of symptoms within 5 days of injury implies a heavy toxin load and severe disease, ranges from 3 to 21 days.
- The disease is self-limiting so treatment is supportive but may need to continue for several weeks.

Management of the wound

If a contaminated wound is present, it should be debrided surgically after 250 IU human tetanus immunoglobulin has been given (in a different site to tetanus toxoid immunization). Benzylpenicillin (1.2 g 4-hrly) and metronidazole (500 mg 8-hrly IV) are appropriate antibiotics. Tetanus-prone wounds include:

- Any wound or burn sustained >6 h before surgical treatment.
- Any wound or burn with a significant degree of devitalized tissue, puncture-type wounds, contact with soil or manure, or clinical evidence of sepsis.

Tetanus toxoid prophylaxis

The disease confers no immunity so patients must be immunized prior to hospital discharge (Table 31.8).

Table 31.8 Tetanus toxoid dose requirements

Last dose of tetanus toxoid <5 years	No further dose
Last dose of tetanus toxoid <10 years	1 dose
No previous immunization	3 doses

Mild tetanus

Patients with mild symptoms, no respiratory distress, and a delayed onset of symptoms should be nursed in a quiet environment with mild sedation to prevent tetanic spasms.

Severe tetanus

- Intubate and ventilate since asphyxia may occur due to prolonged respiratory muscle spasm.
- Sedate with benzodiazepines (high doses may be necessary).
- Muscle rigidity is best treated with magnesium sulfate (starting 2 g/h IV) and benzodiazepines, with addition of muscle relaxants if necessary.
- Autonomic hyper-reactivity (arrhythmias, hypotension, hypertension, and myocardial ischaemia) is often seen. It is minimized by sedation (e.g. clonidine), β-blockade (e.g. labetalol 0.25–1 mg/min), anaesthesia ± atropine 1–20 mg/h IV.
- Human tetanus immunoglobulin 500 units intramuscularly (IM) shortens the course of the disease by removing circulating toxin. Administer as soon as the diagnosis considered. Rapid fixation of the toxin to tissues limits the usefulness of this approach.
- Airway management with intubation and early tracheostomy is often needed as the usual duration of symptoms is 4–6 weeks.

Further reading

Rodrigo C, Fernando D, Rajapakse S. 2014. 'Pharmacological management of tetanus: an evidence-based review'. *Crit Care* 18:217. doi: 10.1186/cc13797

➔ See Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Wound management principles, p152; Antibacterials, p344.

Botulism

An uncommon, lethal disease caused by exotoxins of the anaerobe *Clostridium botulinum*. Botulism is most commonly a food-borne disease, especially associated with canned foods. It may be contracted by wound contamination with aquatic soils or from skin popping (*C. novyi or C. histolyticum* introduced from drug abusers injecting into skin or muscle). Deliberate release of the toxin or contamination of foodstuff with *C. botulinum* is considered a potential biological weapon with the adult lethal dose of toxin being <1 μg. The toxin is carried in the blood to cholinergic neuromuscular junctions where it binds irreversibly. Symptoms begin between 6 h and 8 days after contamination and are more severe with earlier onset. Botulism is diagnosed by isolating *Clostridium* spp. from stool, gastric aspirate, or wound.

Clinical features

- Features include sore throat, fatigue, dizziness, paraesthesiae, diplopia, bilateral cranial involvement, and a progressive, descending flaccid weakness, and rarely gastrointestinal disturbance.
- Fever is usually absent.
- Parasympathetic symptoms are common.
- The disease usually resolves within several weeks.

Diagnosis

Identification of toxin in stool, vomit, or isolation of bacterium stool, wound, or food source.

Management

Antibiotics are not indicated for the management of botulism unless there is a contaminated wound.

Respiratory care

Close monitoring of respiratory failure with prompt intubation and mechanical ventilation if tiring. Patients with bulbar palsy may need intubation for airway protection.

Antitoxin

Prevents further paralysis but does not reverse existing paralysis. May shorten the disease course, if given early. There is a risk of anaphylactoid reactions but, usually, treatment is limited to two doses minimizing the risk.

Toxin removal

If no ileus present, non-magnesium-containing cathartics (e.g. sorbitol) may remove the toxin load. Magnesium may enhance the effect of the toxin.

Wound botulism

Extensive surgical debridement (after antitoxin treatment to neutralize any toxin released during surgery), benzylpenicillin (1.2 g IV 4-hrly), and metronidazole (500 mg IV 8-hrly), and antitoxin are the mainstays of treatment for contaminated wounds.

Further reading

Brett MM, Hallas G, Mpamugo O. 2004. 'Wound botulism in the UK and Ireland'. *J Med Microbiol* 53: pp555–61. doi: 10.1099/jmm.0.05379-0

➲ See Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Wound management principles, p152.

HIV-related disease

Human immunodeficiency virus (HIV) is now considered a chronic medical condition with limited impact on life expectancy with use of combination antiretroviral therapy (cART).

Patients still present *de novo* with 'AIDS-defining' opportunistic pathogen-related infections or as a result of therapy non-compliance. However, the majority now present with conventional infections and illnesses. Lymphoma (Hodgkin's, non-Hodgkin's, Burkitt's) is a well-recognized complication of long-term survivors.

Opportunistic infections to consider include *Pneumocystis jirovecii* pneumonia, CMV, toxoplasmosis, and mycobacteria. Patients may present with cerebral involvement including seizures, e.g. due to lymphoma, typical or atypical central nervous system (CNS) infections, meningoencephalitis, or from complications of the therapy, e.g. acute hypersensitivity reactions or immune reconstitution inflammatory syndrome (IRIS).

Take appropriate samples for microbiology and request an atypical screen depending on presenting features. CD4 count drops with critical illness so is not necessarily reflective of cART compliance. HIV viral load should also be measured.

Seek an HIV specialist opinion regarding continuation or commencement of antiretroviral drugs. Risks of resistance, difficulties in administration of oral medications, possible contraindicated use of proton pump inhibitors, delayed renal and/or hepatic clearance, drug interactions, and toxicity (e.g. IRIS, Stevens–Johnson syndrome, pancreatitis, lactic acidosis) should all be considered. In general, patients well established on cART are continued on this therapy.

Pneumocystis jirovecii pneumonia

- Both incidence and prognosis have improved considerably in recent years, even in those requiring mechanical ventilation. Early support with CPAP and appropriate treatment may avert the need for ventilatory support.
- Diagnose clinically without waiting for laboratory confirmation. Diagnosis is made by respiratory specimen microscopy. Quantitative PCR and a very high β-D-glucan levels are diagnostic if clinically compatible.
- Diffuse, bilateral ground-glass opacity is usually seen on imaging.
- First-line treatment is with high-dose co-trimoxazole (or pentamidine if co-trimoxazole unsuitable or ineffective). Adjuvant high-dose steroids should also be commenced. See Table 31.9 for drug dosages.
- Respiratory support as standard, but there is an increased risk of pneumothorax, so ensure lung protective strategies are performed.
- Avoid excessive fluid loading as marked capillary leak can occur.

Table 31.9 Drug dosages

Co-trimoxazole	120 mg/kg/day in divided doses IV for 10–14 days then PO to complete 21 days
Pentamidine	4 mg/kg/day IV
Methylprednisolone	1 g/day IV for 3 days

Immune reconstitution inflammatory syndrome (IRIS)

IRIS is a hyperinflammatory condition that mainly occurs within 6 months of starting cART, and is related to improvements in immune status and a rising CD4 cell count. It is characterized by paradoxical worsening of symptoms, and results from an exaggerated inflammatory response to *Pneumocystis*, mycobacterial, viral, or other antigens. It can lead to fever, lymphadenopathy, respiratory failure, hepatitis, and CNS and skin manifestations. Diagnosis is by exclusion of other causes. Management includes treatment of infection plus corticosteroids if severe. Consider continuing cART unless life-threatening.

Further reading

Barbier F, Mer M, Szychowiak P, et al. 2020. 'Management of HIV-infected patients in the intensive care unit'. *Intensive Care Med* 46: pp329–42. doi: 10.1007/s00134-020-05945-3

See Ventilatory support—indications, p48; Non-invasive respiratory support, p74; Continuous positive airway pressure (CPAP), p76; Antibacterials, p344; Corticosteroids, p352; Infection control—general principles, p580; Infection control—blood-borne viruses, p582.

Viral critical illness

Better diagnostics have identified a much higher incidence of acute viral illness, ranging from those that predominantly affect the respiratory system (e.g. influenza, coronavirus), the gastrointestinal system (e.g. rotavirus, norovirus, hepatitis), cardiac (e.g. coxsackie, adenovirus), haemorrhagic fevers (e.g. Lassa, Ebola), meningoencephalitis (e.g. herpes simplex), or an HIV-related illness. Other systems may also be involved (e.g. myocarditis from influenza) as the primary condition or as part of multisystem involvement. Reactivation of dormant viruses may also occur with critical illness (e.g. CMV, herpes zoster).

Specific antiviral treatments may be indicated, in addition to supportive care (e.g. mechanical ventilation). Mode of transmission is important to consider, particularly with respect to infection control, e.g. isolation, appropriate personal protective equipment (PPE) for staff.

Respiratory viral infection

Respiratory viruses are a common cause of critical illness, particularly in the elderly and immunocompromised, causing pneumonia and ARDS, and sepsis. In addition to supportive treatment (oxygen, fluids, nutrition, and ventilation) various treatments are postulated for non-COVID-19 respiratory viral infections, e.g. oseltamivir, ribavirin, corticosteroids, interferon, and IVIg, but none have yet confirmed an outcome benefit. Secondary bacterial infection is common, for which prophylactic antibiotics may be useful. Prior vaccination (*Strep. pneumoniae* or *Haemophilus influenzae*) may be advantageous.

Viral haemorrhagic fevers

Viral haemorrhagic fevers are a group of viral infections that cause a severe haemorrhagic disease. They include Lassa, Ebola and Marburg fevers. Treatment is supportive and mortality may be high for these highly contagious pathogens. In developed countries, such patients are managed in a high-risk infectious diseases unit with capability to provide organ support. These units generally have restricted access, lobbied entrance to isolation rooms, negative pressure with HEPA filtration for exhaust air, ensuite facilities, and staff shower and change facilities. Protective suits may limit the time staff can work. These patients may be managed in bed isolator tents (Trexler units) with the provision of all care via invaginated sleeves into the tent.

Further reading

See Oxygen therapy, p40; Endotracheal intubation—indications & equipment, p44; Nutrition—use & indications, p140; Virology, p258; Antivirals, p348; Respiratory failure, p370; Pneumonia—diagnosis, p374; Infection control—general principles, p580; Infection control—dangerous pathogens, p584.

Malaria

Malaria should be suspected in any patient returning from endemic areas with a febrile illness that may have cerebral, abdominal, lung, or renal features. Rarely, people living near airports may be bitten by a transported *Anopheles* mosquito. There may be considerable delay (weeks to months) between the mosquito bite and signs of infection. It is caused by protozoal infection with the *Plasmodium* genus. The most severe form is *P. falciparum* which causes malignant, tertian malaria. Other forms, e.g. *P. vivax, P. ovale*, rarely cause significant life-threatening disease.

Pathophysiology

P. falciparum invades erythrocytes. Even low levels of parasitaemia <2% may be severe in non-immune travellers and patients may be very symptomatic despite low parasite counts. The cells may haemolyse or be destroyed in the liver or spleen. Anaemia may be severe. Increased vascular permeability, cytokine release, red cell agglutination, and coagulopathy may also occur.

Clinical features

Symptoms include headache, fever with rigors, myalgia, abdominal pain, vomiting, and diarrhoea. Paroxysms of fever with 'cold' and 'hot' stages are uncommon. Signs include splenomegaly, jaundice, tender hepatomegaly, and anaemia. Hyponatraemia is common. Features include:

- Cerebral malaria: coma, delirium, seizures, or focal deficits.
- Cough, haemoptysis, or acute respiratory distress.
- Blackwater fever is associated with massive intravascular haemolysis, jaundice, haemoglobinuria, and acute kidney injury. Acute renal dysfunction occurs in a third of adult ICU patients.
- Acute cardiovascular collapse ('algid malaria') and metabolic acidosis.
- Thrombocytopenia, coagulopathy, and spontaneous bleeding.

Diagnosis

- Microscopic examination identifying plasmodia within erythrocytes is the gold standard technique, but low parasitaemia levels may be missed by an inexperienced technician. Parasitaemia intensity may vary from hour to hour and may be scanty. Repeat blood film if doubt persists.
- Rapid antigen tests (immunochromatographic) are useful, but beware of false positives and false negatives.
- Molecular based techniques (PCR) are highly specific and sensitive.
- Leucocytosis is not a feature of malaria.

Treatment

1. Severe or complicated malaria should be managed in critical care.
2. IV artesunate is the treatment of choice if severely ill. Can later switch to oral artemether combination therapy. For *P. vivax* and *P. ovale* infections, add primaquine to treat the liver stage forms. See Table 31.10 for drug dosages.
3. If artesunate not immediately available, give IV quinine. Complications include hypoglycaemia and tinnitus.
4. Exchange transfusion can be considered for high parasitaemia levels, but is now rarely used.

5. Careful attention to fluid and electrolyte balance. Avoid excess fluid as these patients have increased capillary leak which can worsen ARDS and cerebral oedema.
6. Use standard protocols for cerebral oedema, hypoglycaemia, acute kidney injury, coagulopathy, metabolic acidosis, seizures, etc.
7. Steroids are not generally recommended.
8. Malaria patients are immunosuppressed and prone to secondary bacterial infection. Suspect Gram-negative infection if circulatory collapse.

Table 31.10 Drug dosages

Artesunate	2.4 mg/kg IV tds first 24 h, then od thereafter until able to tolerate oral therapy
Quinine	20 mg quinine salt/kg IV over 4 h, then 10 mg/kg infusion over 4 h, repeated 8-hrly until the patient can swallow, then tablets (10 mg quinine salt/kg 8-hrly) to complete a 7-day course. Halve maintenance dose to 5 mg quinine salt/kg 8-hrly if continuing parenteral therapy for >48 h
Primaquine	15–30 mg PO for 14 days

Further reading

➔ See Acute respiratory distress syndrome—diagnosis, p384; Acute respiratory distress syndrome—management, p386; Oliguria, p426; Acute kidney injury—diagnosis, p428; Acute kidney injury—management, p430; Jaundice, p452; Coma, p466; Generalized seizures, p472; Anaemia, p500; Haemolysis, p504; Pyrexia, p654.

Haemophagocytic lymphohistiocytosis (HLH)

Process of hyperinflammation leading to pyrexia, hepatosplenomegaly, lymphadenopathy, and confusion. Initially non-specific. It may be triggered by infectious or non-infectious causes and can mimic sepsis. It may progress into multiorgan failure (lung, liver, renal, cardiac, brain, skin).

Pathophysiology

Excess activation of macrophages leading to disrupted immune homeostasis including phagocytosis of blood cell types and stimulation of a marked pro-inflammatory response.

Diagnosis

Cytopenia (platelets, haemoglobin, white cells), transaminitis, increased ferritin and triglycerides, lactate dehydrogenase, sIL-2R, reduced fibrinogen level, haemophagocytosis (seen in bone marrow ± blood). The H-score (Table 31.11) incorporates these values to provide a probability of HLH.

Table 31.11 The H-score

Score	Points		
Underlying immune-suppression[a]	0 (no)	18 (yes)	
Temperature (°C)	0 (<38.4)	33 (38.4–39.4)	49 (>39.4)
Organomegaly	0 (no)	23 (hepatomegaly or splenomegaly)	38 (hepatomegaly and splenomegaly)
No. of cytopenias[b]	0 (1 cell line)	24 (2 cell lines)	34 (3 cell lines)
Ferritin (μg/L)	0 (<2000)	35 (2000–6000)	50 (>6000)
Triglycerides (mmol/L)	0 (<1.5)	44 (1.5–4)	64 (>4)
Fibrinogen (g/L)	0 (>2.5)	30 (≤2.5)	
AST (IU/L)	0 (<30)	19 (≥30)	
Haemophagocytosis in bone marrow aspirate	0 (no)	35 (yes)	

[a] HIV positive or long-term immunosuppressive therapy.

[b] Haemoglobin <92 g/L and/or leukocytes ≤5 × 10^9/L and/or platelets ≤110 × 10^9/L.

The risk of HLH is >99% with a score of ≥250 and >90% with a score ≥169.

AST = aspartate aminotransferase.

Causes

- Primary (pHLH): familial.
- Infections: e.g. viral (EBV, CMV, human herpesvirus-8), bacterial (mycobacteria, salmonella), fungal (candida, histoplasmosis), parasitic (leishmaniosis, malaria, toxoplasmosis).
- Haematological malignancies, especially lymphomas and solid cancers.
- Autoimmune disease: systemic lupus erythematosus (SLE), adult-onset Still disease.
- Immune deficiency.
- Iatrogenic, e.g. chemotherapeutics, post bone marrow transplantation.
- Idiopathic.

Management

Seek advice from specialist with expertise in HLH (may be rheumatologist, haematologist, or infectious diseases specialist).

- First line: IV steroids (methylprednisolone or dexamethasone) ± IVIg, anakinra (binds interleukin (IL)-1 type receptor antagonist).
- Second line: etoposide IV ± ciclosporin.
- Supportive care and targeted treatment of cause, e.g. antimicrobial, chemotherapy.

Prognosis

Mortality at 30 days 30% and overall mortality 60%.

Further reading

Bauchmuller K, Manson J, Tattersall R, et al. 2020. 'Haemophagocytic lymphohistiocytosis in adult critical care'. *J Intensive Care Soc* 21: pp256–68. doi: 10.1177/1751143719893865

Fardet L, Galicier L, Lambotte O, et al. 2014. 'Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome'. *Arthritis Rheumatol* 66: pp2613–20. doi: 10.1002/art.38690

'Online calculator for HLH risk'. Fardet L, Galicier L, Lambotte O, et al. Accessed June 2023. https://saintantoine.aphp.fr/score/

See Full blood count, p250; Corticosteroids, p352; Immunomodulatory therapies, p354.

Rheumatic disorders

Rheumatoid arthritis

Multisystem disease that may present to critical care with pulmonary involvement or complications of treatment (e.g. acute kidney injury, immunosuppression, bleeding disorders). Pleuro-pulmonary involvement may precede arthritic symptoms; it is more common with active rheumatoid disease. Caution should be taken with intubation, as neck involvement increases the risk of vertebral column subluxation. Seek advice from a rheumatologist about starting/continuing treatment with steroids or other disease-modifiers such as methotrexate, anti-tumour necrosis factor (TNF) antibody, or rituximab.

Rheumatoid pleurisy

May present with effusion and can be asymptomatic. Effusions may be recurrent or chronic and may impede respiratory function. The effusion is an exudate, low in glucose and often high in cholesterol.

Rheumatoid lung

A diffuse interstitial pneumonitis with bi-basal fibrotic changes on chest X-ray or CT. It produces a restrictive pulmonary defect. The mainstay of treatment is early systemic corticosteroid therapy.

Systemic lupus erythematosus (SLE)

A non-organ specific autoimmune disease characterized by antinuclear antibodies with high titres of anti-double stranded DNA antibodies. Vasculitis is prominent, though cutaneous and CNS involvement are not vasculitic in origin. SLE may present to critical care through pulmonary, renal, myocardial, or CNS involvement.

Renal failure

Often vasculitic in origin and may progress to end-stage renal failure requiring long-term dialysis. Early treatment with steroids and immunosuppressives may reverse the disease progress.

Lupus pleurisy and pericarditis

Unlike rheumatoid pleurisy, pleural involvement in SLE is often painful and associated with large pleural effusions.

Pulmonary haemorrhage

This is associated with renal failure and may be life-threatening. Plasma exchange may be helpful.

Interstitial pneumonitis

Interstitial pneumonitis is uncommon. Parenchymal infiltrates are more likely to be infective in origin secondary to immunosuppressive therapy.

Pulmonary thromboembolic disease

Patients typically have a prolonged activated partial thromboplastin time due to circulating lupus anticoagulant, but are more prone to thrombotic episodes. Lupus anticoagulant is associated with anticardiolipin antibodies. Recurrent pulmonary emboli may be associated with chronic pulmonary hypertension. Treatment is long-term anticoagulation.

Further reading

➔ See Respiratory imaging, p178; Anticoagulants—parenteral, p334; Anticoagulants—oral, p336; Corticosteroids, p352; Immunomodulatory therapies, p354; Pulmonary embolus—diagnosis, p394; Acute kidney injury—diagnosis, p428; Acute kidney injury—management, p430; Vasculitis, p620.

Vasculitis

Vasculitis should be suspected in any patient with multisystem disease especially involving the lungs and kidneys.

Granulomatosis with polyangiitis (GPA)

Formerly known as Wegener's disease, GPA is characterized by necrotizing granulomas of the upper and lower respiratory tract, glomerulonephritis, and small vessel vasculitis. GPA is associated with positive core antineutrophil cytoplasmic antibodies (c-ANCA), particularly granular with central attenuation on immunofluorescence. Need for critical care is usually for renal and pulmonary support.

Renal failure

Focal necrotizing glomerulonephritis leads to progressive renal failure. Treatment with steroids and cyclophosphamide may give complete remission.

Upper airway disease

Nasal symptoms include epistaxis, nasal discharge, and septal perforation. Critical care admission may be required for severe epistaxis. Ulcerating lesions of the larynx and trachea may cause subglottic stenosis. This is usually insidious, but may present with difficult intubation.

Pulmonary involvement

Usually associated with haemoptysis, dyspnoea, and cough with rounded opacities ± cavitation on chest X-ray/CT. Nodules may be solitary. Alveolar haemorrhage may be life threatening. The mainstay of treatment is steroids and cyclophosphamide which may produce complete remission. Plasma exchange may be helpful.

Polyarteritis nodosa (PAN)

PAN is a necrotizing vasculitis affecting small and medium-sized muscular arteries. Intensive care admission may be provoked by renal failure, acute coronary syndrome, hypertensive crisis, and bronchospasm although true pulmonary involvement is uncommon. Diagnosis may be confirmed by mesenteric angiography or renal biopsy. Treatment involves renal replacement therapy, high-dose steroids, and cyclophosphamide.

Anti-glomerular basement membrane (GBM) disease (Goodpasture's syndrome)

Anti-GBM antibodies bind at the glomerulus and alveolus. Patients present with a proliferative glomerulonephritis and haemoptysis. Diagnosis is confirmed by positive anti-GBM antibodies and renal biopsy. Treatment is with immunosuppressive therapy and plasma exchange.

Further reading

See Plasma exchange, p122; Corticosteroids, p352; Airway obstruction, p368; Haemoptysis, p402; Acute kidney injury—diagnosis, p428; Acute kidney injury—management, p430; Rheumatic disorders, p618.

Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN) is an acute-onset, potentially life-threatening, idiosyncratic mucocutaneous reaction, usually occurring after starting a new drug, e.g. antibiotics, non-steroidal anti-inflammatory drugs, anticonvulsants, allopurinol, or immunization or less commonly a result of infection such as mycoplasma or CMV. It is often complicated by secondary infection and multiorgan dysfunction.

Stevens–Johnson syndrome is a milder form involving <10% skin surface area whereas TEN involves >30%. It is considered an intermediate form when there is 10–30% skin involvement.

Clinical features

- There is often a flu-like prodrome for 2–3 days.
- Macular rash that may become confluent, with desquamation of skin and mucosae leaving raw, moist denuded surfaces.
- Conjunctivitis may precede skin changes by 1–3 days.
- Relevant drugs started within the previous 4 weeks.

Management

- Clinical diagnosis is usually sufficient; skin biopsy may be needed for atypical cases.
- Stop all potential causative drugs.
- IV catheters should avoid affected skin, if possible.
- A SCORTEN assessment should be made (Table 31.12). Patients with SCORTEN ≥2 or significant comorbidity should be managed in an ICU.
- Fluid loss from desquamation mandates careful assessment and replacement. Requirements approach those needed for an equivalent area burn injury. Nurse in a humidified environment.
- Give PO or IV analgesia.
- Give thromboprophylaxis.
- Regularly assess for infection. Hypothermia may indicate the onset of sepsis and should be managed in protective isolation.
- Manage patients on a pressure-relieving mattress.
- Early attention to eye care is essential. Apply chloramphenicol eye ointment 6-hrly (unless chloramphenicol is a possible causative agent).
- Desquamation may obstruct the tracheobronchial tree or urethra.
- Avoid adhesive tapes and do not debride skin. Detached skin should be left in place and protected.

Table 31.12 SCORTEN indicators of prognosis

Age >40 years
Heart >120/min
Malignancy
>10% body surface area blistered on day 1
Urea >10 mmol/L
Bicarbonate <20 mmol/L
Glucose >14 mmol/L

Score 0–1: 3.2% mortality; score 2: 12.2% mortality; score 3: 35.3% mortality; score 4: 58.3% mortality; score >5: 90% mortality.

Further reading

Lian BS, Lee HY. 2022. 'Managing the ADR of Stevens–Johnson syndrome/toxic epidermal necrolysis'. *Expert Opin Drug Safety* 21: pp1039–16. doi: 10.1080/1744666X.2020.1740591

See Wound management principles, p152; Dressing techniques, p154; Special support surfaces, p156; Basic resuscitation, p358; Fluid challenge, p362; Infection—diagnosis, p588; Infection—treatment, p590; Pain, p660.

Anaphylactoid reactions

Minor reactions to allergens (itching, urticaria) are common before a severe reaction occurs; any such history should be taken seriously and potential allergens avoided. Most reactions are acute in onset and clearly related to the causative allergen. However, some complement-mediated reactions may take longer to develop.

Clinical features

- Respiratory—laryngeal oedema, bronchospasm, pulmonary oedema, pulmonary hypertension.
- Cardiovascular—hypotension, tachycardia, generalized oedema.
- Other—urticaria, angio-oedema, abdominal cramps, rigors.

Management

1. Stop all infusions and blood transfusions and withhold any potential causative drug or food allergen. Blood and blood products should be returned to the laboratory for analysis.
2. Give appropriate oxygen to maintain normoxaemia. If hypoxaemia persists, consider urgent intubation and mechanical ventilation.
3. If there is laryngeal obstruction, bronchospasm, or facial oedema give intramuscular (IM) or nebulized epinephrine. Experienced users may opt for low-dose IV epinephrine, repeated as required. If readily available, Heliox may be helpful. If no rapid relief of airway obstruction, consider urgent intubation with potential need for Front of neck access as per Difficult Airway Society (DAS) guidelines. Persistent bronchospasm may require epinephrine ± salbutamol ± aminophylline infusion, or assisted expiration (manual chest compression).
4. Treat hypotension with epinephrine IV/IM and rapid fluid infusion guided by haemodynamic monitoring. Large volumes of fluid may be required. Severe oedema may coexist with hypovolaemia. Use norepinephrine in high-output vasodilatory shock to divert blood centrally and increase peripheral resistance.
5. Adjunctive treatment includes steroids (e.g. hydrocortisone), antihistamines, i.e. H_1 blocker (e.g. chlorphenamine, IV or PO or cetirizine PO, depending on the severity of the reaction), and an H_2 blocker (e.g. ranitidine). For drug dosages see Table 31.13.
6. After control of the anaphylactic reaction, advice should be sought from the immunology laboratory and appropriate samples such as tryptase taken for confirmation.
7. Reactions to long-acting drugs or fluids will require continued support (perhaps for many hours).

Further reading

'Intubation guidelines'. Difficult Airway Society. 2017. Accessed June 2023. https://das.uk.com/guidelines/icu_guidelines2017

See Endotracheal intubation—indications & equipment, p44; Bronchodilators, p278; Inotropes, p286; Corticosteroids, p352; Basic resuscitation, p358.

Table 31.13 Drug dosages

	Initial dose	Continued treatment
Laryngeal oedema and bronchospasm		
Epinephrine	0.3–0.5 mg IM or 0.5 mg nebulized	Start at 0.05 μg/kg/min IV
Hydrocortisone	200 mg IV	
Hypotension		
Epinephrine	0.5–1.0 mg IM or 0.05–0.2 mg IV	Start at 0.05 μg/kg/min IV
Hydrocortisone	200 mg IV	200 mg IV qds
Chlorphenamine		10 mg IV tds
Urticaria		
Chlorphenamine		10 mg IV tds or 4 mg PO tds
Hydrocortisone		50–100 mg IV tds
Prednisolone		20 mg PO daily

Chapter 32

Trauma & burns

Multiple trauma—initial management

Such patients are admitted either after surgery/interventional radiology, or for close observation and conservative management. The principles of initial intensive care unit (ICU) management are to:

- Continue resuscitation and correct any coagulopathy.
- Adequately restore organ perfusion and oxygenation.
- Control pain.
- Restore and maintain homeostasis (e.g. electrolytes, haemoglobin, pH, temperature).
- Monitor closely and deal promptly with any complications.

Circulatory management

- Institute adequate monitoring at an early stage.
- Patients are often cold and vasoconstricted on ICU admission. This can camouflage hypovolaemia and compromise perfusion. Aim for normothermia; consider fluid warmer, forced air warming blankets.
- Development of a persisting tissue oxygen debt may lead to subsequent multiple organ dysfunction, which may not become clinically apparent for 3–7 days. Therefore, adequate perfusion should be restored promptly by blood and blood products ± vasoactive agents.
- An early increasing hyperlactataemia/metabolic acidosis should prompt suspicion of inadequate resuscitation, covert haemorrhage, or tissue necrosis. Myocardial depression or failure, or an undiagnosed pericardial tamponade, may also be implicated.
- Avoid extremes in blood pressure (BP)to prevent risks of tissue ischaemia or secondary haemorrhage. BP target should reflect need for specific organ protection (e.g. higher with traumatic brain injury (TBI)) with permissive hypotension (systolic BP 80–90 mmHg) until haemorrhage is controlled.

Respiratory management

Management may vary depending on the presence of direct chest injury (e.g. flail chest, pneumothorax), or the need for a protective ventilation strategy (e.g. for head injury). Otherwise, standard lung protective ventilation should be provided.

If spontaneously breathing, maintain gas exchange, encourage deep breathing ± non-invasive support to prevent atelectasis and secondary infection. Ensure good analgesia, consider patient-controlled analgesia and regional blocks (e.g. epidural, paravertebral, or other chest blocks), and mobilize early, if possible.

Weaning from invasive ventilation depends on multiple factors including cardiorespiratory stability, pain control, stabilization of intracranial pressure (ICP), appropriate conscious level, upper airway patency, and likely ability to protect airway and secretion clearance and/or any need for imminent invasive procedures.

Haematological management

- Use blood products early in major haemorrhage with a ratio of fresh frozen plasma:platelets:packed red blood cells of 1:1:1 and at least 1:1:2. Blood transfusion is associated with hypocalcaemia. Monitor and replace ionized Ca^{2+} using calcium chloride.

- In general, aim for haemoglobin >70 g/L, although a higher threshold may be targeted if concerns about further major bleeding or patient has significant cardiorespiratory morbidity. Cross-matched blood should be readily accessible.
- Ensure patient has had tranexamic acid (initial 1 g intravenous (IV) bolus and then 1 g IV infusion over 8 h).
- Correct coagulation as appropriate with platelets, fresh frozen plasma, or other blood products (e.g. cryoprecipitate, Octaplas®, fibrinogen concentrate). Seek advice from a haematologist. Correction may be guided by point-of-care thromboelastography (TEG®) or rotational thromboelastometry (ROTEM®).
- Further surgery or interventional radiological embolization may be needed to stem ongoing or new blood loss.

Peripheries

- Injury to the limb may result in nerve injuries, obstruction of the vascular supply, or muscle damage leading to compartment syndrome and rhabdomyolysis. Check creatine kinase regularly.
- Closely monitor limbs, as well as other compartments (e.g. buttocks). Severe pain, a temperature difference between limbs, nerve palsy, and unilateral poor capillary refill should raise concern. Loss of palpable pulses is a late sign. Surgery (e.g. fasciotomy, revascularization) should be undertaken promptly, as needed.
- Ensure plaster casts or tight compression dressings do not compromise peripheral limb perfusion. Remove if concerned.

Further reading

Holcomb J, Tilley B, Baraniuk S, et al. for the PROPPR Study Group. 2015. 'Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial'. *JAMA* 313: pp471–88. doi: 10.1001/jama.2015.12

Rossaint R, Afshari A, Bouillion B, et al. 2023. 'The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition'. *Crit Care* 27: p80. doi: 10.1186/s13054-023-04327-7

See Trauma score, p36; Ventilatory support—indications, p48; Wound management principles, p152; Dressing techniques, p154; Blood transfusion, p272; Blood products, p274; Coagulants & antifibrinolytics, p340; Basic resuscitation, p358; Multiple trauma—ongoing management, p630; Head injury—general management, p632; Spinal cord injury, p636.

Multiple trauma—ongoing management

Additional consideration to the ongoing ICU management of polytrauma includes:

Analgesia and sedation

- Adequate analgesia is imperative to avoid circulatory instability and decreased chest wall excursion, especially following chest, abdominal, or spinal trauma.
- Use of regional techniques and patient-controlled analgesia, as well as regular paracetamol, facilitates pain relief and weaning. The presence of coagulopathy and infection should be taken into consideration.
- Opiates are often used. Other agents, e.g. ketamine, α_2 agonists, can be given in conjunction. Non-steroidals can be very effective but may worsen coagulopathy, cause stress ulceration, and may worsen risk of acute kidney injury (AKI).
- Other sedating agents may be co-administered, but good analgesia should be the primary consideration. Alcohol excess and illicit drug use are common in patients with trauma. Consider these as a cause of agitation as well as other organic causes such as an intracranial lesion or infection.

Nutrition

- Consider early enteral nutrition, even after abdominal laparotomy. However, depending upon the type of injury, the surgical repair, and risk of ileus, the surgical team may opt for gradual or delayed introduction of enteral feeding. Consider parenteral feeding if enteral nutrition is likely to be delayed by >5 days, especially if the patient is malnourished.

Infection

- Depending on the site of trauma, the type of wound (e.g. open/closed), and the need for surgery, prophylactic tetanus and ongoing antibiotic cover may be required.
- Secondary infection is common so standard preventative measures, strict infection control, sampling, and imaging should be undertaken as necessary.
- Consider replacing intravascular catheters that were inserted during emergency resuscitation under non-sterile conditions.

Prophylaxis

- Attention should be paid to pressure areas; this may involve the use of specialized mattresses or support beds.
- Obtain clear instructions from the trauma team and surgeons regarding care of the wounds, drains, and how much mobilization is permissible or whether precautions are need to be taken (e.g. log-rolling).
- Deep venous thrombosis is common after trauma, especially after orthopaedic procedures on the pelvis and lower limb. Discuss with the surgeon and trauma team when to commence low-molecular-weight heparin prophylaxis in view of any ongoing bleeding risk. Mechanical prophylaxis (thromboembolic deterrent (TED) stockings and

intermittent pneumatic compression) should be started promptly if no contraindications.

Review

- Regular review of the patient is necessary to ensure complications are detected and dealt with promptly. This may require ultrasound or computed tomography (CT)/magnetic resonance imaging scanning, angiography, or repeat laparotomy.
- Later complications include pancreatitis, acalculous cholecystitis, and multiple organ dysfunction (including acute respiratory distress syndrome (ARDS)).

Further reading

Bruns B, Kozar R. 2016. 'Feeding the postoperative patient on vasopressor support: feeding and pressor support'. *Nutr Clin Pract* 31: pp14–7. doi: 10.1177/0884533615619932

See Nutrition—use & indications, p140; Wound management principles, p152; Dressing techniques, p154; Special support surfaces, p156; Non-opioid analgesics, p316; Opioid analgesics, p318; Anticoagulants—parenteral, p334; Infection control—general principles, p580; Infection—diagnosis, p588; Infection—treatment, p590; Multiorgan dysfunction—causes & definitions, p596; Multiple trauma—initial management, p628; Pain, p660.

Head injury—general management

Traumatic brain injury (TBI) can occur in isolation or with other significant trauma. Priorities in management include protecting the airway (if indicated), maintaining adequate gas exchange, and circulatory resuscitation. Any life-threatening injury, e.g. arterial injury, should be managed before definitive treatment for head injury is undertaken.

General management

- Liaise early with regional neurosurgical centre (as required).
- Assume an unstable neck fracture until formally excluded by appropriate investigations. Ideally, the neck should be imaged before ICU admission, particularly if there is altered mentation (Glasgow Coma Scale (GCS) <13), or a need for urgent sedation, intubation, and/or mechanical ventilation. If concerned about an unstable cervical spine injury, agree a management plan with the appropriate surgical teams.
- Most patients with TBI admitted to non-neurosurgical ICUs will have diffuse or local brain injury for which a conservative approach has been recommended. Contact the regional neurosurgery centre if signs of increasing ICP are present for consideration of decompressive craniectomy and/or haematoma drainage (depending on CT findings), ± invasive pressure/tissue PO_2 monitoring.
- Avoid nasal insertion of feeding or endotracheal tubes if a base-of-skull fracture is suspected (e.g. X-ray, rhinorrhoea, otorrhoea, 'Panda eyes', Battle sign).
- Deterioration in conscious level, new neurological deficits, a seizure without full recovery, severe headache or vomiting, or new focal signs (e.g. pupillary dilatation) should prompt urgent evaluation and repeat CT scanning.
- Ensure good glycaemic control, with insulin as needed.
- Antibiotic prophylaxis is not routinely recommended.
- There is no clear evidence base to determine an optimal thromboembolism prophylaxis regimen. An individual risk–benefit approach should be adopted balancing risk of bleeding versus risk of thromboembolism, especially in polytrauma. Discuss with neurosurgical team.

Analgesia

- Adequate analgesia (usually opiates) should be given to patients with TBI; pain and agitation increase ICP, and may cause a secondary insult.
- Short-acting sedation should be used as this enables rapid assessment of the underlying conscious level and any focal neurological deficit.

Respiratory management

- In ventilated patients with TBI, aim for arterial partial pressure of carbon dioxide ($PaCO_2$) of 4.5–5 kPa depending on the severity of injury and cerebral oedema. Discuss with the neurosurgical team.
- Face or neck injuries may have required emergency cricothyroidotomy or tracheostomy to obtain a patent airway. If orotracheally intubated, ensure local swelling has subsided (air leak around deflated cuff) and upper airway is clear (e.g. no residual blood clot) before extubation.

- Severe agitation and confusion may last for several weeks; this often delays weaning and extubation. Seek and treat reversible causes of confusion and delirium (e.g. pain, seizures), and use thiamine in patients with known alcohol excess. Anti-delirium treatment may be necessary.

Circulatory management

- Avoid hypotension with adequate resuscitation ± vasopressor. Target mean arterial pressure >75–80 mmHg or cerebral perfusion pressure 60–70 mmHg if ICP is monitored.
- An elevated BP may be tolerated unless excessive.
- β-blockers are useful in reducing the myocardial and immunosuppressive effects of excessive catecholamine levels.
- No benefit was seen for haemoglobin levels >100 vs >70 g/L.
- A post hoc study found fluid resuscitation with albumin was associated with higher mortality compared to saline.

Other therapeutic interventions

- Aim to clear cervical spine radiologically and remove collar if clear.
- Head-up tilt 30° to improve venous return.
- Correct coagulopathy and reverse anticoagulants.
- Multicentre studies showed no outcome benefit from:
  - high-dose steroid therapy
  - free radical scavengers
  - induced therapeutic hypothermia ('targeted temperature management' (TTM)), in patients with intracranial hypertension or pyrexia >38.5°C. NB: time to target temperature was often prolonged; animal studies suggest this needs to be aggressively instituted post-injury to be most effective
  - erythropoietin

Further reading

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Robertson C, Hannay H, Yamal J-M, et al. 2014. 'Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial'. *JAMA* 312: pp36–47. doi: 10.1001/jama.2014.6490

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➔ See Ventilatory support—indications, p48; Tracheotomy—indications & technique, p86; Minitracheotomy, p90; Neuroprotective agents, p330; Non-opioid analgesics, p316; Opioid analgesics, p318; Sedatives, p322; Tranquillizers, p324; Basic resuscitation, p358; Multiple trauma—initial management, p628; Multiple trauma—ongoing management, p630; Head injury—management of complications, p634; Spinal cord injury, p636; Pain, p660.

Head injury—management of complications

Complications

- Raised ICP.
- (Re-)haemorrhage.
- Seizures. Consider additional causes such as hypoglycaemia, development of a new space-occupying lesion, recreational drugs/alcohol (or withdrawal), and infection.
- Nosocomial infection.
- Diabetes insipidus suggests hypothalamic injury and carries a poor prognosis. Desmopressin (0.5–1 μg IV) is indicated if urine output >250 mL/h for >2 h with supporting serum and urine osmoles.
- Hyperpyrexia should be actively managed, but no added benefit is seen with therapeutic hypothermia compared to normothermia.

Standard approaches should be used for management.

Intracranial pressure monitoring for head injury

Although ICP-guided management has not been shown in randomized trials to improve outcomes after TBI, it may aid management in specific patients.

Indications

- GCS ≤8 and any abnormality on CT scan.
- GCS ≤8 and a normal CT scan but any two of the following:
  - age >40 years
  - hypotension
  - decerebrate posturing.
- GCS >8 but requiring general anaesthesia for treatment of other injuries or requiring treatment likely to increase ICP, e.g. high levels of positive end-expiratory pressure (PEEP).
- Such patients should ideally be intubated and ventilated.

Relative contraindications

- Coagulopathy.
- Infection.

Management of raised ICP

If clinical signs, or direct ICP monitoring evidence (ICP >22 mmHg), or rising ICP, consider the need for urgent repeat imaging to rule out new or extension of previous haemorrhage, and/or worsening cerebral oedema, or hydrocephalus. Additional measures:

- Ensure sedation is adequate and deep. May need boluses of sedation and increasing rates of infusion. May need monitoring using processed electroencephalography devices (e.g. Brainz monitor).
- Nurse head-up at 30–45°, if intubated secure endotracheal tube with loose ties or tape instead.
- Tight $PaCO_2$ control for very acute rises (aim 4.0–4.5 kPa) to reduce vasodilatation and lower ICP.
- Consider paralysing patient to manage ventilation and CO_2.
- Hypertonic saline or mannitol can be used as hyperosmolar therapy to reduce cerebral oedema. There is no strong evidence to show

superiority of one compared with the other. Serum osmolalities should be monitored (aim for 300–320 mOsm/kg) and give no further doses if values >320 mOsm/kg or serum Na^+ >155 mmol/L.

- Discuss with neurosurgical team early for consideration for:
  - craniotomy and clot evacuation
  - decompressive craniectomy
  - insertion of external ventricular drain for cerebrospinal fluid drainage.
- Consider cooling to 36–37°C if pyrexial.
- Thiopental challenge and burst suppression can be considered if ICP remains high.

Further reading

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Chesnut R, Temkin N, Carney N, et al. 2012. 'A trial of intracranial-pressure monitoring in traumatic brain injury'. *N Engl J Med* 367: pp2471–81. doi: 10.1056/NEJMoa1207363

➔ See Intracranial pressure monitoring, p224; Anticonvulsants, p328; Neuroprotective agents, p330; Generalized seizures, p472; Intracranial haemorrhage, p478; Raised intracranial pressure, p484; Multiple trauma—initial management, p628; Multiple trauma—ongoing management, p630; Head injury—general management, p632.

Spinal cord injury

Spinal injury, with or without damage to the cord, may be apparent soon after admission to hospital. However, late deterioration may occur, requiring a high index of suspicion and careful monitoring.

Immobilization

- Immobilize the spine until an expert has cleared the patient of any unstable fractures. Significant spinal injury is excluded following:
  - normal clinical examination in an awake/oriented patient
  - completion of spinal imaging protocols in unconscious or uncooperative patients and in patients with significant distracting injuries.
- Place in a hard cervical collar and immobilize head with lateral supports. This does not stabilize the spine but reminds the staff to take precautions when moving the patient. Either halo-brace or operative stabilization is needed for an unstable fracture.
- Move the patient in spinal alignment ('log-rolling') or straight-lifting, using at least four staff members. Exercise care with neck manipulation; intubation should be performed by an experienced operator with assistance providing manual in-line stabilization.

Circulatory instability

- 'Spinal shock' is the loss of reflexes below the level of the spinal injury and associated with hypotension and 'neurogenic shock' in high spinal injuries where there is interruption of sympathetic outflow. Hypovolaemia should be excluded first. Consider injury to other organs, e.g. spleen.
- Consider vasopressor therapy if evidence of persisting tissue hypoperfusion, e.g. oliguria, metabolic acidosis.
- Postural hypotension and circulatory instability (including symptomatic bradycardia) is commonplace for the first few weeks. Autonomic dysfunction affects 50% of cervical and high thoracic cord injuries. Patients with recurrent bradycardic/asystolic episodes will need temporary/permanent pacemakers.

Respiratory management

- High cervical cord injury (above C5) results in loss of diaphragmatic function. Injuries above T8 result in loss of intercostal function and compromise ability to cough and clear sputum. These will prevent weaning from mechanical ventilation.
- When able, the patient should be managed in an upright posture. However, in the early phase, supine position may allow better respiratory function due to abdominal content facilitating greater diaphragm excursion. Patients often need abdominal binders.
- Regular physiotherapy and cough assist will prevent atelectasis.
- Nosocomial pneumonia is a common complication.
- Early tracheostomy may facilitate support and comfort.

General measures

- Define the severity and level of injury using the American Spinal Injury Association (ASIA) scale.
- Carefully monitor any changes in neurological function to enable early detection of spinal cord compression (including cauda equina syndrome) and referral for urgent remedial surgery.
- Consider thromboprophylaxis early with TED stockings and pneumatic compression as well as low-molecular-weight heparin.
- Gastric protective measures.
- Enteral feeding may be difficult to institute, gastric distension and paralytic ileus are common. A nasogastric (NG) tube should be inserted for gastric decompression. An enterostomy may be needed for long-term feeding.
- Bowel and bladder function will be affected and will require bladder catheterization and regular laxative and enema therapy started early.
- Special care is needed to prevent pressure sores.
- Institute regular physiotherapy to prevent contractures.
- Psychological support is important, particularly if long-term disability is likely. Seek early support from spinal injuries centre who will provide advice for all aspects of spinal care.
- Hyperbaric oxygen therapy is of unproved benefit.
- Avoid suxamethonium for 72 h after a spinal injury as this may cause severe hyperkalaemia.

Further reading

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Roberts T, Leonard G, Cepela D. 2017. 'Classifications in brief: American Spinal Injury Association (ASIA) Impairment Scale'. *Clin Orthop Relat Res* 475: pp1499–504. doi: 10.1007/s11999-016-5133-4

See Ventilatory support—indications, p48; Tracheotomy—indications & technique, p86; Chest physiotherapy, p98; Nasogastric & nasojejunal tubes, p128; Wound management principles, p152; Special support surfaces, p156; Vasopressors, p290; H_2 blockers & proton pump inhibitors, p304; Anticoagulants—parenteral, p334; Corticosteroids, p352; Multiple trauma—initial management, p628; Multiple trauma—ongoing management, p630.

Burns—airway & circulatory management

Major thermal injuries (i.e. >20% body surface area) are often admitted to an ICU, usually specialized burns management, for surgical treatment of the burns, meticulous attention to fluid resuscitation, prevention of infection, and the frequent need for mechanical ventilation.

Airway and respiratory management

- Airway swelling may occur rapidly after burn injury to the face and neck, in particular with evidence of inhalation injury (soot in nares or mouth, carbonaceous sputum, hoarse voice, or stridor). Such patients often need urgent elective intubation as loss of airway may occur within minutes, with maximal airway oedema at 24–36 h.
- Anticipate difficult intubation and have the necessary skills and equipment available. Intubate with an uncut tube (to allow for facial swelling). A decision not to immediately intubate and ventilate should not be taken lightly and must be made by an experienced consultant who has directly assessed the airway. In this case, the patient should be closely monitored for stridor, difficulty in breathing, and any voice change.
- Intubation equipment should be readily available. It is safer to electively ventilate any patient being transferred, especially out of hospital, e.g. to a burns centre.
- Lung protective strategies and humidification should be utilized if invasively ventilating. In addition, bronchoscopy may be helpful to assess extent of inhalation injury and perform lavage.
- Perform blood gas analysis and consider carbon monoxide and cyanide poisoning. Look at the carboxyhaemoglobin % in the oximetry results and treat accordingly.

Haemodynamic monitoring

- Fluid loss requires careful assessment of intravascular volume status. Traditional markers of fluid resuscitation (e.g. central venous pressure, urine output, haematocrit) are often inadequate.
- Invasive or non-invasive cardiac output monitoring allows for accurate titration of fluid. Vasopressors may be needed to maintain an adequate systemic BP.
- Intravascular catheters should be inserted through intact skin. Avoid affected skin areas, if possible.
- Insertion of intravascular catheters, urinary catheters, and NG tubes should be carried out early as rapid onset of swelling in burn areas within a few hours may make these procedures difficult.

Fluid management

- Fluid resuscitation often follows formulae such as the Muir & Barclay (albumin-based) or Parkland (crystalloid-based) formula. These are based on the extent of injury (% burn surface area (BSA)) and the proportion of full-thickness dermal injury to calculate the approximate fluid volume required.

- These formulae only provide an approximate guide; losses into the interstitial spaces and through the lost skin barrier are frequently underestimated. Evaporative losses are about 2 mL/kg/h. Water losses may be increased if wounds are not covered. Losses increase further with inhalation injury.
- Avoid overzealous fluid infusion to minimize oedema.
- The increased permeability and fluid leak phase lasts ~1–2 days. After 2–5 days, a diuretic phase usually commences when excess tissue fluid is lost and the body swelling reduces.
- Electrolyte levels (especially K^+ and Mg^{2+}) can fluctuate widely and should be replaced as necessary.
- Though some haemolysis may occur, blood transfusion requirements are usually low. Debridement often results in major blood loss frequently requiring significant transfusion. Coagulopathy often occurs, in part due to a dilutional effect of fluid infusion and the inflammatory process of the burn injury. Blood products should be given as indicated.
- Limit heat loss as this can be profound in large burns. Use fluid warmers and forced air heating to maintain body temperature.

Fluid resuscitation regimen

These regimens should be used as a guide only. In the critical care setting, haemodynamic monitoring gives a better guide to fluid requirements.

Adapted from Parkland formula

Total volume of Ringer's lactate for the first 24 h:

$$\text{Ringer's lactate (mL)} = 4 \times \text{Body Weight (kg)} \times \text{Burn Surface Area (\%)}$$

Half the volume is administered in the first 8 h, the rest is delivered over the next 16 h.

Adapted from Muir & Barclay formula

Divide first 36 h from the time of burn into six consecutive periods of 4, 4, 4, 6, 6 and 12 h.

For each period, give 4.5% human albumin solution (HAS):

$$\text{HAS (mL)} = \text{Body Weight (kg)} \times \text{Burn Surface Area (\%)}$$

With either formula, give blood as necessary to maintain adequate haemoglobin levels. Reassess cardiorespiratory variables, blood gases, and urine output at frequent intervals to determine whether volume replacement is adequate or not; adjust fluid input accordingly.

Further reading

See Ventilatory support—indications, p48; Tracheotomy—indications & technique, p86; Chest physiotherapy, p98; Nasogastric & nasojejunal tubes, p128; Wound management principles, p152; Special support surfaces, p156; Vasopressors, p290; H_2 blockers & proton pump inhibitors, p304; Anticoagulants—parenteral, p334; Corticosteroids, p352; Multiple trauma—initial management, p628; Multiple trauma—ongoing management, p630.

Burns—general management

Surgery

Escharotomy may be needed on hospital admission to affected limbs, the neck, and/or chest if a circumferential burn is present.

Debridement of necrotic tissue within 48–72 h, with early grafting if necessary, is associated with improved outcome. Coverage may be obtained using split-skin grafts from the patient's unaffected skin, donor skin grafts, or, in extensive burns injuries, dermal substitutes. Blood loss may be rapid and massive, e.g. 100 mL per 1% of body surface grafted.

Wound care

- Early application of dressings and topical creams as guided by local burns/plastic surgery specialists. This may include silver sulphadiazine cream which has antibacterial properties and thus helps prevent secondary infection.
- Early grafting often takes place within the first 2–3 days to provide a skin protective barrier.

Nutrition

- Enteral nutrition should be commenced, as tolerated. If not, the patient should be parenterally fed.
- Target protein intake of 1.5–2 g/kg/day. Supplement with glutamine (0.3–0.5 g/kg/day) for 10–15 days.
- Calorie requirements should be measured by indirect calorimetry or calculated by the Toronto equation:

$$-4343 + (10.5 \times \%\text{BSA}) + (0.23 \times \text{previous day's calorie intake}) + (0.84 \times \text{eBEE}) + (114 \times \text{temp°C}) - (4.5 \times \text{days since injury})$$

  where BSA = burn surface area; e-BEE = estimated basal energy expenditure (Harris–Benedict equation).
- Meta-analysis does not show a profound effect on prognosis from early enteral nutrition.

Infection

- Do not routinely give prophylactic antibiotics to burns patients.
- Body temperature rises on day 1–2 as high as 40°C, may persist for several days, and does not always indicate secondary infection. Infection markers are useful to monitor.
- Likely infecting agents include *Streptococcus* spp., *Staphylococcus* spp., and Gram-negative bacteria such as *Pseudomonas* spp. Appropriate antibiotic treatment should be given as indicated.

Other considerations

- Diagnose and treat any suspected inhalation injury with bronchoscopy. Bronchoalveolar lavage enables removal of soot. Humidified circuits, nebulized bronchodilator ± acetylcysteine (mucolytic) help to keep secretions watery and easy to suction.
- Ensure adequate analgesia (opiates). Ketamine is a useful anaesthetic as it also has analgesic properties.
- Tetanus toxoid should be given soon after hospital admission.
- Reduce heat and fluid losses by placing the patient on a heated air fluidized bed and by early coverage of burned skin through application of occlusive dressings and placing affected limbs in transparent plastic bags.
- Environmental temperature is often elevated to reduce heat loss.
- Stress ulceration can usually be avoided through prompt resuscitation, enteral nutrition, and prophylaxis.
- Prevent pressure sores and contractures by careful nursing and physiotherapy.
- Avoid suxamethonium from 5 to 150 days post-burn because of the risk of rapid and severe hyperkalaemia.
- Increasing resistance to non-depolarizing muscle relaxants may occur.

Mortality

Increases with age >50 years, BSA >40%, and depth of burns injury. Various scores, e.g. Baux and Abbreviated Burns Severity Index (ABSI), provide a mortality risk assessment.

Further reading

Allard J, Pichard C, Hoshino E, et al. 1990. 'Validation of a new formula for calculating the energy requirement of burn patients'. *JPEN* 14: pp115–8. doi: 10.1177/0148607190014002115

Rousseau A-F, Losser M-R, Ichai C, et al. 2013. 'ESPEN endorsed recommendations: nutritional therapy in major burns'. *Clin Nutr* 32: pp497–502. doi: 10.1016/j.clnu.2013.02.012

➔ See Nutrition—use & indications, p140; Wound management principles, p152; Dressing techniques, p154; Infection—treatment, p590.

Blast injury

High-order explosives generate a large supersonic pressure wave (blast or shock wave). An explosion can also cause blast wind, i.e. flow of superheated air, that can also cause injury. The type and severity of blast injury determine the degree of damage. Traditionally divided into four categories:

- *Primary*: caused by the direct effect of blast over-pressure on tissue. Unlike water, air is easily compressible so air-filled structures such as lung, ear, and gastrointestinal tract are often affected. Tympanic membrane rupture indicates high-pressure wave (≥40 kPa) injury and suggests (but does not confirm) the presence of vital organ injury.
- *Secondary*: ballistic trauma related to flying objects. The severity of a ballistic wound is determined by the kinetic energy of the projectile. Velocity has more impact than mass of the object.
- *Tertiary*: occurs with high-energy explosions when people fly through the air and strike other objects, e.g. impalement.
- *Quaternary*: covers all other injuries, e.g. burns, crush injuries, and toxic gas/smoke inhalation.

Death can result quickly from severe lung injury (due to pulmonary haemorrhage or air embolism), head or other internal injury, and/or limb amputation.

Investigations

Assessment should be as for any trauma with focus on airway, breathing, and circulation followed by a primary assessment of:

- Chest—imaging for pneumothorax, fractures ± flail chest. Note contusions may evolve over several hours.
- Heart—electrocardiogram, echocardiography, and troponin for myocardial contusion, and to exclude pericardial tamponade.
- Abdomen—CT scan to assess for injury to both solid and hollow organs; including penetrating objects, perforation, cavitation, and occult haemorrhage. Intestinal haematoma can take up to 36 h to develop. Intestinal perforation is more common with underwater blast injury.
- X-ray/CT to other injured areas—for fractures, shrapnel, gas embolus, etc.
- Blood tests for diagnosis of coagulopathy, rhabdomyolysis.

Management

- Standard surgical management of fractures, burns, wounds, etc.
- If possible, avoid positive pressure ventilation and PEEP due to the risk of alveolar rupture and air embolus. If ventilation is necessary, use low tidal volumes and minimize airway pressure with permissive hypercapnia.
- For arterial gas embolism administer 100% O_2 by tight-fitting face mask. If possible, place the patient in the left lateral position to minimize risk of further air emboli leaving the heart. Consider one-lung ventilation to prevent further air entry into the vasculature. Hyperbaric O_2 treatment is recommended as a definitive treatment.
- Myocardial depression usually self-reverses within hours.

- Consider, and treat as appropriate:
  - coagulopathy
  - carbon monoxide, smoke, and other toxic inhalation
  - rhabdomyolysis and compartment syndrome
  - peripheral compression injuries.
- Follow local protocols for biological, chemical, or radiation contamination if a 'dirty' bomb is implicated in the blast injury.

Further reading

See Respiratory imaging, p178; ECG monitoring, p184; Echocardiography—use & indications, p214; Cardiac function & injury, p242; Pneumothorax, p398; Inhalation injury, p404; Raised intra-abdominal pressure, p448; Multiple trauma—initial management, p628; Multiple trauma—ongoing management, p630; Rhabdomyolysis, p648.

Electrical injuries

Clinical features relate to the effects of the electrical current and the conversion of electrical energy to heat on passage through the tissues.

There are four classes of electrical injury:

1. True: current goes through the patient with entrance and exit sites.
2. Flash: no current through the patient, but superficial arc burns skin.
3. Flame: ignition of clothing by the surface arc.
4. Lightning: high-intensity, ultra-short duration of current may produce cardiac arrest with little tissue destruction.

Important factors are:

- The current is the most important determinant of heat production
- Resistance to current flow: tissues are resistant to current flow in the following decreasing order: bone, fat, tendon, skin, muscle, blood vessels, nerves. A high skin resistance and short duration of contact concentrate the effects locally. However, skin contaminants, moisture, and burning reduce resistance.
- Type of current—alternating current (AC) is more dangerous than direct current (DC). Tetanic muscle contractions may prevent the victim from releasing the current source whereas the single, strong muscle contraction with DC often throws the victim clear. AC is more likely to reach central tissues with consequent apnoea and ventricular fibrillation (with as little as 50–100 mA for 1–10 ms).
- Current pathway—cardiorespiratory arrest is more likely the closer the contact is with the chest and heart.

Clinical features

Related to degree of electrical exposure and type of injury.

- Tachyarrhythmias or heart block/asystole (latter more likely with a high current, e.g. >10 A).
- Myocardial injury.
- Respiratory arrest—tetanic contraction of the diaphragm, cerebral medullary dysfunction.
- Trauma—tetanic muscle contraction, falling or being thrown clear.
- Burns—to skin and internal tissues.

Management

Most severe electrical injuries require urgent pre-hospital treatment:

1. Ensure the source of the electrical injury is not hazardous to rescuers.
2. Manage cardiorespiratory arrest.
3. Prevent further injury, e.g. spinal protection, remove burnt clothes.

After restoration of the circulation, management is directed towards:

1. Ventilatory support.
2. Management of hypovolaemia associated with burn injury. Fluid requirements are usually greater than for victims of thermal burns and require close monitoring.
3. Check cardiac enzymes for degree of myocardial injury. Treat heart failure and/or arrhythmias as indicated.
4. Management of rhabdomyolysis and compartment syndrome.
5. Debride necrotic tissue and fixate bony injury.

Further reading

See Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Electrical cardioversion, p102; Cardiac function & injury, p242; Basic resuscitation, p358; Cardiac arrest, p360; Tachyarrhythmias, p412; Burns—airway & circulatory management, p638; Burns—general management, p640; Rhabdomyolysis, p648.

Near-drowning

The major complications of near-drowning are lung injury, hypothermia, and the effects of prolonged hypoxia. Although hypothermia may protect against organ damage, rewarming carries particular hazards. Have a low index of suspicion for other injuries (e.g. TBI or neck injury from diving into water). A trauma CT series may be able to diagnose these and other injuries, as well as give information about hypoxic brain injury.

Pathophysiology

Prolonged immersion usually results in inhalation of fluid, though 10–20% develop intense laryngospasm leading to so-called dry drowning. Traditionally, fresh-water drowning was considered to lead to rapid absorption of water into the circulation with haemolysis, hypo-osmolality, and possible electrolyte disturbance whereas inhalation of hypertonic fluid from sea-water drowning produced a marked flux of fluid into the alveoli. In practice, there seems to be less distinction between fresh water and sea water as both cause loss of surfactant and severe inflammatory disruption of the alveolar–capillary membrane leading to an ARDS-type picture. Initially, haemodynamic instability is often minor. A similar picture often develops after 'dry drowning' and subsequent endotracheal intubation.

Acute hypothermia often accompanies near-drowning with loss of consciousness and haemodynamic alterations.

Management

1. Give sufficient oxygen to maintain arterial oxygen saturation (SaO_2) >92%. Intubate patients with GCS ≤8 or persisting respiratory failure. Early continuous positive airway pressure or PEEP may be useful. Extracorporeal membrane oxygenation may help in selected patients.
2. Bronchospasm is often present and may require nebulized β_2 agonists ± nebulized or subcutaneous epinephrine.
3. Bronchoscopy may be needed to remove inhaled debris.
4. Direct fluid replacement by appropriate monitoring. Inotrope therapy may be needed if hypoperfusion persists after adequate fluid resuscitation. Fluid overload is uncommon and the role of early diuretic therapy to lower ICP is controversial. Haemolysis may occur and requires blood transfusion.
5. Treat arrhythmias arising from myocardial hypoxia, hypothermia, and electrolyte abnormalities conventionally.
6. Metabolic acidosis may be profound yet bicarbonate therapy is rarely indicated as the acidosis usually corrects on restoring tissue perfusion.
7. Manage electrolyte abnormalities conventionally.
8. Rewarming follows conventional practice; cardiopulmonary bypass may be considered if core temperature is <30°C. Cardiopulmonary resuscitation should be continued until normothermia is achieved.
9. Cerebral protection usually follows raised ICP protocols though the role of diuretic therapy and fluid restriction is controversial. Treat seizures as they arise.
10. Consider antibiotic therapy (e.g. cefuroxime and metronidazole) if strong evidence of aspiration exists. Otherwise, take specimens and treat as indicated.
11. Site a NG tube to reduce the risk of aspiration.

Further reading

See Endotracheal intubation—indications & equipment, p44; Ventilatory support—indications, p48; Positive end-expiratory pressure—principles, p70; Positive end expiratory pressure—management, p72; Continuous positive airway pressure (CPAP), p76; Extracorporeal membrane oxygenation, p84; Bronchodilators, p278; Antiarrhythmics, p294; Basic resuscitation, p358; Cardiac arrest, p360; Hypothermia, p652.

Rhabdomyolysis

Breakdown of striated muscle may result in local swelling leading to compartment syndrome, massive release of myoglobin with AKI, and electrolyte abnormalities (hyperkalaemia, hypocalcaemia, hyperphosphataemia).

Causes

- Trauma, especially crush injury.
- Prolonged immobilization, e.g. after fall, drug overdose.
- Drugs, e.g. opiates, cocaine, ecstasy.
- Hyperpyrexia.
- Vascular occlusion (including lengthy vascular surgery).
- Infection.
- Burns/electrocution.
- Congenital myopathy (rare) or inflammatory myopathies.

Diagnosis

- Suggested by disproportionately high serum creatinine compared to urea (usual ratio ~10 μmol:1 mmol).
- Raised creatine kinase (usually >2000 IU/L).
- Myoglobinuria produces a positive urine dipstick to blood. Urine is usually red or black but may be clear.

General management

- Carefully monitor and ensure prompt, adequate fluid resuscitation. Volumes required may be high.
- Remove/correct inciting cause (if still present).
- Do not treat hypocalcaemia unless the patient is symptomatic; calcium may form crystals with the high circulating phosphate.
- Hyperkalaemia may be resistant to medical management and require urgent haemodialysis or haemodiafiltration.

Complications

Compartment syndrome

- Suspect if limb is tender or extremely painful and peripheries are cool. Note that loss of peripheral pulses and tense, swollen muscles are late signs. Compartment decompression should occur before these develop.
- Muscle manometry reveals pressures >20–25 mmHg.
- Arm, legs, and buttock compartments may be affected.
- Management involves either prophylactic fasciotomies, or monitoring (including regular manometry) with decompression if pressures >25 mmHg or there is concern about limb viability. Fasciotomies may result in major blood loss, especially as concurrent coagulopathy is common.

Acute kidney injury

- AKI is due to a combination of free radical injury causing direct damage, hypovolaemia, hypotension, and myoglobin obstructing renal tubules.
- Urinary alkalinization increases urinary excretion of myoglobin and protects against radical injury.
- AKI may be prevented or attenuated by prompt rehydration and urinary alkalinization with IV 1.26% sodium bicarbonate starting at 100–200 mL/h and continuing for up to 3–5 days. Maintain urinary pH >6,

ideally with blood pH <7.5. Higher infusion rates of 1.26% bicarbonate, or increased concentrations, may be required to achieve this.
- The benefit of a forced diuresis is controversial, but a good diuresis (1.5–2 mL/kg/h) should be maintained. This may require diuretics once the patient is resuscitated.
- Avoid excessive positive fluid balance, especially if oliguric.
- Potassium, sodium, and magnesium levels should be monitored regularly and managed as appropriate.
- If AKI is severe, dialysis or filtration techniques will be required.

Further reading

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Zimmerman J, Shen M. 2013. 'Rhabdomyolysis'. *Chest* 144: pp1058–65. doi: 10.1378/chest.12-2016

➲ See Continuous renal replacement therapy—techniques & indications, p116; Haemo(dia)filtration, p118; Urinalysis, p236; Sodium bicarbonate, p268; Oliguria, p426; Acute kidney injury—diagnosis, p428; Acute kidney injury—management, p430; Poisoning—general principles, p554; Salicylate (aspirin) poisoning, p556; Antidepressant poisoning, p562; Amphetamines & Ecstasy, p564; Multiple trauma—initial management, p628; Multiple trauma—ongoing management, p630; Electrical injuries, p644; Hyperpyrexia, p656.

Chapter 33

Disorders of temperature

Hypothermia

Causes of hypothermia

- Coma and immobility.
- Cold water immersion.
- Exposure.
- Sepsis.
- Rarer causes, e.g. hypothyroidism, hypopituitarism, erythroderma.

Risk factors include alcohol and drug overuse, homelessness, mental health disorder, increasing age, and frailty. Prognosis depends on the degree and duration of hypothermia.

Clinical features

Temperature should be measured centrally with a low reading thermometer. The preferred site is the lower third of the oesophagus.

- *Cold stress* (35–37°C)—normal functioning with shivering.
- *Mild* (32–35°C)—shivering in an attempt to correct body temperature. Mental status may be altered.
- *Moderate* (28–32°C)—neurological signs (dysarthria, decreased conscious level, slowness, hypertonicity, sluggish reflexes) with cardiovascular dysfunction becoming life-threatening.
- *Severe* (<28°C)—unconscious and not shivering, Arterial pulses often impalpable. Hypothermic rigidity is difficult to distinguish from death.
- *Profound* (<24°C).

Electrocardiogram changes

Sinus bradycardia is followed by atrial flutter and fibrillation with ventricular ectopics. The PR interval, QRS complex, and QT interval are prolonged. Atrial activity eventually ceases. 'J' waves most often seen at <31°C; ventricular fibrillation is common at <30°C and asystole at <28°C.

Other investigations

Check lactate, coagulation screen (disseminated intravascular coagulation (DIC)), glucose (NB: insulin ineffective <30°C), creatine kinase (rhabdomyolysis), amylase/lipase (pancreatitis).

Arterial blood gas measurements should not be corrected for temperature (i.e. alpha-stat) as this is a better prognostic indicator compared to temperature-corrected values (pH-stat). Note haematocrit increases by 2% for each degree fall in temperature due to cold diuresis.

Management

1. ABC assessment and appropriate management with CPR if necessary. If cardiac arrest, continue full resuscitation until normothermia achieved. Ventricular fibrillation is usually resistant to defibrillation <30°C, but a single shock may be attempted and repeated if needed for every 1–2°C rise. Epinephrine may be ineffective if core temperature <30°C.
2. Maintain SaO_2 between 94% and 98%; pulse oximetry is unreliable.
3. Remove wet and/or cold clothes.
4. Replace fluid and electrolytes under close monitoring. Severe hyperkalaemia is a poor prognostic sign; values may be raised by haemolysis. Central venous or arterial samples are the most reliable.

5. Rewarming—all hypothermic patients without evidence of other fatal disease should be assumed fully recoverable. The technique used for rewarming depends on the core temperature (measured with a low-reading rectal thermometer) and clinical circumstances. The 'afterdrop' phenomenon may occur with external warming resulting in a further drop in core temperature as cold peripheral blood returns to the central circulation. Another complication is hypotension related to peripheral vasodilation as the patient warms.
6. For frost-bitten areas, avoid rubbing, massaging, or direct warmth as this may cause further mechanical injury. Use warm water (40–42°C) until skin appears red/purple.

Spontaneous rewarming (e.g. space blanket)

Treat cold stress and mild hypothermia with passive external rewarming. Spontaneous rewarming proceeds at a rate inversely proportional to the duration of hypothermia. Rewarming rates of 0.1–0.7°C/h can be achieved. Core temperature may fall during spontaneous rewarming as cold blood is returned from the periphery to the central circulation.

Active rewarming (e.g. forced-air warming blanket, warm bath)

Indicated for moderate-to-severe hypothermia or to augment spontaneous rewarming for mild hypothermia in certain patients, e.g. elderly. Temperature usually increases by >2°C/h.

Central rewarming

For severe hypothermia or moderate hypothermia not responding to external rewarming, central rewarming should be instituted. This may be achieved by continuous endovascular warming circuits, or peritoneal dialysis, gastric or bladder lavage with warmed fluids. Cardiopulmonary bypass, if available, should be used for patients with ongoing cardiac arrest. These techniques generally achieve rewarming rates of 2–3°C/h.

Haemodynamic changes and fluid shifts may be dramatic during active rewarming and this requires careful monitoring and support. If extracorporeal rewarming is available, rates of 3–15°C/h can be achieved.

Complications

- Hypoxaemia due to hypoventilation, ventilation/perfusion mismatch, and possible aspiration.
- Hypovolaemia, hyperkalaemia, and metabolic acidosis.
- Arrhythmias.
- Acute kidney injury, acute pancreatitis, rhabdomyolysis, gastric erosions.
- Frostbite.
- Ataxia, coma.

Further reading

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See Electrical cardioversion, p102; ECG monitoring, p184; Basic resuscitation, p358; Cardiac arrest, p360; Tachyarrhythmias, p412; Bradyarrhythmias, p414; Pancreatitis, p462; Thyroid emergencies, p546; Rhabdomyolysis, p648.

Pyrexia

Fever is common in ICU patients, but only half are related to an underlying infection. Pyrexia reflects an imbalance between heat production and loss. There may be inability to lose heat due to, e.g. high ambient temperature, or due to increased heat generation, e.g. from 'thermostat' dysregulation within the hypothalamus, calcium overload, or mitochondrial uncoupling. Pyrexia may be beneficial for the immune response, heat shock protein activation, and mitochondrial protection. Prognosis is worse in septic patients presenting with a low temperature.

An excessive temperature may be unpleasant to the patient (e.g. rigors). Pyrexia increases metabolic rate and oxygen demand, inducing excessive vasodilatation, salt and water loss. At very high temperatures, cellular function is disrupted with altered enzyme activities and cell damage (e.g. rhabdomyolysis, brain injury).

Causes

Infection

Underlying infection is common, but often over-diagnosed. Antibiotic therapy may itself be a cause of pyrexia. Differentiation between colonizing and pathogenic bacteria may be difficult. Infections of urinary tract or lung are often difficult to diagnose due to early colonization. Seek an underlying source and consider recent travel history (e.g. malaria), opportunistic infections in immunosuppressed patients.

Inflammation

Inflammation unrelated to infection will usually result in pyrexia, e.g. after surgery, burns, myocardial infarction, vasculitis, glomerulonephritis, hepatitis, or acalculous cholecystitis.

Adverse drug reaction

Numerous drugs induce an idiosyncratic pyrexia, including antibiotics, sedatives, paralysing agents, and amphetamines. The neuroleptic malignant syndrome (NMS) is a rare, life-threatening reaction to neuroleptics (e.g. haloperidol) and central dopamine blockers (e.g. metoclopramide). It is characterized by fever (>38°C), muscular rigidity, altered mental status, and autonomic dysfunction. Malignant hyperthermia (MH) is a rare genetic skeletal muscle disorder resulting in extreme pyrexia following exposure to certain anaesthetic agents.

Adverse reaction to blood transfusion

This is due to an immunological reaction to one of the cellular constituents or to contamination with bacterial cell products or other pyrogens.

Physical heating

Excessive heating or prevention of heat loss. Causes include strong sunlight and excess ambient temperature (heatstroke), strenuous exercise, and heat-retaining clothing.

Miscellaneous

Other causes of pyrexia include neoplasm, post-cerebral insult (e.g. head injury, cerebrovascular accident), delirium tremens.

Therapeutic aims

Target normothermia following cardiac arrest or cerebral insults as reducing cerebral metabolic rate may offer neuroprotection.

In sepsis, hypothermia is deleterious, however, optimal temperature target has not been definitively established. A pilot study found improved survival in afebrile septic patients warmed by 1.5°C.

Principles of management

1. Diagnose and remove/treat the precipitating cause. For example, seek and treat infection, stop blood transfusion, discontinue potential causative drug, and treat vasculitis.
2. Cooling aids symptomatic recovery, reduces metabolic rate, and reduces pressor requirements:
   - increase evaporative losses, e.g. tepid sponging, wet sheets, ice packs in groins and axillae
   - increase convective losses, e.g. fanning to improve air circulation
   - cooled intravenous fluids
   - cooling blankets
   - antipyretics, e.g. paracetamol
   - if temperature >40°C consider endovascular cooling, irrigation of bladder/peritoneum with ice-cool fluids, ice-cool baths
   - aim to lower temperature to <38.5°C then reassess.
3. Paralysis and mechanical ventilation may be needed if excess shivering.
4. Seek and treat concurrent rhabdomyolysis, DIC, seizures.
5. Treat NMS by stopping the causative antipsychotic (or antiemetic), cooling and supportive care, and managing complications such as rhabdomyolysis and hypertension.
6. Consider dantrolene for MH.

Further reading

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See Targeted temperature management, p106; Blood transfusion, p272; Blood products, p274; Generalized seizures, p472; Stroke, p482; Infection—diagnosis, p588; Infection—treatment, p590; Sepsis—management, p594; Multiorgan dysfunction—causes & definitions, p596; Head injury—general management, p632; Hyperpyrexia, p656.

Hyperpyrexia

This life-threatening emergency is defined as a very high core temperature, though the threshold varies in the literature from 40°C to 41.5°C.

Clinical features

- Delirium and seizures are associated with temperatures >40°C.
- Coma is usual when temperatures >42°C.
- Tachycardia, tachypnoea.
- Salt and water depletion.
- Rhabdomyolysis.
- Coagulopathy.
- Heart failure with ST depression and 'T'-wave flattening.

Causes

- Hyperpyrexia may be an extreme form of pyrogen-induced fever associated with infection, inflammation, neoplasm, or stroke.
- Heat stroke is associated with severe exercise in high environmental temperatures and humidity. Excess clothing, hypovolaemia, or recent alcohol intake reduces the body's ability to dissipate heat production.
- MH is a genetic drug-induced myopathy associated with a calcium transfer defect in patients receiving volatile anaesthetics or certain muscle relaxants. Heat production is increased by muscle catabolism, spasm, and peripheral vasoconstriction.
- NMS may follow phenothiazine or butyrophenone administration. Muscle rigidity, akinesia, altered mentation, and autonomic dysfunction may continue for 1–2 weeks.

Management

1. Aim to reduce core temperature <40°C within 30 min.
2. Supportive treatment, e.g. fluid replacement, seizure control.
3. Remove clothing and nurse in a cool environment.
4. If available, endovascular cooling is the preferred option. Alternatives include ice-cold bath, whole-body ice packing, ice packs in groins, axillae, and around neck. Surface cool with a fan, tepid sponging, and wet sheets to increase evaporative losses.
5. Stop active cooling when the core temperature falls <38°C.
6. Phenothiazines (though not in NMS) or short-acting benzodiazepines may be used to reduce fever and prevent shivering and agitation.
7. Consider muscle relaxants if the patient is ventilated.
8. For MH, stop causative agent.
9. Monitor and treat hyperkalaemia.
10. Dantrolene inhibits Ca^{2+} ions release from sarcoplasmic reticulum by blocking ryanodine receptors. Consider use for MH.

Further reading

➔ See Ventilatory support—indications, p48; Coagulation monitoring, p252; Basic resuscitation, p358; Heart failure—assessment, p420; Decompensated heart failure: management, p422; Coma, p466; Delirium, p470; Thyroid emergencies, p546; Amphetamines & Ecstasy, p564; Rhabdomyolysis, p648; Pyrexia, p654.

Chapter 34

Pain & perioperative care

Pain

Pain results from many insults, e.g. trauma, invasive procedures, specific organ disease, and inflammatory processes. Pain relief is necessary for recovery from surgery for the following reasons:

- Anxiety and lack of sleep.
- Increased sympathetic activity contributing to an increased metabolic demand and adrenergic stress.
- Immunomodulatory and endocrine effects.
- Inability of the cardiorespiratory system to cope with an increased metabolic demand.
- Physiological attempts to limit pain may include immobility and muscle splinting, and consequent reductions in ventilatory function and cough.

Pain perception

The magnitude of the pain stimulus is related in part to the degree of tissue damage and site of injury. However, perception of pain is also dependent upon other factors, e.g. simultaneous sensory inputs, different pain thresholds, and previous experiences of pain. Surgeons should ensure expectations of postoperative recovery are discussed with patients.

Management of pain

Systemic analgesia

- Opioid analgesics form the mainstay of drug treatment in the intensive care unit (ICU).
- Options include subcutaneous (SC), intramuscular, or intravenous (IV) boluses or continuous infusion, or regional analgesia, e.g. epidural.
- Higher doses are required to treat rather than prevent pain.
- The drug dosage depends on the patient's perception of pain and, perhaps, tolerance due to prior analgesic use. Complex pain patients should be discussed with pain specialist preoperatively.
- Non-opioid drugs may avoid the need for, or reduce the dose, required of opioid drugs. Options include paracetamol (oral or intravenous), non-steroidal anti-inflammatory drugs (NSAIDs), ketamine, and α_2 agonists (e.g. clonidine, dexmedetomidine). Gabapentin may be useful for nerve pain.
- Some operations have pre prescribed pain regimens (particularly arthroplasty).

Patient-controlled analgesia (PCA)

- The patient presses a button on a PCA machine to receive an IV or SC bolus dose of analgesia when required.
- The machine will not give another bolus until a set time has passed (known as the lock-out time, this is usually 5 min):
  - this ensures that the patient does not overdose, as if they are becoming drowsy they are unable to press the button
  - remind family members that they must not press the button for their relative, as this bypasses this safety mechanism.
- Morphine is first line; usual starting dose is 1 mg per bolus. Fentanyl PCA (usual dose 20 μg per bolus) and oxycodone PCA (1 mg bolus) are also available, seek local guidance.

- For patients who are finding it hard to control their pain with 5 min boluses, a background rate can be added, e.g. 1 mg morphine/h. Review the background rate regularly and reduce as patient's pain allows.

Regional analgesia

- Regional techniques reduce the risk of respiratory depression but require experience and expertise to ensure procedures are performed safely and appropriately monitored.
- Local anaesthetic agents may be used to block superficial nerves, e.g. intercostal nerve block with 3–5 mL 0.5% bupivacaine plus epinephrine. Lower concentrations, such as 0.25% bupivacaine, are often used to reduce the risk of significant motor block and to allow early mobilization, e.g. in fascia iliaca compartment block for hip fracture repair.

Non-pharmacological techniques

Explanation, reassurance, positioning, and physical techniques may all reduce drug requirements.

Transcutaneous electric nerve stimulation (TENS) machine may be useful for difficult to manage pain. Similar measures include pillows or hot water bottles to abdomen.

Further reading

See Non-opioid analgesics, p316; Opioid analgesics, p318; Epidural analgesics, p320; Epidural analgesia—management, p662; Postoperative complications, p668.

Epidural analgesia—management

Catheters can be inserted into the epidural space (Figure 34.1) to deliver regional anaesthesia for procedures (e.g. Caesarean section, hip replacement) or to provide regional analgesia. By reducing or avoiding systemic opiate administration, the risk of respiratory complications is reduced.

Local anaesthetics (e.g. bupivacaine) and/or opioid (e.g. fentanyl, morphine) can be administered via bolus and/or continuous infusion via a specially configured, lockable pump (with pre-set limits for maximum infusion rate, bolus dose, and frequency) through a catheter into the epidural space (Table 34.1). Depending on the required level of block, the approach is thoracic or lumbar.

Epidurals should only be 'bolused' by a competent trained individual. It is, however, important for everyone to recognize complications.

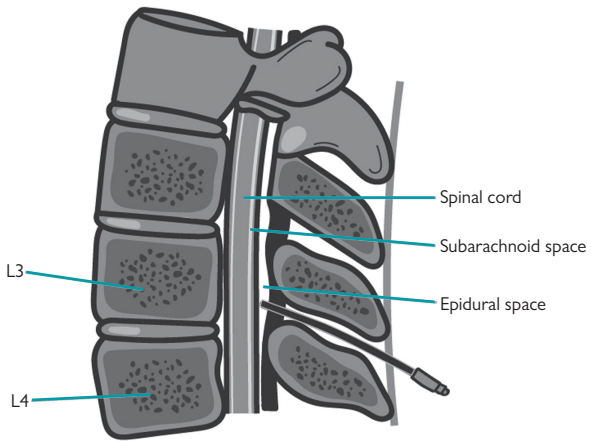

Fig. 34.1 Anatomy of the epidural space.

Management

- Aseptic technique for insertion of catheter.
- Regularly monitor cardiorespiratory variables, sedation and pain, insertion site, and the degree of motor and sensory block.
- In general, avoid concurrent administration of IV and epidural opioids.
- Level of sensory block is determined by testing skin sensation to cold (note C nerve fibres carry pain and temperature) on both sides; adjust dose by bolus ± change infusion rate accordingly:
  - if block is above T4, reduce the rate and review after 30 min
  - if block is as high as T2, the sympathetic supply to the heart may be interrupted and may result in bradycardia

  - if block is unilateral, position patient laterally onto their painful side to improve drug distribution and consider a bolus of the epidural infusion.
- Observe insertion site regularly for catheter displacement (documented catheter length at skin), signs of infection, or leakage of fluid. If a small leak is detected, but the epidural remains effective, apply pads. However, if leakage increases and/or pain becomes severe, remove the epidural.
- Anticoagulation: low-molecular-weight heparin (LMWH) can be given while the epidural is *in situ*, but anticipate time to catheter removal. Table 34.2 in the following topic summarizes insertion and removal timing recommendations.
- When planning removal, an analgesia bridging plan (e.g. PCA, regular oral or IV drugs) is necessary to prevent breakthrough pain.
- Low-concentration, high-volume local anaesthetics are being used increasingly to facilitate ambulatory epidurals. This strategy reduces the chance of motor block.

Table 34.1 Sample regimens for epidural analgesia

Lumbar local anaesthetic	10–15 mL 0.25% bupivacaine followed by an infusion of 5–20 mL/h 0.1% bupivacaine
Thoracic local anaesthetic	4–6 mL 0.25% bupivacaine followed by an infusion of 6–10 mL/h 0.1% bupivacaine
Opioid	1 mg diamorphine gives up to 12 h analgesia
Combined	Low dose mix (0.1% bupivacaine and 2 μg/mL fentanyl in 240 mL 0.9% saline) infusion 6–mL/h—titrate to response

Further reading

'Best practice in the management of epidural analgesia in the hospital setting'. Faculty of Pain Medicine, Royal College of Anaesthetists. 2011. Accessed June 2023. https://anaesthetists.org/Portals/0/PDFs/GuidelinesPDFs/Guideline_best_practice_management_epidural_analgesia_2011_final.pdf?ver=2018-07-11-163752-770&ver=2018-07-11-163752-770

Working Party; Association of Anaesthetists of Great Britain & Ireland; Obstetric Anaesthetists' Association; Regional Anaesthesia UK. 2013. 'Regional anaesthesia and patients with abnormalities of coagulation'. *Anaesthesia* 68: pp966–72. doi: 10.1111/anae.12359

Benzon H, Avram M, Green D, et al. 2013.'New oral anticoagulants and regional anaesthesia'. *Brit J Anaesth* 111 (Suppl 1): pp196–113. doi: 10.1093/bja/aet401

See Opioid analgesics, p318; Epidural analgesics, p320; Fluid challenge, p362; Hypotension, p408; Pain, p660; Epidural analgesia—risks & complications, p664; Postoperative complications, p668.

Epidural analgesia—risks & complications

Relative contraindications and risk factors

- Significant coagulopathy or thrombocytopenia.
- Use of anticoagulants—see Table 34.2.
- Localized infection.
- Sepsis—though confirmatory evidence is lacking, epidurals are not generally used in septic patients due to a perceived increased risk of epidural abscess or haematoma formation.
- Immunosuppression—infectious complications are rare if appropriate precautions are taken.

Table 34.2 Recommended time intervals before or after neuraxial procedure and epidural catheter removal where anticoagulants are used

Drug	Time before neuraxial procedure or catheter removal	Time after neuraxial procedure or catheter removal
Aspirin	None	None
NSAIDs	None	None
Clopidogrel	7 days	After catheter removal
Prasugrel	7–10 days	6 h
Ticagrelor	5 days	6 h
Warfarin	5 days (normal INR)	After catheter removal
Heparin (IV)	4–6 h	1–2 h
LMWH (prophylactic)	12 h	4 h
LMWH (therapeutic)	24 h	4 h
Fondaparinux	36–42 h	6–12 h
Dabigatran	Contraindicated	22–26 h
Rivaroxaban	22–26 h	22–26 h
Apixaban	26–30 h	26–30 h

INR = international normalized ratio.

Complications

- Hypotension due to sympathetic blockade—if not reversed by volume expansion, an α agonist (e.g. metaraminol, phenylephrine) may be needed. Administer with care as excessive vasoconstriction may result in a significant fall in cardiac output (especially with underlying heart disease) and organ ischaemia. Do not assume the epidural is a cause of hypotension, check for surgical bleeding and hypovolaemia. Patients can be mobilized into a chair though the risk of hypotension increases.
- If blockade is as high as T2 then sympathetic supply to heart is interrupted and may result in bradycardia.

- Postdural puncture headache (PDPH)—may result from accidental dural puncture with a cerebrospinal fluid leak. This can be severe and last days (or longer). It is improved by lying supine. If severe, an epidural blood patch (injecting a small amount of the patient's blood into the epidural space to seal the leak) may be considered, consult with local pain team. If worsened by lying supine, consider subdural haematoma or cerebral venous thrombosis.
- Motor block—caused by excessive dosing. Stop the infusion until movement returns then restart at a lower dose. If block does not resolve within 1 h, an urgent magnetic resonance imaging scan is needed to rule out cord compression due to epidural abscess or haematoma. Treat as a medical emergency.
- High doses of local anaesthetic may cause arrhythmias, myocardial depression, perioral numbness, and dizziness, especially with catheter migration. Opioids may cause nausea and vomiting, pruritus, urinary retention, and respiratory depression.
- Infection—introduced by iatrogenic inoculation or haematogenous infection at the needle insertion site, or via the catheter. If a patient is febrile, the epidural should usually be removed even if the epidural site looks clean to avoid epidural abscess. The incidence of epidural abscess, usually caused by *Staphylococcus aureus*, is ~1:100,000. The incidence of meningitis (usually caused by streptococci) is lower. The catheter should generally be removed within 3–4 days.
- Epidural haematoma—can also occur after catheter removal. If large, it may lead to spinal cord compression for which early recognition and surgical decompression are crucial to improve neurological outcome. The risk is greater with antithrombotic use. Suspect with persistent motor block.
- Cardiovascular collapse and respiratory arrest, spinal cord ischaemia, and permanent cord or nerve damage are rare but recognized events. Postoperative monitoring should include checks for nerve injury.

Further reading

Benzon H, Avram M, Green D, et al. 2013. 'New oral anticoagulants and regional anaesthesia'. *Brit J Anaesth* 111 (Suppl 1): pp196–113. doi: 10.1093/bja/aet401

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➔ See Opioid analgesics, p318; Epidural analgesics, p320; Fluid challenge, p362; Hypotension, p408; Pain, p660; Epidural analgesia—management, p662; Postoperative complications, p668.

Perioperative critical care

Patients may be admitted to critical care pre- or post-surgery, either electively or after unexpected perioperative complications. Elective high-risk patients should undergo careful preoperative risk assessment and optimization as part of a protocolized pathway. Perioperative scoring systems may be helpful to identify the high-risk patient population. Perioperative care may include organ support, adequate fluid loading, haemodynamic stabilization, and electrolyte correction. Admission may be required for underlying comorbidities, complex surgical procedures, or for close monitoring for potential complications.

General care

- Shared decision-making between ICU, surgical, anaesthetic, and relevant specialty teams (e.g. haematology) is needed to identify patients requiring ICU admission and agree a postoperative management plan.
- Factors to consider:
  - overnight ventilation
  - planned return to surgery
  - thromboprophylaxis regimen, e.g. bridging plan, LMWH, compression stockings, or intermittent pneumatic compression
  - systemic or local anticoagulation (e.g. post-vascular procedure)
  - drain, nasogastric tube, catheter management (e.g. free drainage, suction)
  - blood pressure and haemoglobin targets
  - positioning and any restrictions on movement, e.g. whole patient, operated limb, neck, spine, etc.
  - oral/enteral intake, need for total parenteral nutrition
  - mobilization plan—early mobilization, if appropriate, reduces complications such as deep vein thrombosis and chest infection
  - antibiotic prophylaxis regimen
  - special precautions, e.g. ready availability of wire cutters if mandible wired, flap monitoring.
- A personalized airway plan should be agreed and documented for management of unexpected airway compromise and reintubation (particularly relevant for patients with an anticipated difficult airway).
- Identify location and identity of all percutaneous drains (especially after chest or abdominal surgery).
- Provide adequate analgesia and patient comfort.
- Maintain normothermia and euglycaemia.
- Determine background fluid need based on volaemic status on arrival and anticipated losses.
- Appropriate monitoring and correction of any physiological (e.g. cardiorespiratory, fluid balance) and biochemical abnormalities (e.g. blood gases, sugar and electrolytes, haemoglobin, coagulation).
- Chronic health conditions, both physical and mental, should also be appropriately managed (e.g. continuation of medicines where possible).

Reasons for elective critical care admission

- Patient risk—assessed to be at high risk of sustaining major complications or death in the perioperative period.
- Airway monitoring, e.g. major oral, head and neck surgery.
- Respiratory monitoring, e.g. cardiothoracic surgery, upper abdominal surgery, prolonged anaesthesia, previous respiratory disease.
- Cardiovascular monitoring, e.g. cardiac surgery, vascular surgery, major abdominal surgery, prolonged anaesthesia, previous cardiovascular disease.
- Neurological monitoring, e.g. neurosurgery, cardiac surgery with circulatory arrest, spinal surgery.
- Flap monitoring, e.g. major plastic and head and neck surgical procedures.
- Elective ventilation, e.g. cardiac surgery, major abdominal surgery, prolonged anaesthesia, previous respiratory disease.

Further reading

'Guidance on establishing and delivering enhanced perioperative care services'. Centre for Perioperative Care. October 2020. Accessed June 2023. https://cpoc.org.uk/guidelines-resources-guidelines/enhanced-perioperative-care

➔ See Critical care unit admission criteria, p10; Oxygen therapy, p40; Airway maintenance, p42; Ventilatory support—indications, p48; Non-invasive respiratory support, p74; Continuous positive airway pressure (CPAP), p76; Chest physiotherapy, p98; Enteral nutrition, p142; Parenteral nutrition, p144; Blood transfusion, p272; Anticoagulants—parenteral, p334; Fluid challenge, p362; Airway obstruction, p368; Respiratory failure, p370; Atelectasis & pulmonary collapse, p372; Hypotension, p408; Oliguria, p426; Vomiting/gastric stasis, p434; Abdominal sepsis, p446; Bleeding disorders—causes & diagnosis, p494; Electrolyte management, p512; Infection control—general principles, p580; Pyrexia, p654; Pain, p660; Epidural analgesia—management, p662.

Postoperative complications

Respiratory complications

- Common in those with pre-existing respiratory disease. Problems include exacerbation of chronic disease, retained secretions, basal atelectasis, infection, and upper airway issues, e.g. laryngeal oedema.
- Anaesthesia and surgery (especially abdominal surgery) reduce functional residual capacity, thoracic compliance, and cough. Both anaesthesia and surgery induce immune suppression increasing the risk of secondary infection.
- Clearance of secretions and maintenance of basal lung expansion are critical. Chest physiotherapy may be needed. Deep breathing and mobilization should be encouraged. This requires effective analgesia, especially after chest or upper abdominal surgery.
- Non-invasive or invasive ventilation may assist basal expansion and secretion clearance if recovery is prolonged, or where surgery ± pre-existing disease increase risk of secretion retention and atelectasis.
- Prior to extubation, check for threats to post-extubation airway patency (e.g. lack of a cuff leak) and potential obstruction, especially when intubation was difficult or after upper airway surgery. At extubation, the patient should (ideally) be cooperative and not over-sedated (compare arterial partial pressure of carbon dioxide ($PaCO_2$), if available, to preoperative values) to reduce the risk of subsequent hypoventilation and atelectasis.

Circulatory complications

- Haemodynamic monitoring should be escalated in both high-risk patients (e.g. pre-existing cardiac and/or renal failure) and in unstable patients to optimize fluid and vasoactive drug management.
- Prevent or correct hypovolaemia to avoid tissue hypoperfusion and subsequent related complications. Subclinical hypovolaemia is common. Hypothermia, pain, and vasopressor infusion may mask hypovolaemia by maintaining central venous pressure and blood pressure. Ensure an adequate stroke volume to maintain adequate organ function.
- Avoid fluid excess, ideally through enhanced circulatory monitoring. Fluid excess may delay recovery and compromise wound healing.
- Urine output and renal function may be affected by perioperative hypotension and hypovolaemia, use of contrast agents, and raised intra-abdominal pressure. Consider intraoperative ureteric injury if oliguria persists and check abdominal drain fluid (if available) for urea.
- Haemorrhage may be covert and should be considered in any patient with haemodynamic instability. Manage by volume resuscitation, correction of anaemia and coagulation disturbances, pressure dressings, and surgery/interventional radiology as appropriate. Consider omitting antiplatelet/anticoagulant drugs.
- Surgery and subsequent immobility increase the risk of venous thromboembolism, which may not be prevented by standard prophylaxis. If concerned, perform relevant Doppler ultrasound or angiography to exclude significant venous thrombi and pulmonary emboli. Discuss management plan with surgeons and haematologists and risk–benefit analysis for different therapeutic interventions.

Renal complications

Monitor for acute kidney injury related to hypoperfusion, drugs (e.g. antibiotics, diuretics). Risk is increased if baseline chronic kidney disease.

Limb complications

- Monitor peripheral perfusion regularly for signs of limb ischaemia (loss of pulses, skin mottling, asymmetric coolness, delayed capillary refill) and swelling. Hands and feet should be frequently exposed and checked.
- Drains, if present, should be checked for patency. If a peripheral abnormality is detected, consider the possibility of fluid imbalance, arterial or venous occlusion from clot/embolus, local haematoma, and compartment syndrome. Remove compression stockings if peripheral circulation is poor and/or oedema is present.
- Manage complications as appropriate, e.g. removing arterial line, contacting appropriate surgical team or interventional radiology.
- Monitor for new neurological abnormalities, e.g. due to perioperative stroke or peripheral nerve compression. Manage as appropriate.
- Monitor vascular line sites for cellulitis, infection, 'tissued' catheters, or extravasation injury. Manage as appropriate.
- Pressure areas should be protected by regularly 'turning' and use of appropriate mattresses and beds, especially for high-risk patients. Pressure areas should be regularly inspected.
- Encourage early mobilization when possible.

Ileus

- Postoperative ileus is commonplace due to intraoperative bowel handling, opiates, and electrolyte (Na^+, K^+, Mg^{2+}) abnormalities.
- Usually resolves with conservative management, IV hydration, bowel rest, and nasogastric tube on free drainage ('drip and suck').
- Reduce opiate use, if possible, and consider non-opioid alternatives.
- For protracted ileus, exclude a mechanical cause of obstruction. If no cause identified and no primary bowel anastomosis, consider neostigmine 2 mg IV (anticholinesterase), repeat 3 h later if required. The μ-opioid receptor antagonist, methylnaltrexone (0.3 mg/kg qds IV) may be successful. Chewing gum is commonly used to reduce ileus.
- Prokinetic agents such as metoclopramide and erythromycin are not helpful for postoperative ileus.
- Post-pyloric enteral feeding can be given if the ileus is proximal, though this should be carefully monitored and discontinued if abdominal pain or distension occurs.
- Severe ileus may lead to considerable bowel distension and raised intra-abdominal pressure with splanchnic ischaemia and oliguria.

Further reading

See Airway maintenance, p42; Ventilatory support—indications, p48; Chest physiotherapy, p98; Fluid challenge, p362; Airway obstruction, p368; Respiratory failure, p370; Atelectasis & pulmonary collapse, p372; Hypotension, p408; Oliguria, p426; Vomiting/gastric stasis, p434; Raised intra-abdominal pressure, p448; Pain, p660; Epidural analgesia—management, p662.

Chapter 35

Oncology

General support of the oncology patient

Prognosis of many cancers has improved significantly over the past few decades. Furthermore, increasing numbers of patients with metastatic disease are now living longer and with reasonable quality of life. Such patients can still be considered for critical care admission after discussion with them and their oncologist(s), recognizing that a ceiling of treatment may be appropriate for some individuals.

Patients may present due to their underlying malignancy, from complications of treatment, or from an unrelated acute problem.

Good communication with the patient and their teams (e.g. oncologists, surgeons, palliative care clinicians) is essential to manage both the medical conditions along with changing patient and family expectations.

Analgesia

Patients with advanced cancer often experience severe pain. Management may be complicated by chronic analgesic dependency necessitating high doses ± sedation for managing acutely painful episodes.

Patients may complain of persistent, continuous, and/or breakthrough pain (brief, rapid-onset flare-ups of severe pain despite regular pain medication). A personalized approach is essential as effective strategies vary between patients. Some will be more affected by side effects, e.g. excess drowsiness from opiates. Seek advice, if necessary, from palliative care or pain teams.

Cancer pain/discomfort may arise from:

- Postoperative pain.
- Organomegaly with stretching of the capsule and pressure discomfort (e.g. splenomegaly).
- Occluded blood vessels causing distal tissue ischaemia.
- Bone fracture(s) from metastases.
- Infection.
- Inflammation (e.g. pleurisy, peritonitis).
- Side effects from cancer therapy (e.g. chemo- or radiotherapy).
- Neuropathy (compression, infiltration, chemotherapy related).

Postoperative pain should be managed in a standard manner, i.e. oral analgesics ± dermal patches graduating to intravenous (IV) infusions/boluses of opiates and/or, if not contraindicated, non-steroidal anti-inflammatory drugs (NSAIDs), epidurals/nerve blocks, and patient-controlled analgesia.

Other than opiate and non-opioid treatment, specific conditions may warrant directed adjunctive therapy. For example, neuropathic pain may respond to antidepressants, anticonvulsants, oral or cutaneous lidocaine, and/or corticosteroids. Local or regional nerve blocks may be useful for somatic or visceral pain. Transcutaneous electric nerve stimulation (TENS) may block pain transmission by low-level stimulation of nerve endings. Complementary medicine may help some patients.

Nausea/vomiting

Commence standard antiemetic therapy (e.g. cyclizine, prochlorperazine, metoclopramide). Treat any precipitating condition, e.g. relief of pain, decompressing a distended stomach or bowel (e.g. nasogastric tube insertion), discontinuing any offending drugs, if possible. If the above fails to

relieve symptoms, consider ondansetron and/or a 3-day course of IV dexamethasone 4 mg bd. If nausea is severe or highly emetogenic chemotherapy is used, consider a continuous infusion of a combination of antiemetics, e.g. ondansetron 24 mg, cyclizine 150 mg, levomepromazine 25 mg infused over a 24 h period.

Psychological support

Many patients manifest signs of clinical depression, anxiety, and/or stress, especially at advanced stages of the disease. The degree of external family/friend support can vary. Admission to critical care may be very frightening. Provision of emotional support and stability can help patients to cope. Assistance can be sought from clinical psychology, oncology, and palliative care teams. Hypnosis and relaxation techniques may prove useful. Adequate provision of information regarding critical care management and prognosis is an important means of allaying anxiety for both patient and family. Discussions should be handled both timely and tactfully.

Further reading

➔ See Communication, p18; Antiemetics & gut motility agents, p308; Non-opioid analgesics, p316; Opioid analgesics, p318; Epidural analgesics, p320; Anticonvulsants, p328; Corticosteroids, p352; Pain, p660; Epidural analgesia—management, p662.

Leukaemia/lymphoma

Such patients may present acutely to critical care with complications arising from either the disease or the therapy, or due to an unrelated condition.

Complications arising from the disease

- Hyperviscosity syndrome due to elevated white blood count. Features include drowsiness, coma, and focal neurological defects.
- Decreased resistance to infection.
- Anaemia, thrombocytopenia, bleeding tendency, coagulopathy.
- Weight loss, lethargy, fever, night sweats.
- Central nervous system involvement.
- Haemophagocytic lymphohistiocytosis (HLH)—follows massive activation of T lymphocytes and macrophages leading to pyrexia, pancytopenia, abnormal liver function tests, elevated ferritin, triglycerides, D-dimer, and C-reactive protein, low fibrinogen, and haemo-phagocytosis in bone marrow/blood film. HLH may be due to the underlying malignancy or can occur following infection. Treatment includes corticosteroids, anakinra, etoposide, or ciclosporin; an optimal treatment regimen has not yet been determined.
- Paraneoplastic syndromes as with other cancers, e.g. lung, breast. Examples include Guillain–Barré syndrome, dermatomyositis-polymyositis, encephalomyelitis, POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin abnormalities).

Complications arising from the therapy

- Infection.
- Thrombotic microangiopathy, e.g. haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), microangiopathic haemolytic anaemia (MAHA).
- Cytokine release syndrome (CRS).
- Engraftment syndrome follows haematopoietic stem cell transplantation (HSCT). This is characterized by non-infectious pyrexia with rash, pulmonary infiltrates, and/or diarrhoea usually occurring within 1–4 days of neutrophil recovery. It is often responsive to steroids.
- Other complications include seizures, diffuse alveolar haemorrhage, posterior reversible encephalopathy syndrome (PRES), graft-versus-host disease (GVHD), neutropenic enterocolitis, idiopathic pulmonary syndrome (pneumonia-like symptoms, e.g. fever, rigors, coughing, dyspnoea but no infection).

Management

1. Hyperviscosity syndrome: raised white cell mass may be reduced rapidly by leukapheresis.
2. Tumour lysis syndrome (TLS) may follow chemotherapy. The risk of TLS can be reduced by pre-emptive hydration and rasburicase.
3. Maintain haemoglobin levels >70 g/L.
4. Platelet transfusions to maintain counts >10 × 10^9/L, or higher if septic (e.g. >20 × 10^9/L), bleeding (e.g. >50 × 10^9/L) or undergoing

an invasive procedure (e.g. >50–100 × 10^9/L depending on the procedure).
5. Fresh frozen plasma and other blood products, as needed.
6. Neutropenia management, including protective isolation, appropriate antibiotic therapy if indicated, ± granulocyte colony-stimulating factor (G-CSF).
7. Rarely, granulocyte transfusion is indicated.
8. Specific treatment as needed, e.g. renal replacement therapy.

Graft-versus-host disease (GVHD)

A T-cell-related immune response following allogeneic stem cell transplantation. It is termed acute within 100 days of the transplant and chronic after 100 days. Features include mucositis, pneumonitis, hepatitis, jaundice, watery diarrhoea, abdominal pain, cytopenia, rash (often pruritic), and blistering. Severity can be graded according to clinical features (Table 35.1).

High-dose corticosteroids are the mainstay of treatment. Other options include ciclosporin, mycophenolate, tacrolimus, rituximab, anti-lymphocytic or anti-thymocytic globulin, and symptom relief. Parenteral nutrition may be needed if diarrhoea is severe.

Table 35.1 Grades of GVHD

Grade	Skin	Liver	Gut
1	Rash <25% body	Bilirubin 35–50 μmol/L	Diarrhoea <1 L/day
2	Rash 25–50% body	Bilirubin 51–100 μmol/L	Diarrhoea 1–1.5 L/day
3	Rash >50% body	Bilirubin 101–250 μmol/L	Diarrhoea >1.5 L/day
4	Desquamation or bullae	Bilirubin >250 μmol/L	Pain or ileus

Further reading

Cox M, Mackenzie S, Low R, et al. 2024. 'Diagnosis and investigation of suspected haemophagocytic lymphohistiocytosis in adults: 2023 Hyperinflammation and HLH Across Speciality Collaboration (HiHASC) consensus guideline.' *Lancet Rheumatol* 6: ppe51–62. doi: 10.1016/S2665-9913(23)00273-4

➔ See Blood transfusion, p272; Blood products, p274; Corticosteroids, p352; Immunomodulatory therapies, p354; Bleeding disorders—causes & diagnosis, p494; Clotting disorders, p498; Anaemia, p500; Thrombotic microangiopathies, p506; Platelet disorders, p508; Infection—diagnosis, p588; Haemophagocytic lymphohistiocytosis (HLH), p616; Effects of chemo- & radiotherapy, p676; Neutropenia & infection, p678; Chimeric antigen receptor T-cell (CAR-T) therapy, p680.

Effects of chemo- & radiotherapy

Bone marrow suppression

Neutropenia, thrombocytopenia, and/or anaemia may be related to the neoplasm, to secondary complications, or to many therapeutic regimens. Impaired immune functionality increases the risk of infection from bacterial, fungal, viral, and atypical organisms, and from bleeding that may range from relatively minor (e.g. petechiae, cannula sites) to catastrophic (e.g. cerebral haemorrhage).

Low platelet counts are generally well tolerated; transfusions aim to achieve counts >10 × 10^9/L though higher levels are targeted for active bleeding (e.g. >50 × 10^9/L), elective procedures (e.g. 50–100 × 10^9/L), and in the presence of sepsis (e.g. >20 × 10^9/L). Avoid excess platelet transfusion as this greatly increases the risk of antiplatelet antibody formation resulting in adverse reactions and/or failure to increment the count. Single donor or human leukocyte antigen-matched pools may be needed to improve the increment.

Anaemia is generally managed by red cell transfusion. In general, haemoglobin levels ≥70 g/L are acceptable though higher target levels may be needed for active bleeding or underlying cardiorespiratory impairment. Check haematinics such as iron, folate, and vitamin B_{12}.

Impaired gas exchange

The lung is often compromised by infection, non-infective pneumonitis, pleural effusion, high- or low-pressure pulmonary oedema (i.e. acute respiratory distress syndrome or left heart failure), haemorrhage, bronchiolitis obliterans with organizing pneumonia (BOOP—now called cryptogenic organizing pneumonia (COP)), GVHD, or fibrosis (especially after busulphan or radiotherapy). Fluid overload is common following renal dysfunction and/or large fluid volumes used for chemotherapy and multiple antibiotics.

- Treat the underlying cause, e.g. antibiotics for infection, steroids for non-infective pneumonitis and COP.
- Aim for arterial oxygen saturation (SaO_2) 90–92% to reduce the risk of 'busulphan lung'.
- Avoid fluid overload as excess capillary leak will worsen gas exchange.
- Mortality remains high if mechanical ventilation is necessary. Non-invasive ventilation or high-flow nasal oxygen may avoid the need for intubation, especially if used early to prevent the patient becoming fatigued. However, intubation should not be delayed unnecessarily.

Cardiomyopathy

Some chemotherapeutics (e.g. doxorubicin, mitoxantrone) can cause cardiomyopathy. This may be dose related or idiosyncratic. Secondary sepsis can also cause myocardial depression. Treatment is based on standard heart failure regimens. Fluid overload should be avoided. Heart failure should be considered if intubated patients fail to wean from mechanical ventilation or require early reintubation.

Renal dysfunction

Many drugs used for chemotherapy (e.g. cisplatin), transplant rejection (e.g. ciclosporin), or antibiotics (e.g. co-trimoxazole, amphotericin, aminoglycosides) are nephrotoxic. Where available, drug levels should be monitored to adjust dosing.

Tumour lysis syndrome

TLS is characterized by hyperkalaemia, hyperphosphataemia, hyperuricaemia, and acute kidney injury. This may follow rapid destruction of bulky tumours, especially leukaemias and lymphomas. Seizures, tetany, and arrhythmias may also occur. The incidence can be reduced with good hydration, a maintained diuresis, and rasburicase (recombinant urate oxidase). Allopurinol or rasburicase can be used as prophylaxis in patients at low/intermediate risk. Once established, renal replacement therapy may be necessary.

Miscellaneous

Multiple other side effects can occur, either in the short term or as a late complication. These may be life-threatening and/or symptomatic. Examples include liver damage (e.g. asparaginase), neuropathy (e.g. vincristine), gastrointestinal toxicity, rash and blistering, lung fibrosis (e.g. busulfan), cystitis (e.g. cyclophosphamide), central nervous system toxicity (e.g. ifosfamide encephalopathy), and radiation fibrosis syndrome (affecting any tissue within the radiation field). Drug-related complications should always be considered with any pathology or patient symptom. Specialist opinion regarding dose adjustment or discontinuation should be sought.

Further reading

➔ See Non-invasive respiratory support, p74; High-flow nasal oxygenation (HFNO), p80; Antibacterials, p344; Corticosteroids, p352; Dyspnoea, p366; Respiratory failure, p370; Acute respiratory distress syndrome—diagnosis, p384; Heart failure—assessment, p420; Acute kidney injury—diagnosis, p428; Bleeding disorders—causes & diagnosis, p494; Anaemia, p500; Platelet disorders, p508; Infection—diagnosis, p588; Neutropenia & infection, p678.

Neutropenia & infection

Though defined as a neutrophil count $<2 \times 10^9$/L, neutropenic patients are not generally placed in protective isolation until counts fall to below 0.5–1 $\times$ 10^9/L. Adequate functionality is still not guaranteed despite restoration of a 'normal' count. Many studies show equivalent outcomes between neutropenic and non-neutropenic haem-oncology patients admitted to critical care. The patient is usually asymptomatic until infection supervenes but can deteriorate very rapidly.

Causes of neutropenia in the oncology patient

- The neoplasm itself (e.g. leukaemia, myeloma, myelofibrosis) or from marrow suppression related to chemo- or radiotherapy.
- Systemic inflammation, infection, and sepsis.
- Nutritional deficiencies, e.g. folate, vitamin B_{12}, malnutrition.
- Adverse drug reaction.
- Part of an aplastic anaemia, e.g. idiopathic, drugs, infection.
- Hypersplenism.

Infections

- Initial infections are often with common bacterial organisms such as *Streptococcus pneumoniae*, *Staphylococcus* spp., and coliforms.
- With recurrent infections or after repeated courses of antibiotics, more atypical and/or multi-resistant organisms may be responsible, e.g. fungi (NB: *Candida* spp.), *Pneumocystis jirovecii*, cytomegalovirus, tuberculosis (atypical or reactivation of *Mycobacterium tuberculosis*).

Management

Stop potentially causative drugs, if possible.

1. Consider protective isolation, ideally in a cubicle equipped with positive pressure laminar flow air conditioning.
2. Adopt strict infection control procedures.
3. Minimize invasive procedures.
4. Maintain good oral hygiene. Apply topical treatment as necessary, e.g. nystatin mouthwashes for oral fungal infection.
5. Apply clotrimazole cream for fungal skin infection.
6. If neutropenic sepsis is suspected, apply a low threshold for starting broad-spectrum parenteral antibiotics promptly. Adjust to targeted therapy if an organism is subsequently isolated or stop if the cause is non-infective. Consult microbiology for advice. Antibacterial cover is frequently augmented by antifungals ± antivirals ± treatment of atypicals (e.g. *Pneumocystis jirovecii*). Problems related to excess/unnecessary antibiotic use include resistance, bacterial overgrowth (e.g. *Clostridioides* (formerly *Clostridium*) *difficile*), liver, renal, and gut toxicity, fluid overload.
7. Neutropenic fever may be due to infection, the antibiotic treatment itself, or to other causes, e.g. drugs/blood products. Consider possible discontinuation of therapy if pyrexia commences during the antibiotic course or fails to resolve. Commencement of antibiotics is not so time critical for uncomplicated neutropenic fever but should be started if clinical deterioration occurs.

8. Remove vascular catheters, if possibly implicated, including Hickman catheters, Permacaths, peripherally inserted central catheters (PICCs).
9. Low neutrophil counts can be managed expectantly as bone marrow recovery after chemotherapy or bone marrow transplantation generally occurs with severe weeks. Sepsis can delay recovery. Marrow stimulants such as G-CSF (filgrastim) may be used. G-CSF should be stopped promptly on recovery of neutrophil counts as very high levels can be generated.
10. White cell transfusions are used occasionally if infection is not responding to antibiotic therapy. Side effects are common, especially pyrexia and pulmonary related, e.g. infiltrates, hypoxaemia.

Further reading

➔ Full blood count, p250; Bacteriology, p256; Virology, p258; Mycology, p260; Antibacterials, p344; Antifungals, p346; Infection control—general principles, p580; Infection—diagnosis, p588; Infection—treatment, p590; Sepsis—definitions & pathophysiology, p592; Sepsis—management, p594; Pyrexia, p654; Leukaemia/lymphoma, p674 Effects of chemo- & radiotherapy, p676.

Chimeric antigen receptor T-cell (CAR-T) therapy

In CAR-T therapy the patient's T-cells are engineered with CARs to target, modify, and destroy cancer cells. These are injected into the patient after cytotoxic leukodepletion. CAR-T therapy is currently offered for certain lymphoma or leukaemia conditions; other indications are being explored.

CAR-T therapy is associated with specific acute toxicities and complications that may be fatal. Prompt identification and treatment are needed, often with organ support requiring critical care.

Table 35.2 Grading of CRS

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	≥38°C	≥38°C	≥38°C	≥38°C
Hypotension	None	No vasopressor	1 vasopressor	≥2 vasopressors
Hypoxaemia	None	O_2 (<6 L/min)	HFNO or high FiO_2 by mask	Positive pressure ventilation

* If received antipyretic or anti-cytokine therapy (e.g. steroids or tocilizumab, interleukin (IL)-6 receptor antagonist), fever is no longer required to grade. CRS grade is determined by the most severe parameter, e.g. 1 vasopressor plus low-flow O_2 = grade 3.

FiO_2 = fraction of inspired oxygen; HFNO = high-flow nasal oxygenation.

Cytokine release syndrome (CRS)

This 'cytokine storm' is the most common complication. Symptoms range from low-grade constitutional to severe hypotension and multiorgan dysfunction. Pyrexia is ubiquitous and can exceed 40°C. Risk factors for severe CRS include high tumour burden, comorbidities, and early-onset CRS (<3 days from infusion). Management is guided by grading (Table 35.2).

Management of CRS

- *Grade 1*: antipyretic, assess for infection and treat as appropriate.
- *Grade 2*: aim systolic blood pressure >90 mmHg with IV fluid boluses up to 1000 mL. Consider anti-cytokine therapy if systolic blood pressure refractory to fluid. First-line therapy is with tocilizumab 8 mg/kg IV (max 800 mg per dose) for up to 3 doses over 24 h. Consider dexamethasone 10 mg IV qds if:
  - high risk for severe CRS
  - signs of hypoperfusion (oliguria, lactate >4 mmol/L)
  - rapid clinical deterioration.
- *Grade 3*: transfer to critical care and start anti-cytokine therapy if not already given. Start dexamethasone 10 mg IV qds.
- *Grade 4*: as per grade 3 but instead of dexamethasone give methylprednisolone 500 mg bd for 3 days, 250 mg bd for 3 days, 125 mg bd for 2 days, then 60 mg bd until CRS grade 1, then taper over 2 weeks. High-dose anakinra (IL-1 receptor antagonist) has been used.

Immune effector cell-associated neurotoxicity (ICANS)

Usually presents within 1–3 weeks of CAR-T therapy but may be earlier or delayed. When occurring concurrently with CRS, more likely to be severe.

May present with aphasia, dysgraphia, lethargy, drowsiness, and/or seizures. For grading, see Table 35.3.

Table 35.3 Grading of ICANS

	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7–9	3–6	0–2	0 (unrousable)
Conscious level	Awake	Responds to voice	Responds to pain	Unresponsive
Seizure (partial or generalized)	None	None	Short, self-terminating	Prolonged (> 5 min)
Motor findings	None	None	None	Hemiparesis or paraparesis
Raised intracranial pressure and neuroimaging	None	None	Focal oedema	Diffuse oedema. Decorticate/ decerebrate posture

* The Immune effector Cell-associated Encephalopathy (ICE) score is similar to a Mini-Mental Score. The ICANS grade is determined by the most severe event.

Management

1. Close monitoring, regular ICE assessment, and neurology consultation.
2. If grades 1–2 start prophylactic levetiracetam 500 mg PO or IV bd.
3. For focal and generalized seizures, lorazepam 1–2 mg IV and repeat as required to a maximum of 4 mg. Start levetiracetam 500–1500 mg IV bolus, follow with maintenance dosing. Aim plasma Mg >1.0 mmol/L.
4. If agitated, consider low-dose haloperidol or lorazepam.
5. Fundoscopy to assess for papilloedema.
6. Imaging (computed tomography or magnetic resonance).
7. Daily 30 min electroencephalogram (if available).
8. Consider corticosteroids and anti-cytokine therapy (anakinra (IL-1 receptor antagonist) or tocilizumab (IL-6 receptor antagonist)).
9. If swallowing impaired, covert PO medicines to IV.

Haemophagocytic lymphohistiocytosis (HLH)

Distinguishing HLH from CRS is difficult and these syndromes share many overlapping features. No trials exist to identify optimal therapy. Anakinra is generally used as a first-line therapy, followed by etoposide or tocilizumab if not responding. Corticosteroids are often given in addition.

Further reading

Santomasso B, Gust J, Perna F. 2023. 'How I treat unique and difficult to manage cases of CAR T-cell therapy associated neurotoxicity'. *Blood* 141: pp2443–51. doi: 10.1182/blood.2022017604

Cox M, Mackenzie S, Low R, et al. 2024. 'Diagnosis and investigation of suspected haemophagocytic lymphohistiocytosis in adults: 2023 Hyperinflammation and HLH Across Speciality Collaboration (HiHASC) consensus guideline.' *Lancet Rheumatol* 6: ppe51–62. doi: 10.1016/S2665-9913(23)00273-4

➲ See Ventilatory support—indications, p48; High-flow nasal oxygenation (HFNO), p80; Lactate, p246; Corticosteroids, p352; Immunomodulatory therapies, p354; Encephalitis, p476; Haemophagocytic lymphohistiocytosis (HLH), p616; Pyrexia, p654; Leukaemia/lymphoma, p674; Effects of chemo- & radiotherapy, p676.

Chapter 36

Obstetric emergencies

Maternity care in ICU

Most individuals remain healthy during pregnancy and in the postpartum period (42 days following birth). Some require enhanced monitoring in labour ward areas and even fewer require specialist critical care input. Recent UK data indicate 2–7 per 1000 maternities require admission to an intensive care unit (ICU). Most ICU stays are often brief with good outcomes. Where and how to manage these patients depends on available local facilities and expertise. Close working between ICU, anaesthetists, obstetricians, and midwives is essential for any obstetric patient in critical care.

Peripartum complications may relate to pre-existing medical conditions (e.g. existing cardiac disease), obstetric-related medical conditions (e.g. pre-eclampsia, HELLP (Haemolysis, Elevated Liver enzymes, Low Platelets), puerperal sepsis), or complex birth injury (e.g. ante- or postpartum haemorrhage (PPH)). Risk factors for ICU admission include maternal age, body mass index (BMI) >35 kg/m², black ethnicity, and parity >3. Maternity early warning scoring systems are recommended to identify the deteriorating obstetric patient in view of their altered physiology.

General considerations

- Hospitals that admit obstetric patients should have a named ICU lead consultant for maternal critical care.
- If prolonged ICU admission is anticipated, consider transfer to a regional unit with appropriate facilities, support, and expertise. Family needs should be appreciated, especially if the unit is distant.
- Ensure emergency access to obstetric and neonatal/paediatric services for those who are >20 weeks' pregnant. A senior neonatologist/paediatrician should be able to attend within 30 min.
- Have equipment available for performing a perimortem Caesarean section in the event of maternal cardiac arrest.
- Consider need for specialist equipment (e.g. neonatal resuscitation).
- Carefully assess fluid status and volume requirements; this is often difficult in the peripartum period.
- If possible, enable the patient to maintain regular contact with baby and family support.
- Explore options to breastfeed or express breastmilk. Review safety of prescribed medications for breastfeeding.

Mortality—direct vs indirect

Direct deaths are those directly related to pregnancy, e.g. pre-eclampsia. *Indirect deaths* relate to causes exacerbated by pregnancy, e.g. cardiac disease. Coincidental deaths from an unrelated event up to 12 months postdelivery (e.g. road traffic accident) are usually not included in maternal mortality and morbidity data.

In the first 6 weeks postpartum, thromboembolic disease is the leading cause of direct death, followed by suicide, sepsis, and haemorrhage. Pre-existing cardiac disease is the main cause of indirect death within the first 6 weeks.

Peripartum planning

Managing chronic medical conditions may become more difficult during pregnancy, e.g. hypertension and diabetes. Maternal medicine specialists should advise on management and any changes in medication.

All complex, high-risk patients should be identified early and referred to specialist centres. A multidisciplinary review including anaesthesia/critical care is essential for the peripartum period, with well-documented plans for mode of birth and postpartum care. The birth should be planned to take place in a centre of expertise with appropriate critical care back-up. Antepartum admission may be required, particularly if the patient has a significant medical history and a risk of severe perinatal decompensation.

Cardiac

In high-resource countries, cardiovascular disease is the leading cause of morbidity and mortality during pregnancy. A changing maternity population with older patients and an increasing incidence of pre-existing hypertension and obesity has resulted in more acquired cardiac disease. Pre-existing structural heart disease remains a significant risk factor though such patients are often well known and specialist input is given early. Patients often require close monitoring in the peripartum period.

Mental health

Maternal suicide is the third largest cause of direct death within 6 weeks of birth and the leading cause (40%) of direct death after a year. Vulnerable women with multiple medical conditions are usually the most susceptible. Healthcare professionals should be vigilant for at-risk patients. Any admissions with attempted suicide should include routine toxicology for prescribed drugs, drugs of abuse, and alcohol. Discuss with a perinatal mental health team if any concerns.

Pre-existing medical conditions

Diabetic ketoacidosis is a medical emergency in pregnancy. Early invasive monitoring and critical support is indicated as fluid balance is often difficult to assess. Also note an increased risk of thromboembolism.

Further reading

Knight M, Bunch K, Patel R, et al. (Eds.) on behalf of MBRRACE-UK. *Saving Lives, Improving Mothers' Care Core Report—Lessons Learned to Inform Maternity Care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2018–20*. Oxford: National Perinatal Epidemiology Unit, University of Oxford, 2022.

See Diabetic ketoacidosis, p542; Pre-eclampsia & eclampsia, p686; HELLP syndrome, p688.

Pre-eclampsia & eclampsia

Pre-eclampsia affects 2–8% of pregnant women in developed countries and is 10- to 30-fold higher in low–middle-income countries. Pre-eclampsia and eclampsia account for a fifth of maternal deaths; the risk is 20-fold higher if presenting before 32 weeks' gestation. Pathological placental blood flow, endothelial activation, oxidative stress, and systemic inflammation are associated with this condition.

Risk factors include age ≥40 years, BMI ≥35 kg/m², family history, multiple pregnancy, history of hypertension, chronic kidney disease, autoimmune conditions (e.g. systemic lupus erythematosus), and diabetes mellitus (type 1 or 2).

Clinical presentation

Usually diagnosed intrapartum but also in early postpartum period. Pre-eclampsia is new-onset hypertension (systolic blood pressure (BP) ≥140 or diastolic BP ≥90 mmHg) commencing after 20 weeks' gestation, plus ≥1 of:

- Proteinuria (protein:creatinine ratio >30 mg/mmol or albumin:creatinine ratio > 8 mg/mmol).
- Maternal organ dysfunction.
- Renal (creatinine ≥90 μmol/L).
- Hepatic (alanine aminotransferase (ALT) >70 IU/L).
- Neurological (altered mental/visual status, clonus, severe headache).
- Haematological (platelets <150, coagulopathy, haemolysis).
- Uteroplacental dysfunction (intrauterine growth retardation, abnormal umbilical artery Doppler, stillbirth).

Eclampsia affects 1 in 100 pre-eclamptics and is characterized by seizures. Both pre-eclampsia and eclampsia are associated with cerebral oedema and, in some cases, haemorrhage.

HELLP occurs in 10–25% of pre-eclamptics. Renal and hepatic failure can occur with reduced plasma volume, raised peripheral resistance, and coagulopathy. Pulmonary oedema may occur secondary to increased peripheral resistance and low colloid osmotic pressure. Placental abruption and intrauterine fetal death affect 1–4% of cases. Multiorgan dysfunction is present in 70% of ICU admissions for severe pre-eclampsia.

Management

Risk prediction models (e.g. Pre-eclampsia Integrated Estimate of Risk (fullPIERS)) can guide interventions and appropriate place of care. Admission criteria to critical care include sustained BP ≥160/110 mmHg, signs of severe pre-eclampsia, and impending eclampsia. Close monitoring, including BP, neurology, and urinalysis (for proteinuria), is essential. Hypertension and seizures may continue for 48 h postpartum. Patients can deteriorate rapidly and without warning.

Circulatory management

- Hypertension—controlled reduction with intravenous (IV) labetalol or hydralazine if oral antihypertensives fail (Table 36.1). Consider up to 500 mL crystalloid with the first hydralazine dose. Target BP <135/85 mmHg.
- Oliguria—controlled volume expansion is usually more appropriate than diuretics.
- Assess fluid balance regularly.
- Limit maintenance fluid to 80 mL/h unless ongoing loss (e.g. bleeding).

- Measure proteinuria regularly. Worsening levels are associated with deterioration and an increased risk of seizures, while improvement (with accompanying polyuria) suggests resolution.

Seizures

- Seizures are best avoided by good BP control.
- Give prophylactic magnesium in severe hypertension, severe pre-eclampsia, or previous eclamptic fit. Consider use in moderate cases.
- Magnesium sulfate is the treatment of choice for eclamptic seizures. Benzodiazepines and phenytoin should generally be avoided.
- Monitor Mg levels to maintain levels between 2 and 3.5 mmol/L. Toxicity with possible cardiorespiratory arrest may occur at higher levels (> 5 mmol/L).
- Excess sedation should be avoided due to the risk of aspiration although continued seizures may require elective intubation and further anticonvulsant therapy (e.g. levetiracetam).

Early fetal delivery

Close fetal monitoring is crucial until delivery has occurred. The definitive treatment for (pre-)eclampsia is delivery but fetal needs must be balanced against those of the mother. The mother's life takes priority. If an acceptable fetal maturity has been reached, immediate delivery should be performed after seizures and hypertension are controlled. Antenatal corticosteroids may aid fetal lung maturation if gestation is <37 weeks.

Table 36.1 Drug dosages

Magnesium	4 g over 5–15 min, followed by 1 g/h by IV infusion for 24 h, or until seizures have stopped for 24 h. Monitor levels regularly Treat recurrent fits with further 2–4 g IV over 5–15 min
Labetalol	Start at 1–2 mg/min IV or faster if a rapid response is required. Labetalol is usually effective once 200 mg has been given after which a maintenance infusion of 5–50 mg/h may be continued
Nifedipine	10 mg sublingually given every 20 min if necessary
Hydralazine	5–10 mg by slow IV bolus, repeat after 20–30 min. Alternatively, infuse starting at 200–300 µg/min and reducing to 50–150 µg/min. Avoid if maternal heart rate >100/min
Glyceryl trinitrate (GTN)	Infusion of 1–10 mg/h, though tolerance may develop after 24 h

Further reading

'Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial'. *Lancet* 1995; 345: pp1455–63.

Magpie Trial Collaboration Group. 2002. 'Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial'. *Lancet* 359: pp1877–90. doi: 10.1016/s0140-6736(02)08778-0

'Hypertension in Pregnancy: Diagnosis and Management. NICE guideline [NG133]'. National Institute for Health and Care Excellence. April 2023. Accessed June 2023 https://www.nice.org.uk/guidance/ng133

See Vasodilators & antihypertensives, p288; Anticonvulsants, p328; HELLP syndrome, p688.

HELLP syndrome

HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low Platelets) is a pregnancy-related disorder associated with endothelial damage and platelet activation. It affects up to 0.9% of pregnancies and is more common with severe pre-eclampsia (10%) and eclampsia (30–50%). HELLP presents before delivery in 70% of cases, and usually between 27 and 37 weeks' gestation. Cases can present up to 48 h post-delivery. It is characterized by:

- Microangiopathic haemolysis resulting from destruction of red cells as they pass through damaged small vessels.
- Hepatic dysfunction with periportal necrosis and hyaline deposits in the sinusoids. Hepatic necrosis or subcapsular haematoma may proceed to haemorrhage or liver rupture, the risk for which exists up to 48 h post-delivery.
- Acute kidney injury occurs in 15% of cases.
- Thrombocytopenia results from increased platelet consumption, though prothrombin time and activated partial thromboplastin time are usually normal. Platelet counts rarely fall below 20×10^9/L. Laboratory markers of disseminated intravascular coagulation may occur in up to 40% of cases.

Approximately half of affected patients have incomplete HELLP with only 1–2 components present. Maternal mortality is around 1%, usually from ruptured subcapsular liver haematoma, haemorrhage, or stroke. Major haemorrhage is uncommon.

Clinical features

- Epigastric or right upper quadrant pain with malaise.
- Nausea and vomiting, headache.
- Generalized oedema is usual though 15% have diastolic BP values <90 mmHg.
- The platelet count nadir usually occurs at 24–48 h postpartum.

Criteria for diagnosis of HELLP syndrome

Table 36.2 lists criteria for diagnosis of HELLP syndrome, the different severity grades, and maternal risk. The differential diagnosis includes other thrombotic microangiopathies (e.g. thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome), and acute fatty liver of pregnancy which tends to be less severe.

Management

- Refer severe cases to a tertiary care centre.
- Priorities for management include basic resuscitation and exclusion of liver haemorrhage or rupture. Early Caesarean section and definitive urgent surgical or interventional radiological repair may be required.
- Delivery of the baby is usually necessary if HELLP occurs >34 weeks' gestation or the fetus and/or mother's condition deteriorates. A conservative 'wait-and-see' approach should not be too prolonged.
- To prevent seizures, give IV magnesium sulfate infusion prophylaxis (4–6 g IV loading dose then 1–2 g/h infusion continued for ≥24 h after delivery, maximum 40 g/day). Check plasma Mg levels frequently (more so if in renal failure) to avoid risk of toxicity or under-dosing.

- If the patient remains hypertensive despite magnesium, give appropriate antihypertensives, e.g. labetalol, hydralazine. Target BP <160/105 mmHg. Aim to reduce systolic BP to <160 mmHg, but not below 130–140 mmHg as this may result in hypoperfusion.
- Corticosteroids increase the platelet count, accelerate fetal lung maturity, and may prevent severity progression. Dexamethasone IV should be given to class I and 2 HELLP patients, and for complicated class 3 patients (e.g. eclampsia, severe epigastric pain, severe hypertension, organ dysfunction).
- Microangiopathic haemolysis and thrombocytopenia may respond to plasmapheresis, fresh frozen plasma ± cryoprecipitate. Repeat blood tests (full blood count, transaminases, LDH, clotting screen) regularly,
- Platelet transfusions should be generally avoided unless there is severe thrombocytopenia (<25 × 10^9/L), active bleeding, or an interventional procedure is planned.
- Blood transfusion is advised when haematocrit <25%.

Table 36.2 Martin/Mississippi classification of HELLP syndrome

Class 1	Severe thrombocytopenia: 0–50 × 10^9/L, LDH ≥600 IU/L or 2× upper limit of normal, AST and/or ALT ≥70 IU/L or 2× upper limit of normal (maternal morbidity 40–60%)
Class 2	Moderate thrombocytopenia: 50–100 × 10^9/L, LDH ≥600 IU/L or 2× upper limit of normal, and AST and/or ALT ≥70 IU/L or 2× upper limit of normal (maternal morbidity 20–40%)
Class 3	Mild thrombocytopenia: 100–150 × 10^9/L, LDH ≥600 IU/L or 2× upper limit of normal, AST ≥40 IU/L (maternal morbidity 20%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase.

Further reading

Aloizos S, Seretis C, Liakos N, et al. 2013. 'HELLP syndrome: understanding and management of a pregnancy-specific disease'. *J Obstet Gynaecol* 33: pp331–7. doi: 10.3109/01443615.2013.775231

American College of Obstetricians and Gynecologists. 2020. 'Gestational Hypertension. American College Obstetricians and Gynaecologists'. *Obstet Gynecol* 135: ppe237–60. Accessed January 2024. https://www.preeclampsia.org/frontend/assets/img/advocacy_resource/Gestational_Hypertension_and_Preeclampsia_ACOG_Practice_Bulletin,_Number_222_1605448006.pdf

See Liver function tests, p244; Full blood count, p250; Vasodilators & antihypertensives, p288; Jaundice, p452; Haemolysis, p504; Platelet disorders, p508.

Postpartum haemorrhage

Postpartum haemorrhage (PPH) is a leading cause of maternal mortality so early recognition of blood loss is critical. As young women may compensate well and initially mask major blood loss, hypotension may be a late sign. Primary PPH is defined as blood loss ≥500 mL within 24 h after birth. Loss of 0.5–1 L constitutes a 'minor' PPH, and more a 'major' PPH. Secondary PPH can occur between 24 h and 12 weeks postpartum. Causes include one or more of the 'four Ts':

- Tone (abnormal uterine contraction)—the commonest cause.
- Tissue (retained products of conception).
- Trauma (of the genital tract).
- Thrombin (abnormalities of coagulation).

Patients with coagulopathy or taking anticoagulants are at increased risk. Maternity units should have a protocol for major PPH that involves urgent communication and involvement of multidisciplinary senior staff, rapidly obtaining blood and blood products, appropriate monitoring, prompt resuscitation, and urgent measures to stop the bleeding.

Management of major PPH

Resuscitation

The principles of resuscitation are similar to any major haemorrhage. Significant concealed retroplacental bleeding may lead to underestimation of blood volume loss.

- Position patient flat and establish ×2 large-bore IV access.
- Close monitoring of ABC and temperature.
- Give tranexamic acid 1 g.
- Give judicious crystalloid until blood becomes available. Fluid input/output should be carefully recorded. Ideally warm fluids, e.g. through a rapid infusion system.
- Transfuse blood based on clinical and haematological end-points. Blood transfusion requirements may be massive. Seek haematology advice regarding use of platelets, fresh frozen plasma, cryoprecipitate etc. Cell salvage can be used, if available. Aim for:
  - Hb >80 g/L
  - platelet count >75 × 10^9/L
  - prothrombin time <1.5× control
  - activated partial thromboplastin time <1.5× control
  - fibrinogen >2 g/L.

Uterine contraction

Begin fundal massage and administer uterotonic drugs, e.g. oxytocin (5 U slow IV bolus, repeated as necessary, or 10–20 U in 1 L normal saline infused quickly). Alternatives include 0.5 mg ergometrine IV (unless the placenta is still *in utero*), Syntometrine®, or a prostaglandin drug. If the uterus does contract, commence an oxytocin infusion (10 U/h), carboprost 0.25 mg intramuscularly (IM) repeated every 15 min to a maximum of 8 doses (except to asthmatics), or misoprostol 1 mg rectally. Prostaglandin F2α injected locally into the uterus or IM can also stimulate uterine contraction.

Surgical/radiological intervention

If pharmacological measures fail, then surgical or radiological intervention should be considered depending on available resources. Intrauterine balloon tamponade is a first-line consideration if uterine atony is the main cause. Conservative surgical techniques may be considered second line.

Temporary reduction of haemorrhage may be achieved by compressing the aorta with a fist pushed firmly above the umbilicus, using the pressure between the fist and vertebral column to achieve compression. This manoeuvre may buy time while definitive surgical repair is organized.

Angiographic embolization or internal iliac artery ligation may avoid the need for hysterectomy in some cases.

Further reading

'Prevention and Management of Postpartum Haemorrhage (Green-top Guideline No. 52)'. Royal College of Obstetricians and Gynaecologists. December 2016. Accessed June 2023. https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.14178

See Blood transfusion, p272; Blood products, p274.

Amniotic fluid embolus

- A rare, but life-threatening complication of childbirth that may present with sudden onset of ≥1 of hypoxaemia, hypotension, coagulopathy, or even cardiac arrest. Tonic–clonic seizures are seen in 50% of cases.
- High early mortality is associated with acute pulmonary hypertension.
- The initial response of the pulmonary vasculature to the presence of amniotic fluid is intense vasospasm resulting in severe pulmonary hypertension and hypoxaemia.
- Right heart function is initially compromised but returns to normal with a secondary phase during which there may be severe left heart failure and pulmonary oedema.
- Amniotic fluid contains lipid-rich particulate material which stimulates a systemic inflammatory reaction. In this respect, the progress of the condition is similar to other causes of multiple organ failure.
- Diagnosis is usually based on clinical features. It may be supported by amniotic fluid and fetal cells in pulmonary artery blood and urine, though this finding is not specific.

Management

Management is supportive. If amniotic fluid embolism occurs prior to delivery, perform urgent Caesarean section to prevent further emboli.

Respiratory support

Provide oxygen to maintain arterial oxygen saturation (SaO_2) at 92–98%. Non-invasive or invasive respiratory support may be required.

Cardiovascular support

Standard resuscitation principles apply with controlled fluid loading and inotropic support as required.

Haematological management

Management of coagulopathy requires blood product therapy guided by laboratory assessment of coagulation parameters and haematology input.

Further reading

See Oxygen therapy, p40; Ventilatory support—indications, p48; Blood products, p274; Basic resuscitation, p358.

Puerperal/maternal sepsis

Defined as an infection between the onset of membrane rupture or labour and the 42nd day postpartum, with ≥2 of the following:

- Pelvic pain.
- Fever.
- Abnormal and often foul-smelling vaginal discharge.
- Delay in uterine involution.

Approximately 1 in 10 maternal deaths are due to infection. Although maternal sepsis is a commonly used terminology, most patients do not have organ dysfunction requiring critical care admission. Risk factors include:

- Pre-existing conditions, e.g. malnutrition, diabetes, obesity.
- Group B streptococcal (GBS) colonization of vaginal tract.
- Birth-associated: e.g. prolonged labour or membrane rupture, invasive perinatal monitoring, surgical assisted birth (e.g. forceps).
- Caesarean section incidence is 5–8-fold higher than vaginal birth.

Causes

The most common causes are chorioamnionitis, pyelonephritis, and endometritis followed by wound infection, mastitis, and pneumonia. Causative organisms are usually polymicrobial including aerobic (e.g. GBS, *Escherichia coli*, *Klebsiella pneumoniae*) and anaerobic bacteria (*Bacteroides fragilis*). Globally, infections such as HIV, tuberculosis (TB), and malaria are more prevalent.

Clinical chorioamnionitis

This is the most common antenatal cause, affecting fetal membranes, amniotic fluid, and/or placenta. It usually originates from ascending infection from the lower genital tract but consider entry from haematogenous spread or invasive procedures. No evidence of bacterial invasion is found in one-third at term, and two-thirds of those with a pre-term clinical diagnosis. A combination of raised C-reactive protein (CRP), fever, and neutrophilia was reported as only 70% predictive of chorioamnionitis.

Fever is almost universally present. Maternal and/or fetal tachycardia and purulent amniotic fluid are common but not always present.

Treatment is with prompt broad-spectrum antibiotics covering both aerobes and anaerobes. A common regimen is amoxycillin + gentamicin, or clindamycin + gentamicin. Seek microbiology advice.

Endometritis

This is a postpartum infection of the endometrial lining of the uterus, with a 1–3% incidence post vaginal delivery and a 10-fold higher incidence after Caesarean section. It is a polymicrobial disease; common isolated organisms include anaerobes and *Chlamydia* and, rarely, herpes or TB. Symptoms include lower abdominal pain, fever, and abnormal lochia. Uterine mobilization may be painful.

Give prompt antibiotics, e.g. clindamycin plus gentamicin. Most improve within 48–72 h, but longer treatment may be needed if sepsis develops.

Group A streptococcal (GAS) sepsis

An increasing cause over the last decade, the risk of invasive GAS infection is 20-fold higher compared to a non-pregnant population. The origin is usually an ascending infection from the lower genital tract. Over 90% occur in the postpartum period, half within 48 h of delivery. Presenting features are fever, abdominal pain, uterine tenderness, and abnormal discharge. Neutrophilia and an elevated CRP are common lab findings. Approximately 10% progress to streptococcal toxic shock syndrome (TSS) which may present as severe hypotension and/or necrotizing fasciitis. Treatment includes antibiotics, e.g. meropenem + clindamycin, urgent consideration of surgical exploration for source control, and supportive treatment with fluid, pressors, ventilatory, and renal support as needed.

Further reading

Conde-Agudelo A, Romero R, Jung E, et al. 2020. 'Management of clinical chorioamnionitis: an evidence-based approach'. *Am J Obset Gynecol* 223: pp848–69. doi: 10.1016/j.ajog.2020.09.044

Chapter 37

Transport of the critically ill

Intra-hospital transport

Critically ill patients are frequently moved out of the critical care unit for investigation or interventional procedures. Balance risks and benefits for the move and whether the procedure should be either postponed or possibly performed in the intensive care unit (ICU).

Transport within hospital requires provision of suitable portable equipment with an adequate battery power supply to cope with unexpected delays, e.g. lift failure. A hospital critical care trolley should be of fixed height with an equipment shelf and other fixed anchorage points below the level of the patient to enable such equipment to be clamped for safe transportation.

Patient preparation for intra-hospital transport

In addition to the usual requirements for provision of bedside critical care medicine, the following are required:

- Assessment of degree of stabilization required before movement.
- Assessment of airway safety. If in doubt, consider intubation.
- Ensure adequate venous access; minimum of two cannulae/catheters are recommended.
- Assessment of security equipment, pacing devices, tubes, and drains.
- Safe storage, and stowage of equipment on the transport trolley.
- Ensure adequate blood gas values on the transfer ventilator before moving the patient.

Required competencies of accompanying staff

The level of organ support required by the patient will determine the skillset of the staff doing the transfer. Competencies to consider:

- Airway device insertion.
- Mechanical ventilation with transport ventilator.
- Chest drain insertion and management.
- Cardiorespiratory monitoring.
- Medications including vasoactive/sedative/paralysing agents.
- Resuscitation skills.
- Lifting and handling.
- Managing access in confined spaces.
- Management during imaging e.g. special issues relating to equipment during magnetic resonance imaging.

If transfer is required to an unfamiliar location (e.g. nuclear medicine), the staff should first familiarize themselves with the area and route, including socket points and piped oxygen availability. A suitably trained assistant is essential.

Specification of transport equipment

The critical care transport trolley must accommodate:

- Portable ventilator with a heat and moisture exchange (HME) filter.
- Oxygen cylinders (ensure sufficient for twice transfer time to include for unexpected delays, e.g. lift breakdown).
- Monitor including electrocardiogram (ECG), invasive & non-invasive blood pressure, temperature, pulse oximetry oxygen saturation (SpO_2), end-tidal CO_2.

- Drugs including emergency/resuscitation agents and fluid, sedatives, neuromuscular blockers.
- Spare cannulae.
- Syringe drivers and volumetric pumps with labelled lines and pre-drawn up replacement infusions (e.g. vasoactives and sedatives).
- Suction.
- Blankets to wrap patient.
- Back-up batteries and plug.
- Mobile phone and charger.
- Personal protective equipment.
- Warm clothing.
- Anchorage for a five-point patient harness.

Further reading

➲ See Endotracheal intubation—indications & equipment, p44; Pulse oximetry, p162; CO_2 monitoring, p164; ECG monitoring, p184; Blood pressure monitoring, p186; Inter-hospital transport—road, p700; Inter-hospital transport—air, p702.

Inter-hospital transport—road

Patients may need transfer to another hospital for clinical reasons including off-site specialist services, repatriation to their local hospital, or non-clinical transfer for bed capacity reasons. Increasingly, dedicated critical care transfer teams perform inter-hospital ICU transfer. However, ICU staff may be required to undertake the transfer, especially if time-critical.

For patients requiring critical care support, at least two attendants should accompany the patient. At least one should be an experienced critical care practitioner, with previous experience of transfer. Pre-transfer the staff must be familiar (or familiarized) with transport equipment and communication systems. Table 37.1 details transport preparation requirements.

Patient preparation

The decision to move a patient between hospitals must be taken jointly by the most senior clinicians available at the referring and receiving hospitals. Evaluate the risk:benefit ratio of transport, staffing, and equipment needs based on the nature of the illness, urgency, vehicle availability, geographical factors, traffic, and weather conditions. Patients should be adequately resuscitated and stabilized as far as is able at the sending facility prior to transport. Consider intubation if concerns about airway safety during transfer, especially over long distances. Intubated patients should be adequately sedated and the need for neuromuscular blockade considered. Chest drains should not be clamped. Patients should be kept warm. Awake patients may require treatment for motion sickness and pain.

Required staff competencies for road transport

In addition to competencies required for intra-hospital transport:

- Ability to assess and resuscitate patients on the move.
- Consider limitations of resource, especially oxygen availability for the duration of the journey and extra to cover delays.
- Familiarity with chains of communication and command.
- Use of diverse modes of communication and protocols.
- Handling emergencies on the road; when to stop or divert.

Table 37.1 Transport preparation (ACCEPT)

Assessment	Be aware of the full patient history and current problems
Control	Identify the leader and allocate tasks
Communication	Make sure all communication is clear, source identified, and involves all staff involved with patient dispatch and receipt
Evaluation	Assess risks and benefits of transport, equipment needed, and urgency
Preparation	Prepare patient, equipment, and staff
Transportation	Having identified mode of transport and completed preparation, transport the patient

Vehicle design

There is guidance covering design, specification, and equipment requirements for road ambulances. A type C ambulance is a mobile ICU designed and equipped for transport, advanced treatment, and monitoring of patients.

Vehicles should have an adequate power supply, two large cylinders containing at least 2000 L oxygen (e.g. two F size cylinders). The vehicle should provide secure, anchorage fixings for the patient trolley, and essential equipment, e.g. a portable ventilator, syringe drivers, volumetric pumps, gas cylinders, etc.

Further reading

➲ See Endotracheal intubation—indications & equipment, p44; Pulse oximetry, p162; CO_2 monitoring, p164; ECG monitoring, p184; Blood pressure monitoring, p186; Sedatives, p322; Tranquillizers, p324; Muscle relaxants, p326; Intra-hospital transport, p698; Inter-hospital transport—air, p702.

Inter-hospital transport—air

Specialist teams are required for air transport with appropriately trained staff.

Aircraft are preferred for longer distance transfers with fixed wing aircraft preferred for distances >150 miles. Time to organize air transport should be taken into account when judging any advantage of speed over longer distances. Road transfer is frequently needed at one or both ends of the journey and must be coordinated and take into account extra transfer time. Helicopters are generally less comfortable and provide a more cramped environment than either ambulance or fixed wing aircraft.

Particular problems of air transport

The lower barometric pressure at altitude reduces alveolar partial pressure of oxygen and increases the volume of gas-filled cavities (beware of an expanding pneumothorax). Noise and vibration may increase pain and discomfort or contribute to nausea. Acceleration and deceleration, particularly in helicopters, may affect haemodynamics. Communication between staff members may be very challenging due to the high-noise environment.

Patient preparation

Assess risk:benefit ratio of air transport and establish staffing and equipment needs based on the nature of the illness, urgency of transfer, availability of transport, mobilization times, geographical factors, traffic, and weather conditions. Notify the receiving team of departure and estimated arrival time—keep them updated with changes en route, including times and patient deterioration that may require urgent intervention.

Monitor SpO_2 and increase fraction of inspired oxygen to target range. Pneumothoraces should generally be drained. Nasogastric tubes should be inserted and placed on free drainage. Pneumoperitoneum and intracranial air are relative contraindications to air transport. Tissues may also swell and plaster casts should be split. Nausea and pain must be adequately controlled.

Required staff competencies for air transport

In addition to the competencies required for road transport, the following are required:

- Understanding the limitations of resource and power in aircraft.
- Understanding the effects of altitude, vibration, noise, acceleration, and deceleration on physiology and monitoring.
- Understanding emergency drills for helicopters and fixed wing aircraft.

Further reading

See Endotracheal intubation—indications & equipment, p44; Chest drain insertion, p92; Nasogastric & nasojejunal tubes, p128; Pulse oximetry, p162; CO_2 monitoring, p164; ECG monitoring, p184; Blood pressure monitoring, p186; Sedatives, p322; Tranquillizers, p324; Muscle relaxants, p326; Intra-hospital transport, p698; Inter-hospital transport—road, p700.

Chapter 38

End of life care

Care of the dying patient in ICU

Despite advances in knowledge, technology, and therapies, mortality in intensive care remains high. Critical care practitioners are thus highly experienced at providing compassionate and supportive care to both patients approaching the end of their lives and their families/friends. The primary goal is to ensure that patient comfort and dignity are maintained. This can be achieved through patient-focused discussions and shared decision-making to ensure that treatment options are aligned with the patient's values and preferences. Relevant colleagues including the parent team, palliative care, psychologists, chaplains, and social workers should be involved as required.

This is often a very difficult period for all involved. Early discussions and expectation setting with patients and their loved ones can aid subsequent difficult conversations. The patient and/or their family may not accept the medical decision of futility of ongoing life-supporting treatment for emotional, cultural, and/or religious reasons. Repeat discussions will be needed and this may include involvement of religious leaders or a second opinion. Rarely, the courts may need to be involved but this should be generally viewed as a last option.

As legal aspects and clinical practices vary between countries, the practitioner needs to be cognizant of national laws, e.g. relating to withdrawal of treatments, brainstem death, and decision-making. In some countries, the patient/family view is paramount. In the UK, a clinician is not obligated to provide life-sustaining care they consider to be futile, despite the patient's and/or family's demands. This may lead to conflict which can be very distressing to all concerned. Conflict should be avoided or minimized wherever possible by skilled discussions and, if needed, offer of external second opinions.

Key aspects of end of life care

Communication

Open and honest communication including likely prognosis, treatment options, and goals of care.

Shared decision-making

Involve the patient (if possible) and their family to establish the patient's values. Decisions needed include a do not attempt cardiopulmonary resuscitation (DNACPR) order, when to escalate or continue invasive support options, and the transition to palliative care and change in focus to comfort measures. Rather than placing the onus of decision-making responsibility on the patient/family, the doctor should take the lead in proposing a course of action and seek their agreement.

Palliative care

Symptom control, e.g. for pain or anxiety, can be provided concurrently with treatments, or as the main focus of care.

Withdrawal or withholding of treatments

It may be appropriate to withdraw or withhold certain interventions (e.g. mechanical ventilation) in accordance with the patient's wishes or advance directives. These decisions are made in conjunction with the patient and/or family and are guided by ethical principles. More often, the doctor will

be proposing such a strategy and sensitive discussions are needed, as highlighted above.

Emotional and spiritual support

Apart from an empathic approach from the ICU team, specialist input can be called upon, including chaplaincy services and counselling, to help patients and families cope with the emotional impact of an end of life situation.

Family presence

Providing opportunity to say goodbye and be with their loved one.

Bereavement support

Ongoing support may include counselling services or referrals to bereavement support groups. Family members may also wish to meet with clinicians after the patient's death seeking answers to outstanding questions.

Organ donation

The patient may offer spontaneously, or already be on an organ donor register. Conversely, organ donation may not have been previously discussed. If the patient is considered potentially suitable for organ donation, discuss with the local transplant coordinator and develop a strategy as to when this should be introduced to the patient (if competent) or their next of kin.

After death

Next of kin should be informed about procedures after death, both verbally and with written leaflets with relevant contact numbers.

Laws and practices vary between countries. In England, a local medical examiner within the hospital will discuss and agree cause of death with the ICU ± primary team. The completed death certificate needs to be registered with the local authority where the patient died. The family may be approached for a postmortem examination. Certain religions (e.g. Jewish, Muslim) require urgent burial of the patient within a few days of death. This should be facilitated by prompt completion of paperwork.

A referral to the coroner is needed where cause of death is:

- Uncertain.
- Violent, unnatural, or suspicious.
- Linked to patient occupation (e.g. prior asbestos exposure).
- Linked to drugs or medications (prescribed or illicit).
- Linked to recent medical treatment, surgery, or an anaesthetic.
- In a patient who was in custody or detained under the Mental Health Act, even if due to natural causes.

The coroner will then decide if the cause of death is clear, if a (compulsory) postmortem examination is needed, and whether an inquest is necessary.

Further reading

➔ See Communication, p18; Advance directives, p708; Withdrawal of life-sustaining treatment, p710; Organ donation, p716.

Advance directives

Any advance care directive (e.g. living will or pre-ICU treatment escalation plan) should be confirmed with the adult patient regarding their preferences. Specific situations may require clarification (e.g. resuscitation during an invasive procedure). The patient should be adequately informed of the risks and benefits of management options, including end of life care where appropriate. Family or close friends may be involved in these discussions if the patient consents.

If a patient lacks capacity then an advocate known to the patient (usually next of kin, but can be a friend or neighbour if no responsible family member can be identified) should be asked to represent the patient's likely views. If an advocate that knows the patient cannot be identified, an Independent Mental Capacity Advocate (IMCA) (England/Wales) or Welfare Attorney (Scotland) should be consulted to represent the patient.

Respecting the patient's decision should be paramount, even if the clinician disagrees. However, the clinician is not obligated to follow the patient/advocate's wishes if care is considered futile, inappropriate, or illegal. A second opinion should be offered if disagreement remains.

Lasting power of attorney

For patients lacking long-term capacity, a legally authorized power of attorney may be in place that allows named people (usually next of kin) to take responsibility for financial and/or medical decisions on behalf of the patient. In such circumstances, the authorized individual(s) should be involved in discussions about treatment escalation. However, this does not give those named people the right to demand treatments considered by the clinician to be futile or inappropriate.

Further reading

➔ See Care of the dying patient in ICU, p706; Do not attempt cardiopulmonary resuscitation (DNACPR), p712.

Withdrawal of life-sustaining treatment

Withdrawal usually involves reduction or cessation of vasoactive drugs and/or respiratory support. In some situations, the patient may be disconnected from the ventilator. Sedation should be increased if necessary such that the patient experiences zero distress or discomfort.

Close family/friends should be offered the opportunity to be in attendance if they so wish. They should be adequately supported throughout and informed in advance as to what to expect.

Withholding involves non-commencement or non-escalation of treatment, e.g. applying an upper threshold dose for an inotrope, not starting renal replacement therapy, and not attempting cardiopulmonary resuscitation (DNACPR).

Discussion with patient and/or family

Before approaching the patient/family, there should be a consensus among ICU medical and nursing staff that duration and/or quality of life are significantly compromised and unlikely to recover. The patient's views should be sought in advance if they have capacity. This should be done as sensitively as possible, trying to minimize distress. Only in very exceptional circumstances should discussions not be held with the patient. If the patient lacks capacity, their advocate (usually their next of kin) should be consulted to represent the patient's views. Discussions should ideally involve the patient's nurse(s) and other clinicians (e.g. primary team, palliative care) as appropriate.

Ethnic, cultural, and religious factors will influence both doctor and patient/family in the timing and frequency of such discussions. Some families find it useful to involve their religious leader. In some countries, doctors take a paternalistic approach with little involvement of patient and/or family in the decision-making process. Others may acquiesce to the family's demands despite obvious futility in continuing care, though this is a legal obligation in some countries.

A series of discussions may be needed over several days, or longer, allowing time for the family to contemplate. Consensus is usually reached with most patients/families by the third discussion.

It should be stressed that pain relief, comfort, hydration, and general nursing care will be continued. Decisions can be amended depending on the patient's progress, e.g. moving from withholding to withdrawal, or re-institution of full treatment. A negotiated process is often a useful interim compromise for families unable to accept a withdrawal decision, whereby treatment limitations are instituted and subsequently reviewed.

Relatives may be distraught and, occasionally, irrational on discussing withdrawal/withholding. For many, this will be their first experience of the dying process. Other factors including guilt, anger, denial, and within-family disagreements may also surface. It should be stressed to the family that the withdraw/withhold decision is a medical recommendation, and their agreement is being sought. The emphasis of the discussion is to inform them of the likely outcome and to seek their view of what the patient would want. Open discussion with both sensitivity and honesty is crucial. Relatives should not feel pressured to give instant decisions.

All communications between caregivers and patient/family members should be accurately recorded. This provides important continuity of

information between team members and over shift changes, and for reference in subsequent discussions.

Further reading

Sprung C, Cohen S, Sjokvist P, et al. for the Ethicus Study Group. 2003 'End-of-life practices in European intensive care units: the Ethicus Study'. *JAMA* 290: pp790–7. doi: 10.1001/jama.290.6.790

See Communication, p18; Care of the dying patient in ICU, p706; Do not attempt cardiopulmonary resuscitation (DNACPR), p712

Do not attempt cardiopulmonary resuscitation (DNACPR)

Different countries have different legislation and guidance so refer to national and local policies. These should take into account legal, organizational, and cultural contexts.

In the UK, DNACPR is a medical decision. The decision and rationale should be explained to the patient (or advocate if the patient lacks capacity) in a sensitive and timely manner, particularly where rapid or unexpected deterioration may occur. The patient (or advocate) cannot demand treatment if the clinician does not consider it to be appropriate. However, it is good practice to have further discussions, if necessary involving ICU colleagues, palliative care, and the primary team, and to offer a second opinion.

Discussions should, ideally, not be left for emergent situations. Routine discussion about DNACPR status on admission to hospital may ensure patients have the opportunity to decline CPR, or to challenge clinical recommendations regarding DNACPR. Patients and/or their advocates should not be given the impression that they are being asked to make the primary decision; rather they are asked to agree with the doctor's recommendation.

Further reading

See Communication, p18; Care of the dying patient in ICU, p706; Withdrawal of life-sustaining treatment, p710.

Brainstem death

- Before brainstem function testing is performed, the patient must have an underlying irreversible condition compatible with brainstem death. Significant abnormalities in temperature and biochemistry must be corrected. There should not be an ongoing effect of depressant or muscle relaxant drugs. If in doubt, wait for a further period of time.
- Before undertaking brainstem death testing, discussions should be held with relevant family, significant friends, and/or advocates. The test itself does not require consent but it is good practice to inform them of the process and the significance of the tests.
- Family and/or friends can be invited to observe testing as this may help to reinforce the very poor prognosis and confirm that death has already occurred. During the procedure, a full explanation should be offered of the tests and their relevance. They should be warned about movement related to spinal reflexes that do not indicate brainstem activity. The patient's dignity should be maintained throughout.
- The legal time of death in the UK is when the first test confirms brainstem death. Brainstem death allows discontinuation of ventilation and organ support.
- If considering organ donation, involve the transplant coordinator early.
- Diagnosis is usually followed by asystole within a few days if ventilation is not discontinued.

Brainstem death testing

Procedures vary internationally. An electroencephalogram or angiography is required in some countries. In the UK, only clinical assessment is necessary. Brainstem testing must be performed by two doctors registered for >5 years, who are competent to perform the tests, and are not members of the transplant team. At least one doctor should be a consultant.

Pupillary light reflex

Pupils should appear fixed in size and fail to respond to a light stimulus.

Corneal reflexes

These should be absent bilaterally.

Pain response

There should be no cranial or limb response to supraorbital pain.

Vestibulo-ocular reflexes

After confirming that the tympanic membranes are clear, unobstructed, and non-perforated, 20 mL iced water is syringed into the ear. The eyes would normally deviate toward the opposite direction. Absence of movement to bilateral cold stimulation confirms an absent reflex.

Gag or cough reflex

The gag reflex is absent in brainstem death. However, the gag reflex is often lost in patients who are intubated. In these patients a cough reflex in response to tracheal stimulation must be absent.

Apnoea test

Before starting the test, reduce minute ventilation to increase arterial partial pressure of carbon dioxide ($PaCO_2$) >6 kPa (>6.5 kPa in those with chronic CO_2 retention).

The patient should be pre-oxygenated with 100% oxygen. Disconnect the ventilator and administer 6–15 L/min oxygen (depending on baseline oxygen saturation) into the trachea via a catheter, or connect to a Mapleson C circuit.

During the apnoea test, the fraction of inspired oxygen (FiO_2) should be adjusted as necessary to maintain pulse oximetry oxygen saturation at acceptable values. The rise in $PaCO_2$ should stimulate respiratory efforts if the brainstem is still functioning. Repeat arterial blood gas after 5 minutes (and repeat as necessary) until $PaCO_2$ rises >0.5 kPa. Any respiratory effort negates the diagnosis of brainstem death.

Further reading

➔ See Blood gas analysis, p174; Hypothermia, p652; Organ donation, p716.

Organ donation

There are several types of organ donation:
- Donation after brainstem death (DBD).
- Donation after circulatory death (DCD).
- Live donation (not relevant for critical care).

Donation after brainstem death

Refers to organ retrieval from patients fulfilling brainstem death criteria. Organ support can continue until retrieval in theatre. Consult local guidelines for up-to-date practices.

Donation after circulatory death

Previously known as non-heart beating organ donation, organs are retrieved from patients where death is confirmed by cardiorespiratory criteria (no breathing effort, no heart beat). Controlled DCD occurs after planned withdrawal of life-sustaining treatments. Uncontrolled DCD occurs after an unexpected cardiac arrest from which the patient cannot be resuscitated. Withdrawal generally occurs in the operating theatre complex with the transplant team on standby.

There is a critical ischaemic time window that differs for each organ. A prolonged time to death after discontinuation of treatment may exceed this window and disqualify that organ from retrieval. The next of kin should be forewarned that retrieval may not be possible in this situation. As national guidelines and procedures vary, seek local guidance from the organ donation team.

Care of the potential organ/tissue donor

Patients with suspected brainstem death should be considered candidates for organ or tissue donation. Tissue donation is excluded if there is:
- Systemic malignancy (other than for eye donation).
- HIV, human T-cell lymphotropic virus, or hepatitis B or C positive or behavioural risk.
- Syphilis.
- Creutzfeldt–Jakob disease (CJD) or family history of CJD.
- Progressive neurological disease of uncertain pathophysiology.
- Previous transplantation.

There are few absolute contraindications to solid organ donation:
- HIV positive (unless recipient HIV positive).
- CJD or suspected CJD.

The transplant coordinator should be contacted early (before next of kin are approached) to confirm likely organ and tissue suitability. If the next of kin are amenable, the transplant coordinator will then initiate organ donation procedures. Do not reject potential donors who, for example, have fully treated infections or acute kidney injury without consultation with the transplant coordinator.

Management

1. Confirm suitability for organ donation, discussion with next of kin.
2. Confirm organ donation is allowed by the coroner (or equivalent), and which organs may be potentially retrieved.

3. Laboratory tests for electrolytes, blood group, HIV, and hepatitis status and drug screen if indicated.
4. If DBD, follow local guidelines to maintain optimal cardiorespiratory status with fluid ± inotropes and vasopressin, optimal ventilation, low positive end-expiratory pressure, and physiotherapy.
5. Diabetes insipidus should be treated with desmopressin and fluids to maintain adequate volaemic status.
6. Maintain euthermia.
7. Contact operating theatre and anaesthetic teams.

Further reading

See Renal function, p234; Electrolytes (Na^+, K^+, Cl^-, HCO_3^-), p238; Virology, p258; Brainstem death, p714.

Excellence at the end of life

After a decision has been made to focus on symptom control, optimizing patient's comfort should be the main priority of care. The patient can range from being awake and alert to unresponsive. Management should be tailored to the individual and modified accordingly.

Symptom control

Palliative care advice may be sought regarding appropriate medications (Table 38.1) including analgesia, antiemetics, anxiolytics, and/or antisialagogues. These may be administered in a continuous syringe driver/pump either intravenously or subcutaneously.

Oxygen and respiratory wean

Consider weaning respiratory support (reducing FiO_2, removing non-invasive ventilatory support). Hypoxaemia and/or hypercarbia can be distressing so anticipatory comfort measures should be commenced.

Nutrition

Continuing nutritional support should be considered on a case-by-case basis, and with discussion with the family.

Skin and eye care

Continue care to pressure areas with regular repositioning and barrier creams if needed.

Environment

Disconnecting machines, monitoring, and alarms will provide a more peaceful environment for the patient and their loved ones. Consider moving into a single room or quiet ward area if available. Reducing the frequency of observations aids comfort and privacy; however, appropriate sedation and comfort should be regularly assessed and managed.

Table 38.1 Drugs commonly used for palliation

Pain	Morphine, diamorphine, fentanyl, NSAID, paracetamol
Agitation	Haloperidol, midazolam
Nausea and vomiting	Cyclizine, metoclopramide
Anxiety	Midazolam
Breathlessness	Midazolam, morphine, fentanyl
Secretions	Hyoscine butylbromide, glycopyrronium
Constipation	Lactulose, senna

NB: drug dosages should be titrated to effect and will depend on prior use.

Spiritual considerations

The patient and/or family may have particular religious or spiritual needs that should be accommodated if possible. A visit from a religious leader, placing special objects around the bedspace, or playing particular music are important considerations.

Discharge from ICU

Discussions should be held with patient and family regarding the preferred location of death. This may be a suitable ward, hospice, or home. Transfer does depend on availability, anticipated duration of decline, and necessary resources and support. Community palliative care nurses, social care, and primary care teams should be involved if the patient requests to die at home.

Further reading

➲ See Wound management principles, p152; Antiemetics & gut motility agents, p308; Anti-constipation agents, p312; Non-opioid analgesics, p316; Opioid analgesics, p318; Sedatives, p322; Tranquillizers, p324; Pain, p660; Symptom relief, p672; Care of the dying patient in ICU, p706.

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