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Pediatric Inflammatory Bowel Disease

Fourth Edition

Springer

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We dedicate this book…
To our families.
To Gordana-Dana, to David and Sue; to Melissa, Joanne, and Kay for their love, understanding, and encouragement.
To Niko; to Alex and Matthew, Julie, Steven, Chris, Linda, Keisha, William, and Andrew; and to Jack, Leo, and Benjamin for helping us believe the best is yet to come.
To our colleagues everywhere, past and present for working hard each day to make a difference.
To our patients for constantly inspiring us.
In memory of our dear colleague Dr. Gabor
Petar, Judith, Andrew, Bob, and Jon

Foreword

Pediatric inflammatory bowel diseases (IBD) are the most common and most significant chronic disorders in pediatric gastroenterology. The onset of Crohn disease and ulcerative colitis in the first two decades of life presents a number of diagnostic and therapeutic challenges that are unique to pediatric patients. Although the studies available for pediatric diagnosis have improved dramatically in the past three decades, the improvement in technology alone cannot account for the increased frequency of IBD recognized in early childhood. While therapy for older patients has improved dramatically with the development of exciting biologic and small molecule strategies, rarely if ever have comprehensive studies of the pharmacokinetics, safety, and efficacy of any of the IBD medications been performed in pediatric patients. A number of excellent medications are not available in liquid preparations that can be swallowed by children, and others, such as timed-release formulations, are developed for delivery to an adult gastrointestinal tract. It is unfortunate that the care we provide to children is often an extrapolation of what is known about and available for adults with IBD.

Pediatric patients with IBD face a number of unique challenges. The onset of disease before puberty can be devastating. Growth failure is a particularly difficult problem with potentially permanent consequences. Much of the pediatric-specific research has focused on the role of nutritional therapy to treat growth failure and induce remission. Strategies such as nocturnal nasogastric administration of supplements are widespread in most pediatric centers and are surprisingly well tolerated even by the youngest patients, particularly when the value of nutritional therapy is presented in advance to both the family and the child. Nutrition must be strongly advocated for pediatric patients, as it has great therapeutic value and it is the only therapy for which there are no serious potential complications.

The long-term consequences of medical and surgical therapy are particularly troubling for pediatric patients. While most of the cosmetic side effects are reversible, the psychological trauma to an adolescent can be overwhelming. We are only beginning to understand and address the long-term consequences of therapy given at an early age. Bone mass accumulation and linear growth are critical processes that are age dependent, with peaks in early adolescence. Failure of therapy at this stage will have permanent and possibly debilitating consequences. However, the advances in biologic and small molecule therapies have resulted in a dramatic shift in the therapeutic armamentarium. In adults, the "therapeutic pyramid" has been turned on all of its sides, leading to improvement in quality of life and a decrease in overall corticosteroid exposure, but with a potential new set of adverse events from therapy. While pediatric patients undoubtedly benefit from the adult data supporting the "top-down" strategies, the data in adults does not necessarily predict the optimal strategies for children. The effects of more "aggressive" therapy are being recognized for their positives and negatives, and the risks and benefits are undoubtedly different in children and adolescents. Whether it is the

state of the immature immune system, the effect of rapid growth, or the background susceptibility to different malignancies at different ages, the incidence of profound problems such as hepatosplenic T-cell lymphomas reminds all practitioners that we do not understand the unique aspects of the younger patient that may confer increased susceptibility.

The incredible scientific advances have generated exciting insight into IBD with subsequent newer therapies and fully warrant a fourth edition of this book. In the decades since the first IBD gene association was discovered, another 200 loci have been identified, and the individual characteristics and functions of these sites are increasingly understood. This is only the beginning of the synergy that can be achieved from the combination of the human genome project results and the availability of genome-wide arrays. The increased focus on the unique aspects and causes of very early onset IBD (VEO-IBD) has led to an exciting and new group of diseases that are more likely to be monogenic. Sequencing technology, including targeted panels, whole exome and whole genome sequencing have moved the field forward with the identification of causative monogenic defects and new therapeutic targets. This has translated into a precision medicine approach for children with VEO-IBD, resulting in remission and in some cases even cure of the disease. Identification of monogenic defects has also led to the prevention of catastrophic sequelae of the disease, such as malignancy, as in the case of allogenic stem cell transplant in *IL10R* deficiency. To complement these advances, there is incredible progress in the technology available to study the microbiome, its role in immunomodulation, and the effects of prebiotic, probiotic, antibiotic, and nutritional therapy for gastrointestinal diseases. This work has given insight into the complex relationship between the human immune system and the enteric inhabitants that reside within us. This work will likely identify one important group of environmental triggers that comprise part of the cause of IBD, and through that understanding, we may have one more route for the prevention of IBD in genetically susceptible individuals. A better understanding of the resident microbiota will undoubtedly inform better enteric therapy for IBD.

There is no better care than that given by a well-educated and experienced practitioner who considers all aspects of a patient's problems. This book is designed for those practitioners who care for children. IBD therapy must be customized for each individual patient. There is no more ultimate "individual" patient than a child or adolescent with IBD. The many challenges of growth, nutrition, psychology, and adaptation weigh heavily upon the profound challenges of pediatric Crohn disease and ulcerative colitis. In addition to the need for induction and maintenance of remission, the pediatric gastroenterologist must be obsessed not only with the benefits of early achievement of mucosal healing but also with the long-term consequences of therapy, not just a decade away, but hopefully a half century or more hence. Although these patients will move on to adult gastroenterologists, the problems may only accumulate and multiply. "Above all else, do no harm" is a wise admonition for pediatric IBD, where therapies are rapidly improving, and there is a great potential for a cure of these devastating illnesses. These therapies and ultimate cures for Crohn disease and ulcerative colitis will come from the extraordinary advances in immunology and immunogenetics that are well detailed in this book. Until that time, we must rely on the conventional approaches developed in adults, but with the conviction to verify their efficacy for children with IBD.

This book is a landmark step toward better understanding of pediatric IBD and the challenges of IBD therapy in children. The editors are highly respected clinical scientists who have each contributed substantially to the knowledge about pediatric IBD. In addition, the knowledge gained from their extensive clinical experience is reflected in this book. They have assembled a truly extraordinary group of authoritative leaders whose contributions to this volume will guarantee that this will be a reference for all who care for pediatric IBD. The book is a tribute to those authors but is dedicated to the children and adolescents with Crohn disease and

ulcerative colitis. It is remarkable how far we have come since the first edition yet sobering how far the journey is yet to go. It is a sign of the times that increased focus at every level is directed toward children, and this book is one significant step along that road toward improving care for the hundreds of thousands of children and adolescents with inflammatory bowel diseases. It should be a required reading for all those who care for these children.

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Preface

We are pleased to present the fourth edition of *Pediatric Inflammatory Bowel Disease.* Since the publication of the last edition, there has continued to be an explosion of discoveries and advances in the areas of genetics, immunology, pharmacogenomics, microbiome, optimization of therapeutic delivery, and epidemiologic knowledge, particularly regarding our youngest pediatric patients afflicted with inflammatory bowel disease. These advances have resulted in improved understanding of the etiology and pathogenesis of inflammatory bowel disease and have provided mechanisms to optimize therapeutic management of our patients.

The focus of the textbook remains unchanged. We hope to provide a reference that assists clinicians from multiple disciplines, including primary care, pediatric, internal medicine, and gastroenterology—all healthcare providers who care for children with inflammatory bowel disease. This textbook will augment other utilized references, focusing on pediatrics while also incorporating the adult evidence and experience that has informed and influenced the care of children.

The format of the textbook is similar to the last edition, with sections dedicated to etiology and pathogenesis, epidemiology and clinical features, diagnosis, medical and nutritional therapy, surgical therapy, research, and special considerations—a section that includes topics which have become increasingly important and challenging for the experienced clinician, including addressing the psychological aspects of pediatric inflammatory bowel disease, legislative advocacy, transition from pediatric to adult care, and quality improvement. We are pleased to offer topical new chapters regarding immune dysregulation in very early onset pediatric inflammatory bowel disease, fecal markers of disease activity, therapeutic drug monitoring, dietary therapies, complementary and alternative therapies, management of intra-abdominal complications, postoperative surveillance, and fostering self-management and patient activation, coauthored by two parents of patients with pediatric inflammatory bowel disease.

As with the previous three editions, we are indebted to the internationally recognized experts who contributed to this book, inculcating the latest research- and evidence-based clinical opinion to the updated chapters. This edition would not have been possible if not for their generous contributions and dedication.

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Part IV Medical Therapy

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Part I

Etiology and Pathogenesis

Genetics of Inflammatory Bowel Diseases

1

Christopher J. Cardinale and Hakon Hakonarson

Introduction

The inflammatory bowel diseases (IBD), Crohn disease and ulcerative colitis, are immune-mediated disorders resulting in chronic, relapsing inflammation of the gastrointestinal tract. The etiology of IBD is multifactorial, influenced by both genes and environment. It has been hypothesized that environmental factors and maladaptive immune responses to gastrointestinal flora generate a dysregulated inflammatory cascade, creating mucosal injury in genetically susceptible individuals. The identification of genetic linkage between Crohn disease and the pericentromeric region of chromosome 16 by Hugot et al. in 1996 spawned a series of genome scans and linkage analyses in search of susceptibility and phenotypic modifier genes [1]. In 2001, the discovery that specific polymorphisms in the *NOD2* were the underlying variants on chromosome 16 introduced a new era of genotype-phenotype investigations [2, 3]. The advent of genome-wide association studies has resulted in the successful identification of new, well-replicated disease associations, now encompassing 240 independent regions of the genome (loci) [4].

The field of IBD genetics is of special interest to pediatric gastroenterologists for both practical and investigational reasons. From a clinical practice standpoint, pediatric gastroenterologists are often faced with questions from concerned parents regarding the risk of IBD among current or future siblings, as well as the eventual offspring of the affected child. Understanding genetic associations of IBD can provide patients and their families with useful information that may help them cope with the disease. Furthermore, as our knowledge of genotype-phenotype associations grows, it is anticipated that genotyping at the onset of disease may enable physicians to predict disease course and tailor medical therapies specific for each patient. Studies of pediatric IBD lead to a better understanding of the disease because children have been exposed to fewer environmental confounders, which can provide insights into intrinsic genetic mechanisms that may not be detected in adult studies. This may be especially important in children with very early onset IBD (<5 years), whose disease course and phenotypes are the most discordant with those of adult-onset IBD.

Genetic Epidemiology

Ethnic and Racial Variations of Disease

The genetic underpinnings of IBD are supported by ethnic and racial variations in disease prevalence. The highest rates of IBD are found in Caucasian individuals, especially those of Jewish heritage. Among Jewish subgroups, Ashkenazi Jews have a two- to ninefold greater prevalence of IBD over non-Jewish counterparts [5, 6]. While the vast majority of genetic investigations in IBD have been conducted in Caucasians, it is apparent that it can occur in all racial and ethnic groups. African Americans and Asians have a lower risk of IBD, although there appears to be a trend toward growing prevalence in these populations [7].

Evidence is mixed on the question of phenotypic differences in IBD presentation between races. Basu et al. reported that African Americans and whites were more likely to have Crohn disease, whereas ulcerative colitis predominated among Mexican Americans [8]. While intestinal manifestations did not appear to vary based upon race or ethnicity, there were differences in extraintestinal manifestations between groups. Among Crohn's patients, African Americans were more likely to develop arthritis and uveitis than whites, whereas joint symptoms and osteoporosis were more com-

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mon among whites with UC than Mexican Americans. On the other hand, other researchers have reported no major differences in disease location, behavior, upper gastrointestinal tract involvement, perianal involvement, and extraintestinal manifestations among races and ethnic groups [7, 9, 10].

Family Studies

Family studies have demonstrated that 5–30% of probands with Crohn disease and ulcerative colitis identify the presence of IBD in a family member [5]. This association appears to be stronger for Crohn disease than ulcerative colitis. Phenotypically, relatives of probands with IBD are more likely to develop the same form of disease as the affected family member, with a concordance between family members in the localization of disease but not disease severity. With regard to age of disease onset, patients with a family history of IBD are more likely to develop disease at an earlier age than affected individuals lacking a family history [11]. Among family members, the risk of developing IBD is the greatest among first-degree relatives, especially siblings. The relative risk (RR) for a sibling of a Crohn's patient developing disease is 13–26; for ulcerative colitis patients, the RR for a sibling is 7–17 [12]. Orholm et al. reported that 6.2% of children born to a parent with ulcerative colitis developed IBD and 9.2% of children born to a parent with Crohn disease developed IBD [13]. In the rare instance that both parents have IBD, studies estimate that their children have a 33% chance of developing IBD by age 28 [12]. While second- and third-degree relatives of IBD probands have a lower likelihood of disease, their risk is still elevated compared to the background population.

In all but rare individual patients and in VEO-IBD, the incidence of IBD is multifactorial and highly polygenic. This complex genetic architecture was illustrated by a study of two large Ashkenazi Jewish families, one with over 800 members and one with over 200 members containing 54 cases of Crohn disease and 26 cases of ulcerative colitis [14]. No monogenic, Mendelian locus was identified, but there was an enrichment in these families of risk alleles that are common in the human population.

Twin Studies

Twin studies are based upon the premise that, in the setting of a similar environmental milieu, rates of disease concordance between twins correlate with the influence of genetic factors. To date, three large studies of twin pairs with IBD from Scandinavia and the United Kingdom have consistently identified higher concordance rates among monozygotic twins with Crohn disease and ulcerative colitis than dizygotic twins [15–17]. The influence of genetics appears to be greater in Crohn disease than ulcerative colitis with reported cumulative monozygotic concordance rates of 30% and 15%, respectively [18]. Concordance rates for dizygotic twins are approximately 4% in both Crohn disease and ulcerative colitis. Co-twins with IBD are more likely to develop the same disease type, although mixed pairs of dizygotic twins with ulcerative colitis and Crohn disease have been reported. With regard to disease-specific characteristics, Scandinavian twin registries demonstrated concordance of 40–77% for disease location; however, there appeared to be no association of disease behavior or extent among co-twins [15, 17]. A trend toward concordance for age at diagnosis was identified with 40–67% receiving a diagnosis of IBD within 2 years of one another. The fact that monozygotic concordance is not 100%, and the low concordance between dizygotes demonstrates that genotype alone is not sufficient for disease evolution.

NOD2 Gene and Crohn Disease

The *NOD2* gene (formerly *CARD15*) located on the *IBD1* locus of chromosome 16 is associated with an increased susceptibility to Crohn disease, but minimally with ulcerative colitis. It is the highest risk gene for Crohn disease, and its share of the heritability is several times greater than other loci. Among the more than 30 known amino acid polymorphisms identified in the *NOD2* gene [19], the most common variants are two missense mutations, p.Arg702Trp and p.Gly908Arg, and one frameshift mutation p.Leu1007fsinsC. NOD proteins are mammalian pattern recognition receptors which serve the innate immune system as bacterial sensing molecules. NOD2 is a cytosolic protein found in a variety of cells including monocytes, macrophages, B and T lymphocytes, dendritic cells, and intestinal epithelial cells. Stimulation of NOD2 by its ligand, the bacterial cell wall component muramyl dipeptide (MDP), propagates signal transduction pathways leading to nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) activation [20]. These three polymorphisms impair activation of NF-κB [21]. Studies of NOD2's role in mucosal immune homeostasis remain controversial in explaining how a loss-of-function mutation can paradoxically lead to increased inflammation. Some evidence suggests that deficient bacterial sensing by NOD2 leads to excessive activation of parallel pathogen-sensing pathways such as IL-1β/NRLP3 [22, 23].

Epidemiology of *NOD2* Mutations

A *NOD2* risk allele confers a two-to-three-fold relative risk of developing Crohn disease; this risk is increased to 17-fold if two alleles are present [24]. Ten to thirty percent of patients with Crohn disease are heterozygous for one of the three mutations, while 3–15% are homozygous or compound heterozygotes [25]. Although these variants are associated with an increased risk of Crohn disease, 8–15% of the healthy population possesses at least one of these mutations and 1% of healthy individuals are homozygous or compound heterozygotes. The widespread prevalence of risk alleles in the healthy population is explainable by polygenic factors, variable penetrance, and other environmental mediators.

Studies worldwide have revealed that the association of *NOD2* polymorphisms with Crohn disease varies between different ethnic populations. North American adult Caucasian cohorts report carriage rates of 10–30% for the three common *NOD2* variants, while minority groups were found to have lower allele frequencies. A North American, multicenter study of pediatric patients with Crohn disease identified *NOD2* polymorphisms among 25% White, 1.6% African American, and 1.6% Hispanic participants [26]. Significant diversity in allele carriage has been described among Crohn's patients in European countries and background control populations [27]. *NOD2* variants are virtually absent in Japanese, Korean, Chinese, and sub-Saharan African individuals. High rates of *NOD2* mutations have been seen in the Jewish Ashkenazim with one Israeli group reporting the presence of variants in 51% of pediatric and 37.5% of adult Crohn's patients studied [28].

Human Leukocyte Antigens in Ulcerative Colitis

The major histocompatibility complex (MHC) locus on chromosome 6p encodes genes in the human leukocyte antigen (HLA) family, which present peptide antigens to T-cells. Associated polymorphisms between HLA types and IBD have included the Class I type HLA-B and the Class II types HLA-DRB1, HLA-DQB1, and HLA-DP [29]. The polymorphism-rich nature of the HLA region as well as its complex linkage disequilibrium has resulted in heterogeneous findings among investigators across over a hundred studies. It is consistently shown, however, that the amount of trait heritability for Crohn disease conferred by the HLA locus is modest, but for ulcerative colitis it is the greatest genetic risk factor [30].

Class II alleles DRB1*0103, DRB*1502, and DRB*401 have been consistently associated with ulcerative colitis [31]. Phenotypic analyses have identified DRB1*0103 to be predictive of a more aggressive form of ulcerative colitis with shorter time to colectomy than those without the allele. In Crohn's patients, a particular link between DRB1*0103 and isolated colonic disease has been reported [32]. The correlation of DRB1*0103 with both colonic Crohn disease and ulcerative colitis has been postulated to provide a unifying molecular mechanism for colonic involvement in IBD. HLA associations with extraintestinal manifestations of IBD have also been evaluated. HLA-B*27, HLA-B*35, and HLA-DRB*103 have been associated with type I peripheral arthropathy, whereas HLA-B*44 is associated with type II peripheral arthropathy [33, 34]. Symptoms of uveitis have been linked with HLA-B27 and DRB*0103.

High-density genotyping using microarrays in the MHC region has reinforced the importance of HLA-DRB1*0103 in both Crohn disease and ulcerative colitis in a study by Goyette, et al. Their study genotyped 7,406 single nucleotide polymorphisms in 32,000 IBD cases and an equal number of controls [35], finding that DRB1*0103 gave by far the strongest association. The fine resolution of mapping allowed localization to specific amino acid substitutions in the MHC molecule which revealed that the causal variants are located within the peptide-binding groove and thereby influence antigen presentation directly [35].

Genome-Wide Association Studies in IBD

The use of linkage studies was prevalent during the 1990s and early 2000s because of the cost and labor associated with producing genotypes. The family-based design allows the genome to be scanned for associations using a few hundred markers, since closely related individuals will share large segments of chromosome. A major development in the field of human complex-trait genetics occurred in the mid-2000s with the introduction of genotyping millions of single nucleotide polymorphisms (SNPs) using microarrays. This technology has made possible the performance of genome-wide association studies (GWAS). These studies survey a large fraction of the common human genetic variation, testing each of millions of SNPs for direct association with the trait of interest by comparing the population allele frequency between IBD cases and healthy controls [36]. This direct association testing approach has the advantage of greater power to detect small effects. Risch and Merikangas estimated that 17,997 affected sibling pairs would be necessary to detect a risk allele with 50% frequency and odds ratio of 1.5 by linkage analysis [37]. By contrast, direct association analysis would require only 484 cases and controls.

IL23R Polymorphisms in Crohn Disease and Ulcerative Colitis

One of the first GWAS, in a North American Crohn disease cohort, identified new gene associations including multiple polymorphisms within the *IL23R* gene on chromosome 1p31 [38]. In particular, an amino acid polymorphism, p. Arg381Gln, located in the cytoplasmic domain of the *IL23R* protein, demonstrated highly significant evidence for association. The low-frequency allele conferred significant protection against developing IBD in non-Jewish and Jewish Crohn disease cohorts, as well as in non-Jewish ulcerative colitis cohorts. Additional independent association signals were observed indicating the presence of multiple associations within the *IL23R* gene [38]. As the second-strongest signal, after *NOD2*, this association has been extensively replicated by subsequent GWAS.

The functional IL-23 heterodimeric receptor is comprised of the IL23R and IL12RB2 [39] subunits, with the latter subunit being shared with the functional IL-12 receptor. Similarly, the IL-23 cytokine is comprised of a unique subunit, p19, as well as a p40 subunit which is common to the IL-12 functional cytokine. Additional support for the role of the IL-12/IL-23 pathway in mediating end-organ inflammation has been generated in mouse models demonstrating requirement for IL-23 in murine colitis [40–43] and experimental autoimmune encephalitis [44]. The monoclonal antibody therapy ustekinumab inhibits the p40 common subunit of IL-12 and IL-23 and was approved for the treatment of Crohn disease in 2016 [45] and is promising in the treatment of ulcerative colitis [46].

Association of the *ATG16L1* Autophagy Gene with Crohn Disease

A GWAS focusing on amino acid-altering polymorphisms identified the p.Thr300Ala substitution in *ATG16L1* in Crohn disease. The *ATG16L1* gene is part of the autophagosome pathway and is involved in the processing of intracellular bacteria [47]. *ATG16L1* is expressed in intestinal epithelial cells, as well as in $CD4^+$, $CD8^+$, and $CD19^+$ primary human lymphocytes [48]. Of interest is that no association was observed to ulcerative colitis suggesting that *ATG16L1*, like the *NOD2* polymorphisms, represent Crohn's-specific risk alleles. The *ATG16L1* association demonstrated that autophagy and host cell responses to intracellular microbes are involved in the pathogenesis of CD. Before the discovery of this genetic association, the role of autophagy in IBD was not as well appreciated, and this example demonstrates how genetic investigation can advance new treatment approaches and understanding of disease pathophysiology.

Non-Coding Variation

The IBD risk variants described to this point have been coding mutations which alter the amino acid sequence of a protein such as NOD2, HLA-DRB1, IL23R, or ATG16L1. These signals were the first to appear in the early days of GWAS is an indication of how impactful coding variants can be consistent with their overwhelming role in Mendelian genetics. However, at least 95% of the known loci associated with IBD are SNPs located in introns or intergenic regions. It is widely presumed that these non-coding variants alter transcription factor-binding sites, chromatin structure, or other regulatory processes to influence the expression of protein- and RNA-coding genes. A major focus of the post-GWAS era has been to identify the target genes and the mechanism of the non-coding variants [49].

SNPs located in close proximity on the same strand of DNA tend to be inherited together because they are unlikely to be separated by meiotic recombination. This DNA linkage results in the phenomenon of linkage disequilibrium (LD), where the population's history of meiotic recombination's demarcates stretches of chromosome—blocks—with an unbroken haplotype of variants shared among the individuals in the population. LD allows the geneticist to genotype a sampling of SNPs representing each of the haplotypes in each of the blocks, thereby capturing a sizeable fraction of all the common genetic variations in the population [50]. Consequently, it is usually not possible to identify the causal SNP distinctly from other SNPs that are in LD. The LD blocks tend to be small enough, around 30,000 base pairs, that the locus will contain a small number of potentially causal protein-coding genes near the associated LD block (Fig. 1.1). The examples discussed below highlight some instances where strong associations were found in proximity to genes with a functional role consistent with IBD risk.

Meta-Analysis

The associated common variants identified by single GWAS usually have modest individual effects, often with odds ratios of smaller than 1.2 for binary traits, or with explained variance of less than 1% for quantitative traits [51]. To discover common variants with even smaller effects, a sample size larger than that of single studies is required. Meta-analysis combines large datasets and is an economical way to improve sample size. An early meta-analysis of three genome-wide scans in Crohn disease identified 21 new Crohn susceptibility loci. It increased the number of independent loci conclusively associated with Crohn to 32, explaining approximately 20% of Crohn disease heritability [52]. Including three additional GWAS scans, a subsequent meta-analysis added 39 new confirmed Crohn disease

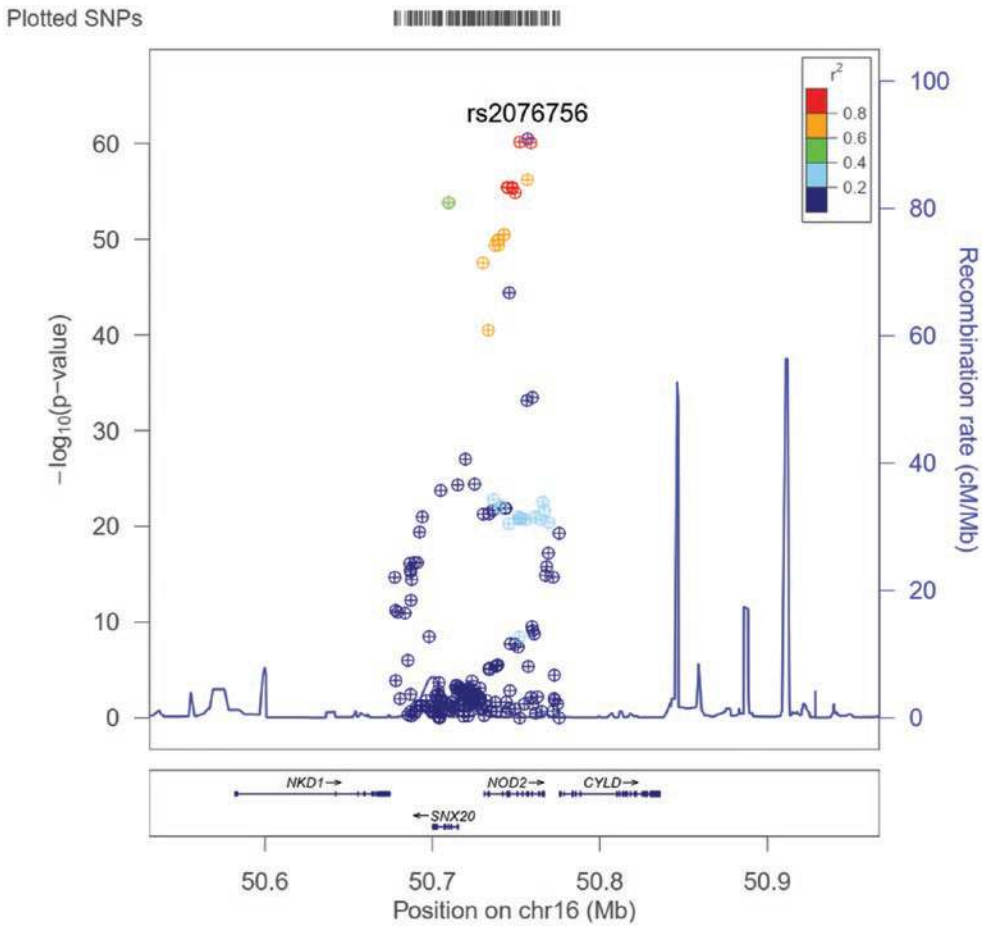

Fig. 1.1 The *NOD2* gene is an example of "synthetic association" in a GWAS locus. The regional association plot displays the sequence coordinates of the chromosome 16 locus (*x*-axis) *versus* the inverse logarithm of the association *p*-value for the Crohn disease trait (*y*-axis) in a published GWAS [4]. Genes situated in this locus include *NKD1*, *SNX20*, *NOD2*, and *CYLD*. The color coding of the SNPs in the plot reflects the strength of linkage disequilibrium (LD) with the lead variant. The lead SNP shown is a non-coding intronic SNP, and is non-causal. It is associated with the Crohn disease trait through its LD to the ensemble of amino acid mutations in the *NOD2* gene which sit disproportionately on this haplotype

susceptibility loci [53]. These 39 new loci increase the proportion of explained heritability to only 23.2% indicating their rather modest effects. While some of these newly identified loci contain a single gene, others contain multiple genes or none at all. Some functionally interesting candidate genes in the implicated regions include *STAT3*, *JAK2*, *ICOSLG*, *ITLN1*, and *SMAD3*.

Signal transducer and activator of transcription 3 (STAT3) and Janus kinase 2 (JAK2) are members of the JAK-STAT signaling pathway. This major signaling pathway transmits information from cell surface receptors stimulated by cytokines and growth factors to the nucleus to regulate transcription of genes involved in immune cell division, survival, activation, and recruitment [54].

Inducible T-cell co-stimulator ligand (ICOSLG) is a co-stimulatory molecule homologous to B-7 which is expressed on intestinal epithelial cells. Signaling through its receptor, ICOS, may have a key role in controlling the effector functions of regulatory T-cells [55]. Maturing plasmacytoid dendritic cells express ICOSLG to modulate the activity of IL-10-producing regulatory (Treg) T-cells [56].

Intelectin-1 (ITLN1) is a secreted protein expressed in human small bowel and colon, hence its name as an intestinal lectin, a carbohydrate-binding protein. ITLN1 binds to the surface carbohydrate chains of numerous bacterial species, implicating it in immune defense [57]. More recently, it has been identified as a circulating anti-inflammatory adipokine expressed in visceral fat and is associated with obesity, diabetes, and cardiovascular disease [58].

Mothers against decapentaplegic homolog 3 (SMAD3) is a transcription factor which binds to specific DNA sequences in the promoter region of many genes that are regulated by transforming growth factor beta (TGF-β), and on formation of the SMAD3/SMAD4 complex, activates transcription. SMAD3 deficiency will enhance Th17 differentiation during the TGF-β-mediated induction of Foxp3+ regulatory T-cells [59].

GWAS Meta-Analysis in Ulcerative Colitis

A meta-analysis combining data from six GWAS identified 47 risk loci in ulcerative colitis [60]. Some noteworthy candidate genes identified by this effort include *PRDM1*, *TNFRSF14*, *TNFRSF9*, *IL1R2*, *IL8RA*, and *IL8RB*.

PR domain containing 1 (PRDM1) is the master transcriptional regulator of plasma cells and drives the matu-

ration of B-lymphocytes into immunoglobulin-secreting cells [61].

Tumor necrosis factor receptor superfamily 14 (TNFRSF14), also known as herpes virus entry mediator (HVEM), transduces signals from the cytokine LIGHT and has an important role in preventing intestinal inflammation in a murine colitis model [62].

Tumor necrosis factor receptor superfamily 9, (TNFRSF9) encoding receptor 4-1BB, is a co-stimulator in the regulation of peripheral T-cell activation. This receptor is expressed by T-cells, dendritic cells, granulocytes, and endothelial cells at inflammation sites and enhances their proliferation and activation [63].

Interleukin 1 receptor 2 (IL1R2) is a non-signaling decoy receptor that reduces IL-1β activity by competing with the high-affinity receptor IL1R1. IL-1β is a pro-inflammatory cytokine produced by lamina propria macrophages and is increased in patients with ulcerative colitis [64].

Receptors for IL-8 (IL8RA and IL8RB) mediate the chemokines' role as a neutrophil chemotactic and activation signal. IL8RA may play a role beyond neutrophil recruitment in mediating the immune response in UC [65].

Association of *TNFRSF6B* and *IL27* with Pediatric Age of Onset IBD

Pediatric age of onset IBD is an attractive target for GWAS for several reasons. Early-onset IBD is characterized by unique phenotypes and increased severity, suggesting the possibility of loci specific to early-onset disease. Early-onset IBD also has a stronger association with family history of IBD, and the childhood population may also be less affected by exogenous factors implicated in adult-onset IBD, such as diet, smoking, and medication [66]. Therefore, GWAS in children provides additional power to reveal genetic risk variants with only modest effects in pediatric- and adult-onset IBD.

GWAS have been performed focusing on pediatric cases. One of these involved 3426 affected individuals and 11,963 genetically matched controls [67]. The study nominally replicated 29 of 32 loci previously associated with adult-onset Crohn disease, as well as 13 of 17 adult-onset ulcerative colitis loci. Further, it identified seven new regions associated with childhood IBD susceptibility.

Kugathasan et al. found an association located on chromosome 20q13 containing tumor necrosis factor superfamily receptor 6B (*TNFRSF6B*) [68]. The protein product of *TNFRSF6B*, decoy receptor 3 (DcR3), binds to and neutralizes signaling by pro-inflammatory cytokines LIGHT, TL1A, and Fas ligand [69–72]. Serum DcR3 levels were elevated in pediatric cases of IBD relative to controls, particularly in patients harboring the 20q13 minor allelic variants [68]. Follow-up studies by our group led to the launch of a clinical trial with an anti-LIGHT monoclonal antibody to treat Crohn's patients who have failed other therapies beginning in 2020.

The second locus of interest is the in 16p11 region, in a LD block containing several genes including *IL27*. The IL-27 cytokine regulates T-cell differentiation in adaptive immune responses, influencing the balance between pathogenic Th17 cells and inflammation-suppressing T-cell subsets [73]. Identification of *IL27* as a candidate gene is consistent with the involvement of the Th17 pathway in the pathogenesis of Crohn disease, corroborating findings from other genome-wide scans (*IL23R*, *STAT3*, *JAK2*, and *IL12B*).

Genome-wide significant association results throughout the IL12/IL23 and IL27/Th17 pathway genes support the relevance of these T-cell subsets in the pathogenesis of IBD (Fig. 1.2).

Impact of the Immunochip

Common immune disorders such as ankylosing spondylitis, celiac disease, multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes often share overlapping susceptibility loci in GWAS studies [74]. Motivated by this observation, the Immunochip Consortium was formed to produce an inexpensive genotyping array that could be used to analyze hundreds of thousands of samples in autoimmune disease. The chip interrogates approximately 200,000 SNPs at 186 loci to enable dense genotyping so that SNPs located close together in the loci of interest including those at low allele frequencies can be included in analyses [75]. The results gained from this effort played a large role in the meta-analysis of Jostins et al. which raised the tally of IBD-associated loci to 163 [76]. The Jostins study revealed that 113 of the 163 loci are shared with other complex diseases including 66 loci shared with other autoimmune diseases [74]. The economic cost of the Immunochip allowed many samples to be genotyped so that loci could be identified at a genome-wide significance level, where in the previous meta-analyses they showed only marginal significance.

A further goal of the Immunochip effort is to fine-map variants so that, by using Bayesian statistical analyses, the individual causal variant can be identified rather than a large ensemble of variants that are in linkage disequilibrium with each other [77]. For instance, this fine mapping was used to show that there are additional amino acid substitutions in *NOD2* and *IL23R* which are the causal SNPs that drive the genetic association signal.

Huang et al. applied Bayesian conditional analysis to the Immunochip data to identify credible sets, that is, a defined

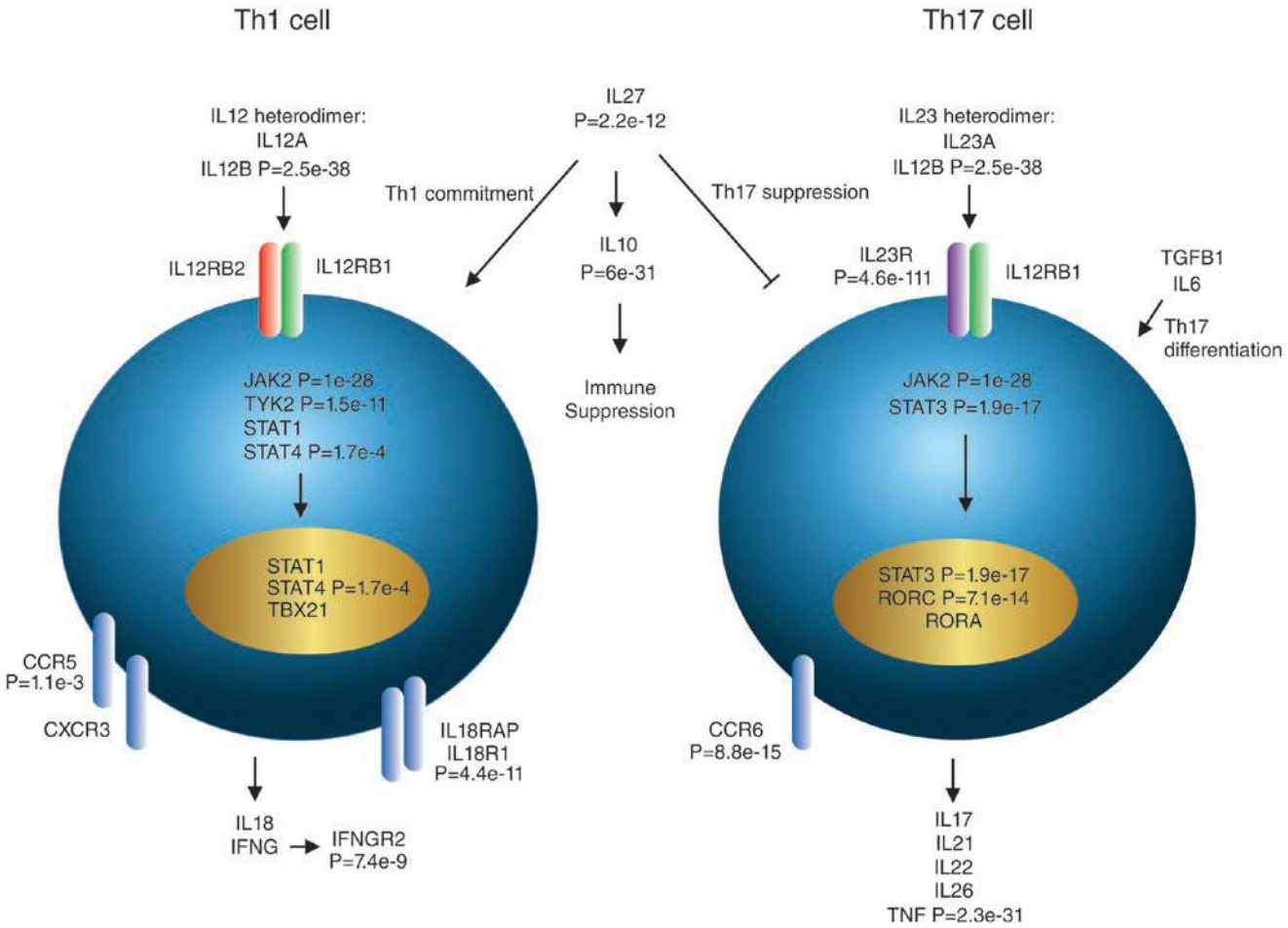

Fig. 1.2 Genes involved in cytokine signaling and T-cell differentiation are highly enriched in IBD GWAS. The competing pathways of Th1-type versus Th17-type helper T-cell differentiation are influenced by cytokines and their signaling cascades. The *p*-values for the genes shown are from a recent GWAS meta-analysis [93]

number of SNPs accounting for at least 95% of the posterior probability of causality at the locus of interest [78]. Eighteen loci were identified in which the 95% credible set consisted of a single variant, i.e., the causal variant was identified specifically. A revealing outcome of this analysis is that the causal SNPs frequently do not have functional annotations that would ordinarily implicate them in disease, such as an expression quantitative trait locus (eQTL) association, transcription factor-binding motif, or epigenetic modification.

Trans-ancestry Association Studies

A majority of genetic studies in IBD have been conducted in European ancestry populations. However, the expansion of these studies into Asian populations has yielded some insights. In the Japanese population, the well-known *NOD2* polymorphisms are virtually absent [79]. GWAS in Japan has shown that the single largest association signal is located in the *TNFSF15* gene encoding the pro-inflammatory cytokine TL1A [80].

Liu et al. conducted a trans-ethnic meta-analysis including 86,640 individuals of European ancestry and 9,846 individuals from East Asia, India, or Iran [4]. This study implicated 38 new loci, raising the tally to 200 total loci, and determined that there were significant differences in the frequency of risk alleles in the different populations. Nevertheless, the direction and magnitude of the effect at the shared loci were very similar between ancestries, suggesting that the casual variants are likely to be common (minor allele frequency greater than 5%). In addition to the large impact of TL1A in the Asian population, the HLA locus was also found to have a greater influence in ulcerative colitis [4].

A GWAS focusing on the African-American population not only replicated many of the known loci from the European population, but also yielded additional African-specific SNPs in *ZNF649*, *LSAMP*, and *USP25* [81]. These results demonstrate that different ancestries can have population-specific

variants and that predictive medicine based on genotypes will need to incorporate data from diverse backgrounds.

Next-Generation Sequencing

The traditional method of DNA sequencing was developed by Sanger et al. using dideoxy-nucleotides as chain terminators [82]. This technology has become quite efficient and can be run on an automated instrument to generate 700-bp sequence reads with fluorescently labeled terminators, but with very low throughput. In the last decade, a new generation of DNA sequencing technology has emerged which uses sequencing-by-synthesis on a massively parallel scale. The current generation of these instruments can generate up to 6 trillion raw bases in the form of 20 billion reads of sequence every two days, sufficient for 48 whole-human genomes (Illumina Inc., San Diego, CA). This technology has revolutionized the field of Mendelian genetics, that is, rare monogenic diseases, by enabling the identification of rare variants in a family setting. Interestingly, inflammatory bowel diseases can have Mendelian mimics that can be detected by next-generation sequencing, particularly in the very early onset (VEO) patients [83]. More attention will be given to the diagnosis of these genetic phenocopies and well as the management of the very young patients in the chapter of this textbook on very early onset IBD.

Sequencing in High-Risk Individuals and Families

Currently, the most cost-effective approach to massively parallel sequencing in IBD patients is to target the exome, that is, the 1% of the genome that encodes the amino acids of proteins. Congenital deficiency of the receptor for the immunomodulatory cytokine IL-10 was the first monogenic defect identified as causative of VEO-IBD in 2009. While refractory to medical therapy, these patients responded to bone marrow transplant [84]. Exome sequencing has revealed additional patients with IL-10 receptor deficiency [85], Since that time, multiple monogenic defects have been identified through exome sequencing. An early example of the success of this approach was seen in a 15-month-old child who presented with perianal fistulae and failure to thrive unresponsive to standard treatments which progressed to pancolitis. The patient underwent many surgical procedures and genetic tests that did not resolve his disease. Exome sequencing revealed that this patient carried an exceedingly rare mutation on the X chromosome in the *XIAP* gene, a potent regulator of the inflammatory response [86]. Since this protein acts in cells of the hematopoietic lineage, he was treated by a bone marrow transplant resulting in resolution of his disease. Other monogenic cases of VEO IBD have been identified and have resulted in life-saving therapy [87].

Features that suggest a patient may be a candidate for exome sequencing include early onset of disease, unusual severity, familial pattern of transmission, and refractory response to standard therapies. It is recommended to obtain DNA samples from the parents in addition to the proband because some probands may be compound heterozygotes, that is, inheriting a different defective allele of the gene from each parent. The trio of exomes is useful in identifying de novo mutations in either the parental germ line or in the child which may be pathogenic.

Next-Generation Sequencing in Research

It is hypothesized that some fraction of the heritability of complex genetic disorders, such as IBD and particularly VEO-IBD, is due to rare or low-frequency variants [88]. Due to their rarity, these variants are not in strong linkage disequilibrium with proxy SNPs, which is required to make the GWAS approach feasible. Therefore, discovery of additional genes and low-frequency variants will require direct sequencing of hundreds of thousands of genomes [89].

Initially, the approach to finding rare or coding variation has been to sequence-specific genes in a large cohort based on the gene's status as a GWAS candidates. Rivas et al. identified additional coding mutations in *NOD2* and *IL23R* as well as novel coding variants in *CARD9*, *IL18RAP*, *CUL2*, *C1orf106*, *PTPN22*, and *MUC19* [90]. Beaudoin et al. performed amplicon sequencing on 55 genes in 200 cases and 150 controls for ulcerative colitis. They confirmed the previous associations with *CARD9*, *IL23R*, as well as a novel association in *RNF186* [91].

Efforts are currently underway to extend sequencing to thousands of exomes to search for pathogenic coding variants. A difficulty to this approach is that any individual variant is so rare that there is insufficient statistical power to identify the variant at genome-wide significance. As a result, many statistical methods have been developed which aggregate all the discovered variants in a gene into a single supervariant to test the burden of rare mutations or to test the variance in allele frequencies between cases and controls [92].

As sequencing technology improves, it has become feasible to obtain a whole-genome sequence (WGS), including the 99% of the genome that is non-coding, for less than $1000. WGS has been used to expand the catalog of variation that can be assessed and thereby has led to GWAS studies on an increasing scale. The largest GWAS meta-analysis to date contained 59,957 IBD cases and yielded 240 genome-wide significant loci [93]. A companion study sequenced whole genomes at low depth in 4280 cases and found an additional rare variants in *ADCY7*, but essentially replicated

the known loci, suggesting that rare or low-frequency variants explain little heritability in IBD [94].

Risk Prediction

Encouraged by the notable success of GWAS in Crohn disease and ulcerative colitis, it is logical to ask if these advances can deliver sufficiently accurate predictions to make targeted intervention realistic. Several efforts have been made, but most results are modest [95]. As in meta-analysis, it is possible to compile a large sample size by combining as many cohorts as possible, yielding a boost in prediction performance. Using the large sample size and wide variant spectrum of the Immunochip dataset in combination with advanced machine learning methods, Wei et al. were able to achieve an area under the receiver–operator curve (AUC) of 0.86 for Crohn disease and 0.83 for ulcerative colitis [96]. Genotypes from the Immunochip were useful in predicting durable responders *versus* primary non-responders to anti-TNF therapy in ulcerative colitis [97]. The efficacy of these models depends on the status of the limited number of high-risk variants, with little contribution from the low frequency or rare variants present on the Immunochip [98]. Machine learning methods such as the study by Wei et al. run the risk of being "over-fit" to the training dataset, and encounter difficulty generalizing to other cohorts. A comprehensive catalog of variation from WGS combined with a massive number of subjects may be the way to overcome these challenges.

Genotype-Phenotype Correlations in Pediatric IBD

Cleynen et al. analyzed subphenotypes of IBD in 34,819 patients who were genotyped on the Immunochip [99]. For Crohn disease, the phenotypes examined were age at diagnosis, disease location, disease behavior (penetrating, stricturing, inflammatory), and requirement for surgery. For ulcerative colitis, the phenotypes examined were age of onset, disease extent, and colectomy. Across all 186 loci on the Immunochip, only SNPs in *NOD2*, the HLA locus, and 3p21 (*MST1*) were found to have genome-wide significance, influencing all subphenotypes [99]. The disease location was essentially fixed over time and was the main independent determinant of the patient's disease process, while disease behavior and requirement for surgery were largely markers of disease progression. A composite polygenic genetic risk score based on the 163 known loci was associated with all disease subphenotypes but only the three loci named above were individually significant. The authors concluded that the binary classification of IBD into Crohn disease and ulcerative colitis is not supported by genetic data and that a ternary classification should be used: ulcerative colitis, colonic Crohn disease, and ileal Crohn disease [99].

Genetic Sharing Between Pediatric Age of Onset IBD and Other Autoimmune Diseases

As the Immunochip genotyping effort amply demonstrated, there is a shared genetic architecture for a wide variety of autoimmune diseases. Li et al. performed GWAS in 6,035 cases of 10 different pediatric autoimmune diseases and 10,718 shared controls. This effort identified 27 genome-wide significant loci which had shared risk among multiple pediatric autoimmune diseases, for instance, a novel role for *CD40LG* in Crohn disease, ulcerative colitis, and celiac disease [100]. The main pathways identified as responsible for this shared risk were cytokine signaling (JAK/STAT and helper T-cell), antigen presentation, and T-cell activation [100]. A study of SNP-h^2, also called narrow-sense heritability, across these 10 pediatric autoimmune diseases showed that the heritability explained by common SNPs was 45.4% for Crohn disease and 38.6% for ulcerative colitis [101]. In pairwise analysis, Crohn disease and ulcerative colitis showed the strongest similarity to each other of all pairwise combinations of the 10 autoimmune diseases [101].

Summary

Family-based, twin, and ethnicity-based studies lend strong support for a genetic basis of IBD as a model complex mode-of-inheritance trait. The recent advent of GWAS has markedly advanced the identification of well-replicated IBD associations, leading to an abundance of genomic regions with individually modest amounts of heritability. As whole-genome sequencing, polygenic scores, and machine learning progresses, it will be possible to identify rarer variants, gene interactions, and networks that contribute to the pathogenesis of IBD allowing for stratification of IBD patients into different therapeutic pathways and interventions.

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Immunologic Regulation of Health and Inflammation in the Intestine

2

Anees Ahmed and Gregory F. Sonnenberg

Introduction

The major functions of the gastrointestinal (GI) tract is digestion and nutrient absorption. To conduct these functions, this organ system has an enormous surface area to facilitate absorption and is also colonized with trillions of normally beneficial microbes, termed the microbiota, which are important in aiding in digestion and other important functions [1, 2]. This poses unique challenges of how to protect this large barrier from infectious microbes, while simultaneously establishing tolerance to the microbiota and preventing detrimental responses to these non-harmful stimuli. The immune system plays a central role in coordinating these diverse responses and maintaining a state of health in the GI tract.

For that reason, the GI tract contains a substantial portion of the entire human immune system [3]. Complex and dynamic interactions occur in this organ system between immune cells that are of hematopoietic origin (such as macrophages, dendritic cells, B-cells, or T-cells), as well as numerous other non-immune and tissue-resident cell types (such as epithelial cells, stromal cells, or neuronal cells) that are integral to the immune response and will be discussed in this chapter. It is also a niche for trillions of microbes ($\sim 10^{12}$ viable bacteria per gram of colonic content), consisting of roughly 500–1000 microbial species that are collectively known as the gut microbiota [4]. The microbiota comprises bacteria, as well as bacteriophages, viruses, fungi, and occasionally protists, which form a complex ecosystem thought to have co-evolved with mammalian hosts over time [5]. The co-existence of microbiota and host immune system is mutually beneficial, but a careful balance must be maintained to establish a state of health or homeostasis. Intestinal homeostasis is mediated in part by physical separation of microbiota from the immune system through various biochemical and biophysical barriers, such as the epithelial layer, mucus, and the production of antimicrobial factors by different cell types [6–8]. A breakdown in these protective barriers results in chronic activation of the immune system by intestinal microbiota and is a hallmark of IBD as well as various bacterial infections and cancer [9–11].

Despite this physical separation in the healthy intestine, there is a complex, dynamic, and bidirectional crosstalk between the microbiota and immune system, which is essential for normal development of the immune response, intestinal physiology, and regulation of intestinal health [12–15]. The impact of the microbiota in shaping the proper development of the immune system can be studied in the context of germ-free mice. Germ-free animals are born and raised in a completely sterile environment that is free from live microbial stimuli. Mice in these settings exhibit impaired development of the mucosal immune system and gut-associated lymphoid tissues [16]. In addition to altered cytokine secretion and numerous defects in antibody production, germ-free mice have relatively fewer and smaller lymphoid tissues, including Peyer's patches (PPs) and mesenteric lymph nodes (MLNs) as compared to specific pathogen-free (SPF) mice that are typically utilized in the laboratory. Germ-free mice also have reduced total numbers of peripheral $CD4^+$ T-cells, including both T helper (Th)17 [17] cells and regulatory T (Treg) cells [18, 19], two cellular subsets discussed below that critically impact intestinal health and inflammation. These developmental defects can be partially reversed following the introduction of live gut bacteria, demonstrating the existence of a dynamic relationship between mucosal immunity and the microbiota. Conversely, the intestinal immune system also actively shapes the composition and anatomically restricts microbiota through various mechanisms [20]. For example, the mammalian immune system

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recognizes and responds to the members of the intestinal microbiota by promoting protective immune responses that reinforce barrier integrity, prime protective immunity to invading pathogens, and prevent over-reaction to beneficial microbes or food antigens, thus establishing a state of tolerance [21, 22]. Defects in these responses or microbial composition (termed dysbiosis) can rewire immune cell populations and their functionality, resulting in chronic inflammation or increased risk of infection.

IBD is a multifactorial disease caused by dysregulated immune responses to microbiota resulting in chronic intestinal inflammation [9, 11, 12, 23, 24]. This disease also impacts a growing number of children worldwide, and in addition, can manifest in a unique form of the disease in children younger than 5 years of age. The latter is termed very early onset IBD (VEO-IBD), which is phenotypically and genetically distinct from traditional-onset IBD [25]. The risk for developing VEO-IBD is strongly correlated with host genetics, displays aggressive progression with increased disease severity, and unfortunately these patients are often associated with poor responsiveness to conventional therapies [26, 27]. Studies with these patients, as well as numerous mouse models, have defined specific components of the immune system that are essential to establish and maintain a state of health in the GI tract. Here, we focus on these specific immune pathways that are essential to regulate intestinal health and homeostasis, as well as examine how these findings have shaped our understanding of host–microbiota interactions and created a foundation to develop future therapeutic strategies for treating chronic inflammatory diseases. Further, we discuss several unique features of the mucosal immune response in children that will be important in our understanding of IBD.

The Anatomy of the Intestinal Immune System

The intestine should not be perceived as a single homogeneous organ but rather as a combination of several anatomically distinct and functionally specialized compartments with different environmental pressures [28, 29]. Each compartment is divided into four major layers: the innermost mucosa, the submucosa, the muscularis, and the serosa. The mucosa is the most proximal part to the lumen of the intestine or outside environment and is composed of a single layer of columnar epithelial cells along with an underlying lamina propria (LP) region which contains the vast majority of intestinal immune cells. Immune cells within the intestine are primarily located within the organized lymphoid structures known as gut-associated lymphoid tissues (GALTs). GALTs collectively include the MLNs, PPs in the small intestine, colonic patches, caecal patches, and comparatively smaller structures which include cryptopatches (CPs) and isolated lymphoid follicles (ILFs). To maintain local tissue homeostasis, different intestinal segments (such as the small intestine that includes the duodenum, jejunum and ileum; and the large intestine that includes the cecum and colon) have developed physical barriers and unique defense strategies of appropriately responding to the complex variety of foreign substances in the GI tract, including the commensal microbiota, potential pathogens, and dietary antigens, while simultaneously facilitating the major functions of the GI tract that are necessary at each segment.

The Intestinal Epithelium: Structure and Functional Subsets

The intestinal epithelium is a large single layer of columnar cells that differs enormously in architectural structure and cellular composition between the small and large intestine (Fig. 2.1). In the small intestine, the epithelium protrudes into the lumen with brush border-like structures called villi, which increases the mucosal surface area for nutrient absorption. Villi are absent in the colon, limiting the potential damage that can be caused by transition of semi-solid stool through the large intestine. This may have important consequences in the context of IBD, where different forms of the disease impact distinct anatomical locations, such as Crohn disease (CD) that impacts the entire GI tract, while ulcerative colitis (UC) primarily impacts the large intestine. The epithelium layer itself has many invaginations termed “crypts of Lieberkühn” that contain specialized types of intestinal epithelial cells (IECs) [30]. The intestinal stem cells at the base of the crypts give rise to transient proliferative epithelial cells [31]. Under homeostatic conditions, these intestinal crypts undergo constant cycles of IEC replenishment and renewal every 4–5 days [32]. Various differentiated cell types are present in the epithelium, and each is attributed to specialized and unique functions. The number and distribution of these cell types differ markedly between the small and large intestine. These cell types are as follows: (a) Enterocytes, the most prominent cells specialized for water and nutrient absorption [33]. (b) Goblet cells, the most dominant secretory cells responsible for mucin secretion [34]. (c) Enteroendocrine cells, responsible for secreting different hormones [35]. (d) Paneth cells that release antimicrobial peptides to protect nearby cells [36, 37]. (e) M cells, that are integral to the luminal antigen uptake and presentation to the immune system [38, 39]. Finally, the different intestinal enteroendocrine cells are responsible for the production of hormones in the gut such as 5-HT/serotonin by enterochromaffin cells, somatostatin by D cells, and gastrin by G cells [35]. Enterocytes, the absorptive epithelial cells, have microvilli at their apical surface to enhance digestion and nutrient

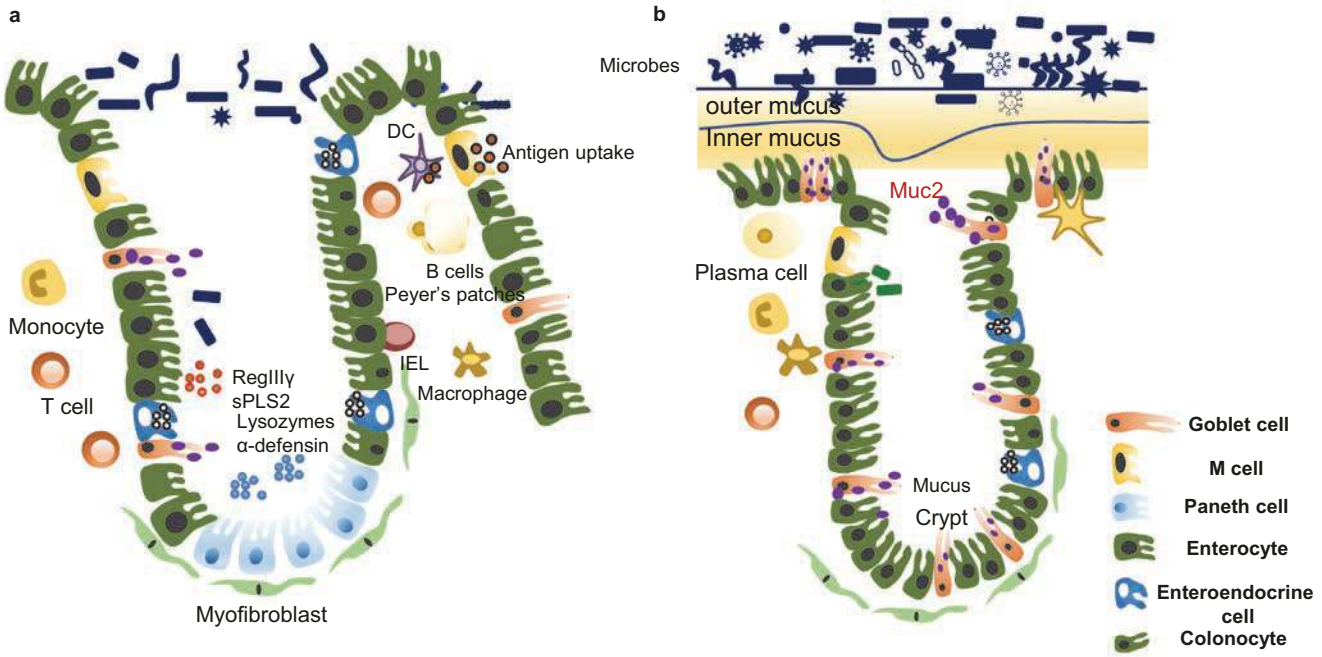

Fig. 2.1 Anatomy of the small and large intestinal mucosa. The small intestine (**a**) and large intestine (**b**) exhibit distinct anatomical features that have important consequences on host-microbiota interactions. These include structural differences, changes in abundance of epithelial cell types, and distinct mucus layers that control the physical separation of microbiota. The small intestine contains fewer microbes but is more permeable, while the large intestine is microbial-dense and has more physical separation between the microbiota and intestinal tissues

absorption. Mono-, di-, and tri-saccharides, amino acids-, fat- and water-soluble vitamins (A, D, E, K, B, and C) are primarily absorbed in the duodenum and jejunum, whereas vitamin B12 and bile salts are absorbed in the ileum of the small intestine. Mucus-producing goblet cells make up around 10% and 25% of epithelial cells in the small and large intestines, respectively [40]. As a result of that, the mucous layer (glycocalyx) is diffused and permeable to bacteria in the small intestine, whereas it forms a thick bilayered structure in the colon, creating a more robust barrier to the microbiota [41].

Epithelial Cell Function: Interlinked Connection with Microbiome and Dysfunction in IBD

Located in between the luminal microbiota and the underlying immune cells, the intestinal epithelium plays a pivotal role in detecting and differentiating beneficial microbiota from external pathologic microbial insult during infection. IECs express innate receptors, including the Toll-like receptors (TLRs) and Nod-like receptors (NLRs), including TLR2, TLR3, TLR4, TLR5, and TLR9 with different anatomical distributions and developmental expression patterns [42, 43]. A majority of these receptors are present at the basolateral membrane, while TLR2 and TLR9 are also expressed at the apical surface [44–46]. TLR activation by cognate ligands initiate a signaling cascade that drives nuclear translocation of nuclear factor kappa B (NF-kB) and expression and secretion of various cytokines and chemokines, including tumor necrosis factor (TNF), interleukin- (IL-)6, IL-8, IL-18, the chemokine CCL20, antimicrobial peptides including RegIIIβ, RegIIIγ, and α-defensins which signal and prime nearby immune cells [47–49].

Studies in germ-free mice has made it clear that microbes play an essential role in shaping normal intestinal architecture and function. The intestinal mucosa of germ-free mice is thin with reduced IEC proliferation and has compromised production of protective IEC-derived mediators including mucins and antimicrobial peptides [50, 51]. In 2004, groundbreaking studies showed that in the absence of innate recognition receptors that sense the microbiota (including TLR2, TLR4, or the signaling adaptor MyD88), mice become highly susceptible to the direct toxic effects of the colitogenic chemical agent dextran sodium sulfate (DSS), which could be attributed in part to reduced IEC proliferation and repair [52]. Additionally, IECs express all of the molecular machinery required to process and present luminal antigens to intraepithelial lymphocytes via either major histocompatibility complex (MHC) class I or class II. It is widely accepted that the host intestinal commensal microbiota

works in concert with IECs to maintain tissue homeostasis. For example, butyrate, produced by Clostridia species of the microbiota, is transported through the apical membrane of IECs by short-chain fatty acid transporters (SMCT1 and MCT1), and is subsequently metabolized through beta-oxidation and the tricarboxylic acid pathway [53]. This results in a positive feedback loop by which IECs limit the oxygen availability and thus favor butyrate-producing obligate anaerobes over facultative anaerobes such as *Escherichia coli*, a hallmark microbe of intestinal dysbiosis and tissue inflammation [54]. Mechanistically, the activation of the nuclear sensor, peroxisome proliferator-activated receptor (PPAR-γ), during β-oxidation mediates nuclear export of the NF-kB subunit RelA thereby limiting pro-inflammatory responses to non-commensal bacterial infection [55]. Butyrate is also known to increase the peripheral differentiation of Treg cells [19, 56]. Naïve $CD4^+$ T-cells treated with butyrate had increased histone H3 acetylation of the critical transcription factor FoxP3 at its promoter and intrinsic enhancers CNS1 and CNS3 DNA sequence [57]. Overall, microbiota-derived butyrate critically regulates pro- and anti-inflammatory responses in the intestine. During antibiotic treatment or IBD, this communication between host and microbiota is perturbed, which substantially impacts gut homeostasis [58, 59]. Together, these observations paint a picture of a dynamic and functional epithelium that is essential for maintaining barrier integrity, promoting tolerance, and providing active defense against pathogenic organisms.

Several lines of evidence suggest that the normal functions of the intestinal epithelium are disrupted during chronic intestinal inflammation such as IBD. Firstly, some of the IBD-susceptibility genetic loci have been linked to various aspects of epithelial function including hepatocyte nuclear factor 4α *(HNF4α)* and E-cadherin [60], which regulates epithelial tight junction formation; meprin 1A (*MEP1A*) [61], a brush border enzyme; and NOD2 (*CARD15*) which recognizes bacterial muramyl dipeptide [62, 63]. There are additional lines of evidence suggesting that patients with IBD have compromised epithelial barrier integrity, including reduced goblet cell numbers and mucus secretion as compared to healthy individuals. Abnormal intestinal permeability has been established among patients with CD, which can promote excessive antigen uptake, continuous immune stimulation, and eventually chronic mucosal inflammation [64]. Finally, epithelial cell death, particularly loss of Paneth cells, contributes to intestinal inflammation in mice and is associated with CD in humans [65–67]. Interestingly, increased cell shedding with gap formation and local barrier dysfunction is observed in intestinal biopsies of patients with IBD, and this dysfunction is predictive of disease relapse. In addition to the genetic factors discussed above, environmental insults may predispose to impaired intestinal barrier function in IBD. The view that IECs are a dynamic cell types that are central to the maintenance of intestinal homeostasis is consistent with IEC dysfunction contributing to IBD pathogenesis.

Gut-Associated Lymphoid Tissues

Immune cells within the GI tract are primarily located within organized lymphoid structures known as GALTs that can be found diffusely localized within the LP, the sub-mucosa, or throughout the epithelium. GALTs, together with intestinal draining MLNs, serve as the primary sites for the priming and initiation of adaptive immune responses, and collectively include the PPs in the small intestine, colonic patches, caecal patches, and comparatively smaller structures which include CPs and ILFs. Each of these sites plays an important role in recognizing luminal antigens and facilitating innate and adaptive immune responses. Conversely, effector immune cells are also diffusely present throughout the lamina propria and upper epithelium.

The GALT constitutes subepithelial lymphoid structures in the mucosa and submucosa with signature overlying follicle-associated epithelial cells. These are primarily microfold cells (M cells), specialized for the luminal antigens uptake and subsequent delivery to underlying dendritic cells (DCs) for presentation to adaptive immune cells [68, 69]. M cells also serve as a major entry site for multiple intestinal pathogens [70]. Macroscopically visible PPs located in the small intestine are the most well-characterized GALT tissue. The size and density of PPs vary along the intestine, increasing from the jejunum to the ileum. They are highly concentrated in the distal ileum and are fewer in the duodenum. PPs contain numerous B-cell lymphoid follicles (~10 in mice and ~100 hundred in humans), surrounded by smaller T-cell-rich areas [71]. In contrast to MLNs, PPs have constitutively active germinal centers indicative of continuous immune surveillance and stimulation by luminal antigen. Comparable to PPs in small intestine, the large intestine has cecal patches at the appendix and colonic patches throughout the colon serving as important sites for T-cell priming and immunoglobulin A (IgA) production [72, 73]. The development of PPs and colonic patches is initiated during the early embryonic life and is completed shortly after the birth. The GALT also includes microscopically visible small lymphoid structures including small cryptopatches that mature to ILFs and are collectively known as solitary isolated lymphoid tissues (SILTs). In contrast to PPs, ILFs primarily contain B-cells with no distinct T-cell zone. ILFs serves as important sites for T-cell-independent IgA class-switched antibody response due to the activity of the cytokines BAFF (B-cell-activating factor) and APRIL (a proliferation-inducing ligand) [74]. Mice and humans are estimated to have 1000–1500 and 30,000 SILTs, respectively [75, 76]. In mice, most

of the cryptopatches are developed within the first 2 weeks of postnatal life [77, 78]. DCs within the small intestinal SILTs express CXC-chemokine ligand 13 (CXCL13) which acts on B-cells through CXC-chemokine receptor 5 (CXCR5) to maintain cellular localization in SILTs [79, 80]. Also, mice deficient in RANK ligand (RANKL; also known as TNFSF11) have fewer small intestinal SILTs with very few B-cells [81]. Finally, the microbiota plays a major and dynamic role in the presence and maturation of SILTs, as studied in germ-free mice and discussed above.

Compartmentalized Gut Lymph Node Drainage

MLNs are the largest lymph nodes in the body and develop independently from the other GALT structures. The lymphatic drainage in the intestine is essential for appropriate immune cell trafficking and the development of adaptive immunity to luminal perturbation. Lymphocytes circulate to the MLNs as a result of expression of both L-selectin and $\alpha_4\beta_7$ integrin. L-selectin mediates lymphocyte migration into peripheral tissues, whereas $\alpha_4\beta_7$ mediates migration of lymphocytes into the intestinal mucosa. Separate segments of MLNs are attributed to drain the different sections of intestines [82, 83]. Seminal studies experimentally demonstrated that duodenum primarily drains to a small lymph node embedded in the pancreatic tissue; jejunum drains to the middle section of the MLNs, whereas the distal ileum, ascending colon and caecum drain to the distal segments of the MLNs [82]. Similar regional differences in lymph drainage are also observed in humans, and these differences in compartments have substantial consequences for how the immune response may react. For example, it has been shown that an identical luminal antigen in mice will give rise to distinct tolerogenic or inflammatory immune responses depending on delivery to distinct compartments of the MLN. Those delivered to the proximal small intestine-draining LNs give rise to tolerogenic responses, whereas delivery to distal LNs are more likely to elicit pro-inflammatory T-cell responses [84].

Innate Immune Cell-Dependent Regulation of Intestinal Health

The innate immune response comprises our first line of defense against the invading pathogens. Relative to the adaptive immune response discussed below, innate immune responses are generally rapid, non-specific, and lack long-lasting immunological memory. Innate immune cells, such as macrophages and DCs, have a unique ability to sense and respond to the intestinal microbiota and external pathogenic insults through the recognition of conserved structural motifs known as pathogen-associated molecular patterns (PAMPs) by pattern-recognition receptors (PRRs). These receptors include the membrane-bound TLRs and intracellular NLRs. This recognition allows the generation of effective inflammatory responses against microbial invasion. Furthermore, antigen presentation by professional antigen-presenting cells (APCs) such as DCs and other mono-nuclear phagocytes mediates T-cell activation and induction of adaptive immune responses. Neutrophils (or polymorphonuclear leukocytes) are the most common granulocytes in our circulation. They are highly capable of phagocytosing and killing invading microbes and play a major role in protecting the intestine, while also having the ability to be a major driver of intestinal inflammation.

Dendritic Cells

DCs are the most efficient APC of the immune system. DCs express a wide array of surface TLRs and intracellular NLRs that can detect environmental stimuli and modulate antigen-specific adaptive immune responses [85]. DCs in the gut samples luminal antigen through extended dendrites [69], encounter antigen via M cells [86], or through goblet cell-associated antigen passages [87]. Upon antigenic stimulation, activated DCs migrate toward the T-cell areas in lymphoid structures and present MHC-peptide complexes and co-stimulatory signals to naïve T-cells. DCs also dictate the effector T-cell function and polarization through secreting immunomodulatory cytokines or chemokines. In homeostatic conditions, intestinal DCs express low levels of co-stimulatory molecules and promote the induction of Tregs. In contrast, during pathogen encounter, DCs secrete inflammatory cytokines and promote effector T-cell polarization (Th1, Th2, and Th17 cells, discussed below) [88]. $CD103^+$ $Sirp\alpha^+$ DCs in humans and $CD103^+$ $CD11b^+$ DCs in mice play a prominent role in inducing Treg differentiation [89, 90]. Human studies have also indicated that $CD103^+$ DC subsets play a significant role in Th17 cell differentiation, while $CD103^-$ $Sirp\alpha^+$ DCs promote Th1 cell responses [91]. Gut-tropic migratory DC precursors through retinoic acid-dependent upregulation of α4β7 integrins and CCR9 induce their homing back into the intestine after priming in the MLN [92].

Abnormal DC functions have been attributed to the pathogenesis of several diseases including IBD [93]. Based on a series of studies in different clinical settings and experimental models, a novel paradigm has been proposed for DC functions. Depending upon the stage of inflammation DCs can promote regulatory or inflammatory responses. During the early inflammatory state, intestinal DCs play a protective role as their depletion in the intestinal mucosa leads to exac-

erbation of DSS-induced colitis, partly caused by the increased neutrophil influx [94]. In chronic immune dysregulation due to the absence of TGF-β signaling, DCs fail to gain a regulatory phenotype and promote inflammatory T-cell responses [95]. During IBD in humans, intestinal DCs can drive pathogenic phenotypes. DCs have higher expression of TLR2, TLR4 and the activation marker CD40 in patients with CD or UC relative to healthy individuals [96]. Furthermore, colonic DCs from IBD patients have higher expression of inflammatory cytokines such as IL-12 and IL-6 at steady state, suggesting DCs from patients with IBD exhibit a hyperactive phenotype [96]. Together, these observations highlight the importance of DCs in maintaining intestinal health and its contribution in IBD pathogenesis.

Macrophages

Macrophages are described as "the phagocytic cell of the immune system." Macrophages are fundamentally important for the phagocytosis of microbial pathogens, the degradation of apoptotic cells, and the production of inflammatory chemokines and cytokines [97]. However, macrophages also constantly surveil the residing tissue and actively participate in maintaining homeostasis [98, 99]. Due to these key functions, abnormal macrophage responses have been implicated in the pathophysiology of numerous human clinical conditions, including IBD [100]. It is estimated that an average human body contains approximately 200 billion macrophages throughout the body and they can be found in every tissue compartment. Macrophages can originate from their embryonic precursors or can be replenished from the bone marrow-derived monocytes at the site of infection during tissue inflammation [101]. Under the steady state, macrophages are primarily tissue resident and specialized to function specific tasks. Tissue-resident macrophages in the GI tract and GALT promote tolerance to commensal microbiota and food antigens. This unique ability is partly due to their relative hypo-responsiveness to TLR stimulation and reduced ability to prime adaptive immune responses (relative to DCs) [102]. It has been observed that during IBD, the number of macrophages is dramatically and significantly increased in the intestinal mucosa. These macrophages also exhibit enhanced expression for a large number of T-cell co-stimulatory molecules such as CD80 and CD86 [103]. It has been also observed that macrophages recruited during intestinal inflammation have upregulated expression for triggering receptor expressed on myeloid cells-1 (TREM-1) and further blocking TREM-1 leads to dampening in pro-inflammatory mediators such as TNF, IL-6, IL-8, IL-1 beta, and MCP-1 [104]. These results indicate that macrophages play a critical role both in intestinal health and in mediating the pathogenesis of IBD.

Granulocytes: Neutrophils, Eosinophils, Basophils, and Mast Cells

Granulocytes are a group of leukocytes that differentiate from myeloblasts in the bone marrow and are characterized by the presence of lobulated nucleus and granular cytoplasm. It includes mast cells, neutrophils, eosinophils, and basophils. Neutrophils (or polymorphonuclear leukocytes) are the most abundant form of all granulocytes and circulatory immune cells in humans [105]. PMNs are primarily phagocytes which actively engulf and degrade invading microbes, or dead cells in the body [106]. As a result, PMNs play an important role in early antimicrobial immunity. Unlike PMNs, eosinophils, basophils, and mast cells can mediate allergic inflammation. Both eosinophils and basophils are predominantly circulatory cells, whereas mast cells are primarily tissue-resident. Eosinophils and basophils along with mast cells are recruited at the site of inflammation and exert their effector functions through release of cytoplasmic granules containing enzymes, cytokines, chemokines, and growth factors [106]. There is a substantial body of evidence indicating that PMNs play an important role during the effector stages of IBD pathogenesis. In line with the importance of neutrophils in clearing invading microbes, mice lacking neutrophils have higher intestinal microbial burden during colitis [107]. Higher neutrophil infiltration is observed in inflamed colonic tissue in UC patients along with elevated fecal calprotectin (a neutrophilic inflammation marker) [108]. In an adoptive $CD4^+$ T-cell transfer mouse model of colitis, neutrophils are reported to have enhanced expression of major histocompatibility complex-II and CD86, which is indicative of immune activation [109]. Such neutrophils can induce $CD4^+$ T-cell activation in MHCII- and antigen-dependent manner. It has also been observed that inhibiting PMN recruitment at the sites of tissue inflammation, using CXCR2 antagonists or anti-CXCR2 monoclonal antibodies, is associated with reduced intestinal inflammation in animal models [110]. In contrast, additional evidence supports a role for neutrophil dysfunction in IBD pathogenesis. For example, evidence suggests that there is impaired neutrophilic infiltration and IL-8 production in CD patients [111]. Furthermore, treatment of CD patients with growth factor GM-CSF that mediates neutrophil development and function has been explored as a therapeutic approach and currently is under further investigation [112, 113].

Adaptive Immunity and Their Contribution to Intestinal Health and Inflammation

The lamina propria contains different populations of adaptive immune cells (particularly T-cells and B-cells) that interact and are regulated by numerous innate immune cell

populations including macrophages, DCs, granulocytes, and innate lymphoid cells (ILCs). Collectively, the intestinal epithelium and lamina propria account for the largest population of antibody-secreting plasma cells and T-cells in the body. However, the presence and distribution of different immune cell populations vary along the length of the intestine and this facilitates distinct functions.

T-cells

In the lamina propria, $CD4^+$ T-cells and $CD8^+$ T-cells are derived from conventional T-cells that undergo priming in secondary lymphoid organs and display an effector-memory phenotype. $CD4^+$ T-cells are highly diversified and instructed by the innate immune system to differentiate into distinct effector states including T-bet^+ Th1 cells that produce IFN-γ, RORγt $^+$ Th17 cells that produce IL-17 and IL-22, $GATA3^+$ Th2 cells that produce IL-4, IL-5, and IL-13, as well as FoxP3-expressing Treg cells that produce IL-10 and TGF-β (Fig. 2.2).

T-cells mediate a wide range of functions including cell-mediated killing of virus-infected cells, providing help in antibody class switching, differentiating into effector cell types to provide immunity against pathogens, and restraining inflammatory responses. Dysregulated adaptive immune response leading to breakdown of tolerance toward the commensal microbiota has been proposed as a major driver of IBD pathogenesis [114, 115]. For example, effector $CD4^+$ T-cells such as Th1, Th2, and Th17 cells provide defense against pathogens, but if left unchecked, can mediate distinct forms of intestinal inflammation [116]. On the other hand, regulatory states such as Tregs and T regulatory type 1 (Tr1) cells are critical for limiting the differentiation of effector $CD4^+$ T-cells and controlling inflammation. Therefore, a tight balance between effector and regulatory T-cells holds an important key for maintaining intestinal homeostasis. Homing of T lymphocytes from the lymph nodes is also dependent on $\alpha_4\beta_7$ integrin and their expression is regulated by all-trans retinoic acid synthesized by gut-associated DCs [117].

IBD can be a result of hyperactivation of effector T-cells and/or defects in the immunosuppressive function of Treg cells. IBD has been associated with altered T-cell responses including Th1 (IFN-γ), Tregs (IL-10), and more recently Th17 (IL-17A, IL-17F, IL-22 and GM-CSF) cells [114, 118]. In human IBD, Th17 and Th1 cells have been associated with CD pathogenesis, while UC can include an atypical Th2 cell response, as well as other mixed effector T-cell responses [119]. Microbiota drives the differentiation of RORγt expressing Th17 cells and in part through induction of the upstream cytokine IL-23 that supports Th17 cell responses and a population of IL-$17A^+$IFNγ^+ T-cells in the inflamed mucosa [120]. Th17 cells also combat bacterial infection by promoting the neutrophilic inflammatory response [114]. Therefore, Th17 cell effector responses can be both protective and pathogenic in the intestine [121, 122]. In this similar line, treatment with anti-IL-17A blocking antibody (secukinumab) worsened the symptoms of active CD in some patients, while it has provided therapeutic benefits in

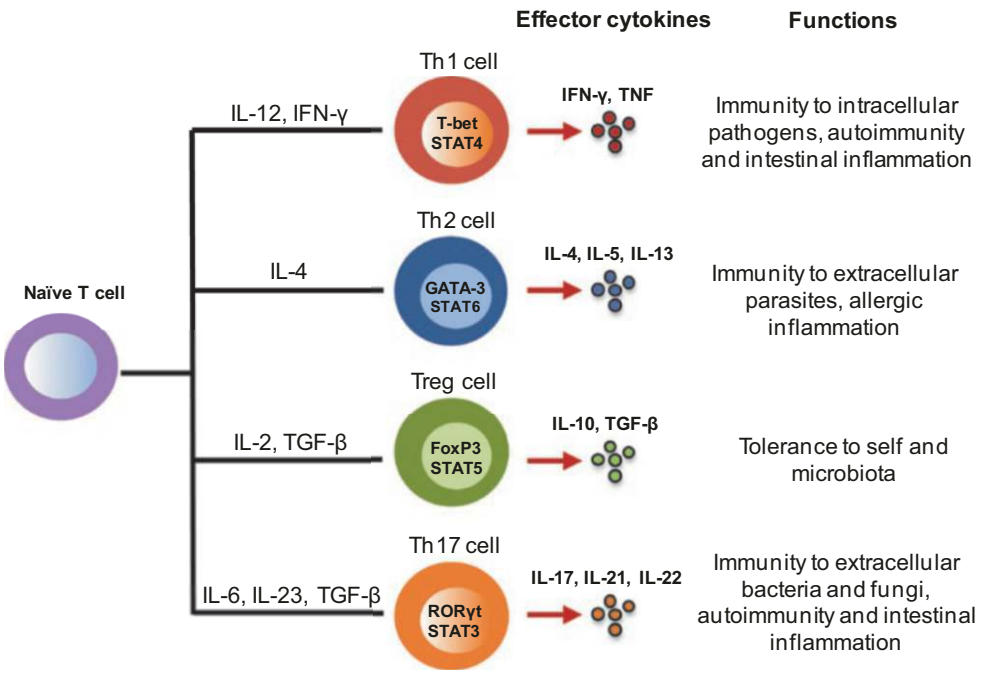

Fig. 2.2 Activation pathways, transcription factors, and effector cytokine profiles of the major T helper cell subsets. Activated $CD4^+$ T-cells differentiate into different lineages of T helper cells depending on the cytokine milieu of the microenvironment. For each lineage, a distinct transcription factor has been identified. Furthermore, each T helper subset produces a different set of effector cytokines, mediate distinct beneficial functions, or if dysregulated, can cause distinct types of diseases

other pathophysiological-related diseases [123]. Therefore, Th17 cells provide many beneficial and inflammatory functions in the intestine that must be tightly regulated.

Treg cells play an essential role in restraining effector T-cell responses and innate inflammatory mechanisms [9]. This restraining function is regulated in part by IL-10 and TGF-β produced by these cells, as well as through direct cellular contact that include pathways like CTLA-4 [124, 125]. Treg cells can adopt specialized fates and employ transcriptional or homing receptors that are utilized by effector T-cells, such as RORγt, to mediate their suppressive functions. In this context, Treg and Th17 cell differentiation are reciprocally regulated in the intestine. In an inflammatory milieu (such as by enhanced IL-6 and IL-23), Th17 cells expand at the expense of Treg cells and promote effector T-cell function [126]. There is also substantial evidence that Treg cells become fundamentally altered in the context of IBD. For example, T-cells from IBD patients have shown to be refractory to TGF-β [127]. Loss-of-function mutations in *FOXP3* (a key Treg cell transcription factor) is strongly correlated with intestinal inflammation [128]. Furthermore, Treg cells expand in the intestine of IBD patients, but exhibit a pro-inflammatory phenotype including expression of the inflammatory cytokine IL-17A [129, 130]. The pathways accounting for these phenotypic and functional changes in Tregs remain poorly understood and additional research in this area will be important for defining novel mechanisms coordinating intestinal tolerance.

B-cells

B-cells are an important constituent of mucosal immune responses in both healthy and diseased states. B-cells are primarily developed in the bone marrow but it can also originate via extramedullary hematopoiesis. During early embryonic development, pluripotent hematopoietic stem cells migrate to the fetal liver where mature B-cells develop and migrate to the intestine. Studies in experimental models of IBD have suggested that B-cells suppress mucosal inflammation either by secreting cytokines, antibodies or by directly dampening effector T-cell functions [131, 132]. During inflammation, an inducible regulatory B-cell subset (Breg cells) develops in GALT which restrains T-cell expansion through the production of IL-10 [133]. Antibody-mediated immunity is the most important arm of the mucosal immune system in mediating microbial exclusion and tolerance. However, the relationship between secretory antibodies and microbiota is not unidirectional. Studies from germ-free mice have shown that IgA production is acutely dependent on the presence of intestinal microbes [134]. This humoral defense mechanism also relies on cooperative interaction between secretory epithelial cells and local plasma B-cells. Plasma cells in the intestine primarily secrete dimers and larger polymers of IgA (pIgA) [135]. This induction of mucosal IgA responses can occur either in a T-cell-dependent or T-cell-independent manner (via the cytokines BAFF and APRIL) and these antibodies can bind through their J chains to the epithelial secretory component (pIg receptor) to get transported into the intestinal lumen [136]. This transmembrane glycoprotein receptor (pIgR) also mediates the translocation of pentameric IgM antibodies. Secretory antibodies mediate immune exclusion during microbial colonization and restrict mucosal recognition of soluble antigens. During IBD, local production of pIgA is significantly downregulated and has strikingly decreased J chain expression [137]. Individuals with IgA deficiency may have an increased risk of developing IBD [138]. However, the total deficit in pIgA level can be compensated by increased populations of plasma B-cells secreting other types of antibodies in IBD lesions (such as IgG and IgA1) [139].

During IBD, activation of mucosal APCs and a dramatic increase of IgG-producing B-cells may result in altered immunological homeostasis and can jeopardize the mucosal integrity. Luminal cytotoxic complement (C3b) deposition and complement activation are observed in relation to epithelium-bound IgG1 in UC [140]. This C3b deposition can be a sign of persistent immune activation. The early events that trigger B-cell driven immunopathology in IBD remains unknown. However, abrogation of oral tolerance to commensal microbial antigens has been presumed as an early mechanism, and GALT neogenesis and hyperplasia in the inflamed lesions enhance aberrant microbial stimulation of the local B-cell population. Under homeostasis, the production of IgA is primarily restricted to the mucosal surfaces and does not occur at systemic secondary lymphoid structures. However, breakdown of this normal compartmentalization can result inappropriate B-cell responses contributing to intestinal inflammation [141]. Indeed, systemic humoral responses to bacterial membrane and flagellar proteins have been detected in children with IBD [142].

Essential Immunologic Pathways that Regulate Intestinal Health

A balanced communication between populations of immune cells is necessary to maintain intestinal health, and impairment of the immune response or altered T-cell populations can directly promote intestinal inflammation. In 1993, seminal studies unequivocally established three pathways that are essential to regulate this balance and mediate intestinal health. These include the cytokines IL-2 and IL-10, as well as MHC class II and subunits of the T-cell receptor (TCR), which coordinate how T-cells receive signals from other immune and non-immune cell types [143–145]. Loss of any

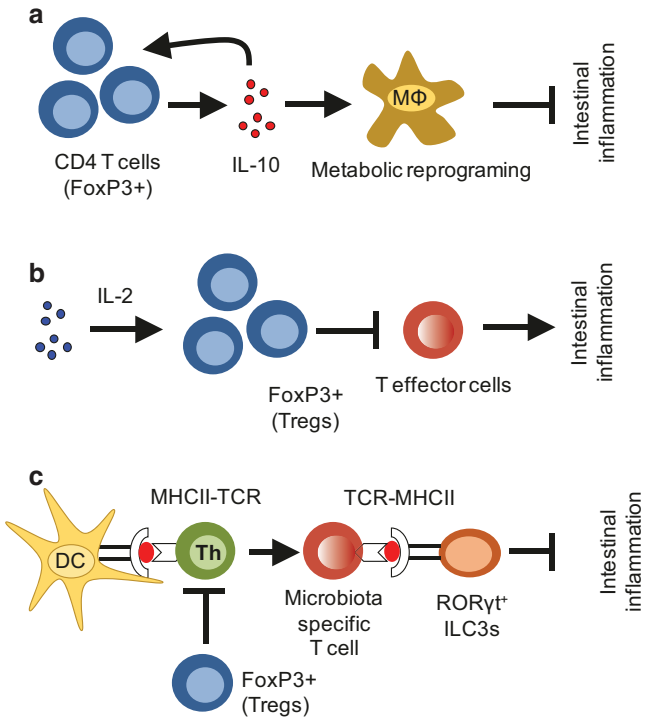

Fig. 2.3 Essential immunologic pathways that regulate intestinal health. Preclinical models and translational studies have revealed a number of immune pathways that are necessary to maintain a state of healthy in the mammalian intestine. (**a**) FoxP3⁺ T-cells (Treg cell) are the major cellular source of IL-10 in the mammalian intestine. Treg cell-derived IL-10 is essential to promote intestinal health by imprint tolerogenic phenotype in macrophages other T-cells. (**b**) Under homeostasis, IL-2 produced by activated CD4⁺ T-cells, DCs, and other unknown cells and it is essential for IL-2 to bind to the IL-2R on Treg cells, which subsequently limit T effector cell responses to coordinate intestinal health. (**c**) MHC class II on conventional DCs activate naïve CD4⁺ T-cells by presenting commensal bacterial antigens in MLNs. This supports the generation of Tregs cells. Further, MHCII⁺ ILC3s limit microbiota-specific T effector cells via apoptosis, a process termed intestinal selection

one of these pathways in mice is sufficient to results in spontaneous and chronic intestinal inflammation, and substantial investigation since this discovery has delineated the cellular and molecular mechanisms by which these pathways coordinate intestinal health (Fig. 2.3).

Previously, IL-10 was perceived as a critical immunoinhibitory cytokine that restricts effector function of Th1 cells, Th17 cells, NK cells, and macrophages [146]. In humans, polymorphisms in IL-10 and IL-10R are strongly correlated with IBD disease pathogenesis. Kühn et al. developed a genetically engineered model by targeted mutation in the IL-10 gene disrupting its function, which continues to be widely used to dissect IBD etiology in preclinical models [143]. IL-10 knockout mice develop spontaneous colitis after weaning and have impaired gut mucosal barrier function characterized by discontinuous and transmural inflammatory lesions and display extensive mucosal hyperplasia accompanied by increased immune cell infiltration [143]. Colitis in IL-10- and IL-10 receptor (IL-10R)-deficient mice is primarily driven by increased CD4⁺ T-cell Th1 responses and IFN-γ production. IL-10 is also known to directly inhibit IL-12 production from the myeloid cells and therefore restricts Th1 cell differentiation [147, 148]. In addition to IL-12, IL-10 suppresses IL-23 production from mononuclear phagocytes through transcriptional inhibition of the shared IL-12 p40 subunit, which is critical for driving pathologic Th17 cell responses during mucosal inflammation [148]. Critically, intestinal inflammation in IL-10-deficient mice can be completely prevented by treatment with antibiotics or deriving the mice in germ-free conditions, highlighting that a major function of this pathway is to promote immunologic tolerance to the microbiota.

Despite these advances, the exact cellular source and molecular pathways by which IL-10 maintains intestinal health remained unclear from these initial studies. Several hematopoietic cells such as T-cells, B-cells, macrophages, and DCs, as well as several non-hematopoietic cells are all capable of producing IL-10 in the mammalian intestine. The use of selective genetic models to specifically delete the IL-10 gene revealed that CD4⁺ T-cells are a crucial non-redundant source of IL-10, and many of the phenotypes in IL-10-deficient mice could be recapitulated in mice having a selective lineage-specific deletion of IL-10 only in Foxp3⁺ Treg cells [149]. In addition, expression of IL-10R and signal transducers and activators of transcription 3 (STAT3) are critical in Foxp3⁺ Treg cells to limit Th17 cell response [150, 151]. Ablation of the IL-10R or STAT3 in Treg cells resulted in selective dysregulation of Th17 cell responses and colitis. Treg cell-derived IL-10 also drives macrophages toward a tolerogenic phenotype through metabolic reprogramming to maintain mucosal homeostasis [152]. This is critically important to maintain intestinal health, as selective deletion of IL-10R on myeloid cells revealed this population as a critical target of IL-10. During inflammation, IL-10 suppresses mammalian target of rapamycin (mTOR) activity in myeloid cells through the induction of its inhibitor, DDIT4 (DNA damage–inducible transcript 4 protein) and preventing glucose uptake while promoting oxidative phosphorylation of essential signaling molecules [152]. In IL-10-deficient mice, dysfunctional mitochondria get accumulated in the macrophages, resulting in production of IL-1β through overactivation of the NLRP3 inflammasome [152]. Consistent with this, inhibiting caspase-1 activity or deficiency could partially protect IL-10-deficient mice from developing spontaneous intestinal inflammation.

IL-2 was discovered more than 30 years ago and studies with IL-2 or IL-2 receptor (IL-2Rα) deficient mice have highlighted the crucial role of IL-2 in maintaining Treg cell homeostasis and peripheral immune tolerance. Under steady-state conditions, IL-2 is mainly produced by activated CD4⁺

T-cells in secondary lymphoid organs and gets consumed by cells expressing the high-affinity IL-2R subunit CD25 (also known as IL-2Rα), which is robustly expressed by Treg cells. IL-2-deficient mice develop spontaneous colitis with striking clinical and histological similarity to IBD in humans [145]. Colitis in IL-2-deficient mice is also associated with higher infiltration of activated T- and B-cells, elevated immunoglobulin secretion, and aberrant expression of MHC class II molecules [153]. Similar findings were also observed with mice lacking IL-2Rα and IL-2Rβ. IL-2-deficient mice crossed with Rag2-deficient mice or raised in germ-free conditions were disease free, demonstrating an essential requirement of adaptive immune cells and the microbiota in disease progression [153, 154]. The importance of IL-2 in regulating $CD4^+$ T-cells was later refined with the identification of additional heterogeneity in this T-cell subset. It is now well appreciated that IL-2 promotes Th1, Th2, and Treg cells, while inhibiting Th17 cells function [155]. IL-2 plays a crucial role in the maintenance of $Foxp3^+$ Treg cells [126, 156]. Treg cells subsequently suppress $CD8^+$ T-cell and other $CD4^+$ effector T-cell responses via IL-2 sequestration. IL-2-, IL-2Rα-, and IL-2Rβ-deficient mice have a significantly low proportion of Tregs with impaired suppressive function [156]. Consistent with this, lineage-specific deletion of the IL-2R on only $Foxp3^+$ Treg cells was sufficient to result in spontaneous intestinal inflammation with enhanced activation and proliferation of $CD8^+$ T-cells [157]. The relevant cellular sources of IL-2 are yet to be fully defined, but expression has been observed in various immune cells such as T-cells, DCs, NK cells, and ILCs. Recently, ILC3s are shown to be the dominant source of IL-2 uniquely in the small intestine and ILC3-intrinsic IL-2 expression is essential to promote intestinal Tregs differentiation and function selectively in this anatomical compartment [158].

Beyond IL-10 and IL-2, chronic intestinal inflammation was also observed in mice lacking different components of the TCR, such as TCRα-deficient, TCRβ-deficient, TCRβ- and TCRδ-double deficient, as well as MHC class II-deficient mice [144]. The intestinal disease in these mice exhibits similarities to ulcerative colitis in humans. However, athymic or mice lacking T-cell and B-cells (*Rag1*$^{-/-}$) mice did not exhibit disease onset, suggesting that dysfunction of αβ T-cells, especially MHC class II-restricted $CD4^+$ T-cells contributes to the pathogenesis of intestinal inflammation in these models [144]. A recent study found that lineage-specific deletion of MHC class II on DCs and not on epithelial cells is sufficient for development of robust intestinal inflammation, but mice used in this study also target ILC3s. [159, 160]. Collectively, these seminal findings highlight the importance of different immunoregulatory molecules, cytokines, T-cell subsets, and innate immune populations in maintaining intestinal immunity and health.

A common theme among these findings is that a fine tuning of communication between the innate immune system, adaptive immune system, and intestinal microbiota is essential to coordinate intestinal health. Disruption of these pathways can manifest in overactivation of the immune response and spontaneous intestinal inflammation. These studies have critically informed our understanding of IBD, as it is now known that there are patients with loss-of-function mutations in many similar pathways (including IL-10, IL-10R, IL-2, and IL-2R) that also manifest in VEO-IBD [161, 162]. Furthermore, the appreciation that this can be an entirely hematopoietic phenotype (such as in the case of IL-10 or IL-10R) has allowed the development of hematopoietic stem cell transplantation as one viable therapeutic approach to stop intestinal inflammation in VEO-IBD patients with specific mutations [163]. A more advanced understanding and refinement of these pathways, as well as other novel pathways by which the immune system orchestrates intestinal health, will likely yield novel preventative, therapeutic, and curative treatment strategies to IBD.

Innate Lymphoid Cell-Dependent Regulation of Intestinal Health

ILCs are recently appreciated cell types of the innate immune system in mice and humans. They were first identified at barrier surfaces by their ability to secrete IL-22 and drive antimicrobial responses in the gut, but it is now well accepted that ILCs populate almost every tissue and are critical regulators of immunity, inflammation, and homeostasis [164–166]. ILCs are predominantly tissue-resident and highly enriched in mucosal barrier tissues. Therefore, they are well poised to be the first immune cells to react to colonizing microbiota or invading pathogens by the induction of inflammatory responses to infection, orchestrating the ensuing adaptive immune response and the resolution of inflammation after infection [165]. Critically, ILCs also play a major role in lymphoid organogenesis and maintenance of barrier integrity [20, 167].

Despite the resemblance to T-cells, ILCs lack somatically recombined antigen-specific receptors and are innate counterparts to different T-cell subsets [168]. They are also predominantly tissue resident and colonize tissues, such as the GI tract, early during developmental life [169]. ILCs are subdivided into three subgroups on the basis of their transcription factor expression and cytokine secretion profile: group 1 ILCs (ILC1s) express T-bet, are responsive to IL-12, and produce IFN-γ in response to intracellular pathogens; group 2 ILCs (ILC2s) express GATA-3, are responsive to IL-33, IL-25, and TSLP and secrete IL-5, IL-13, and amphiregulin in response to helminth infection; while ILC3s express RORγt, are responsive to IL-23, TL1A, IL-1α, and IL-1β and produce IL-17 and IL-22 in response to extracellular bacteria or fungi [168]. ILC3s are the most heterogeneous ILC popu-

lation in mice and humans, and encompass a subset of CCR6$^+$ lymphoid tissue-inducer (LTi)-like cells and a subset of T-bet$^+$ ILC3s that express the natural cytotoxicity receptors NKp46 or NKp44. Further, ILC3s have been the most closely studied in context to human IBD since they play a major role in intestinal homeostasis, repair, and immunity in various animal models of acute injury, and also their numbers are reduced in intestinal biopsies of IBD patients relative to healthy controls [170, 171]. The latter may be the result of substantial plasticity among these ILC subsets in which under inflammatory conditions, ILC3s can transition to an ILC1 or ex-ILC3 phenotype [171].

ILC3s regulate intestinal homeostasis, innate immunity and tissue inflammation through several distinct pathways, that occur at distinct developmental timepoints. During embryogenesis, a subset of CCR6$^+$ ILC3s known as LTi cells are considered as the initiators of lymphoid organ formation. RORγt-deficient mutant mice lacking LTi cells fail to develop lymph nodes, PPs or CPs [167]. RORγt$^+$ LTi cells secrete lymphotoxin (LT)-$\alpha_1\beta_2$ which engages LTβR on mesenchymal cells and bring about release of the chemokines CXCL13, CCL19, and CCL21. These chemokines recruit adaptive immune cells and enhance expression of the adhesion molecules VCAM-1, MadCAM-1, and ICAM-1, resulting in proper development of lymphoid tissues [167]. Indeed, ILC3s can represent up to 30% of the total hematopoietic cells within the developing human intestine [169]. This sets the stage for these cells to coordinate multiple developmental pathways and control the early immune response to colonizing microbiota. However, there is evidence that ILC3s are then replaced by other adaptive immune cells and greatly reduced in numbers over time, with even greater depletions occurring during intestinal infection or inflammation as noted above.

After birth, ILC3s maintain a bidirectional communication with the microbiota. For example, the proper development, activation, and effector functions of ILC3s are dependent on the signals derived from microbiota. ILC3s then produce IL-17, IL-22, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF) in response to IL-23 and IL-1β secreted by myeloid cells after recognition of microbial PAMPs or microbial metabolites (such as aryl hydrocarbon receptor ligands) [172, 173]. Among these, IL-22 has been most well studied and is dominantly produced by ILC3s. IL-22 mediates resistance to intestinal infection by directly acting on non-hematopoietic cells in the intestine. IL-22 binding on epithelial cells through the IL-22Rα1–IL-10Rβ receptors induce fucosylation of epithelial cells and secretion of antimicrobial peptides such as RegIIIβ and RegIIIγ [174]. Fucosylation of the epithelial cells has been shown to be important for resistance against *Salmonella typhimurium* infection [174]. IL-22 is also shown to be critically important for protection against intestinal inflammation elicited by *Citrobacter rodentium* infection or DSS administration, in part by promoting mucus production, protecting intestinal epithelial stem cells, and promoting the above antimicrobial responses [175, 176].

ILC3s also regulate intestinal immunity through direct and indirect interactions with adaptive immune cells. Activation of stromal cells by LTi cells derived lymphotoxin-α3 mediates the recruitment of B-cells and stimulates the production of T-cell-dependent or -independent IgA which in turn shapes the composition of the intestinal microflora [74, 177]. Engagement of IL-1R on ILC3s brings about release of GM-CSF. ILC3-derived GM-CSF triggers retinoic acid and IL-10 production from the myeloid cell, which promotes the induction and expansion of Treg cells [173]. These GM-CSF-primed APCs promote Treg cell responses to food antigens and help maintain oral tolerance. ILC3s also contribute to Treg maintenance since IL-2 production by ILC3s is critical to support Treg homeostasis selectively in the small intestine [158], while MHC class II expression by a subset of ILC3s is an essential tolerogenic signal that limits exacerbated microbiota-specific T-cell responses in the large intestine of mice and promote microbiota-specific RORγt$^+$ Tregs [166, 178, 179]. Critically, both of these pathways were found to be reduced in the inflamed intestine of children with IBD and associated with changes in the adaptive immune response, indicating that disruption of this pathway contributes to disease pathogenesis. Although we are still in the early stages of investigating ILCs, their importance to intestinal health is apparent and may hold important keys for better understanding mucosal immunity.

Causes and Immunologic Drivers of Intestinal Inflammation in Humans

The cause of IBD in most individuals remains incompletely understood, but it is considered to be the result of dysregulated immune responses to environmental factors including luminal and microbial antigens. Human IBD is an outcome of a complex interplay between host genetic risk factors and extrinsic environmental stimuli. Over the past decade, genome-wide association studies (GWAS) have identified about 215 susceptibility genes loci associated with the pathogenesis of IBD, which are important for regulating intestinal barrier integrity, pro-inflammatory signaling pathways, modulation of immune cell responses and host–microbiota interactions [27]. These analyses have revolutionized our current understanding of IBD. For example, polymorphisms in IL-10 and IL-10R were reported early on as a human IBD risk allele through GWAS [180]. Further these studies also identified variations in IL-2, IL-2R signaling and HLA, a molecule critical for antigen presentation, that increases susceptibility to IBD [27, 181]. Homozygous, loss-of-

function mutations in *IL10*, *IL10RA*, *and IL10RB* are associated with a unique and rare form of IBD that develops at younger than 5 years of age, termed VEO-IBD [161, 182]. GWAS in adult IBD and studies of VEO-IBD have elucidated many novel pathways that are reviewed more in depth by others [183–185].

Various therapeutic interventions using broadly immunosuppressive glucocorticoids, antibiotics, and biologics have been applied to clinically manage and treat IBD patients. Beyond the frontline use of glucocorticoids, TNF blockade remains the most important therapeutic approach and is shown to exert its effect through increased IL-10 production from the macrophages [186]. However, a subset of patients become refractory to this blockade over time and these immunosuppressive therapies are often associated with an increased risk of opportunistic infections, malignancies, or autoimmunity. Thus, there is an urgent need to develop safer and more efficient approaches. Antibodies targeting IL-23-Th17 cell pathways or delivery of exogenous regulatory cytokines (IL-2) show promising initial clinical results, but several failed to achieve desired therapeutic benefits [123, 187]. Recently, Ustekinumab, an antagonist of the p40 subunit of both IL-12 and IL-23, was approved by the FDA for the treatment of Crohn disease and ulcerative colitis [188]. Recent clinical trials have also demonstrated success of selective blockade of IL-23 [188, 189]. Other promising therapies that can have potential therapeutic benefits, include using the small molecule inhibitors targeting transcription factors or kinases employed by various cytokine receptors and cells, are currently in the pipeline for clinical testing. Finally, clinical trials with idea to specifically increase and activate Treg cells using low-dose IL-2 therapy have provided a promising strategy and is under investigation [190]. Other groups are also harnessing the beneficial effect of the microbiota or microbial metabolites, and efficacy of probiotic or healthy human fecal microbiota in transplantation strategies is under clinical stages of investigation for treating IBD.

Understanding Intestinal Immunity and IBD in Children

IBD is most often diagnosed in adolescence and young adulthood, but there are rising number of incidences in pediatric populations. Pediatric IBD affects approximately 10 per 100,000 children in the US. Among children with IBD, 4% are below the age 5 years and 18% are under 10 years of age with the peak onset in adolescence [25]. Normally, children diagnosed with IBD have classic symptoms such as weight loss, abdominal pain, and bloody diarrhea but many children can present with overall poor growth, compromised bone health, and anemia [25]. In GWAS studies, no difference exists in the commonly known risk genetic loci between pediatric and adult IBD. However, early onset of IBD in children may be associated with a higher burden of common risk alleles and the presence of rarer variants with high penetrance [26]. Host genetics plays an important role in onset of VEO-IBD. Using advanced sequencing technology, monogenic defects have been identified in a variety of primary immunodeficiency genes such as CARD8, IL-10, IL10R, XIAP, and FoxP3 in some children with VEO-IBD [180, 191], and active investigations could further identify primary immunodeficiencies associated with VEO-IBD [192].

There are several unique considerations for host–microbiota interactions that exist in early life. The composition of microbiota that are the first to colonize the mammalian intestine promotes proper development of GALT and function of immune cells. Similarly, intestinal microbiota composition is also shaped by early dietary and introduction of solid-food antigens during weaning. Immune responses during this critical time point are vigorous and termed a "weaning reaction." Further, microbial metabolites, such as short-chain fatty acids and retinoic acid, critically promote the differentiation of RORγt$^+$ Treg cells during the early stages of life and imprint long-term tolerance to dietary antigens and microbiota [56, 193]. Alterations in this critical developmental window, "weaning reaction" and immunological imprinting can lead to enhanced susceptibility to immune pathologies later on in life, including IBD [194]. This can occur through a number of different ways, and as an example, limited evidence indicates that early-life exposure to antibiotics may increase the likelihood of developing pediatric IBD [195].

Finally, the clinical care of pediatric IBD is being advanced by development of new drug and collaborative research networks. Vedolizumab, a monoclonal antibody against α4β7 integrin, inhibiting lymphocyte trafficking back to the intestine can provide therapeutic benefits [196]. Using advanced scRNA-seq technology and whole-genome sequencing technologies, investigators are obtaining a more robust understanding of the cellular and genetic diversity to cell types involved in the healthy and inflamed pediatric intestine [26].

Summary

Deciphering the complexities of the mucosal immune system has revealed how defects in specific pathways can directly cause intestinal inflammation, as well as the critical mediators that drive this outcome. This has informed our understanding of IBD and provoked the development of novel therapeutic strategies. However, we remain at the early stages of understanding the full spectrum of cross-talk between the mucosal immune system, other resident non-immune cells, and the intestinal microbiota. It will also be important to continue to define the unique immunologic,

microbial, and developmental differences in the pediatric GI tract relative to the adult GI tract. Research of these pathways in pre-clinical mouse models and translational patient-based studies will not only advance our understanding of intestinal health and inflammation, but also provoke the development of novel preventative, diagnostic, therapeutic, and potentially curative treatment strategies in IBD.

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Cytokines and Inflammatory Bowel Disease

3

Edwin F. de Zoeten and Ivan J. Fuss

Introduction

The etiology of inflammatory bowel diseases (IBD) is generally described as multifactorial including genetic predisposition, dysbiosis, and a dysregulated immune response. The immune response is the only one of these which is currently amenable to therapy. Understanding the factors that go into the activation of inflammation, and those that perpetuate this effect is improving greatly. With this mastery, we are able to define the cytokines that are important in the etiology of IBD. Over the past 20 years, many of the newest and arguably the most successful therapies for Crohn disease (CD) and ulcerative colitis (UC) have been due to an increased understanding of the immune response and specifically the cytokines essential to this response.

As stated above, IBD is in part due to a dysregulated or an inappropriate immune reaction, which has been thought in part to be against the microflora of the gut. Upon activation of the immune system, cytokines and chemokines, which are proteins produced by the cells involved in the immune response, are produced and trigger a cascade of downstream reactions. These cytokines are increasingly being defined as important molecules in the pathogenesis of IBD as well as putative and known targets for the therapy of IBD.

With the advent of murine models of mucosal inflammation, a great deal of knowledge has been acquired which has advanced our understanding of inflammation in IBD. In these models, it has been initially noted that the inflammation is due either to an excessive Th1 T-cell response or an excessive Th2 T-cell response, with the former characterized by increased IL-1, IL-2, IL-6, IL-12, IL-18, IFN-γ, and TNF-α production and the latter by increased IL-4, IL-5, IL-10, and/or IL-13 production. An example of a murine Th1 colitis is that induced by the haptenating agent TNBS [1], colitis in which the predominant immune response is dominated by IL-12, IFN-γ, and TNF-α. This correlates with human studies, which have shown increased levels of TNF-α, IFN-γ, IL-1, and IL-6 in the intestinal tissues and the peripheral blood of CD [2]. Similar to what has been observed in UC patients [3, 4] the oxazolone model of colitis in mice, which has similar histologic features as those seen in UC, is associated with a Th2 response that is dominated by IL-13. Thus, murine models have given important insights into the IBD entities; however, questions of whether CD and UC are "true," Th1- or Th2-mediated disease processes remain. These will be discussed later in this chapter.

In the immune cascade, cytokines help to determine the nature of the immune response; they can act in a dual nature as either pro- (IL-1, IL-6, TNF-α) or anti-inflammatory (IL-4, IL-5, IL-10, TGF-β) molecules. They can affect the synthesis or secretion of reactive oxygen species, nitric oxide, leukotrienes, platelet-activating factor, and prostaglandins. In addition, they can have differing qualities depending on when they are present in the inflammatory cascade. Finally, it is important to understand that pro- and anti-inflammatory responses are required to maintain the integrity of the intestinal mucosa due to the environment in which it exists. The intestinal mucosa is constantly bombarded with antigens from food, commensal bacteria and pathogenic bacteria and therefore it is important to be able to mount an inflammatory response to rid itself of harmful bacteria yet, at the same time, the mucosal immune system must be able to regulate itself either by the action of specific regulatory cells or by the action of cytokines such as IL-4, IL-5, IL-10, TGF-β, IL-1ra, and TNF-α.

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Pro-Inflammatory Cytokines

Tumor Necrosis Factor-Alpha

For most gastroenterologists, TNF-α is the most recognized cytokine due to the increasing use of the monoclonal anti-TNF-α antibodies, infliximab, adalimumab, certolizumab, and golimumab, for the treatment of CD and UC. TNF-α is secreted by macrophages, monocytes, neutrophils, T-cells, and NK cells following their stimulation by bacterial lipopolysaccharides. $CD4^+$ T-lymphocytes secrete TNF-α, while $CD8^+$ T-cells do not. The synthesis of TNF-α is induced by many different stimuli including interferons, IL-2, and GM-CSF. The production of TNF-α is inhibited by IL-6 and TGF-β.

TNF-α can signal through two different cellular receptors (TNFR1 and TNFR2), both of which are an agonist of the NFKB, p38, and c-jun N terminal kinase (NK) cascades, important signaling pathways involved in the generation of the inflammatory responses [5]. An additional effect of TNF-α signaling is the induction of intermediate molecular complexes, via signaling through the TNFR1, that lead to the downstream activation of necroptosis and apoptosis pathways; mechanisms which are dependent on MLKL and caspase 8 [6, 7]. Of note, these processes both lead to effects on epithelial cell survival, therefore, epithelial barrier function.

It is a potent pro-inflammatory cytokine that exerts its stimulatory effect on cells that produce IFN-γ. Indeed, TNF-α in synergy with factors from non-lymphocyte lamina propria mononuclear cells can act with prostaglandin E2 to stimulate IL-12-mediated T-cell production of IFN-γ. In resting macrophages, TNF-α induces the synthesis of IL-1 and prostaglandin E_2, which can act in concert to potentiate the inflammatory cascade. TNF-α can also enhance the proliferation of T-cells induced by various stimuli in the absence of IL-2; in fact some subpopulations of T-cells only respond to IL-2 in the presence of TNF-α. Beyond its effect on the immune response, TNF-α activates osteoclasts and thus induces bone resorption and this effect may be associated with decreased bone mineral density in patients with CD.

Although TNF-α is required for normal host immune responses, the over expression can have severe pathologic consequences as exemplified by mice in which the over expression of TNF by a transgene is associated with a severe colitis [8].

In animal models, TNF-α knockout mice do not develop significant colitis [9], and as proof of principle that TNF-α is important for the pathogenesis of IBD, TNF-α neutralizing antibodies have been shown to be effective in ameliorating intestinal inflammation. Associated human studies have reported elevated levels of TNF-α in serum, stool, and mucosal tissue [10, 11] correlating with clinical and laboratory indices of intestinal activity. Furthermore, dramatic effects have been noted in clinical studies in patients with Crohn disease treated with infliximab [12, 13]. These effects have been observed in both disease amelioration and induction of clinical remission. Important for the understanding of some of the critical side effects of infliximab, TNF-α mediates a part of the cell-mediated immunity against obligate and facultative bacteria and parasites by stimulating phagocytosis and the synthesis of superoxide dismutase in macrophages. It confers protection against *Listeria monocytogenes* infections and tuberculosis. Anti-TNF-α antibodies have been shown to weaken the ability of mice to cope with these infections. Infection with these organisms is a possible risk of using anti-TNF-α monoclonal antibody therapy in the treatment of IBD and a reason that patients are screened for tuberculosis prior to initiation of therapy with infliximab.

Interferon-gamma

IFN-γ is produced mainly by $CD4^+$, $CD8^+$ T-lymphocytes and natural killer cells activated by antigens and mitogens. IFN-γ synergizes with TNF-α in inhibiting the proliferation of various cell types; however, the main biological activity of IFN-γ appears to be immunomodulatory in contrast to the other interferons (IFN-α or β), which are mainly antiviral. IL-2 and IFN-γ appear to be intricately interwoven in their functions. In T-helper cells, IL-2 induces the synthesis of IFN-γ and other cytokines. IFN-γ acts synergistically with IL-1 and IL-2 and appears to be required for the expression of IL-2 receptors (CD25) on the cell surface of T-lymphocytes. Blocking of the IL-2 receptor by specific antibodies inhibits the synthesis of IFN-γ. IFN-γ is a modulator of T-cell growth and functional differentiation, a growth-promoting factor for T-lymphocytes, and it potentiates the response of these cells to growth factors. Most importantly, IFN-γ can increase the expression of MHC class molecules allowing greater antigenic recognition. Furthermore, it can increase permeability at epithelial tight junction barriers, thereby allowing further antigenic exposure [14]. Finally, in concert with TNF-α, IFN-γ can cause direct tissue destruction as it increases local inflammation [14, 15].

IFN-γ secretion is one of the few cytokines that correlates with severity of disease in patients with CD. As a known pro-inflammatory cytokine, it would appear to be an obvious choice to target for treatment of IBD. IFN-γ has been targeted in CD using fontolizumab, a humanized monoclonal antibody against IFN-γ [16, 17]. In studies using these antibodies, positive results were found in patients with moderate to severe CD when compared to placebo. Although the studies did not reach statistical significance, the results did indicate a trend toward effect. This suggests a potential benefit of blocking IFN-γ in patients with CD.

Interleukin-1

This cytokine consists of IL-1α and IL-1β subunits, both are produced predominately by antigen-presenting cells such as monocytes and macrophages. In addition to these pro-inflammatory cytokines, there is an IL-1 receptor antagonist (IL-1ra) produced by intestinal epithelial cells, which is capable of inhibiting the pro-inflammatory actions of IL-1 by binding the IL-1 receptor and competitively blocking the interaction with IL-1. IL-1rα is considered to be one intestinal mechanism for downregulation of the immune response and has been shown to be elevated in the serum of patients with CD. Stimulation of IL-1rα secretion is activated by IL-1, forming a negative feedback loop.

Furthermore, in combination with TNF-α, IL-1 appears to be involved in the generation of lytic bone lesions. IL-1 activates osteoclasts thereby suppressing the formation of new bone, suggesting another etiology for decreased bone density in CD. Low concentrations of IL-1, however, can promote new bone growth.

IL-1 was one of the first cytokines targeted for therapy in animal colitis models. In these studies, administration of IL-RA led to amelioration of colitis, in a rabbit model. Thus, it was also one of the first demonstrations that blockade of a single cytokine could be effective in therapy of colitis [18]. In patients with IBD, increased serum levels of IL-1 are seldom detected. However, in intestinal lesions in patients with both CD and UC, IL-1 levels are elevated [19]. IL-1Ra is a possible intestinal mechanism for downregulation of the immune response and is elevated in the serum of patients with CD. IL-1Rα determines the biological effects of IL-1, as increased concentrations of this mediator will decrease IL-1 activity. In the inflammatory lesions of IBD patients, levels of this mediator are increased, although not as much as IL-1, leading to a disproportionate increase in IL-1 activity [20] overcoming competitive inhibition.

IL1-α and -β are essentially biologically equivalent pleiotropic factors that act locally and systemically. IL-1 has a multitude of effector functions, some of which are mediated indirectly by the induction of the synthesis of other mediators including ACTH, PGE_2, IL-6, and IL-8 (a chemotactic cytokine in the chemokine family). The main biological activity of IL-1 is the stimulation of T-helper cells, which are induced to secrete IL-2 and to express IL-2 receptors. IL-1 can also act on B-cells, promoting their proliferation and the synthesis of immunoglobulins. IL-1 stimulates the proliferation and activation of other immune cells such as NK-cells and fibroblasts, thymocytes. The IL-1-mediated proliferative effects can be inhibited by the suppressive cytokine, TGF-β.

The synthesis of IL-1 can be induced by other cytokines including TNF-α IFN-α, β or γ, and also by bacterial endotoxins and viruses. Furthermore, IL-1 activity is not only limited to stimulation of T-cells but it also promotes the adhesion of neutrophils, monocytes, T-cells, and B-cells by enhancing the expression of adhesion molecules such as ICAM-1 (intercellular adhesion molecule) and ELAM (endothelial leukocyte adhesion). All of which can contribute to the pathogenesis of CD. IL-1 is also a strong chemoattractant for leukocytes, as demonstrated by the local accumulation of neutrophils at the site of injection of tissue with IL-1. Beyond activation of other inflammatory factors, IL-1β can have direct inflammatory effects. It can be secreted in response to select microbial components (i.e., LPS or ATP derived from bacterial breakdown) via stimulation and activation of the NLR inflammasomes [21]. The importance of the inflammasome pathway previously has been overlooked as prototypic Crohn disease patients have not responded to blockade with anti-IL-1β therapy. In examination of IL-1β role in intestinal inflammation, murine models of colitis have demonstrated that inhibition of inflammasome function through use of knockout animals carrying deletions of NLRP3 has had mixed effects on colitis with both amelioration and increased colitis reported. However, overactivation of the NLRP3 inflammasome function has led to enhanced colitis induction [22]. Finally, several monogenic mutations leading to increased NLRP3 inflammasome activation are accompanied by severe Crohn disease that appears amenable to treatment with IL-1β inhibition therapy [23]. Therefore, IL-1β may play a central role in a subset of Crohn disease patients if the predominate dysregulated cytokine, the latter due to genetic influence of inflammasome activation.

Interleukin-2

IL-2 is a major T-cell growth factor, secreted by activated T-cells and acts via the high-affinity IL-2 receptor (CD25) on T-cells. This binding to CD25 promotes cell proliferation. Under physiological conditions, IL-2 is produced mainly by CD4+ T-lymphocytes following cell activation. Resting cells do not produce IL-2. In T-helper cells, IL-2 induces the synthesis of IFN-γ and other cytokines. IFN-γ acts synergistically with IL-1 and IL-2 and appears to be required for the expression of IL-2 receptors on the cell surface of T-lymphocytes. Blocking of the IL-2 receptor by specific antibodies also inhibits the synthesis of IFN-γ. IFN-γ in return is a modulator of T-cell growth and functional differentiation. It is a growth-promoting factor for T-lymphocytes and potentiates the response of these cells to growth factors.

IL-2 is a growth factor for all subpopulations of T-lymphocytes including importantly suppressive T regulatory cells. It is an antigen-unspecific proliferation factor for T-cells that induces cell cycle progression in resting cells and thus allows clonal expansion of activated T-lymphocytes.

In patients with CD, it has been demonstrated in many studies that IL-2 secretion from lamina propria cells is

decreased as compared to normal patient samples. Daclizumab, a humanized monoclonal antibody to CD25, produced in an effort to block the binding of IL-2 to the IL-2R was tested in patients with UC and initially appeared promising in a small open label study [24] but upon testing in a placebo controlled study the therapy did not show efficacy [25]. This effect could be related to the fact that IL-2R (CD25) is also present on T regulatory cells. The inhibition of binding of IL-2 to its receptor present on Treg cells thereby inhibits the proliferation of these cells, which are important in down regulation of the immune response. This highlights a common problem in the targeting of the cytokine pathway for treatment of inflammatory diseases, in that, cytokines frequently have multiple effects and can function in both a pro-inflammatory as well as an anti-inflammatory capacity.

Interleukin-6

IL-6 is a pleiotropic cytokine considered to be a major player in inflammation, regulation of T-cell responses and apoptosis. Many different cell types produce IL-6. The main sources in vivo are stimulated monocytes, fibroblasts, endothelial cells, macrophages, T-cells, and B-lymphocytes. IL-6 is a B-cell differentiation factor in vivo and in vitro and an activation factor for T-cells. In the presence of IL-2, IL-6 induces the differentiation of mature and immature T-cells into cytotoxic T-cells. IL-6 also induces the proliferation of thymocytes and likely plays a role in the development of thymic T-cells. Most significantly, IL-6 and TGF-β together can induce the development of the inflammatory Th17 cell lineage. Finally, in opposition, if IL-6 is present, there is decreased propensity to development of FOXP3-positive Treg cells.

IL-6 activity as a pro-inflammatory cytokine lies in its ability to affect NF-κB signaling [26]. Furthermore, IL-6 can signal via its receptor directly or by binding to soluble IL-6R to form a IL-6/sIL-6R complex that binds membrane-bound signal transducer (gp130), by-passing membrane-bound receptor (trans-signaling). IL-6 trans-signaling of hematopoietic cells is the predominate manner IL-6 relates its pro-inflammatory effects [27].

Interestingly, IL-6 levels are increased in the serum of patients with active CD and UC compared to normal controls. A study looking at a known functional polymorphism of the IL-6 gene and the site of disease in CD patients did not demonstrate an association of IL-6 functional polymorphisms with CD or protection from CD. It did demonstrate that patients with the high producer genotype were more likely to have ileocolonic disease, while those with the low producer genotype had primarily colonic type disease, whereas those with intermediate producer genotype were more likely to have isolated ileal disease. These studies indicated an association of IL-6 production and site of disease [28]. The activity of IL-6 has made it an obvious target for clinical trials not only due to its pro-inflammatory effects but also due to its involvement in T-cell apoptosis [29]. A pilot study was performed [30] to investigate safety and efficacy of a humanized anti-IL-6R monoclonal antibody in patients with CD. This target appeared to be promising in these studies with 80% of the patients treated for 12 weeks demonstrating clinical improvement as compared to 31% treated with placebo.

Interleukin-12

IL-12 is a heterodimeric molecule composed of IL-12 p40 and IL-12 p35 subunits. IL-12 is secreted by antigen-presenting cells such as monocytes, macrophages, and dendritic cells, and to a lesser extent by NK cells. The most powerful inducers of IL-12 are bacteria, bacterial products, and parasites.

IL-12 is a pro-inflammatory cytokine that is important in the differentiation of naïve T-cells into IFN-γ producing pathogenic $CD4^+$ Th1 cells [15, 31]. In peripheral lymphocytes of the Th1 T-helper cell type, IL-12 induces the synthesis of IFN-γ, IL-2, and TNF-α. TNF-α also appears to be involved in mediating the effects of IL-12 on natural killer cells since an antibody directed against TNF-α inhibits the effects of IL-12. IL-12 and TNF-α are co-stimulators for IFN-γ production with IL-12 maximizing the IFN-γ response; the production of IL-12, TNF-α, and IFN-γ is inhibited by IL-10. In Th2 T-helper cells IL-12 reduces the synthesis of IL-4, IL-5, and IL-10.

This cytokine is considered a driving force behind chronic intestinal inflammation. Evidence for this comes forth from murine models of colitis by demonstrating that disease development could be inhibited by treatment with anti-IL-12p40 monoclonal antibodies [31]. In human studies, this master T-cell differentiating cytokine has been shown to be produced in large amounts in the intestines of patients with CD [32]. In addition, this cytokine has been targeted in human CD using various anti-IL-12p40 monoclonal antibodies and found to be effective in Phase 2 and Phase 3 multicenter trials [33, 34]. In the latter, significant clinical response and remission could be achieved in patients with moderate-to-severe active Crohn disease. Furthermore, the phase III UNITI trial also included a cohort of patients which failed TNF-α mAb, with significant response and remission rates demonstrated in this patient population. The long-lasting clinical effect observed may be due in part to the induction of apoptosis of the inflammatory effector cells. These studies suggest that in addition to IL-2, IL-12 is a necessary growth and survival factor for T-cells [35]. It also brings forth the point that the mechanism of action of the various anti-

biologic therapies lies not only in their capability to neutralize their respective cytokines but due to their ability to induce cell death of the inciting inflammatory effector cells. Interestingly, the p40 subunit is also found to be a portion of another significant pro-inflammatory master cytokine, IL-23. The positive effects observed in the anti-IL-12 p40 antibody may indeed be due to both the effects on IL-12 and IL-23 [32]. Further studies in models of colitis indicate that IL-23 is important in the inflammatory response in IBD in that it plays a significant role in the maintenance of Th-17 effective inflammatory cells [36].

Interleukin-17

The discovery of the Th17 cell lineage revolutionized our understanding of IBD pathogenesis. The Th17 type secretes IL-17 and IL-22. IL-17 has been associated with multiple immune regulatory functions. Most notably, IL-17 is involved in inducing and mediating pro-inflammatory responses. IL-17 induces the production of many other cytokines, such as IL-6, G-CSF, GM-CSF, IL-1β, TGF-β, TNF-α, chemokines including IL-8, GRO-α and MCP-1 and prostaglandins (e.g., PGE_2) from many cell types (fibroblasts, endothelial cells, epithelial cells, and macrophages). IL-17 expression is stimulated and/or maintained by IL-23 expression. These IL-17 expressing cells appear to be derived by a subset of CD4+ T-cells called T-helper-17 (Th17) cells, which are distinct from Th1 and Th2 cell lineage and need to be derived in the presence of IL-23; in addition, IL-17 may be derived to a lesser degree from monocytes and neutrophils [37]. Increased expression of IL-17 has been reported in the intestinal mucosa of IBD patients [38]. Some reports suggest that IL-17 alone is capable of inducing autoimmune tissue reactivity, whereas other groups suggest that IL-17 and IFN-γ synergize to stimulate this autoimmune reactivity [39, 40]. In these studies, it was indicated that T-cells and monocytes in the intestinal mucosa produce IL-17. IL-17 binds to the IL-17 receptor on endothelial cells and epithelial cells to promote secretion of pro-inflammatory substances that recruit inflammatory cells to the site [41]. In studies where the genes for either IL-17A or IL-17F were deleted, mice continued to develop severe colitis but when RORγτ (the transcription factor important for expression of all IL-17) genes was deleted minimal inflammation occurred in colitis models which suggests that the different forms of IL-17 are redundant but IL-17 together are important for the development of colitis. In addition, if both IL-17A and IL-17F were deleted, the colitis was ameliorated. Interestingly, as noted with other cytokines, it appears that IL-17 is not just simply an inflammatory cytokine. Recent murine studies in both chemically induced colitis as well as adoptive transfer colitis indicate that IL-17 plays a complex role in the inflammatory response. These studies showed that transfer of IL-17 deficient T-cells into an immunodeficient mouse led to more rapid onset of colitis that transfer of cells from WT mice. One explanation of this could be that Th1 cells bear IL-17 receptors and signaling through these receptors inhibits Th1 differentiation by suppressing the transcription factor T-bet. Thus, IL-17 may have pro- and anti-inflammatory properties. As a result of these roles, the IL-17 family has been linked to many immune/autoimmune-related diseases including rheumatoid arthritis, asthma, and lupus. IL-17 expression is increased in patients with a variety of allergic and autoimmune diseases, such as RA, MS, inflammatory bowel disease (IBD), and asthma, suggesting the contribution of IL-17 to the induction and/or development of such diseases. It must be stated that IL-17 may not appear to be the main cytokine important for inflammation in IBD, in those studies evaluating the effect of anti-IL-17A antibody, secukinumab for the treatment of Crohn disease have been disappointing and do not appear to have a therapeutic effect and may have worsened outcomes in CD, similarly in the use of the IL-17 receptor inhibitor, brodalumab, worsening of CD was noted compared to placebo. In a realm that is of interest in the development and progression of IBD, IL-17 has been identified as a key mediator of fibrosis in multiple organs including the intestine. As fibrosis is an important issue in IBD this makes understanding of IL-17 even more critical. Recently, Biancheri et al. demonstrated that IL-17 is upregulated in strictured tissue and that myofibroblasts express receptors for IL-17A [42]. An understudied area is the role of another IL-17 family member, IL-17C, which unlike its more studied relative IL-17A and F, does not appear to be produced by leukocytes but by epithelial cells. This cytokine shows increased concentrations in the tissues and serum of patients with UC and CD [43] and appears to activate the expression of multiple antimicrobial peptides [44]. While not a potent activator of the expression of pro-inflammatory cytokines, it has been shown to induce expression of IL-1β, TNFα, and IL-6 and likely enhance inflammation. It remains the current hypothesis that while IL-17 plays a role in inflammation in Crohn disease, the role is complex, and it appears that Th1 cytokines such as IFNγ may play a greater role.

Interleukin-23

IL-23 and IL-17 changed our view of the cytokines important in the development of IBD. Multiple murine colitis studies demonstrated that development of colitis appeared to be more dependent on IL-23 than on IL-12. IL-23 is a pro-inflammatory cytokine secreted by activated dendritic cells and macrophages that share structural homology with IL-12; specifically, it is composed of the p40 subunit and a unique p19 chain. Initial studies indicating an ameliorating effect of

an anti-p40 antibody in murine models of inflammation was felt to be due to its effect on IL-12. However, this effect was reevaluated and studies suggest that this ameliorating effect may be due to a decrease in IL-23 mediating effect. In these studies, mice deficient in the p19 subunit of IL-23 displayed attenuated inflammation in colitis models, whereas mice deficient in the p35 chain of IL-12 (therefore deficient in IL-12 but not IL-23) had no effect on colitis. These studies together suggest that the initial effects observed with anti-p40 in a variety of animal models may have been due to a decrease in IL-23. IL-23 promotes and stabilizes a novel subset of $CD4^+$ T-cells (TH17 cells) that is characterized by the production of IL-17, IL-6, and TNF-α and has been associated with autoimmune tissue inflammation [39]. Without IL-23, it has been noted that Th17 cells produce the cytokine IL-10. The exact mechanism by which IL-23 promotes The TH17 response has not been defined but it appears that TGF-β and IL-6 are important for the commitment into a TH17 cell and IL-23 is important for the proliferation of this cell type [45, 46]. Furthermore, recent studies may indicate a separate role for IL-23 in the occurrence of IL-17 expressing cells [47] whereby IL-23 may have a direct effect on regulatory T-cell development. Thus, in these animal studies mice that lack IL-23 fail to develop colitis, however this may not be secondary to the inability to produce IL-17 but rather because of the development of a dominant regulatory T-cell response. Moreover, Sunjino et al. demonstrated a dominant role for T regulatory cells in the suppression of colitis by blocking differentiation of TH17 into alternative TH1 type cells, therefore, establishing a significant role for this suppressive pathway [48].

IL-23 effect is not limited to TH17 cells but appears to have an effect of the innate immune system inducing monocytes and macrophages to produce pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α as well. In murine colitis studies where either IL-23 or the IL-23 receptor were deleted, it was shown that IL-23 plays a major role in the development of colitis. These studies also have shown an increase in the number of anti-inflammatory Treg cells suggesting that IL-23 may play a role in suppressing this cell type.

In addition, in a genome-wide association study in adults [49] as well as in a pediatric population [50], the IL-23 receptor (IL-23R) gene on Chromosome 1p31 has been shown to have a highly significant association with CD, specifically, an uncommon coding variant of the IL-23R gene was shown to confer protection. These data indicate that the IL-23 pathway may have a causal link to CD.

Interleukin-18

This cytokine initially identified as Interferon-gamma-inducing factor (IGIF), is like the IL-1 family in structure, processing, receptor and pro-inflammatory properties. It is produced by intestinal epithelial cells and induces other pro-inflammatory cytokines and Th1 polarization. IL-12 and IL-18 have a synergistic relationship. Their production by activated macrophages appears to drive the development of Th1 CD4+ T-cell predominance in the intestinal mucosa. Recombinant IL-18 alone is able to induce a proliferative response in vitro in freshly isolated mucosal lymphocytes from patients with CD. The synergistic effect is likely due to the up regulation of the IL-18 receptor by IL-12.

Intestinal mucosa from patients with CD have been evaluated and found to have increased expression of IL-18 [51] and this was also noted in experimental murine colitis [52]. Tissues from CD patients have been shown in vitro to decrease suppressive cytokine IL-10 expression after treatment with IL-18 indicating one possible effector mechanism. IL-12 and IL-18 together appear to synergize to drive the lamina propria lymphocytes into a Th1 type response. IL-12 appears to induce increased IL-18 expression thus the synergistic effect [53, 54]. Using models of colitis multiple laboratories have tried to block IL-18 and the results indicate that IL-18 may have a role in the initiation of intestinal inflammation, while others have shown that IL-18 acts to reduce inflammation.

An additional source for IL-18 production is the inflammasome pathway. The role, however, of the inflammasome to induce secretion of cytokines such as IL-1β and IL-18 is complex. While IL-1β appears to function as a pro-inflammatory cytokine in murine models of colitis [55–58], the function of IL-18 remains a duality. Thus, whereas studies have demonstrated that IL-18 is necessary for the induction of DSS colitis [55, 59, 60], further studies have shown that a deficiency in IL-18 secretion affords mice more susceptibility rather than more resistance to DSS colitis [61–63]. This correlated to studies which show that a deficiency in NLRP3 inflammasome pathway leads to increased susceptibility to DSS colitis, which appears to be secondary to decreased IL-18 expression [61, 62]. Alternatively, the NLRC4 inflammasome assembles in response to detection of bacterial invasion, and NLRC4 activation leads to the production of IL-18 and IL-1β which have been implicated in inflammation [64]. In fact, hyper inflammation found in patients with NLRC4 mutations can be treated with inhibition of IL-18 [65, 66], suggesting a pro-inflammatory function of IL-18. identifying a dichotomous effect of IL-18 including pro-inflammatory properties as well as an important role in epithelial cell restitution and repair after injury [63, 67].

In a separate but similar role IL-6, a cytokine that can also affect epithelial cells acts as a tumor promoter by affecting the carcinogenicity of these intestinal epithelial cells [68]. IL-18 can have effects on these cell types since $IL18^{-/-}$ and $Il18r1^{-/-}$ mice display increased susceptibility to DSS colitis-

associated cancer [63]. This effect of IL-18 may be through the cytokine IL-22 and its IL-binding-protein (22 bp), the latter a decoy protein that neutralizes IL-22. The interplay between these various cytokine pathways is shown by the fact that IL-22 and IL-22 bp can regulate epithelial cell growth/repair and control tumorigenesis while these aforementioned factors can be regulated by IL-18 and the NLRP3, NLRC4 or NLRP6 inflammasomes [67].

Interleukin-13

IL-13 can have a dual functional role in that it can downmodulate macrophage activity, reducing the production of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-10, IL-12) and chemokines (MIP-1, MCP) in response to IFN-γ or bacterial lipopolysaccharides. IL-13 can also enhance the production of the IL-1 receptor antagonist and decrease the production of nitric oxide by activated macrophages, leading to a decrease in parasiticidal activity. Yet, it appears that IL-13 is important in the development of Th2 type colitis such as the murine model of colitis oxazolone and its human component, UC [69]. In these studies, it was found that IL-13 produced by Natural Killer (NK) T-cells, when neutralized, led to decreased inflammation in the oxazolone model of colitis. Furthermore and most importantly, in human studies, these IL-13 secreting type II NK T-cells, (NK T-cells with non-invariant TCRs) recognize lyso-sulfatide glycolipid antigen; these cells bore IL-13Rα2 receptors and exhibited an increased cytolytic function against epithelial cell lines. Moreover, IL-13 itself has been shown to be directly toxic to epithelial cells as well as to cause increased permeability barrier functional defects [70]. Most recently, a correlative study of UC patients demonstrated that there were two divergent groups: a predominate group with high tissue IL-13 mRNA levels and a smaller group containing normal tissue IL-13 mRNA levels [71]. Of significance, the cohort group with high IL-13 expression exhibited more severe intestinal inflammation and extension of disease than their lower IL-13 counterparts.

Thus, in the oxazolone model of colitis and its human counterpart ulcerative colitis, it is believed that IL-13 secreting NK T cells play a role in the etiology of this disease entity. This is in contrast to the Th1/Th17 disease process discussed in the pathogenesis of CD. Although IL-13 can function as a pro-inflammatory molecule in UC it may also play a role in innate tumor surveillance pathways. In studies by Schiechl et al., tumor formation was accompanied by the co-appearance of F4/80 + CD11bhigh Gr1low macrophages, cells that undergo differentiation and activation by IL-13 and subsequently produce a source of tumor-promoting factor such as IL-6 after such activation [72]. In a similar vein, F4/80 + CD11bhigh Gr1intermediate macrophages after activation through IL-13 produced increased amounts of TGF-beta, a cytokine that inhibits tumor immunosurveillance.

Finally, clinical trials aimed at the IL-13 pathway have been performed. Although these trials did not meet their primary endpoints, they did reveal interesting findings concerning the IL-13 signaling pathway. In an initial trial, Anrukinzumab, an agent that binds to the IL-4/IL-13Rα1 complex and blocks signaling of IL-13 via the IL-13Rα1 pathway, was utilized [73]. As noted by the authors, these complexes consist of study drug and IL-13, which may be subsequently cleared through another IL-13 receptor pathway, IL-13Rα2. More recent findings demonstrate that the latter IL-13 receptor pathway, IL-13Rα2 and not the IL-13Rα1 pathway appear to be involved in the activation and secretion of IL-13 in ulcerative colitis [74]. Thus, the decreased efficacy of this trap molecule antibody directed against the IL-13Rα1 pathway may be expected based upon the former findings. The dose–response curves demonstrate some efficacy at low doses but not at higher levels. This might be explained by clearance of IL-13 initially but subsequently binding and activation of the aforementioned IL-13Rα2 pathway leading to decreased responses at higher doses. Finally, another monoclonal antibody, Tralokinumab directed at IL-13 itself had a significant remission rate as compared to placebo but did not achieve significance for response rate [75]. These results may demonstrate that a subgroup of patients may achieve a remission response; however, additional screening markers are necessary to evaluate these responder patients.

Interleukin-33

IL-33 is part of the IL-1 family and is expressed in various non-hematopoietic cells as well as in inflammatory cells (e.g., macrophages and dendritic cells) [76]. Similar to other IL-1 family members such as IL-1 and IL-18, IL-33 was originally thought to be synthesized as a 30-kDa-precursor molecule and then subsequently cleaved by caspase-1 upon inflammasome activation to its mature/bioactive 18-kDa form [77]. However, more recent studies have suggested that the full-length 30 kDa IL-33 (f-IL-33) is the bioactive form with decreased active forms (20–22 kDa) resulting from caspase cleavage [78, 79]. In addition, further reports indicate that the bioactive form may not depend upon any caspase cleavage [80]. Thus, IL-33 bioactive form can be regulated by cleavage through proteases, in particular, neutrophil serine proteases cathepsin G or elastase C, both released from neutrophils. Therefore, the inflammatory milieu may play a role in the generation of highly active mature forms of IL-33. This cytokine has both intracellular effects, as a transcrip-

tional repressor [81], and more classical cytokine-like extracellular effects.

The IL-1 receptor-related protein, ST2, is the IL-33 receptor and exists in two different splice variants. ST2L is a transmembrane receptor that confers IL-33's biologic effects, and sST2 is a soluble molecule that serves as a decoy receptor [77]. Signaling through ST2 receptor can drive cytokine production in a host of cell populations, which include type 2 innate lymphoid cells (ILCs) (natural helper cells, nuocytes), T-helper lymphocytes, mast cells, basophils, eosinophils, natural killer (NK), and invariant natural killer T (iNK T) cells [82, 83]. Thus, the IL-33/ST2 axis appears to play an important role in several chronic inflammatory disorders through the regulation of Th2 and/or Th17 cytokines responses such as IL-5, IL-9, IL-13, and IL-17 [76, 77, 84, 85]. Interestingly, studies on the effects of IL-33 have identified a regulatory effect on NFκB-induced pro-inflammatory signals, identifying an anti-inflammatory effect of overexpression of IL-33. Yet even more recent studies have demonstrated that IL-33 from intestinal epithelial cells in the setting of inflammation plays an active role in downregulating the Th17 cells and their secretion of IL-17 [86] and upregulation of Tregs and expression of IL-10 [87, 88].

Increased IL-33 production has been noted in murine models of colitis (i.e., oxazolone colitis, SAMP1-yit) as well as in ulcerative colitis [89, 90] when compared to healthy controls. Further studies of active UC patients reveal IL-33 production was localized to intestinal epithelial cells (IEC) and cells in colonic inflammatory infiltrates [84, 85, 89, 90]. This increase appears to be regulated in part by TNF-α as the latter can upregulate both IL-33 and sST2 and treatment of patients with anti-TNF-α monoclonal antibody decreases circulating levels of these molecules [84]. Of note, when assessing severity of ulcerative colitis, it has been shown that there is decreased expression of IL-33 noted in more severe ulcerative colitis [91] compared to less effected individuals suggesting an anti-inflammatory effect in UC. Further understanding of the dichotomous effects of IL-33 is critical to our understanding of how to target this cytokine in therapeutic studies.

Interleukin-37

IL-37 is an IL-1 family-related cytokine; however, in contrast to IL-1 related pro-inflammatory action of this gene family, it is anti-inflammatory in function. IL-37 is predominantly expressed by antigen-presenting cells such as macrophages or dendritic cells and can suppress a variety of inflammatory cytokine pathway signaling; IL-1β, IL-18, TNF, and IL-6 [92]. The IL-37 is a heterodimeric receptor which consists of the IL-1R8 (SIGIRR) and IL-18R1, both highly expressed within the gastrointestinal tract [93]. In prior studies, it has been demonstrated that although mice do not normally express IL-37, mice which carry a transgene to overexpress human IL-37 are protected from experimental dextran sodium sulfate (DSS) intestinal colitis [92, 94]. Furthermore, knockout mice that carry mutations in the IL-1R and IL-18R1/IL-18BP are more susceptible to the development of increased intestinal inflammation [95].

In related studies, silencing interleukin-37 (IL-37) in human $CD4^+CD25^+$ Tregs reduced the suppressive function of $CD4^+CD25^+$ Tregs. In addition, supplementation of rhIL-37 enhanced the suppressive function of $CD4^+CD25^+$ Tregs in naïve mice T-cells. Treatment with rhIL-37 was associated with increased expression of cytotoxic T-lymphocyte-associated antigen (CTLA)-4 and forkhead winged helix transcription factor p3 (FOXP3) on $CD4^+CD25^+$ Tregs. Finally, rhIL-37 increased the secretion of transforming growth factor-β1 (TGF-β1) but no other suppressive cytokines such as IL-10 in the $CD4^+CD25^+$ Tregs [96].

In human-related studies, patients with heterozygous IL-37 variants may have increased joint inflammation [97]. In addition, expression levels of IL-37 may be associated with a more modified IBD disease course [98]. In a more recent report, an initial case of a homozygous loss of function human IL-37 mutation was observed in a two-year-old child from a consanguineous family [99]. He presented at four-month old with recurrent bloody diarrhea with mucous eight to nine times per day and significant cachexia. As an infant, he was maintained on a hypoallergenic diet but continued to demonstrate inflammatory changes which encompassed on colonoscopy findings of diffuse ulcers with wide-based crater formation throughout the colon and rectum, but a normal appearance to the ileum, supported a diagnosis of infantile onset inflammatory bowel disease. In addition, significant lymphocytic infiltration with cryptitis and apoptotic crypt abscesses were also observed throughout the colon and rectum.

No abnormalities were found on immunophenotyping profile studies. Given the familial consanguinity and infantile onset IBD findings, a whole-exome sequencing analysis was performed which a *IL37* chr2: g.113676259 T > C (p.Ile177Thr) missense variant, thought to be pathogenic by Combined Annotation Dependent Depletion (CADD) scoring. This mutation destabilizes the protein structure to promote accessibility of the mutated amino acid change. IL-37 protein expression and stability studies demonstrated higher levels of IL-37 protein within cells albeit less stable in structure and therefore targeted for degradation. In functional analysis studies, as mutant IL-37 cannot be stably expressed, it was found that it did not properly inhibit pro-inflammatory cytokines generation.

These studies gives additional insight into monogenic VEO-IBD and in the long-term further studies may shed light on the significance of IL-37 effects on T regulatory sup-

pressive function and role of the IL-1, IL-18 and IL-37 axis in colonic homeostasis.

Interleukin-9

IL-9 is another Th2-related cytokine that appears to be involved in IBD pathogenesis. Production of IL-9, by Th9 cells, is induced in naïve T-cells by TGF-β and IL-4 in concert with additional cytokines (i.e., IL-1β and IL-25). This cytokine was initially identified as a Th2-type cytokine by its ability to induce Th2 inflammation in disease states such as parasitic infection, allergy, or autoimmune states [100–102]. Recent studies have elucidated the role of IL-9 in IBD, which demonstrated increased levels of this cytokine in UC and in CD [103, 104] both in the serum of affected patients as well as in intestinal biopsies. Studies of the murine colitis model, oxazolone colitis, revealed that mice lacking IL-9 develop no or reduced disease. However, mice deficient in IL-9 also manifest amelioration of several Th1/Th17murine colitis models, including cell-transfer colitis; thus, IL-9 contributes to inflammation in a variety of Th1/Th2/Th17 intestinal inflammatory conditions [105]. The mechanism by which IL-9 may have broad effects on intestinal inflammation is the ability to alter epithelial barrier function via effects on tight junction proteins. The junction complex protein Claudin 8 (CLDN8) was identified as a critical downstream component of the IL-9 inflammatory cascade [104].

Tumor Necrosis Factor-Like Ligand (Tl1a)

TL1A is a cytokine that appears to contribute to intestinal inflammation; however, it does not appear to be uniquely associated with TH1/TH2 or TH17 cells and appears to be within the category of cytokines that can bridge the T-cell spectrum. This cytokine is secreted by T-cells, antigen-presenting cells, and endothelial cells [106]. Studies involved in elucidating the exact function of TL1A indicate that TL1A enhances baseline T- and B-cell activation by T-cell receptor activation.

The significance of TL1A to intestinal inflammation is demonstrated in the studies where exogenous administration of TL1A to mice with Dextran sodium sulfate (DSS)-colitis increased both TH1 and TH17 responses. Furthermore, the administration of antibodies to TL1A led to the amelioration of colitis in the DSS and TNBS model of intestinal inflammation [107, 108]. While effects on TH1 and TH17 production have been associated with TL1A, in recent studies of mice carrying a transgene for TL1A, intestinal inflammation of the small intestine was developed, which appeared dependent on IL-13 [108]. In separate studies, TL1A was found to inhibit the induction of new $FOXP3^+$ regulatory cells and or the expansion of existing subsets [109]. Thus, these studies suggest that TL1A is a cytokine that optimizes both TH1/TH2 and TH17 responses either through direct effects on these cell lineages or through effects on suppressor T regulatory cell pathway.

The costimulatory activities of TL1A induces cytokines associated with inflammation, such as IL-2, IFNγ, IL-13, and IL-5 from T-cells, while the latter (IL-5/IL-13) can also be generated from innate lymphoid cells (ILC type 2) [110–114]. TL1A can also costimulate additional intestinal innate lymphoid cell groups (ILC3), with divergent effects. In combination with the ILC stimulatory cytokine IL-23, TL1A can enhance the secretion of the regulatory cytokine IL-22 [114, 115]. IL-22, as noted above, can induce antimicrobial peptides, which can affect intestinal barrier homeostasis [113–115]. Therefore, TL1A can play a role in both pro-inflammatory and regulatory function through costimulation of ILC populations.

Turning to human studies, elevated TL1A has been noted in both CD and UC indicating again that TL1A is not associated with a unique T-cell differentiation cell lineage [106]. Furthermore, lamina propria CD14+ macrophages in CD patients produced increased amounts of TL1A and the latter increased T-cell production of IFN-gamma and IL-17 from allo-antigen-stimulated T-cells (but had no significant effect as a lone stimulus reiterating the mouse model data demonstrating a co-stimulatory effect of TL1A) [116]. Finally, polymorphisms in the TL1A gene have been observed in CD patients indicating a possible significant clinical function to this cytokine [117].

Anti-Inflammatory Cytokines

As the host requires a pro-inflammatory response in the presence of a stimulating antigen, so too, the host requires a balancing anti-inflammatory response once the antigen has been dealt with or the offending infection has been cleared. Without the ability to turn off or downregulate the immune response the inflammation becomes overwhelming and can be detrimental to the host. This issue is exemplified in patients with the disease known as IPEX (immune dysregulation, polyendocrinopathy, and enteropathy, X-linked). This syndrome is characterized by the development of overwhelming systemic autoimmunity in the first year of life. It is associated with mutations identified in the *FOXP3* gene. FOXP3 is a member of the forkhead/winged-helix family of transcriptional regulators known to be specific to regulatory T-cells and important for their function. Without functional Treg cells, the activated immune system has little or no halt to the inflammatory process. Tolerance, in normal hosts, is mediated by these regulatory T-cells, as well as B lymphocytes, natural killer T-cells and dendritic cells that secrete

transforming growth factor (TGF-β), interleukin (IL)-10, interferon (IFN)-α/β, and prostaglandin J2. Another mechanism for regulation is the secretion of anti-inflammatory cytokines. As these cytokines are defined, they are being evaluated for methods to increase their secretion or for systemic therapy with the cytokine itself to treat IBD.

Transforming Growth Factor-Beta

TGF-β belongs to a family of multifunctional polypeptides produced by a wide variety of lymphoid and non-lymphoid cells. They exist in five different isoforms, three of which are expressed in mammals and designated as TGF-β1, TGF-β2, and TGF-β3 [1].

TGF-β can act in both autocrine and paracrine modes to control the differentiation, proliferation, and state of activation of immune cells. TGF-β can inhibit the production of and response to cytokines associated with CD4+ Th1 T-cells and CD4+ Th2 T-cells [118]. TGF-β inhibits the proliferation of T-lymphocytes by downregulating predominantly IL-2 mediated proliferative signals. It also inhibits the growth of natural killer cells in vivo and deactivates macrophages. Of significance, TGF-β has been shown to be important in stimulating the development of FOXP3$^+$ T regulatory cells from naïve CD4+ T-cells.

These activities have been verified by animal models of IBD [119]. These studies indicate that TGF-β production is relevant in the pathogenesis of experimental colitis. In two different models of Th1-mediated murine experimental colitis, it has been shown that protection from colitis development is strictly associated with the presence of increased numbers and/or upregulation of TGF-β1-producing cells. In these studies, T-regulatory cells were first characterized by the surface marker CD25 and that transfer of CD4$^+$ T-cells depleted of CD4$^+$CD25$^+$ cells into recipient mice recovered their ability to induce intestinal inflammation in a murine cell transfer colitis model [120]. Recently, further studies revealed that these CD25+ T-cells are indeed the same T regulatory cells which bear the more familiar marker FOXP3. In addition, it has also been shown that TGF-β can be expressed on the surface of CD4$^+$CD25$^+$ T regulatory cells in association with latency-associated peptide (LAP), and it is LAP molecule, which mediates CD4$^+$CD25$^+$ T cell suppression in in vitro suppression assays, and furthermore, that CD4$^+$LAP$^+$, but not CD4$^+$LAP$^-$, T-cells can convey protection against the development of colitis in murine intestinal inflammatory models [121]. Recently, a novel therapy targeting TGFβ expressing cells has been evaluated [122]. The target of this therapy is the expression of Smad7; Smad7 has been shown to inhibit the signaling of TGFβ in the setting of inflammation [123, 124]. The pharmaceutical Mongersen (GED0301) has been developed as an anti-sense RNA to inhibit the expression of Smad7. By inhibiting the expression of Smad7, there is an increase in TGFβ expression and concurrent decrease in inflammation. Unfortunately, treatment with Mongersen did not meet the Phase III study endpoints.

The Th17 T-cell pathway or specifically a major component of this pathway, IL-23, has been demonstrated to negatively influence regulatory T-cell development and/or responses. It has been demonstrated that IL-23p19-deficient mice exhibit an increased number of T regulatory cells in the colon [125]. Furthermore, the numbers of FOXP3$^+$ T regulatory cells in the colon of Rag$^{-/-}$-recipient mice (mice lacking T- and B-cells) reconstituted with IL-23 receptor-deficient T-cells are increased [47]. Thus, these findings show that IL-23 skews the development of inflammation by mediating Th17 effector cell responses and by inhibiting FOXP3$^+$ regulatory T cell differentiation. Recent studies, however, have demonstrated that a cytokine constitutively expressed by epithelial cells, in the response to tissue damage, namely IL-33, enhances regulatory T cell stability and function in murine transfer cell colitis [80]; moreover, T regulatory cells, which lacked the IL-33 receptor (ST2) were shown to be unable to protect mice from development of colitis in the aforementioned transfer colitis model [126]. Of note, an important role for the transcription factor GATA-3 was found in regulatory T-cell function [127, 128] as ST2 expression in T regulatory cells was significantly dependent on GATA-3 [126]. Importantly, as noted above, IL-33 is found in inflamed tissues of IBD patients and may function to bring inflammation under control via T regulatory cell differentiation.

In humans, the data pertaining to regulatory cells remain sparse. Maul et al. [129] have shown that there exists a decrease in FOXP3-expressing cells in the periphery of IBD patients. However, examination of mucosal tissue reveals that as compared to controls, IBD patients had a relative increase in these cells albeit this increase was less than that seen in other inflammatory disorders such as diverticulitis. The authors postulated that there is a relative lack of counter-regulation in IBD patients at the mucosal level and therefore an inability to increase the number of local resident regulatory cells in the face of inflammation. Similarly, in studies conducted in children naïve to treatment, it was demonstrated that the percentage of CD4+ T regulatory of the inflamed CD or UC intestine is increased as compared to that from control individuals [130]. Furthermore, in CD, an increase in Treg numbers could be secondary to affects from local dendritic cell subpopulation, which expresses increased amounts of the integrin αVβ8, an integrin that activates TGF-β [131].

More recently, transcriptional gene network analysis revealed a close association of FOXP3 with EZH2 [132]. EZH2 is a gene that participates in DNA methylation and

therefore transcriptional repression. Mutation or overexpression of EZH2 has been associated with many forms of cancer as EZH2 inhibits genes responsible for suppressing tumor development. In studies pertaining to regulatory cell generation and function, potential coordinated functions between FOXP3 and EZH2 were identified. Genetic ablation of EZH2 resulted in T regulatory instability and conversion to Th1/Th17 effector cells in a murine model. Furthermore, these T regulatory cells failed to ameliorate DSS or T-cell-mediated colitis. Thus, it was suggested given the above information that the defect in IBD may not be due to a failure in regulatory cells enumeration but suppressive function. In follow-up studies, however, FOXP3+ Tregs from IBD patients have been demonstrated to have normal capacity to suppress effector cells [133].

This, however, led to further studies to elucidate whether a deficiency in other suppressor TGF-β associated cells might cause disease. This appears not to be the case, as Butera et al. demonstrated that FOXP3-negative suppressor cells occur that bear surface TGF-β in association with latency-associated peptide (LAP) and that these cells regulate the extension of disease in UC [134].

Interleukin-4

IL-4 is produced mainly by a subpopulation of activated T-cells (Th2), which are the biologically most active helper cells for B-cells and which also secrete IL-5 and IL-6. Another subpopulation, Th1 also produces IL-4 albeit to a lesser extent. IL-4 is a stimulatory molecule for both B and T cells that has known immunosuppressive effects in the intestine and it promotes the proliferation and differentiation of activated B-cells and the expression of MHC class 2 antigens.

IL-4 enhances the expression of MHC class 2 antigens on B-cells. It can promote their capacity to respond to other B-cell stimuli and to present antigens for T-cells. While IL-4 is frequently described as an anti-inflammatory cytokine, recent studies have shown its capacity to perpetuate inflammatory diseases. Specifically, in a murine model of ileitis, a monoclonal antibody against IL-4 was shown to suppress disease severity [135]. Interestingly, IL-4-mediated disease in certain animal models appears to be most important in inflammation limited to the ileum and small intestine [136]. In the aforementioned oxazolone model of colitis, IL-4 is the predominant initial cytokine to appear in the mucosal lesions; however, this is subsequently superseded by an IL-13 response. This coincided with what one sees in the IBD disease entities as no significant measurable secreted levels of IL-4 have been found in either UC or CD patients to suggest a pathogenic role. Thus, IL-4, as with IL-13, displays both anti-inflammatory and inflammatory cytokine properties. Its targeting it for therapy in animal studies has had some beneficial effects. Its targeting in human disease is not as clear.

Interleukin-10

IL-10 is a critical regulator of intestinal homeostasis and has been shown to inhibit pro-inflammatory cytokines and activate regulatory T-cell function and gene expression. IL-10 is produced by activated $CD8^+$ peripheral blood T-cells, by T-helper $CD4^+$ T-cell clones after both antigen-specific and polyclonal activation. IL-10 is also produced by macrophages, dendritic cells, and B-cells. IL-10 affects both innate and adaptive immune cells modulating multiple functions of pro-inflammatory cells. IL-10 inhibits the synthesis of a number of cytokines such as IFN-γ, IL-2, and TNF-α in Th1 T-helper subpopulations of T-cells but not of Th2 T-helper cells. This activity is antagonized by IL-4. The inhibitory effect on IFN-γ production is indirect and appears to be the result of a suppression of IL-12 synthesis by accessory cells. In the human system, IL-10 is produced by, and downregulates the function of, Th1 and Th2 cells. In macrophages stimulated by bacterial lipopolysaccharides, it inhibits the synthesis of IL-1, IL-6, and TNF-α by promoting, among other things, the degradation of cytokine mRNA. It also leads to an inhibition of antigen presentation. The activation of macrophages can be prevented by IL-10. In human monocytes, IFN-γ and IL-10 antagonize each other's production and function. IL-10 has been shown also to be a physiologic antagonist of IL-12. In macrophages stimulated with bacterial lipopolysaccharides, IFN-gamma increases the synthesis of IL-6 by inhibiting the production of IL-10.

In B-cells activated via their antigen receptors or via CD40, IL-10 induces the secretion of IgG, IgA, and IgM. This effect is synergized by IL-4, while the synthesis of immunoglobulins induced by IL-10 is antagonized by TGF-β. It has been shown that human IL-10 is a potent and specific chemoattractant for human T-lymphocytes. Finally, IL-10 also inhibits the chemotactic response of CD4(+) cells, but not of CD8(+) cells, toward IL-8. In support of its role in IBD, mice deficient in IL-10 (IL-10−/−) gene spontaneously develop chronic colitis. In humans, patients with mutations in IL-10 or the IL-10 receptor (IL-10R) develop a severe form of IBD presenting in the first year of life demonstrating a critical anti-inflammatory pathway in IBD [137, 138]. Identifying one of the first known etiologies for Very Early Onset Inflammatory Bowel Disease (VEOIBD). Understanding of the etiology of this monogenic IBD identified a therapy for patients with defects in IL-10 or IL-10R using allogeneic hematopoietic stem cell transplant [139]. With this information, recombinant IL-10 has been used as therapy in patients

with CD. While initial studies appeared positive, upon further evaluation in larger clinical trials, results were not noted to be significant. Due to the concern that IL-10 was not delivered in significant quantities to the local mucosal level, another approach was attempted using "Turbo Probiotics." This was done by engineering *Lactobacillus lactis* to secrete IL-10 specifically at the intestinal level. A similar construct has been tried in patients with IBD, but results are lacking.

Interleukin-22

Interleukin-22 (IL-22) is a member of the IL-10 cytokine family [140]. IL-22 has been shown to induce proliferative, anti-apoptotic pathways as well as assist in tissue repair [141] and production of antimicrobial peptides [142]. IL-22 is secreted by both innate immune cells (NK cells and dendritic cell) as well as adaptive immune cells such as $CD4^+$ and $CD8^+$ cells. However, because its receptor is predominantly found on innate cell populations, it appears to regulate these cells and not adaptive immune cells [143]. IL-22 has been identified as an antimicrobial and pro-regenerative cytokine in IBD. This cytokine activates its function via the JAK/STAT pathways, specifically the STAT3 activation [144] appears to be quite strong similar to other IL-10 family members.

IL-22 is produced by a wide variety of cells, in innate lymphoid cells [145] in an IL-23-dependent manner, while it is produced by $CD4^+$ T-cells in an IL-6-dependent manner. Specifically, Th1 and Th17 cells [146] have been shown to secrete IL-22 after exposure to IL-6 and this secretion is somewhat inhibited by TGF-β. In addition, there is another Th cell type identified in human peripheral blood, which is defined by IL-22 secretion without IL-17 or IFNγ secretion now termed the Th22 cell [147], although their role is not well understood in the intestinal immune response.

Recent studies have identified a protective effect of IL-22 in IBD. In multiple models of colitis including epithelial cell disruption models as well as T-cell-mediated models of colitis, lack of IL-22 expression worsened the colitis or delayed recovery [148] and injection of IL-22 could ameliorate severe colitis. IL-22 also affects the production of antimicrobial proteins, which can protect against pathogenic bacteria and other infectious agents [149]. Although increased levels of IL-22 have been observed in patients with IBD, its effect may be altered in that it is accompanied by increased production of antagonistic IL-22 Binding Protein (BP) [150]. In humans, IL-22 has been associated by GWAS with multiple susceptibility genes including IL-23, IL-23R [151], as well as the IL-22 gene location within the ulcerative colitis risk locus at 12q15 [152]. No human studies to affect IL-22 expression or function are ongoing at this time in IBD, but studies in other diseases such as psoriasis are ongoing [153].

Summary

As evidenced above, there are a multitude of cytokines that are involved in the inflammatory response of the mucosa in inflammatory bowel disease. These cytokines can have pleiotropic effects including pro- and/or anti-inflammatory effects and are important in the pathogenesis of IBD as well as other autoimmune diseases. The above described cytokines are those that were deemed most significant to inflammatory bowel disease, but there are multiple other cytokines that are currently being evaluated or are as yet unknown that may in the future be targets for therapy of IBD.

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The Gut Microbiota and Inflammatory Bowel Disease

4

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Abbreviations

AIEC	Adherent and invasive *E. coli*
AMP	Antimicrobial peptide
CD	Crohn disease
CDI	*C. difficile* infection
EN	Enteral nutrition therapy
FMT	Fecal microbiota transplantation
GWAS	Genome-wide array studies
IBD	Inflammatory bowel disease
ILC	Innate lymphoid cells
MAP	*Mycobacterium avium* subspecies *paratuberculosis*
NLR	Nucleotide-binding domain and leucine-rich repeat-containing receptor
NOD1	Nucleotide-binding oligomerization domain protein 1
PAMP	Pathogen-associated molecular pattern
PRR	Pattern recognition receptor
SCFA	Short-chain fatty acids
TLR	Toll-like receptor
TNF	Tumor necrosis factor
UC	Ulcerative colitis

Introduction

Inflammatory bowel disease (IBD), comprised of Crohn disease, ulcerative colitis, and indeterminate colitis, is a chronic inflammatory disease of the gastrointestinal tract. It is due to an aberrant immune response to environmental factors in a genetically susceptible host. The gut microbiota and its metabolites are thought to be critical environmental factors in the development of IBD. As a result of these different disease drivers, within the IBD subtypes, the phenotype and disease course are quite heterogeneous [1].

There is significant evidence to support the role of gut microbes in the development of IBD. Animal studies of IBD have demonstrated that germ-free animals show little sign of inflammation [2]; however, inflammation develops with exposure to microbes [3]. Adaptive immune responses to bacterial antigens have been shown to lead to the spontaneous development of colitis through immune activation and/or the loss of immune tolerance in various models [4]. From a clinical standpoint, inflammation in CD and UC occurs predominantly in the terminal ileum (in CD) and colon (both UC and CD) where the greatest concentrations of bacteria are found. Antibiotics can have efficacy in the treatment of IBD [5–7], and recently, therapy using a combination of antibiotics has been shown to be effective in patients with severe colonic disease [8, 9]. Furthermore, the fecal flow exacerbates IBD, and surgical diversion of the flow ameliorates the disease [10, 11]. From a more descriptive standpoint, studies have found that there are increased amounts of bacteria in the mucus layer in biopsy specimens of patients with IBD as compared to controls [12]. However, genetic studies have provided some of the strongest support for the role of microbiota in the development of IBD. Genome-wide association studies (GWAS) have identified >200 genetic risk loci, with 28 shared between CD and UC [13, 14]. Many of the genes and genetic loci identified involve pathways which are critical for the protection of the host against the gut microbiota, such as regulation of the epithelial barrier, microbial defense, and autophagy, as well as pathways involving regulation of the innate and adaptive immune systems [13]. Together, these aberrations support the notion that IBD is due to the inability of the host to protect against microbial invasion combined with an unrestrained immune activation.

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Characteristics of the Gut Microbiome

The human gut microbiome is one of the most densely populated bacterial communities on Earth with up to 10^{11} organisms per gram of fecal weight composed of over 1000 species, most of which are obligate anaerobes [15, 16]. The bacterial concentration, as well as complexity, increases proximally from the stomach and duodenum, where there are approximately 10^2–10^3 aerobic organisms/gram luminal contents, to 10^{11}–10^{12} distally where anaerobic organisms predominate in the cecum and colon [4]. Throughout, the collective genome of the bacteria is 100-fold greater than that of its human host [17]. Indeed, humans should be viewed as a biologic "supraorganism" that is dynamic and carries out functions in parallel or cooperatively. Roles of the microbiota include immune education and metabolism. Although there are over 50 bacterial phyla on Earth, a majority of the bacteria in the human adult gut largely belong to one of four phyla, *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteroidetes* [18, 19].

Most gut microbes are obligate anaerobes, many of which are fastidious and difficult to grow in vitro making traditional culture techniques of limited value in characterizing the composition of the gut microbiota. The development of culture-independent methods, mainly through the use of high-throughput DNA sequencing, has provided new means to evaluate the gut microbiome and its relationship to IBD. There are two primary methods that utilize deep-sequencing technologies to characterize the microbiome. The first approach uses small-subunit ribosomal RNA (16S rRNA gene sequences (for Archaea and Bacteria) or 18S rRNA gene sequences (for eukaryotes)) as stable phylogenetic markers to define the lineages present in a sample [20]. Another approach uses shotgun metagenomic sequencing. This sequences the total community DNA, thereby allowing for the microbial community structure and genomic representation of the community to be evaluated. The genomic community evaluation provides an understanding of the functions encoded by the genomes of the gut microbiota [17]. Metatranscriptomics and metaproteomics provide a deeper understanding of microbial function through direct evaluation of gene expression [21].

These advances in sequencing technologies have allowed investigators to characterize the bacterial composition of the gut throughout different stages of life, a critical step in the study of health and disease. Colonization of the gut begins at birth, and individual characteristics of the gut microbiome begin to arise during infancy and throughout the first year of life. This process is dependent on several factors including the mode of delivery and form of infant feeding. During the first year of life, the human gut microbiome becomes more stable and adult-like [22] concurrent with the introduction of solid foods into the diet [23]. Interindividual differences in the characteristics of the bacterial microbiota observed early in life, within months, persist at 1 year of life [22]. Indeed, interindividual differences in the gut microbiome are the largest source of variance among healthy individuals that appear to be relatively stable over time, at least in the short term [18].

Characteristics of the Gut Metabolome

With ongoing characterization of the composition of the gut microbiota community structure, further studies have interrogated how it actively impacts host function through their produced metabolites. These are central to the mutualistic relationship that can ultimately result in a state of health or disease.

The metabolic products of the microbes are likely even more diverse than the microbiome, and they function as regulators of the immune system, neuronal signaling molecules, and even maintain homeostasis in the microbial community structure of the gut through their antimicrobial properties. These functions are carried out in part through fermentation of indigestible carbohydrates to produce short-chain fatty acids (SCFA) that are utilized by the host, biotransformation of conjugated bile acids, synthesis of certain vitamins, degradation of dietary oxalates, and education of the mucosal immune system [24]. Butyrate, along with other SCFA, is a primary energy source of enterocytes that can be transported intracellularly and activate anti-inflammatory signaling to maintain homeostasis. Bile acids, on the other hand, require bacteria for deconjugation. Bile acids have direct antibiotic effects on microbes in the intestine and indirect effects through FXR-induced antimicrobial peptides. Generated insight into the dynamic microbial environment in the gut has shown that the mutualistic relationship is mediated through the host microbe cross-talk at the mucosal interface.

Targeted and untargeted metabolic profiles can be obtained with various chromatographic techniques, including mass spectrometry systems and high-performance liquid chromatography. Targeted metabolomics allows for absolute quantification of a specific set of metabolites, such as bile acids, short chain fatty acids, or amino acids. Untargeted evaluation of the low-molecular weight molecules uses biochemical features such as retention time and mass to charge ratio for annotation and to determine the relative abundances. However, there remains a lack of standard reference material for many metabolites and identification cannot be inferred from fragments of the metabolites [25].

Diet and the Gut Microbiome

Together with increase in incidence of certain diseases, many environmental changes have occurred over the last several decades. These changes in modern lifestyle have been implicated in the alteration of the gut microbiome, including improved sanitation, increase in antibiotic use, less crowded living conditions, decline in *H. pylori*, smaller family size, vaccinations, refrigeration, decline in parasite infections, sedentary lifestyle, cesarean section, food processing, and diet changes [26].

The development of agriculture and domestication of animals have been major factors in recent human evolution [27] with the resultant changes in diet perhaps altering the host–gut microbiome relationship [28]. Over time in industrialized nations, there has been a reduction in fiber consumption with an increase in simple sugars, fats, and proteins. It has been hypothesized that this change in diet may have altered the interaction of the host and the microbiota in a manner that has played a role in the increasing incidence of metabolic disorders [28]. Furthermore, fluctuations in diet may have consequences for the bacteria and the host, allowing for predisposition to invasion or inflammation [29].

There has been recent evidence demonstrating the relationship between the gut microbiota and diet. An analysis of fecal 16S rRNA sequences from 60 mammalian species indicated clustering according to host phylogeny as well as clustering according to diet (herbivore, carnivore, and omnivore) [30]. Cross-sectional studies using shotgun metagenomic sequencing have suggested that there has been a functional evolution of the gut microbiome in relation to diet [31]. Microbial genes encoding for enzymes involved in carbohydrate and amino acid metabolism are dissimilar between herbivores and carnivores [31].

A study by Wu et al. focusing on the effect of diet on the gut microbiome revealed differences in the impact of habitual long-term versus short-term diet [32]. Long-term diet, similar to a "Westernized" diet (high in meats and fats, low in carbohydrates), was associated with high levels of *Bacteroides* and low levels of *Prevotella* genera. Diets high in carbohydrates but low in animal protein and fat had higher levels of the *Prevotella* and lower levels of *Bacteroides*. These results provide an explanation for previously described clustering of individuals into "enterotypes" dominated by *Bacteroides* and *Prevotella* based on the composition of the gut microbiota and not correlated to host properties such as age, gender, ethnicity, or body mass index [33]. These observations are also consistent with a study comparing the gut microbiome of children from a village in the West African country of Burkina Faso to those in Europe [34] where the inverse relationship between *Bacteroides* and *Prevotella* genera was also noted. These three studies suggest that long-term diet helps to distinguish a gut microbiota community or enterotype that is associated with a "Westernized" diet rich in *Bacteroides* from an enterotype associated with an agrarian diet where the bacteria of the *Prevotella* genus predominate. In addition, studies of monozygotic twins to assess host genotype influences on enterotypes showed most twin pairs had similar enterotypes longitudinally, although many of these subjects likely share similar diets and environments [35]. Enterotypes may function as a marker of disease; however, further studies are needed.

Gut Microbiota–Host Interactions at the Mucosal Interface

The alteration of the gut microbiota has a direct effect on the host's immune system. Mammalian hosts have coevolved to exist with our gut microbiota through a mutualistic relationship, where the host provides a uniquely suited environment in return for physiological benefits provided to the host by its gut microbiota [24]. Indeed, when viewed as a whole, the "supraorganism" of the gut can carry out enzymatic reactions distinct from those of the human genome and harvest energy that would otherwise be lost to the host. The consequences of these enzymatic reactions suggest that over the millennia, mammalian metabolism, physiology, and disease have shaped and have been shaped by the gut microbiota. Commensal bacteria may also directly inhibit the growth of specific pathogens, such as *Clostridium difficile*, by competitive inhibition thus preventing an adequate niche for expansion.

Relevant to pediatric IBD, the gut microbiota develops between birth and the first few years of life and each exposure during this time impacts the microbial structure. This may be particularly germane to very early onset IBD, as this dynamic period is the time that the disease develops. Further evidence supporting the role of the microbiome in VEO-IBD is the drastic increase in incidence of this population, which cannot be explained alone by the strong genetic drivers identified in this population. The relationship between host genetics and developing microbiome has been shown through germ-free (GF) murine models. GF mice have underdeveloped gut-associated lymphoid tissue. In an environment with specific defined flora, the gut microbiota elicits host-specific T-cell response and differentiation [36]. Concurrently, the aberrant T-cell development of GF mice shapes the gut microbiome, as seen by the different phylogenetic compositions of the microbiota in Rag1-deficient mice [37]. Zebrafish models show similar findings, in which Rag1-deficient zebrafish had overgrowth of *Vibrio* species [38].

In general, the interaction between the gut microbiota and the mammalian host is complex but can be roughly divided into

three major categories: the innate immune system, the adaptive immune system, and the intestinal epithelial interface.

The Innate Immune System

The innate immune system rapidly responds as the first line of defense against invading microbes. It encompasses receptors that recognize the microbial patterns, pattern recognition receptors (PRRs), serve as sensors of pathogen-associated molecular patterns (PAMPS) and reside in the lumen of the intestine [39]. The most studied PRRs are the Toll-like receptors (TLRs). PRRs are expressed on many cell types and activate an inflammatory response via NF-κβ activation, cytokine production, and recruitment of acute inflammatory cells [40]. TLR signaling in the intestine is important in homeostasis of the intestine through a variety of functions including epithelial cell proliferation [41], IgA production [42], antimicrobial cytokine production and peptide expression, and maintenance of tight junctions [43]. Nucleotide-binding domain and leucine-rich repeat-containing receptors (NLRs), another class of innate immune receptors, have the ability to respond to different stimuli with an inflammatory response. Examples of NLRs include nucleotide-binding oligomerization domain protein 1 (NOD1) and NOD2. NOD2 is highly expressed in monocytes and Paneth cells, and its ligand is common to both Gram-positive and Gram-negative bacteria. Rehman demonstrated via murine models that NOD2 is integral in the interaction between the host and the microbiota and for the development of the intestinal flora [44]. Disruptions in TLR and NLR expression have also been associated with intestinal dysbiosis [45, 46]. Notably, *NOD2* was the first gene associated with the susceptibility for Crohn disease.

The Adaptive Immune System

Innate immune signaling through the activation of PRRs or NLRs cannot distinguish between commensal and pathogenic bacteria. The adaptive immune system, involved in both humoral and cell-mediated immunity, has evolved to regulate immune responsiveness by selectively responding to or ignoring individual antigens based on previous encounters [47]. A lack of this immune tolerance results in unrestrained immune activation and subsequent inflammation in the absence of a microbial pathogen, the hallmark of immune-mediated diseases such as IBD. Studies in germ-free mice demonstrate that the gut microbiota plays a critical role in helping to shape adaptive immune function through the production of IgA [48], development of Th17-producing lymphocytes [49], as well as T regulatory cells [50], which play a critical role in the maintenance of immune tolerance [51].

In addition, innate lymphoid cells (ILCs) are innate immune cells without antigen-specific responses. There are three types, and they are functionally associated with T-cells with lymphoid lineage that also regulate effector T-cell response against commensal organisms. Group 3 ILCs are RORγt+ and produce IL-22 and/or IL-17 with stimulation by IL-23 and IL-1ß. ILCs are regulated by commensal organisms as the production of IL-22 is reduced in the absence of the microbiota [52]. Similar to the innate immune system, multiple gene variants associated with IBD involve components of the adaptive immune response including T- and B-cell regulation and the IL-23/Th17/T regulatory cell axis [13].

The Intestinal Epithelium

The intestinal epithelium functions as a physical and chemical barrier to separate the luminal gut microbiota from the host, by example through mucus secretion, and functions as an immune response. It produces antimicrobial peptides (AMPs) such as defensins, lysozyme, C-type lectins, and cathelicidin, some of which are produced by Paneth cells located at the base of small intestinal crypts [53]. Human genetic variants associated with IBD have been identified in a number of these pathways demonstrating that alterations in host innate immune protection from the gut microbiota play a role in the development of IBD. Among these include genes involved in epithelial barrier function, restitution, and solute transport as well as genes known to have an effect on the biology of Paneth cells [13, 54]. With respect to the latter, genetic polymorphisms in ATG16L1, associated with Crohn disease, lead to alterations in Paneth cells in both mice and humans that have functional consequences predisposing mice to the development of intestinal inflammation in response to bacteria and viruses [54, 55]. Paneth cell products, such as defensins, not only protect the host mucosal surface but can also help to shape the composition of the gut microbiome [56].

IBD and the Human Gut Microbiome

Epidemiological evidence provides strong evidence for the role of the environment in the pathogenesis of IBD. Over the last several decades, there has been an increase in the incidence of inflammatory bowel disease that is too rapid to be attributed solely to genetic factors. The association with residence in or immigration to industrialized nations [57], the consumption of a "Westernized" diet rich in fat and red meat [58], and the use of antibiotics at a young age [59] all implicate an alteration in the gut microbiota as a possible etiologic factor that may be playing a role in the increased incidence of IBD. Further support of this notion is the "hygiene hypothesis" suggesting that humans living in more

industrialized societies are exposed to fewer microbes or less complex microbial communities at an early age leading to the development of an immune system less able to "tolerate" exposure to the microbial-laden environment in later life resulting in inappropriate immune activation [60].

Several theories have been suggested to explain the role of the gut microbiota in the pathogenesis of IBD: (1) specific microbial pathogens that induce intestinal inflammation, (2) host genetic defects in containing commensal microbiota in combination with defects in host mucosal immunoregulation, and (3) dysbiosis of commensal microbiota (4). Multiple studies have been performed evaluating the role of specific bacteria in the development of IBD, such as *E. coli* and *Mycobacterium avium* subspecies *paratuberculosis* (MAP). In CD, there have been consistent findings of increased mucosa-associated *E. coli* in both the ileum and colon. The *E. coli* isolated in CD is often an adherent invasive *E. coli* (AIEC) phenotype, which is characterized by the invasion of epithelial cells and replication within macrophages [61] without causing cell death and induces the secretion of the tumor necrosis factor (TNF)-α [61, 62]. CD-associated AIEC strains are also capable of adhering to ileal enterocytes in patients with CD, however, not from control enterocytes [63].

MAP has also been implicated as a causal organism in the development of IBD. It is the known cause of Johne's disease in cattle which, similar to the histologic appearance of human CD, leads to chronic granulomatous enteritis. Multiple studies have explored the role of MAP in CD; however, controversy remains whether this organism indeed has a causal role. Some studies have shown remission in patients who have been treated with anti-MAP therapy; however, many argue that this has not proven causality. A large randomized controlled trial using combination antibiotics which have proven efficacy against MAP was performed by the Australian Antibiotic in Crohn Disease Study Group, but there was no significant effect on long-term maintenance of remission [64]. The recent Phase 3 clinical trial of RHB-104 for the treatment of Crohn disease in the United States also showed an increase in clinical remission as compared to those on placebo and mildly increased durable clinical remission through 52 weeks (RHB104 18.7% vs. placebo 8.5% $p = 0.0077$). Criticism of these studies remain that patients were not assessed for the presence of MAP prior to initiation of therapy. Thus far, the use of cutting edge sequencing technology has not yet identified improved our ability to detect MAP in patients with Crohn disease. As further studies are performed in MAP and IBD, perhaps a better understanding of this relationship will come to light [61].

The intestinal microbiome in patients with IBD is characterized by decreased microbial diversity and increased abundance of pro-inflammatory organisms. Multiple studies in patients with CD have demonstrated a reduction in the abundance of the phylum *Firmicutes* [62, 65–69]. Specifically, *Faecalibacterium prausnitzii*, a *Firmicutes*, has been found to be decreased in IBD, including pediatric Crohn disease [70–72]. Furthermore, a decrease in *F. prausnitzii* was predictive of recurrence of disease in patients with CD undergoing ileal resection. There have also been studies that have shown a decrease In the presence of *Faecalibacterium prausnitzii* in fecal samples and biopsy specimens [70, 73]. In animal studies, *F. prausnitzii* can induce an anti-inflammatory response by increasing IL-10 as well as produce short-chain fatty acids, both of which may protect against the development of intestinal inflammation [62]. Concurrent with a reduction in *Firmicutes*, multiple studies have reported a concomitant increase in the abundance of *Proteobacteria* (including *E. coli*) [69, 74, 75] and *Enterobacteriaceae* [76, 77].

To control for the influence of genetics on the microbiome, there have been several studies performed comparing the microbiota of twin pairs. Dicksved and colleagues compared the intestinal microbiome of identical twins concordant or discordant for CD. Total bacterial diversity was decreased among patients with CD. Within twin sets, both healthy twins and twins concordant for CD had closely matched bacterial community profiles. In comparing the twin pairs discordant for CD, however, there was a difference between the fecal microbiome of those with CD and the healthy twin. This suggests that the structure of the bacterial communities is more closely associated with the disease activity rather than the genetics of the host [78]. In another study focusing on twins, Willing and colleagues characterized gut microbial communities in 40 twin pairs who were concordant or discordant for CD or UC. There were differences in the bacterial communities of patients with CD, and there were phenotypic differences as well among ileal and colonic disease as compared to the healthy subjects. There was a decrease in two genera of core commensals in patients with ileal CD, *Ruminococcaceae* family (including *Faecalibacterium*) and *Roseburia* (a member of the *Firmicutes* phylum) [79]. Consistent with prior studies, there was an increase in *Enterobacteriaceae*, including *E. coli* in some of the patients with ileal CD [80].

The alterations in the gut microbiome that are associated with IBD are often described as being "dysbiotic," implying that there is a functional imbalance between enteric bacteria with potentially pathogenic influences and bacteria who have a benign or beneficial effect on the host [81]. There is currently no clear evidence to confirm this notion in humans. An alternative explanation is that the observed alteration in the gut microbiome of patients with IBD is simply a consequence of the intestinal inflammatory response without consequence to the host. Additionally, in a human study of pediatric ulcerative colitis, evaluation of normal terminal ileum biopsies revealed a loss of goblet cells, depletion of

the mucous layer, and loss of bacterial diversity despite a lack of inflammation in the sampled location, which may be due to a systemic effect to the gut epithelial lining independent of local inflammation [82].

There is, however, evidence for a functional effect of a "dysbiotic" intestinal microbiota in animal models. Investigators studying mice deficient in the immune regulatory transcription factor T-bet observed alterations in the intestinal microbiome that occurred simultaneously with the development of spontaneous colitis. Transfer of this bacterial community induced colitis in wild-type mice [83]. In a follow-up study, the investigators identified the presence of *Klebsiella pneumoniae* and *Proteus mirabilis* correlated with colitis in these mice [84]. Mice deficient in another immune regulator, the NLRP inflammasome, also develop spontaneous colitis, the susceptibility to which can also be transferred to wild-type mice [45]. Together, these studies suggest a causal role for the microbiota in IBD.

Beyond understanding the microbial contribution to the onset of IBD, longitudinal observational studies have begun to elucidate how the gut microbiome of children with inflammatory bowel disease changes over time. These changes may be able to be used as biomarkers in conjunction with clinical, genomic, and immunologic profiles for monitoring disease progression and stratifying risk of disease complications. Multiple studies have identified dysbiosis patterns in fecal microbial communities in a subset of treatment naïve pediatric IBD subjects [85–87]. Predictors of response to treatment, disease severity, and remission or progression of disease would greatly improve clinicians' ability to personalize therapy for this complex disease. The RISK study, a large multicenter inception cohort of pediatric Crohn disease, followed newly diagnosed patients for 3 years in order to create a risk stratification model using clinical, genomic, and serologic markers for complicated Crohn disease phenotype. In addition, they identified ileal microbiota signatures associated with these complicated disease phenotypes, but integration of microbiota data into the risk stratification model requires future studies [88, 89]. The PROTECT study of treatment naive children with ulcerative colitis collected stool samples for 52 weeks after diagnosis and identified microbial changes at baseline and shifts during follow-up that were associated with achieving remission as well as progression to colectomy within the first year [90]. There was expansion of *Veillonella dispar* and other organisms typically detected in the oral microbiome along with the previously described pro-inflammatory microbes, including *Enterobacteriaceae*, with more severe disease, more extensive disease, and higher risk of colectomy within the first year after diagnosis.

Diet, IBD, and the Gut Microbiome

Several investigators have examined the association of dietary patterns and the incidence of IBD [58, 91]. A systematic review of this subject found consistent results showing that high dietary intake of total fats, polyunsaturated fatty acids, Omega-6 fatty acids, and meat was associated with an increased risk of CD and UC; high fiber and fruit intakes were associated with a decreased CD risk; and high vegetable intake was associated with a decreased UC risk [91]. These studies support a potential role for dietary patterns in the pathogenesis of IBD. Together with the recent data characterizing the impact of diet on the gut microbiome and its association with enterotypes [32], it is tempting to speculate that the alteration of gut microbiota community structure through the consumption of agrarian versus a "Westernized" diet may play a role in either reducing or increasing, respectively, the risk for the development of IBD. This notion would be consistent with the increased incidence of IBD localized globally in more industrialized societies.

The Gut Microbiota as a Therapeutic Strategy

Probiotics and Prebiotics

Possible beneficial strategies for the treatment of IBD include probiotics, prebiotics, or a combination of both, synbiotics. Probiotics are defined as living microorganisms that, when administered in adequate concentration, confer a health benefit on the host [92]. Probiotics have been shown to be effective in the treatment of pouchitis and possibly in other forms of UC, but the benefits are often not sustained for the long term [93–96]. Although evidence for the efficacy of probiotics, mainly *Lactobacillus* and *Bifidobacterium*, in the treatment of IBD is currently equivocal, their beneficial effect in animal models is more consistent [97]. Possible mechanisms of action include the production of bacteriocins [98], the alteration of luminal pH of the intestine thereby altering the growth characteristics of some bacteria [99], the enhancement of epithelial barrier function through the production of SCFA, a primary source of energy for colonocytes [100], and mucosal and systemic immunomodulation by inducing anti-inflammatory cytokines, T and B regulatory cells, and reducing inflammatory cytokines [51, 101]. Numerous other proposed mechanisms of action have recently been reviewed [93, 100]. Prebiotics have also been investigated in the use of treatment of inflammatory bowel disease. Prebiotics are nondigestible food substances that stimulate the growth and/or activity of bacteria as well as the production of SCFA

[100]. Prebiotics have been used with probiotics; this combination is called synbiotics. Several prebiotics that have been studied extensively and accepted in the European Union include fructooligosaccharides, galactooligosaccharides, and lactulose. The difficulty with these substances is ensuring the bacteria selectivity, i.e., only bacteria beneficial to the host will ferment the oligosaccharide and that the products of fermentation will promote the growth and activity of nonpathogenic organisms [102]. There have been several clinical trials using prebiotics, including inulin and curcumin, as therapy [103–106], and some have shown promising results.

Enteral Nutrition Therapy

Enteral nutrition (EN) therapy, which has shown efficacy in the induction and maintenance of remission in patients with CD [107, 108], may ultimately provide additional support for the role of diet and the gut microbiota in the pathogenesis of IBD. As discussed in a separate chapter, EN is an attractive therapeutic option compared to pharmacological agents, as there are no serious associated side effects. While proven to be effective as therapy in CD, the mechanism of action of nutritional therapy has not been fully characterized. A recent study of pediatric CD patients on exclusive EN (at least 90% of total caloric intake by dietary formula) compared to partial EN (53% by formula) was superior at improving symptoms and quality of life as well as inducing mucosal healing, suggesting that the elimination of solid table foods may be the key to why EN is therapeutic [109]. In addition, the alteration of the gut microbiota may be another possible mechanism of action. In the same study of pediatric CD patients, effective EN therapy changed the microbiota within 1 week and reduced the dysbiosis seen initially [86]. Further investigation into the metabolic profiles of these patients' stool implicated the role of nitrogen metabolism in the disease-associated dysbiosis and its correlation with the presence of Proteobacteria species [110]. Leach and colleagues evaluated the fecal microbiome of patients with CD who were treated with EN and compared them to healthy control subjects on a regular diet [89]. Prior to initiation of EN, the two cohorts had similar diversity of bacteria present. At the 8-week follow-up, there was a significant reduction in diversity in the stool of the patients treated with EN that was sustained for several months following completion of therapy. Small studies have demonstrated shifts in the microbiota coincident with trends toward remission but larger controlled studies of dietary therapeutic interventions, such as the Crohn disease exclusion diet, specific carbohydrate diet, or anti-inflammatory diet are still needed [111, 112]. The success of nutritional therapy highlights the importance of characterizing the interactions among diet, the gut microbiota, and the mucosal immune system.

Bacterial Engineering

Another treatment in IBD utilizing the microbiome is bacterial engineering. In 2000, *Lactococcus lactis* was genetically engineered to secrete hIL-10 into the intestinal tissue in murine models. Colitis was prevented in IL-10 knockout mice, and there was a 50% reduction in inflammation in DSS-induced chronic colitis [113]. Additionally, *L. lactis* expressing IL-27 has been more effective than the IL-10 producing bacteria or systemic administration of IL-27 in mouse models of colitis by increasing production of IL-10 in the intestinal epithelium [114]. Similarly, *Bacteroides ovatus* has been engineered to deliver TGF-β with good results in murine models [115]. Other bacteria have been modified to counteract TNF-alpha and reactive oxygen species [116, 117]. There are ongoing trials of several live biotherapeutics in humans for the treatment of IBD.

Fecal Transplantation

Fecal microbiota transplantation (FMT) is another microbiota-based therapy that involves collecting stool from a healthy donor, preparing it in one of several ways, and transferring it to a patient with a disease or dysbiotic condition. The goal of FMT is to restore bacterial diversity through the microbiota of a healthy person. This healthy flora outcompetes *C. difficile* and produces secondary bile acids and antimicrobials that inhibit its growth. There remains no clear consensus regarding the mode of administration of fecal material. Possible delivery methods include upper endoscopy, nasogastric tube, nasointestinal tube, pill ingestion, colonoscopy to deliver to proximal colon, sigmoidoscopy, rectal tube, retention enema, or a combined approach. Patient comfort, safety, and cost-effectiveness should be considered when choosing how to deliver the material.

FMT was first safely described in humans in 1958 in the treatment of fulminant pseudomembranous enterocolitis [118]. Since then, there have been many published cases of *C. difficile* infection (CDI) and FMT, specifically for the treatment of recurrent or refractory CDI, which have been successful [119–121]. Multiple systemic reviews of fecal transplantation for CDI have demonstrated it to be well tolerated, and effective with a mean cure rate of 87–90% and as high as 100% worldwide [122–124]. Moreover, the new healthy microbiota environment appears to be durable [121, 125]. While there have been few serious adverse events associated with FMT especially in children, there are risks related to infections and the still unknown risks associated with changing the recipients' microbiota in the long term. In June 2019, the FDA issued a safety alert regarding the transmission of extended-spectrum-beta-lactamase-producing *E. coli* to two adult patients, one whom died, which prompted more

stringent screening requirements from the FDA. In addition, further screening has been recommended for SARS-CoV-2 due to concern for transmission as well. These developments have highlighted the importance of careful consideration of the indication for FMT and screening before proceeding. In pediatric cases of recurrent CDI, there is limited data regarding safety and efficacy, but an 86–92% cure rate has been reported without serious adverse events [126–128].

The effect seen in CDI may be possible in other dysbiotic conditions, particularly IBD. In 1989, Bennet and Brinkman published the first report of successfully treating UC with FMT, when Bennet successfully treated his own colitis [129]. In 2003, Borody and colleagues treated six patients with moderate to severe UC with FMT. All patients responded and remained in remission from 6 months to 13 years and had mucosal healing on endoscopy [130]. A review of several small studies of FMT as therapy for IBD showed mixed results, although the majority achieved clinical remission at least in the short term, none had serious adverse events, but there were several accounts of fever, chills, and gastrointestinal symptoms after, and one study reported worsening UC after FMT [131]. The largest studies of FMT for UC were randomized, placebo-controlled trials using FMT to induce remission in patients with mild to moderate UC which had mixed results regarding efficacy [132, 133].

A recent study showed that adult patients with IBD and parents of children with IBD were willing to consider fecal transplantation as therapy and felt that this was a safer option than many of the standard therapies [133]. In pediatric IBD, the use of FMT has shown clinical benefit for a small cohort of 7/9 subjects with CD via nasogastric administration but not for UC subjects [134]. As with most pediatric therapies, the long-term consequences of FMT are unknown and should be better understood before implementing in conventional practice. There are currently no standard protocols, and further larger controlled studies are necessary; however, this therapy, perhaps with a more targeted microbiota, may hold promise for IBD as we learn more about the role of the gut microbiota and IBD pathogenesis.

Conclusions

Inflammatory bowel disease has been associated with both genetic and environmental factors. It has shown a dramatic increase in incidence over the past several decades. Effects of environmental changes in modern lifestyle, such as diet, sanitation, vaccinations, and antibiotics, have contributed to an alteration in the gut microbiome. While gut microbes very likely play a large role in the pathogenesis and propagation of the disease, their exact role requires further elucidation. The challenge remains to identify genetic, immunologic, environmental, and microbial triggers of disease development. As technologies such as DNA sequencing, metagenomics, transcriptomics, proteomics, and metabolomics continue to advance, along with the development of more sophisticated biocomputational tools, mechanisms by which the gut microbiota plays a role in the pathogenesis IBD will be better elucidated. In turn, this may provide novel insights into microbial-based methodologies that can be used to effectively prevent or treat IBD.

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5 Immune Dysregulation Associated with Very Early-Onset Inflammatory Bowel Disease

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Introduction

The immunologic component to IBD has been recognized for many years. The strong association with specific MHC haplotypes underlies the presumption that T cells are involved in the pathogenesis [1, 2]. Additionally, the serologic biomarkers also acknowledge that B cell responses are aberrent [3–5]. Nevertheless, the exact pathogenesis of IBD remains elusive and even more so for VEO-IBD. Two lines of recent evidence support the hypothesis that immunologic dysfunction is fundamental to both the development and perpetuation of IBD. Genome-wide association studies have identified over 160 variants in teenage and adult cohorts and the majority of those variants map to immunologically relevant genes [6–8]. These common variants are thought to synergistically interact with the microbiome to induce a state of susceptibility to IBD [9]. Some of these variants have independently been demonstrated to be associated with either impaired epithelial function or activation of immunologically competent cells [10, 11]. The effect size of each variant is rather small, however, and it has been difficult to define the precise pathophysiologic contribution related to each independent variant. On the other side of the spectrum, monogenic disorders occur in which the penetrance of IBD is high. Understanding the mechanisms driving these rarer monogenic disorders has dramatically enhanced our understanding of IBD. A critical aspect of VEO-IBD is the hypothesis that genetic variants with a high penetrance for IBD dominate the susceptibility in young children, while adult-onset IBD is dominated by common variants with much lower relative risks for disease (Fig. 5.1).

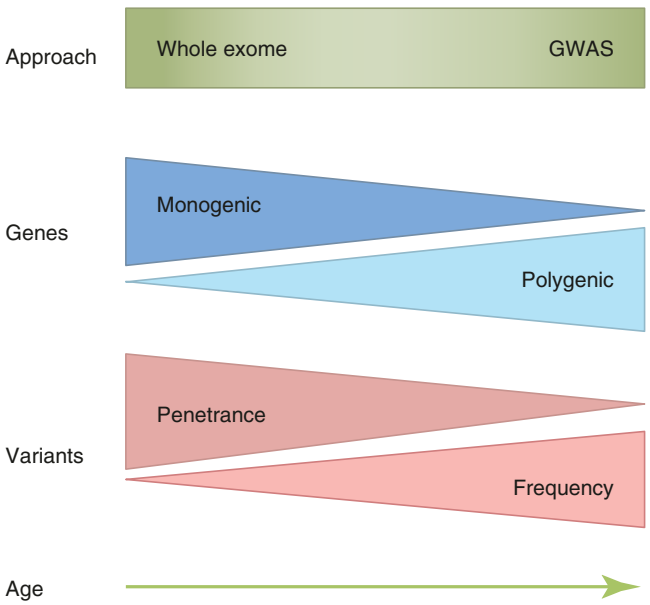

Fig. 5.1 Inheritance and penetrance of variants related to IBD. VEO-IBD is thought to be enriched for monogenic disorders, whereas adult-onset IBD has a polygenic inheritance with contributions from multiple variants, each of which may confer only a small increase in risk

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Genomics and VEO-IBD

Inflammatory bowel disease (IBD), comprised of Crohn disease, ulcerative colitis, and indeterminate colitis, is a multigenetic and environmentally triggered disease resulting in a dysregulated immune response to commensal or pathogenic microbes that reside in the gastrointestinal tract [6, 12–17]. Patients with IBD exhibit local and systemic immune reactivity to various microbes, and as a result or inherently, have significant alterations in the composition of intestinal commensal bacteria, and can become colonized with pathogenic or opportunistic bacteria [18–25]. The multifactorial nature and environmental contribution to IBD are largely responsible for the increased incidence over the last several decades [26]. It is not surprising, therefore, that the genetic contribution to the disease largely involves host defense with recognition and response to microbes. Genome-wide association studies (GWAS) have supported this host–microbe relationship, and most of the identified >230 IBD-associated risk loci [8] are involved in host defense. Several genes located within the IBD-associated loci are critical in regulation of host defense, involving both the innate and adaptive immune response toward microbes [8]. However, GWAS studies were primarily performed in adult-onset IBD and children 10 years of age and greater, whose disease, as noted above, is most frequently a polygenic complex disease. Furthermore, GWAS often do not capture rare variants, specifically those with minor allele frequency (MAF) less than 5%. Therefore, these studies do not account for the subset of children with VEO-IBD who underlying rare or novel monogenic defects [6, 27–29].

While VEO-IBD is a heterogeneous population, including children with mild disease, some patients with VEO-IBD can present with distinctive disease phenotypes, including extensive and more severe disease than older children and adults [30, 31], as well as systemic disease manifestations. In addition, due to poor response to conventional therapies, severity of inflammation, and greater duration of disease, there are higher rates of morbidity in this population [29, 30, 32]. The aggressive disease phenotype, early age of onset and strong family history of disease, led to the identification of causal monogenic defects, often involving genes associated with primary immunodeficiencies and epithelial barrier in a proportion of children with VEO-IBD [33, 34]. Monogenic VEO-IBD was first recognized in 2009 with the discovery that mutations in IL-10R, and subsequently several *IL-10* [35], *IL-10RA, and IL-10RB* [29] variants, led to the specific phenotype of neonatal onset IBD with severe perianal disease, extraintestinal disease, and colitis. Since that time, numerous additional underlying immunodeficiencies or genetic disorders have been identified in children with VEO-IBD [30, 34]. Some examples include variants in genes that cause common variable immunodeficiency (CVID), Wiskott–Aldrich syndrome (WAS), Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), X-linked inhibitor of apoptosis (XIAP), and chronic granulomatous disease (CGD) [30, 32, 36].

Studying consanguinity and targeted genetic sequencing has been an extremely valuable approach to allow the identification and characterization of genetic variants associated with VEO-IBD. However, these approaches alone may not identify novel and rare gene variants. Increasingly, whole-exome sequencing (WES) has led to the discovery of additional genes and pathways associated with the disease [36–40], and expanded our understanding of the pathogenesis of VEO-IBD. In recent years, whole-genome sequencing (WGS) has been incorporated into the pipeline for genetic discovery in VEO-IBD to further investigate variants in non-coding, regulatory regions of the genome that may be pathogenic as well.

While WES and WGS have revolutionized our ability to study rare variants and determine the genetic basis of disease, understanding the relevance of identified variants has remained challenging. The individual patient's phenotype may be shaped by mode of inheritance, epigenetics and gene–gene interaction. Environmental modifiers, such as the intestinal microbiota, antibiotic exposure, infection or diet, also significantly impact disease phenotype [27, 37]. Due to the clinical presentation, often of severe disease, together with the challenge of identifying the unique pathogenesis of the disease, the appropriate evaluation is critical patients with VEO-IBD. Indeed, in the setting of increasing recognition of the challenges of evaluation and treatment for this unique group of patients, a recent position paper from North American Society for Pediatric Gastroenterology Hepatology and Nutrition reviews factors that should trigger concern for underlying immunodeficiency in VEO-IBD, suggests immunological assays and genetic studies that can facilitate identification of underlying diagnosis and emphasizes the importance of targeted treatment approaches in the right context. [41].

Clinical Presentation of Very Early-Onset (VEO) IBD

Pediatric IBD has increased in incidence and prevalence and this phenomenon has included very young children [26, 42, 43]. VEO-IBD remains relatively uncommon, approximately 6–15% of the pediatric IBD population is less than 6 years old, and disease in the first year of life is rare [26, 43]. A subset of patients with VEO-IBD present with a phenotype that is distinct from older children and adults, including extensive colonic disease (pancolitis) that it is frequently difficult to differentiate ulcerative colitis (UC) from Crohn disease (CD). Due to the frequent extension of disease, to involve small bowel and perianal disease, (Table 5.1) [30, 43], indeterminate colitis is diagnosed more often in patients with VEO (11–31%) [44] as compared to older onset IBD (4–10%) [45–48]. In comparison, in older onset IBD (older children >6 and adults), CD is more prevalent (55–60%), while approximately 30–35% of VEO-IBD patients are diagnosed with CD [44].

Table 5.1 Differences between VEO-IBD and older-onset IBD

VEO-IBD	Older-onset IBD
Disease presentation Predominately colonic Ileal involvement <20% Extensive at presentation	Disease presentation Ileocolonic Less extensive at presentation
Disease classification CD: 30–35% UC: 35–39% IC: 11–22%	Disease classification CD: 55–60% UC: 40–45% IC: 4–10%
Histology Villous blunting Apoptosis	Histology Villous blunting/apoptosis rarely seen
Positive family history 40–50%	Positive family history 10–20%
Therapeutic response to conventional therapy Decreased	
Surgical intervention 70%	Surgical intervention 55%

The work-up in this population, similar to older patients, includes laboratory, radiologic, and endoscopic evaluation (Table 5.2). The laboratory studies should include not only routine screening utilized for IBD diagnosis, but also an immunological evaluation as well. This includes vaccine titers, immunoglobulin profiles, analyses of B and T cell function, and a dihydrorhodamine (DHR) flow cytometry assay for chronic granulomatous disease. Potential further targeted phenotyping and functional profiling of the systemic and mucosal immune system will be guided by the individual patient presentation. Diagnosis at a very young age should trigger concern for a monogenic-driven disease, particularly in IBD diagnosed less than 2 years of age. Marked growth failure and poor response to conventional therapies are more commonly seen in children with VEO-IBD than in older children with IBD as well [44, 49]. Furthermore, extensive family history, including history of disease in male family members (such as in X-linked disease), history of infection, skin disease, or autoimmunity can help guide appropriate laboratory screening. As shown below and in Table 5.2, initial screening laboratory studies such as inflammatory markers and complete blood count may point to the underlying defect, such as elevated inflammatory markers or neutropenia, which may represent a monogenic disorder causing functional defects in neutrophils, such as glycogen storage disease type 1b, leukocyte adhesion deficiency, or congenital neutropenia.

Table 5.2 Primary immune deficiencies associated with IBD

Category	Gene name	Name of immune deficiency	Prevalence of IBD	Characteristics of IBD in this syndrome	Other features of the disorder	Other autoimmune manifestations
Central tolerance	AIRE	APECED	≈10%	Enteropathy with villous blunting	Candida, malabsorption	Autoimmune polyendocrinopathies
	RAG1/2	SCID, Leaky SCID	≈50%	Not reported	Low CD4/CD45RA cells, infections	Autoimmune cytopenias, skin disease, vasculitis, neuropathy, interstitial lung disease
Peripheral tolerance	FOXP3	IPEX	≈90%	Villous atrophy		Diabetes, autoimmune polyendocrinopathies
	STAT5b	STAT5b deficiency	Unknown	Villous atrophy	Post-natal growth retardation, lymphocytic interstitial pneumonitis, severe varicella	Arthritis, thyroiditis
	CD25	IL-2RA deficiency	≈90%	Villous atrophy	Viral infections	Various autoimmune manifestations
	CTLA4	CTLA4 haplosufficiency	≈80%	Villous blunting	Hypogammaglobulinemia, infections	Cytopenias, arthritis, thyroiditis, dermatologic manifestations, granulomatous lung disease
	LRBA	LRBA deficiency	≈60%	Typical IBD and small bowel disease	Hypogammaglobulinemia, infections	
Apoptosis defects	FAS (TNFRSF6), FASLG (TNFSF6), somatic mutations of FAS in 30%	ALPS	≈1%	Not reported	Adenopathy, hepatosplenomegaly	Autoimmune cytopenias
	CYBA, CYBB, NCF1 < NCF2, NCF4	CGD	≈10–50%	Villous blunting with acute inflammation common, pigmented macrophages in half, granulomas in half, eosinophils prominent in 25%	Fungal infections, abscesses	ITP rarely
	XIAP	XLP2	≈20%	Granulomas	HLH, hypogammaglobulinemia	None
Lymphocyte signaling defects	PLCG2	PLAID	≈5%	Not reported	Skin granulomas, cold urticaria, infections, hypogammaglobulinemia	Autoantibodies, thyroiditis, vitiligo
	AID	AR Hyper IgM syndrome	≈5–10%	Not reported	Adenopathy, high IgM, low IgG	Autoimmune cytopenias, arthritis, hypothyroidism, kidney disease
	DOCK8	DOCK8 deficiency	≈5–10%	Not reported, may be secondary to infection	Severe infections	Vasculitis, autoimmune hemolytic anemia

Category	Gene name	Name of immune deficiency	Prevalence of IBD	Characteristics of IBD in this syndrome	Other features of the disorder	Other autoimmune manifestations
	WAS	Wiskott–Aldrich syndrome	≈5–10%	Not reported	Small platelets with thrombocytopenia, infections, eczema	Hemolytic anemia, vasculitis, arthritis, neutropenia
	NEMO (IKBKG), NFKB1A	Ectodermal dysplasia with immune deficiency	≈25%	Paucity of lymphocytes and relatively superficial neutrophil infiltrate	Infections are severe	Limited
	BTK	XLA	≈5–10%	Not reported	No B cells, hypogammaglobulinemia	Arthritis
Interferon hyper-production by lymphocytes	STAT1 GOF	STAT1 GOF	≈50%	Villous atrophy	Candida and other fungal infections	Diabetes common but other autoimmunity seen frequently
	STAT3 GOF	STAT3 GOF	60%	Villous atrophy	Short stature	Diabetes and other autoimmunity
	STAT3 LOF	Hyper IgE syndrome	≈1-5%	Can be due to infection	Infections, eczema	Rare
Unknown mechanism		CVID	10-20%	Villous atrophy, collagenous colitis, typical IBD all seen	Usually adult-onset, sinopulmonary infections	Autoimmune cytopenias, lymphoproliferation, granulomas
	DNMT3b, ZBTB24	ICF	50% have diarrhea	Not reported	Mild developmental delay, IgA deficiency	Rare

APECED autoimmune polyendocrinopathy, candidiasis, ectodermal dysplasia, *SCID* severe combined immune deficiency, *IPEX* immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, *ALPS* autoimmune lymphoproliferative syndrome, *CGD* chronic granulomatous disease, *XLP2* X-linked lymphoproliferative syndrome 2, *PLAID*, phospholipase C-γ2–associated antibody deficiency and immune dysregulation, *XLA* X-linked agammaglobulinemia, *ICF* immunodeficiency, centromeric instability, facial anomalies syndrome

Genetic Variants Associated with VEO-IBD and Their Immunologic Consequences

Monogenic diseases that can present with the phenotype of intestinal inflammation include those that cause defects of intestinal epithelial barrier function, phagocyte bacterial killing, development and function of the adaptive immune system, and hyper or autoimmune inflammatory disorders [28]. These genetic alterations may differentially influence the development and progression of intestinal inflammation, and therefore these patients will likely exhibit significant heterogeneity in their responsiveness to therapeutic interventions. Below we discuss what we have learned from mouse models and translational patient-based studies, which should be considered when developing therapeutic strategies for these unique patient populations. Increasingly, there is a recognition that treatment strategies for children with VEO-IBD, particularly in those with immunologic alteration, should be personalized based on the individual patient's clinical and immunophenotype, as well as genetic data when available, and management may include therapies not standardly used for the treatment of IBD.

Genetic Variants Influencing Intestinal Epithelial Barrier Function

Mutations in genes associated with maintaining integrity of the intestinal epithelial barrier can present with intestinal inflammation in patients with VEO-IBD. These include loss-of-function mutations in *ADAM17* resulting in ADAM17 deficiency [50, 51], *IKBKG* (encoding NEMO) resulting in X-linked ectodermal dysplasia and immunodeficiency [52], *COL7A1* resulting in dystrophic epidermolysis bullosa [53], *FERMT1 resulting in* Kindler syndrome [54–56], *TTC7A resulting in multiple intestinal atresia* [39], and *EGFR* leading to neonatal skin and inflammatory bowel disease [57]. Gain-of-function mutations may also lead to similar epithelial barrier defects, as seen in the case of *GUCY2* resulting in familial diarrhea [27, 58] and *TGFBR1* and *TGFBR2* leading to Loeys–Dietz syndrome, type 1 and 2, respectively [59, 60]. Mutations in these genes may all lead to an impairment of the intestinal epithelial barrier through distinct pathways, such as limiting epithelial regeneration (*ADAM17*) [61], loss of signaling pathways involved in gene expression (*IKBKG, EGFR, and TGFBR1/2*) [57, 60, 62, 63] altered cell adhesion, barrier formation and apoptosis (*COL7A1*, *FERMT1,* and *TTC7A)* [39, 53–56], or impaired bacterial sensing and ion homeostasis (*GUCY2*) [27, 58]. The intestinal histology of patients with epithelial defects can be helpful in distinguishing the disease from other etiologies of intestinal inflammation. Patients with *IKBKG* (NEMO) defects may have villous atrophy or epithelial cell shedding on pathology [64]. Histology in patients with *ADAM17* mutations may demonstrate hypoplastic crypts in small bowel secondary to a low rate of epithelial production as *ADAM17* is necessary for TGF-α to be cleaved from the cell membrane [65, 66].

The intestinal barrier is necessary to maintain a physical separation between commensal bacteria and the mammalian immune system, and a breakdown in this barrier through multiple distinct pathways can directly promote chronic intestinal inflammation [12, 14]. In addition to genes listed above, intestinal barrier function is maintained through a number of physical and biochemical structures, including mucus production, intestinal epithelial cell tight junction proteins, Immunoglobulin A (IgA), and antimicrobial peptides. In mice, chemical disruption of the intestinal barrier, through administration of dextran sodium sulfate (DSS) in the drinking water, results in dissemination of commensal bacteria and activation of the innate immune system [67]. Chronic exposure to DSS can lead to activation of the adaptive immune response and the development pro-inflammatory, commensal bacteria-specific, B and T cell responses [18, 68], which are similar to those observed in IBD patients [18, 69]. Intestinal epithelial cells play a significant role in directly regulating immunologic homeostasis in the intestine, as mice with intestinal epithelial cell lineage-specific deletion of factors regulating the NFκB pathway, including NEMO and IKKβ, result in susceptibility to chronic intestinal inflammation [62, 63]. Although we know that loss of intestinal barrier function can directly cause intestinal inflammation, additional mouse models and translational patient-based approaches are required to further define how mutations in the above genes specifically lead to a break down in the barrier, and whether we can develop more targeted therapies to restore barrier integrity and limit chronic inflammation.

Genetic Variants Impairing Development of the Adaptive Immune System

Several genetic variants can alter the development or function of adaptive immune cells in a cell-intrinsic or -extrinsic manner. Defects that affect development or function of B cells and T cells occur with loss-of-function mutations in recombination activating genes (*RAG1* or *RAG2*) or the IL-7R (*IL7R*) causing Omenn syndrome, or the *PTEN* gene causing PTEN syndrome. Defects in *RAG1*, *RAG2,* or *IL-7R* can cause cell-intrinsic defects in the development of both T cells and B cells, by blocking either early lymphocyte survival or recombination of the B cell receptor (BCR) or T cell receptor (TCR) [70–72]. Defects in B cell development lead to an absence of circulating mature B cells and antibody production, which have been linked to an IBD phenotype [73]. This includes agammaglobulinemia, which can also occur in

X-linked agammaglobulinemia (XLA) [74] and common variable immune deficiency (CVID), a complex and heterogeneous disease, with the responsible mutations known for only a minority of cases [75]. Loss-of-function mutation in *LRBA* may lead to multiple defects in immune cell populations (including lymphoproliferation, autoimmune cytopenias, and immune deficiency), along with enteropathy and endocrine dysfunction [76]. Related to CVID, antibody deficiency associated with IBD manifestations include IgA deficiency and severe combined immunodeficiency (SCID), which can be secondary to multiple variants that influence the development or function of the adaptive immune system (including *RAG1, RAG2, JAK3, CD45, CD3G, ZAP70, ADA, DCLRE1C, DOCK8*) [28, 73, 77]. Omenn syndrome, a recessive form of SCID, involves abnormal development of B cells and T cells, and can also be associated with intestinal disease as well as severe eczematous rash [77, 78]. In these patients, laboratory studies are significant for increased oligoclonal T cells and reduced B cells, and histology can show an intestinal graft versus host appearance [79, 80]. Aberrant function of immunoglobulins, such as in hyper IgM and Hyper IgE syndromes, can also result in intestinal inflammation and an IBD phenotype [81]. It is currently unclear exactly how these selective impairments of the adaptive immune system can manifest in intestinal inflammation. There is a potential involvement of altered regulatory pathways, or chronic infections with pathogenic and opportunistic microbes. Therefore, additional lines of study are required to further interrogate the link of these mutations to intestinal inflammation.

Wiskott–Aldrich syndrome (WAS) results from a loss of function mutation in Wiskott–Aldrich syndrome protein (*WASP*), and patients can exhibit thrombocytopenia, eczema, immune deficiencies, and intestinal inflammation [82]. The clinical manifestation of patients with VEO-IBD with this genetic defect can be pancolitis in addition to other autoimmune processes. *WASP* is a critical cytoskeleton protein expressed in hematopoietic cells that are required for the normal development and function of multiple cell types [83, 84]. WASP is also requited for peripheral B cell development and function, with subsequent ability to respond to antigens [85, 86]. Laboratory studies of these patients may show thrombocytopenia, low IgM levels, low marginal B cells, and lymphopenia [87]. Snapper and colleagues identified that intestinal inflammation in WASP-deficient mice was critically dependent on inflammatory T cells [88], and may result from an impaired development of regulatory T cells (Tregs) in the thymus and periphery [89]. Surprisingly, these defects are likely occurring in a cell extrinsic manner, as the absence of WASP in cells of the innate immune system directly contributed to the development of inflammatory T cell responses in mice [90]. The causes of intestinal inflammation in other similar patient populations are less well understood, but defects in regulatory T cells, IgA, and abnormal selection of T cell and B cell specificities likely contribute. The clinical manifestations of Wiskott–Aldrich syndrome, including bowel inflammation, have successfully been managed with HCT and, more recently, with gene therapy [91, 92]. Similarly, HCT is an effective management strategy for the systemic manifestations of SCID, hyper-IgM syndrome, and other defects of adaptive immunity [93, 94]. Additional immunological analyses and mouse models, such as those described above, are required to further define the causes of disease and potential therapeutic options in these patient populations.

Genetic Variants Impairing Regulatory T cells

Defects in regulatory T cells can clinically present as colonic disease and well as an enteropathy. The prominence of villous atrophy is a clue to these disorders. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is most often secondary to mutations of Forkhead box protein 3 (*FOXP3*) gene, a transcription factor that is essential for the development and immunosuppressive activity of CD4 FOXP3$^+$ Tregs [78, 95–97]. There are over 20 mutations in *FOXP3* that have been identified in patients with IPEX [96], and patients frequently present with neonatal severe secretory diarrhea, failure to thrive, infection (due to defects in immunoregulation), skin rash, insulin-dependent diabetes, thyroiditis, cytopenias, and other autoimmune disorders [78]. Tregs are absent or dysfunctional in these patients, and in the intestine, histologic analyses may reveal infiltration of inflammatory cells in the lamina propria and submucosa of the small bowel and colon as well as changes in the mucosa of the small bowel [98]. Other genetic defects have been found to cause IPEX-like disease, including loss of function mutations impacting IL-2–IL-2R interactions, STAT5b, and ITCH, or gain-of-function mutations in STAT1, all of which critically influence the development and function of Tregs [78]. Further, Blumberg and colleagues have identified in a novel loss of function mutation in *CTLA4,* a surface molecule of regulatory T cells that directly suppresses effector T cell populations, in VEO-IBD [99].

The mechanisms by which regulatory T cells limit intestinal inflammation are well characterized in mice. Regulatory T cells can develop in the thymus as "natural Tregs" and directly contribute to limiting pro-inflammatory T cells in the intestine [100]. The composition of commensal bacteria influences the repertoire of Tregs [100] and commensal bacteria-specific "induced Tregs" can also be generated in the periphery following sampling of commensal bacteria by dendritic cells in the intestine and migration to the mesenteric lymph node [12, 16, 97, 101]. Once generated, Tregs can then promote intestinal homeostasis through direct regu-

lation of innate and adaptive immune cell responses to commensal bacteria, a process which involves cytokine production, direct cell–cell contact (in part through CTLA4) and sequestering of growth factors [12, 16, 97]. Consistent with a major role for regulatory T cells in limiting pro-inflammatory immune cell responses to commensal bacteria, mice deficient in IL-2 or FoxP3 develop significantly less intestinal inflammation when maintained in germ-free versus conventional housing conditions, but exhibit comparable levels of systemic autoimmunity [102, 103]. Evidence also suggests that the balance of tissue-specific IL-23 and IL-33 expression in mice is critical in regulating the function of regulatory T cells in the intestine and ability to limit chronic inflammation [104], although the role of these pathways in human VEO-IBD has not been extensively examined.

Genetic Variants in the IL-10-IL-10R Pathway and Related Cytokine Family Members

Homozygous loss of function mutations in *IL-10* ligand and receptors *IL-10RA* and *IL-10RB* are associated with significant intestinal inflammation, particularly in neonatal or infantile VEO-IBD, with a phenotype of severe enterocolitis and perianal disease [29, 35]. In addition, compound heterozygote loss of function mutations of *IL-10RA* have been reported with neonatal Crohn disease and enterocolitis [105]. IL-10 is an anti-inflammatory cytokine secreted by a variety of cells, including dendritic cells, natural killer (NK) cells, eosinophils, mast cells, macrophages, B cells, and $CD4^+$ T cell subsets (including Th2 cells, Th1 cells, Th17 cells, and Treg) [106, 107]. IL-10 maintains homeostasis through suppression of an excessive pro-inflammatory response and exerts its effect through binding to the IL-10 receptor, IL-10R, which is a tetrameric complex [108]. It is composed of 2 distinct chains, 2 molecules of IL-10R1 (α chain) and 2 molecules of IL-10R2 (β chain) [109]. IL-10 binding to IL-10R activates the JAK1/STAT3 cascade, which subsequently limits pro-inflammatory gene expression [109]. In addition to intestinal inflammation, IL-10 defects are associated with arthritis, folliculitis, and predisposition to large B cell lymphoma [105, 110]. Given that the defects in IL-10–IL-10R interactions predominantly influence the immune system, a potential treatment for these patients is successful hematopoietic stem cell transplantation [111]. Although this can be challenging and typically requires an HLA-identical donor, there has been recent success reported with haploidentical stem cell transplantation; however, non-engraftment complications can occur [112].

An essential role for IL-10 in limiting intestinal inflammation was demonstrated by the spontaneous development of severe colitis in IL-10-deficient mice [113], and studies by Sartor and colleagues identified that the intestinal inflammation in IL-10-deficient mice was entirely dependent on the presence of commensal bacteria [114]. Therefore, IL-10 plays a critical role in limiting dysregulated immune cell responses to intestinal commensal bacteria. The exact cellular sources and targets of IL-10 that contribute to the maintenance of intestinal homeostasis have been less well defined until the recent development of mice that permit conditional deletion of IL-10 and IL-10R. These critical studies have revealed an essential role of regulatory T cell-intrinsic IL-10 expression in preventing intestinal inflammation in mice [115, 116]. Furthermore, IL-10R expression on myeloid cells in mice is critical to elicit anti-inflammatory responses and limit T cell-dependent intestinal inflammation [117, 118]. Critically, patients with loss-of-function mutations in *IL-10RA* or *IL-10RB* also exhibited an impaired ability to differentiate anti-inflammatory myeloid cells in vitro, and rather exhibited increased pro-inflammatory properties, such as elevated expression of IL-6, IL-12, TNFα, MHCII, and co-stimulatory molecules [117]. Although mouse models have provided invaluable insight into human health and disease, it should be noted that mice deficient in *IL-10* do not completely replicate the phenotypes of humans with loss-of-function mutations in *IL-10*, likely due to many confounding factors.

IL-22 is a cytokine that is related to IL-10, shares the IL-10R2 chain with a unique IL-22R1, signals through predominantly STAT3, and also plays a critical role in mediating intestinal homeostasis [119]. However, unlike IL-10, the complete IL-22R is restricted to non-hematopoietic cells, and in the intestine, IL-22 acts almost exclusively on intestinal epithelial cells to mediate innate immunity and intestinal barrier function [119]. IL-22 can be produced by Th17 cells, and more recently has been identified to be predominantly expressed by a previously unrecognized cell type of the innate immune system, termed group 3 innate lymphoid cells (ILC3) [119, 120]. This breakthrough in immunology has led to the identification of other members of the innate lymphoid cell (ILC) family, including group 1 ILCs (ILC1) that express T-bet and pro-inflammatory cytokines TNFα and IFNγ, and group 2 ILCs that express GATA3 and type 2 cytokines IL-4, IL-5, IL-9, and IL-13 [120, 121]. The ILC family exhibits a heterogeneity comparable to that of differentiated CD4 T cell subsets, and plays a profound role in regulating intestinal health and disease in mouse models [119–121]. Critically, recent reports suggest that ILC3 is a dominant source of IL-22 in the intestine of healthy humans, and that dysregulated ILC responses are observed in adult patients with IBD [122–128]. ILC3 expresses MHCII, and that selective deletion of MHCII on ILC3 results in dysregulated CD4 T cell responses and spontaneous intestinal inflammation, suggesting that these cells are essential for regulation of T cell-mediated inflammation in the gut [123]. $MHCII^+$ ILC3 selectively induces cell death of pro-inflammatory, commen-

sal bacteria-specific, CD4 T cells in the intestine. MHCII was reduced on ILC3 from intestinal biopsies of pediatric IBD patients versus non-IBD controls and inversely correlated with levels of pro-inflammatory Th17 cells [129]. In recent years, there is increasing understanding about the role of IL-22 in inflammatory bowel disease [130, 131]. However, much remains to be learned about ILC and IL-22 responses in VEO-IBD, and given the importance of these pathways in mediating intestinal health and disease, it is likely the genetic variations associated with VEO-IBD may differentially influence ILC responses.

Genetic Variants Influencing Bacterial Recognition and Clearance

Chronic granulomatous disease (CGD) is a result of defective intestinal phagocytes, specifically the granulocytes responsible for bacterial killing and clearance [132]. The NADPH oxidase complex is responsible for killing of ingested microbes through its production of the respiratory burst. Mutations in any part of the complex molecules (CYBB, CYBA, NCF1, NCF2, NCF4) can result in intestinal inflammation as well as autoimmune disease [133, 134]. Intestinal inflammation can be observed in as high as 40% of patients with CGD [135–138]. Several variants have been associated with VEO-IBD, in particular, defective NCF2 results in altered binding to RAC2 [139]. These patients can present in the neonatal or first year of life with colitis, severe fistulizing perianal disease, and tructuring [139]. Histology frequently demonstrates multiple granulomas that may not have associated inflammatory change [37]. Critically, a recent study by Muise and colleagues identified that heterozygous loss of function mutations in components of the NADPH oxidase complex can determine susceptibility to VEO-IBD, without directly causing overt immunodeficiency [140]. Other neutrophil defects that are associated with VEO-IBD include Leukocyte Adhesion Deficiency Type I and II caused by mutations in *ITGB2* and *SLC35C1,* respectively [141, 142]. These patients can present with an IBD phenotype, history of bacterial infection, and laboratory studies remarkable for increased peripheral granulocytes [143]. Glycogen storage disease Type 1b, with hallmark features of neutropenia and neutrophil granulocyte dysfunction, can present with intestinal inflammation [144]. The reasons for why CGD and other bacterial processing defects may manifest in intestinal inflammation are poorly understood and warrant additional research. It is possible that the causes include bacterial overgrowth or dysbiosis in the intestine, dysregulated activation of the innate and adaptive immune system, or both. Further, the therapies used to treat such patients need to be carefully considered. For example, anti-TNFα therapy is contraindicated in CGD. Though effective for intestinal disease can increase the risk of severe infections in these patients [145]. Other therapies include leukine, antibiotics, and allogenic hematopoietic stem cell transplantation, which have demonstrated some success [146]. In addition, IL-1R antagonists may be particularly attractive approach to limit disease in mouse models and patients with CGD by restoring autophagy and directly limiting inflammation [147].

Autoimmune and Autoinflammatory Disorders

Several autoimmune/autoinflammatory diseases have been linked with intestinal inflammation in children with VEO-IBD. (Fig. 5.2) These include mevalonate-kinase deficiency [148], familial Mediterranean fever (FMF) [149, 150], Hermansky–Pudlak syndrome [151] X-linked lymphoproliferative syndrome (type 1 and 2) [36, 152, 153], and mutations in *NLRC4*. [154, 155] These diseases occur due to loss of function mutations in an enzyme critical for metabolism (mevalonate-kinase deficiency), cytoskeletal proteins (FMF), proteins involved in organelle fusion or biogenesis (Hermansky—Pudlak syndrome), or proteins involved in

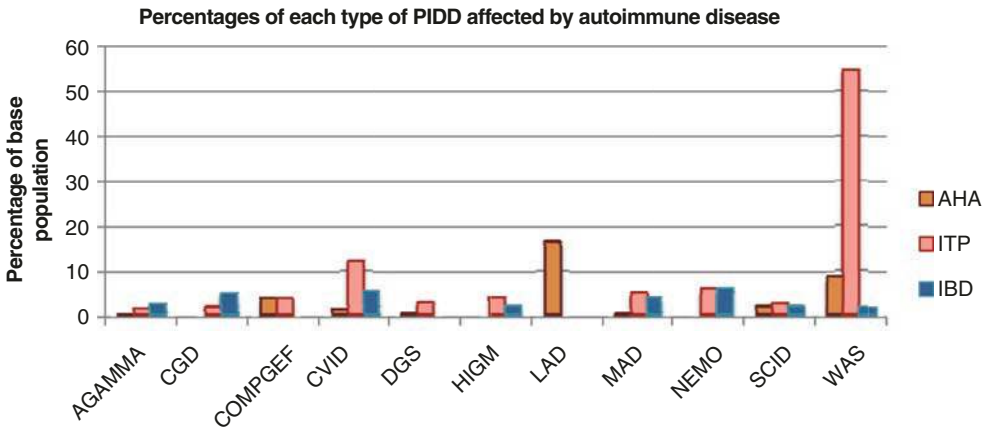

Fig. 5.2 Primary immune deficiencies have an increased frequency of autoimmune disease. The USIDNET registry was used to identify three types of autoimmune manifestations among different types of immune deficiencies. IBD occurs at a low frequency in many of the primary immune deficiencies. There is no strong relationship among the three types of autoimmune disease, suggesting distinct mechanisms of disease

cell signaling or apoptosis (X-linked lymphoproliferative syndrome) or from gain-of-function mutation in *NLRC4* leading to constitutive interleukin-1 family cytokine production and macrophage cell death. While there are many additional clinical manifestations in these patients, twenty percent of patients with X-linked lymphoproliferative syndrome with loss of function defect in the gene X-linked inhibitor of apoptosis protein (*XIAP*), present with VEO-IBD [156]. *XIAP* is involved in NOD2-mediated NFKB signaling, and therefore these children may have an impaired ability to sense bacteria. In addition, as an inhibitor of apoptosis, it prevents apoptosis of activated T cells, thus allowing for expansion and survival of T cells in response to pathogens [157, 158]. Therefore, in XIAP deficiency, due to the inability to clear pathogens, there is a hyperinflammatory state, with increased production of cytokines resulting in an IBD phenotype [156, 158]. Children with these mutations can present with severe colonic and perianal fistulizing disease [36, 159], and of great concern, EBV infection can result in fatal hemophagocytic lymphohistiocytosis [159].

While this is not an exhaustive description of the rare genomic drivers of VEO-IBD, it highlights the different components of the immune system, including innate and adaptive response, involved in this disease. Treatments guided toward the specific defect, such as IL-1 antagonists, colchicine, HSCT, or leukine can be used if the defect is determined. Additionally, monitoring for potential complications associated with a genetic defect is essential, such as in XIAP, IL-10 gene variants, and CGD. In addition to these monogenic diseases, VEO-IBD has been shown to have a high degree of genetic heterogeneity. It is therefore likely that there are more pathways involved in VEO-IBD, and the outcome of therapeutic intervention can be improved through further study and identification of the associated variants. Utilizing next-generation sequencing (NGS) such as WES can improve detection of variants and diagnosis of disease. Further, there is an urgent need to also directly translate genes-to-function and functionally profile the immunological significance of known genetic variations in intestinal inflammation.

Immunologic Considerations

Autoimmune disease in general is strongly associated with variants related to immune deficiency. In a meta-analysis of rheumatoid arthritis, 377 candidate genes were identified as risk loci for rheumatoid arthritis. Among 98 genes with a relative risk greater than 2, 15 of those genes were related to primary immune deficiencies [160]. Therefore, it should come as no surprise that VEO-IBD is similarly enriched with gene defects related to primary immune deficiencies. The study of primary immune deficiencies and their association with VEO-IBD has illuminated the critical and delicate interaction of the immune system with the luminal contents of the gastrointestinal tract. Primary immune deficiencies undoubtedly increase the susceptibility to IBD through multiple mechanisms. Even a mild immune deficiency such as IgA deficiency has a significantly higher rate of IBD than the general population [161]. This may reflect changes to the microbiome due to the lack of selective pressure [162] increased microbial translocation, compromised signaling within the gastrointestinal tract, or stimulation of an aberrant response due to active infection. There are two compelling reasons to further understand defects in genes related to immunologic function in cohorts of patients with IBD. From a purely clinical perspective, identification of patients with monogenic disorders is critical to deliver optimal care. Whether it be through the use of targeted biologic therapy or hematopoietic stem cell transplantation, these patients clearly require a precise, targeted approach to their specific disease state. The second reason for the focus on monogenic disorders is the critical perspective that they provide for the population overall. As was shown above, many of the common variants as well as the monogenic disorders can be categorized according to pathologic pathways that drive the development of VEO-IBD. Even in those patients for which a monogenic cause is not found, these pathways contribute to greater insights and allow better selection of therapeutic approaches.

While defects in epithelial barrier function, lymphocyte signaling defects, regulatory T cell defects, innate responses to infection, and autoinflammatory disorders may seem to represent highly diverse types of defects leading to VEO-IBD, they come together at the epithelial surface where immune responses must be perfectly tuned to prevent inappropriate responses. Increased translocation of bacteria or translocation of inappropriate bacteria, as is the case in dysbiosis, drives an inflammatory loop. An important component of the integrity of the epithelial surface is the contribution of innate lymphoid cells. There are no known monogenic disorders that affect innate lymphoid cells; however, in murine models, their role is now firmly established. These cells contribute to the maintenance of the epithelial layer as well as secretion of antimicrobial peptides and mucins. When this carefully constructed epithelial barrier is penetrated, cells of the innate immune system are activated and recruit additional cells to the inflammatory process. It may be that some of the signaling defects that have been described for conventional T cells also impact the function of innate lymphoid cells and contribute to the susceptibility of IBD through their roles in innate lymphoid cells more substantially than is currently appreciated. Within the lamina propria, T cells and innate lymphoid cells perform an intricate

choreography mediated by the secretion of cytokines. Many of the recognized cytokines are already being targeted through biologic therapies. From this framework, the high impact of the monogenic disorders may be appreciated.

One of the initial strategies to identify patients with primary immune deficiencies is to simply survey their immunologic function, as described above. While many of the defects may not have demonstrable effects on cells within the peripheral blood, many of the monogenic disorders will have an impact that can be appreciated through simple screening studies. Obtaining lymphocyte subsets, testing neutrophil oxidative burst, and evaluating immunoglobulin levels and function represent a reasonable first step. In patients with phenotypic features of specific monogenic conditions, additional functional studies may also be indicated. When suspicion for monogenic disease is high, targeted sequencing panels or whole-exome sequencing (and in some cases whole-genome sequencing) may be pursued. This strategy is now sufficiently available and the consequences of identification of a primary immune deficiency are sufficiently large, that it is appropriate to expend the energy and effort to obtain this type of sequencing.

Perspective and Future Directions in Genetic and Immunologic Analyses of VEO-IBD

In order to advance our understanding of VEO-IBD, sequencing technology must be utilized to completely understand the genetic landscape of this disease, and immunologic studies spanning basic mouse models and translational patient-based approaches are required to determine the contribution of those genetic variations to human disease. Given that dysregulated interactions between the immune system and commensal bacteria underlie the pathogenesis of intestinal inflammation, it is also important to include analyses of composition and function of the microbiome. As these patient populations are studied worldwide, and sometimes in small numbers, international collaborations are needed to integrate genetic, immunologic, and environmental results pertaining to VEO-IBD patients to better understand the effects of different variants within known genes, and identify new gene defects causing IBD through the study of mutations that arise in the same genes of multiple unrelated individuals. With increased understanding of the disease processes operating in VEO-IBD, we can begin to individualize therapies to the specific patient as well as employ unconventional therapies that are not routinely part of the IBD therapeutic arsenal. These approaches could provide a roadmap to establishing a standard of care for this disease and improving patient quality of life.

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Part II

Epidemiology and Clinical Features

The Epidemiology of Pediatric Inflammatory Bowel Disease

6

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Introduction

The global epidemiology of pediatric-onset inflammatory bowel disease (IBD) is rapidly evolving. Based on studies of adult-onset IBD, a four-stage model has been proposed to describe this evolution: (1) emergence of IBD; (2) acceleration in incidence; (3) compounding prevalence; and (4) prevalence equilibrium (Fig. 6.1) [1]. Compounding prevalence occurs when the incidence of IBD is relatively stable over time, while prevalence continues to grow because the incidence of IBD exceeds mortality rates among IBD patients [2]. If the incidence of IBD were to sufficiently decline in a region such that it approaches the mortality rate, prevalence equilibrium would be reached. Much of the developing world has evolving incidence rates of adult-onset IBD consistent with either the first or second stage of this epidemiologic model; the developed world is in the third stage [1]. Thus far, no world region has reached prevalence equilibrium.

The evolution of IBD in children has lagged the evolution in adults. Specifically, many developed, high-income regions in the Western world remain in a stage of accelerating incidence, with many countries describing a rapidly rising incidence of childhood-onset IBD. Further, a lack of data on the epidemiology of childhood IBD in other regions of the world suggests that the emergence of IBD in children may be anticipated in low- and middle-income countries. This chapter will describe our current knowledge of the epidemiology of IBD, including changing age demographics of IBD within children and ethnocultural (including racial) differences and summarize the importance of studying children to understand how environmental exposures influence the pathogenesis of IBD.

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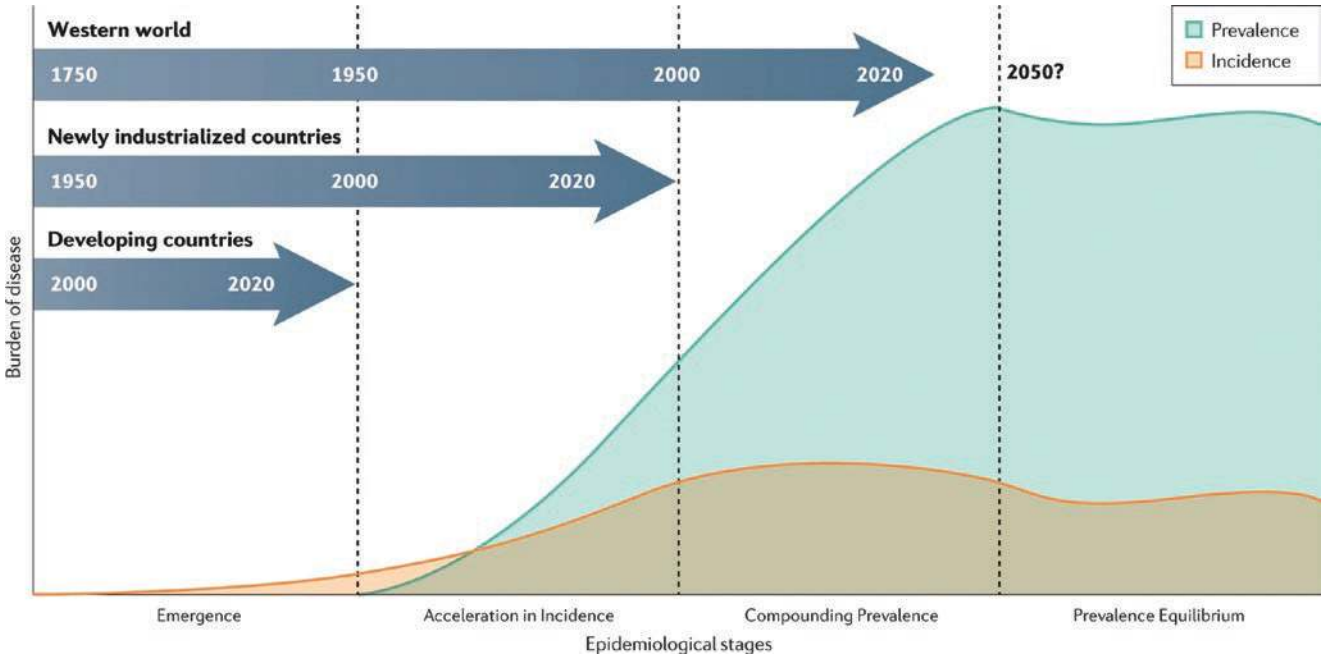

Fig. 6.1 The proposed four-stage model describing the evolution in the epidemiology of inflammatory bowel disease (IBD). Reprinted from Kaplan and Windsor [1] with permission

Incidence and Prevalence

There are two metrics that describe the epidemiology of a disease: incidence and prevalence. Incidence is defined as the number of newly diagnosed people in a given time period, most frequently reported as annual incidence per population. Prevalence is defined as the number of people living with a disease at one point in time. A frequently used analogy to describe incidence and prevalence is water filling and draining from a sink. Incidence is analogous to the water flowing from the tap into the sink—higher incidence is analogous to faster flow of water from the faucet resulting in the sink filling more quickly with cases. Prevalence is analogous to the total volume of water in the sink. For a lifelong chronic disease, like IBD, the only mechanism for cases to "drain away" is death or migration out of the population under study. In pediatric studies where prevalence is often defined as number of children living with IBD in the population, aging out of the population (i.e., becoming an adult) will also remove cases from the sink. Because mortality from IBD is low and is far exceeded by the number of new cases, the number of cases accumulating in the sink continues to grow—resulting in a growing total burden of disease.

Regional incidence and prevalence estimates of pediatric-onset IBD are summarized in Table 6.1 and Fig. 6.2. There is wide geographic variation in the incidence and prevalence rates of pediatric IBD internationally. Systematic reviews indicate that the highest incidence rates of pediatric IBD occur in Canada, Northern Europe, the Northern United States, and Israel, but there remains a paucity of data on the epidemiology of pediatric IBD in the developing world [3, 4]. In general, Crohn disease (CD) is more common among children than ulcerative colitis (UC). More recent studies confirm this geographic distribution of IBD with North America, Northern Europe, and Israel continuing to have the highest rates of IBD and the number of countries reporting rates continues to grow. A longitudinal gradient can be observed, with prevalence being much higher in northern regions of Europe than southern regions. Australia and New Zealand have intermediate rates of IBD. Where data are available, countries in Asia and the Middle East indicate lower rates of IBD in children. Pediatric IBD is rapidly emerging in these regions where it was previously unreported or underreported. Despite our growing knowledge of the epidemiology of pediatric IBD, gaps in knowledge remain for many parts of the world.

Changes in Incidence and Prevalence Over Time

Incidence rates of childhood IBD are increasing globally. These increases have been long established in North America and Europe [3, 4]. As more data on the global incidence of IBD come to light, these rates are continuing to increase in North America [5, 6] and Europe [7–11] and being mirrored

Table 6.1 Summary of the most recently reported incidence and prevalence of pediatric inflammatory bowel disease summarized by world region

Region	Countries reporting incidence and/or prevalence	Incidence per 100,000 person-years	Prevalence per 100,000 people
Africa			
Northern Africa	Libya [16]	**IBD:** 0.9	**IBD:** 3.6
Americas			
Caribbean	French West Indies (Guadeloupe, Martinique) [91], Puerto Rico [92]	**IBD:** • <10 years at diagnosis: 0.3 (French West Indies) • 10–19 years at diagnosis: 3.1 (French West Indies)	**IBD:** 24 (Puerto Rico) **CD:** 7 (Puerto Rico) **UC:** 11 (Puerto Rico)
Central America	Costa Rica [93]	**IBD:** 2.96	
North America	Canada [5, 20], United States of America [94] (California [95], Minnesota [96], Texas [27], Wisconsin [19])	**IBD:** 2.4 (Texas) to 10 (Canada) **CD:** 1.3 (Texas) to 6.5 (Canada, Minnesota) **UC:** 0.5 (Texas) to 4 (Minnesota)	**IBD:** 38 (Canada) to 62 (Canada) **CD:** 25 (Canada) to 43 (United States) **UC:** 11 (Canada) to 28 (United States)
South America	Colombia [97]		**CD:** 0.4 **UC:** 0.9
Asia			
Eastern Asia	China [12], Japan [23], South Korea [98], Taiwan [99]	**IBD:** 0.6 (China) to 3.3 (South Korea) **CD:** 0.25 (Taiwan) to 2.8 (South Korea) **UC:** 0.6 (South Korea)	**CD:** 7.2 (Japan) **UC:** 1.5 (Japan)
South-Eastern Asia	Singapore [17]	**IBD:** 4.3 **CD:** 2.1 **UC:** 1.0	
Southern Asia	Sri Lanka [100, 101]		**CD:** • <10 years: 0 to 0.2 • 10–19 years: 0.44 to 3.9 **UC:** • <10 years: 0 to 0.93 • 10–19 years: 1.8 to 2.73
Western Asia	Bahrain [13, 14], Israel [15, 22], Kuwait [102], Saudi Arabia [18]	**IBD:** 0.49 (Saudi Arabia) to 21.6 (Kuwait) **CD:** 0.34 (Saudi Arabia) to 15.3 (Kuwait) **UC:** 0.15 (Saudi Arabia) to 6.0 (Kuwait)	**IBD:** 373 (Israel) **CD:** 9.32 (Bahrain) to 245 (Israel) **UC:** 128 (Israel)
Europe			
Eastern Europe	Czech Republic [103, 104], Hungary [105], Poland [106]	**IBD:** 2.7 (Poland) to 12.5 (Czech Republic) **CD:** 0.6 (Poland) to 6.8 (Hungary) **UC:** 1.3 (Poland) to 4.0 (Hungary)	
Northern Europe	Denmark [107, 108], Faroe Islands [109], Finland [110, 111], Iceland [11], Ireland [112], Norway [113], Sweden [114–117], United Kingdom (England [9], Scotland [118, 119])	**IBD:** 5.0 (Iceland) to 41.5 (Faroe Islands) **CD:** 2.2 (Faroe Islands) to 10.0 (Sweden) **UC:** 2.4 (Iceland) to 12.5 (Finland)	**IBD:** 46.3 (Scotland) to 75.0 (Sweden) **CD:** 29.0 (Sweden) to 39.5 (Scotland) **UC:** 12.5 (Scotland) to 30.0 (Sweden)
Southern Europe	Croatia [120], Italy [121], Malta [122], San Marino [123], Slovenia [124], Spain [10]	**IBD:** 1.4 (Italy) to 9.4 (Slovenia) **CD:** 0.62 (Malta) to 8.69 (Croatia) **UC:** 0.9 (Croatia, Spain) to 9.1 (San Marino)	**IBD:** 31.0 (San Marino) **CD:** 15.5 (San Marino) **UC:** 15.5 (San Marino)
Western Europe	Austria [125], France [7], Germany [126], Netherlands [127]	**IBD:** 5.2 (Netherlands) to 17.4 (Germany) **CD:** 2.1 (Netherlands) to 10.6 (Germany) **UC:** 1.6 (Netherlands) to 6.2 (Germany)	**IBD:** 66.3 (Germany) **CD:** 37.7 (Germany) **UC:** 23.7 (Germany)
Oceania			
	Australia [29, 128–130], New Zealand (NZ) [131, 132]	**IBD:** 5.2 (NZ) to 6.8 (Australia) **CD:** 3.5 (NZ) to 5.9 (Australia) **UC:** 1.0 (NZ) to 1.6 (Australia)	**IBD:** 21.7 (NZ) to 46.0 (Australia) **CD:** 16.5 (NZ) **UC:** 3.3 (NZ)

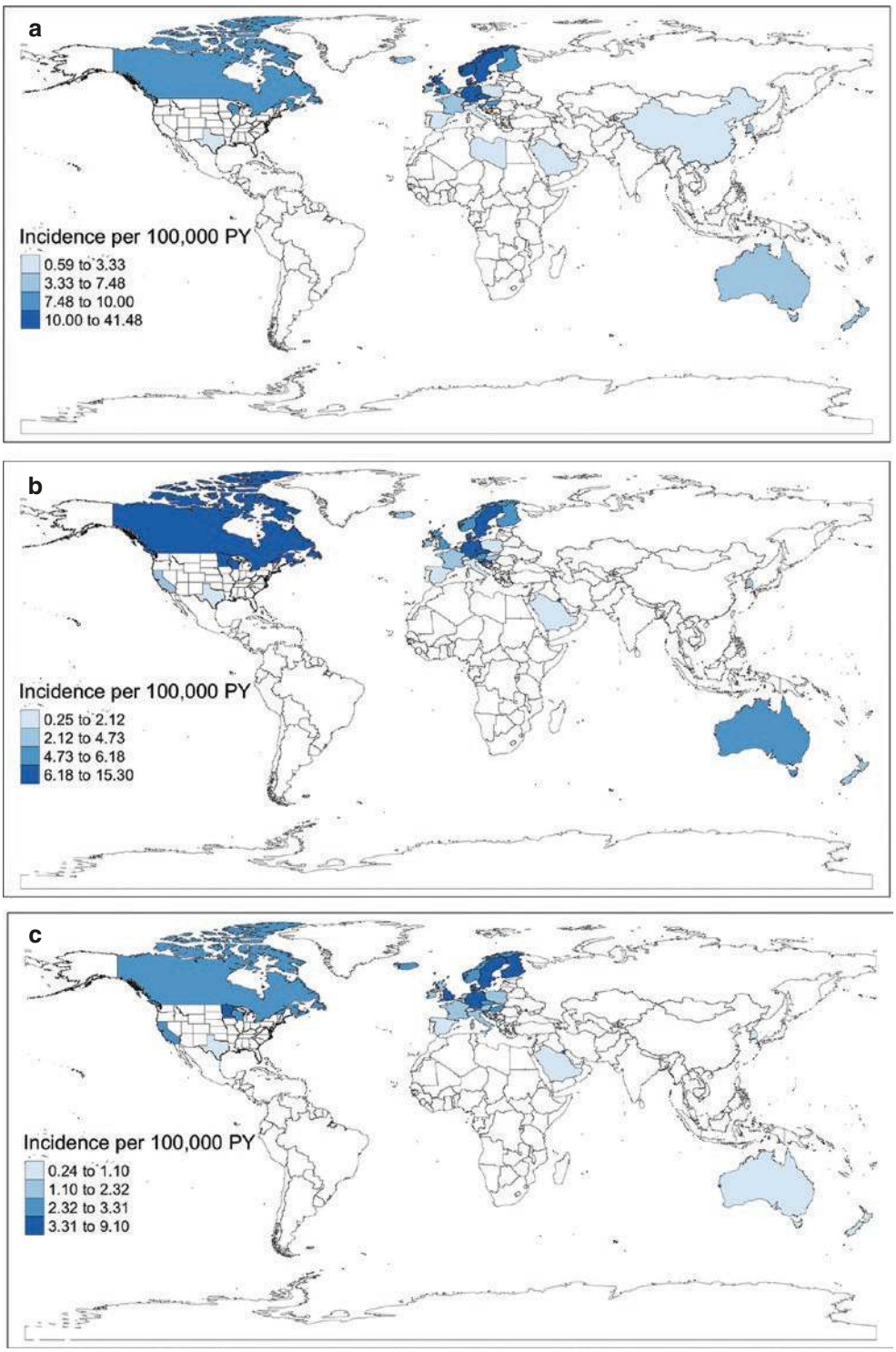

Fig. 6.2 Maps describing global patterns in the incidence of pediatric-onset (**a**) inflammatory bowel disease (IBD); (**b**) Crohn disease (CD); and (**c**) ulcerative colitis (UC)

in other parts of the world, including in China [12], Bahrain [13, 14], Israel [15], Libya [16], Singapore [17], and Saudi Arabia [18]. Incidence rates in Wisconsin, USA remained stable between 2000 and 2007 [19].

Changes in incidence vary by age. For example, incidence of IBD is increasing among Canadian children of all ages [6]; however, this is largely driven by increases in Very Early-Onset IBD (VEO-IBD), defined by IBD diagnosed in children <6 years of age [5]. In Saudi Arabia, incidence of VEO-IBD and VEO-CD have declined over time, but incidence of IBD, CD, and UC have increased among all those diagnosed before their 15th birthday; the incidence of

VEO-UC was stable over this period [18]. France has reported stable rates of VEO-IBD but increasing rates of IBD diagnosed between the ages of 6 and 16, before age 10, and among children of any age [7, 8].

Canada [5, 6, 20, 21], Israel [15, 22], Libya [16], and Japan [23] have reported significant increases in the overall prevalence of childhood IBD over time. Japan reported an increase of 71.4% in the prevalence of CD (4.2 to 7.2 per 100,000) and 36.4% increase in the prevalence of UC (from 11 to 15 per 100,000) between 2004 and 2013 [23]. The prevalence of IBD in Libya increased from 1.2 per 100,000 to 3.6 per 100,000 between 2002 and 2006 [16]. Israel similarly reported increases in the prevalence of CD and UC, with prevalence increasing faster among Arabs than Jews [15]. In Canada, increases in prevalence differ by age group. The most notable increases in prevalence were reported for those <5 years of age and was specific to overall IBD (average annual percentage change [AAPC] +10.7%, 95% CI +3.32 to +18.09) and CD (AAPC +13.14, 95% CI +7.24 to +19.04) [5]. Changes in the prevalence of VEO-UC were not statistically significant (AAPC +5.48, 95% CI −5.01 to +15.98). Increases in the prevalence of CD and UC were similar among Canadian children 5 to 9 years of age (CD: AAPC +9.11, 95% CI +4.38 to +13.84; UC: AAPC +9.98, 95% CI +5.91 to +14.05). The prevalence of overall IBD and CD significantly increased among those 10 to 13 years of age, though the annual increases in this age group were much smaller in magnitude relative to the other age groups (IBD: +3.14%, 95% CI +1.61 to +4.67; CD: +2.99, 95% CI +0.79 to +5.20). There were no significant changes in the prevalence of IBD, CD, or UC among those 14 to 15 years of age.

Projecting the Future Epidemiology of Pediatric Inflammatory Bowel Disease

The availability of large population-based cohorts of IBD patients derived from routinely collected health data has enabled investigators to predict the future burden of IBD. In Canada, the overall prevalence of IBD in children (<18 years) will rise from 62 per 100,000 in 2008 to 159 per 100,000 (prediction interval [PI] 133 to 185) in 2030 [20]. This same degree of projected increase in the prevalence of pediatric IBD (<17 years) was not replicated in Scotland, where the 2018 prevalence was reported to be 106 per 100,000 and the 2028 prevalence is predicted to be 124 (95% CI 80 to 169) per 100,000 [24]. The prevalence of IBD in Portugal is expected to be 4–6-times higher in 2030 than in 2003; however, this study did not forecast pediatric-specific prevalence estimates [25]. These studies predicting future trends in epidemiology are important to understand the future global burden of IBD, as well as to plan for health system changes required to meet the needs of children with IBD. The rising prevalence in some regions will be accompanied by increasing health services utilization and use of biologic medications, resulting in alarming increases in direct health care costs and other resource needs.

Changing Age at Inflammatory Bowel Disease Diagnosis

The differing trends in incidence rates across age groups begs the question: Is the age at which children are being diagnosed with IBD changing? The data needed to answer this question are not clear. An Israeli study reported that the mean age at IBD diagnosis among Jewish children significantly decreased from 15.0 ± 2.8 years for those diagnosed between 2002 and 2008 to 14.3 ± 3.1 years for those diagnosed between 2009 and 2016 [22]. A second study from Israel conducted between 2005 and 2017, including both Jews and Arabs, reported significant increases in the incidence of both CD and UC in children diagnosed between 10 and <18 years but no change in the incidence of CD and UC diagnosed <10 years [15]. In France, an increasing proportion of children were diagnosed with an inflammatory phenotype (64% in 1988–1990 to 87% in 2009–2011) with notable declines in fibrostenotic disease behavior at diagnosis (33% in 1988–1990 to 11% in 2009–2011) [7]. These changes in phenotype over time implies earlier identification of disease, prior to progression from inflammatory to fibrostenotic disease. However, this was not reflected in the analysis assessing age demographics: the proportion of children diagnosed before 10 years of age did not significantly change between 1988–1990 (17.0%) and 2009–2011 (18.7%) [7]. Changes in the age at IBD diagnosis likely resulted from a combination of factors including early disease onset and earlier diagnosis resulting from increasing awareness of IBD in young children and improved access to specialist pediatric gastroenterologist care, endoscopy, and imaging [26].

Ethnocultural Differences in the Epidemiology of Inflammatory Bowel Disease

There are notable differences in the epidemiology of IBD among children of different ethnocultural backgrounds living in the same geographic regions. A study from Texas reported incidence of 4.15 (95% CI 3.48 to 4.82), 1.83 (95% CI 1.14 to 2.51), and 0.61 (95% CI 0.33 to 0.89) per 100,000 person years in White, African American, and Hispanic children, respectively [27]. These rates increased in all groups over the course of the study but the relative increase in incidence was the greatest for Hispanic children. This same study reported a higher incidence of CD relative to UC in all

groups; however, this difference was most pronounced in African-American children. A Wisconsin study reported a similar ethnic distribution among children with IBD to the general population of the state [19].

In Israel, both the incidence and prevalence of pediatric IBD are substantially higher in Jews than in Arabs. However, one study found that the gap has decreased between 2005 and 2018. The prevalence of both CD and UC increased much faster among Arab children (CD: AAPC +6.0%, 95% CI +3.8 to +8.3; UC: AAPC +7.0%, 95% CI +5.0 to +9.2) than among Jewish children (CD: AAPC +1.4%, 95% CI +0.9 to +1.9; UC: +2.9%, 95% CI +2.5 to +3.4) [15].

A study from British Columbia, Canada, described significantly higher incidence of IBD in South Asian children relative to non-South Asian children [28]. In South Asian children, the incidence of IBD increased from 5.95 per 100,000 person-years in 1996 to 18.01 per 100,000 person-years. In non-South Asian children, the incidence increased from 4.44 to 7.73 per 100,000 person-years over the same period. Although the incidence of all IBD types was higher among South Asian children, this difference was highest for UC (South Asians: CD 6.41 per 100,000 person-years, UC 6.70 per 100,000 person-years; non-South Asians: CD 3.69 per 100,000 person-years, UC 0.96 per 100,000 person-years). The majority of IBD cases presenting in South Asian children occurred in second-generation residents (the children of immigrants).

There is a paucity of data on the incidence and prevalence of IBD in indigenous populations, such as Native Americans, Canadian First Nations, and Australian Aboriginal people, although it has been suggested that the risk remains lower in these populations. In Australia, 0.56% of children with IBD have at least one parent of Aboriginal or Torres Strait Islander origin; 4.13% of Australian children are of Aboriginal or Torres Strait Islander origin [29]. Regions of Manitoba, Canada with the lowest per capita rates of First Nations peoples have the highest rates of IBD [30, 31]. The penetrance of IBD susceptibility genes differs in Canadian First Nations peoples and individuals of European ancestry. For example, mutations in *ATG16L1* and *NOD2*—two genes important for bacterial recognition and autophagy—are less common in healthy Manitoba First Nations peoples than Caucasians [32].

Studies of migrants from low to high prevalence countries can also provide valuable information about the risk of IBD in individuals of differing ethnocultural backgrounds. Individuals migrating from low prevalence regions to Western countries remain at lower risk of IBD compared with other residents of those Western countries [33–35]. However, age at immigration may mediate this effect, with those immigrating during childhood or adolescence having an increased risk of IBD relative to those immigrating at older ages [33]. This implies that earlier life exposure to environmental factors in high-prevalence countries increases the risk of IBD. However, even Canadian-born children of immigrant mothers were less likely to develop IBD than children born to non-immigrant mothers [33]. Being an immigrant or child of an immigrant was associated with significantly lower risk of CD, but was less protective for UC. This implies that even in-utero and early-life exposure to the Canadian environment are insufficient to convey risk, despite the high prevalence of IBD in Canada. However, this risk modulation is associated with ethnic background, and therefore genetic risk or protective factors. In the Canadian study, the decreased risk of IBD was most pronounced for those born to parents migrating from East Asia. Children born to parents from the Middle East, South Asia, Sub-Saharan Africa, and Western countries had the same risk of developing IBD as children born to non-immigrant parents [33]. Second-generation immigrants to Sweden were at similar risk to non-immigrants notwithstanding their region of origin [35]. However, there were regional differences in the risk of IBD subtypes, such as in second-generation immigrants from Eastern Europe (increased risk of CD, but decreased risk of UC), Southern Europe (increased risk of UC), and Latin America (decreased risk of CD). No significant associations were identified among second-generation immigrants from other regions, including Asia (although migrants from South and East Asia were not distinguished) [35]. The findings of differential risk of IBD in migrants from different regions indicate important differences in host susceptibility to Western environmental factors and may aid in our understanding of the complex pathogenesis of IBD.

Environmental Risk Factors

IBD results from a complex interaction between an individual's genetic background, environmental exposures, microbiome, the epithelial lining of their intestine, and their immune response to commensal bacteria [36]. This is further complicated by the number of lifestyle and other environmental exposures associated with IBD. A recent umbrella review of meta-analyses identified 43 lifestyle and environmental exposures that were either associated with an increased or decreased risk of IBD [37]. Therefore, the contributing factors in one individual may not have the same impact to another individual's risk of IBD. As a result, identifying environmental risk factors that predispose to the development of IBD remains a challenge. The evolving epidemiology of pediatric IBD will provide extraordinary opportunities to study how shifts in environmental exposures in developing and newly developed regions contribute to IBD pathogenesis.

The Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS) was designed to describe the emergence of IBD across Asia and identify environmental risk factors associated with IBD in regions where the prevalence of IBD was

previously low [38–40]. Australia was included in ACCESS to allow for comparisons between risk factors in Asians and those in a Westernized country primarily composed of people of European origin. Although the data generated from this cohort are not specific to IBD in children, they enhance our understanding of how the same environmental risk factors may play differing roles in individuals across ethnocultural backgrounds.

Many environmental exposures that have been hypothesized to be associated with the development of IBD likely modify the intestinal microbiome and these factors may act in concert to influence the microbiome. For example, the development of the intestinal microbiome is jointly influenced by mode of delivery (vaginal or cesarean section), breastfeeding, early-life antibiotic exposure, and other environmental exposures [41]. Because the microbiome is established early in life [42], and children have been exposed to fewer environmental risk factors than adults, we may be able to more clearly identify environmental risk factors contributing to IBD pathogenesis in those diagnosed with IBD in childhood.

The Hygiene Hypothesis

The "Hygiene Hypothesis" has long been postulated to be an explanation for the emergence of IBD and other immune-mediated inflammatory diseases (IMIDs) in developed countries in the twentieth century, and the ongoing emergence of IBD in low- and middle-income countries more recently. This hypothesis posits that early exposure to unhygienic circumstances early in life is important for proper immune system development, with a focus on the role of various environmental microscopic organisms in priming the immune system. Without these exposures, aberrant immune responses develop. In IBD, this is exemplified by excessive immune responses to the commensal intestinal bacteria resulting in intestinal inflammation.

The impact of environmental hygiene on the risk of IBD is often studied by evaluating exposures such as availability of indoor plumbing (e.g., tap water, flush toilets), household crowding (e.g., family size, bed sharing, number of siblings), and household pets. However, studies describing associations between these environmental factors have reached inconsistent conclusions and have not always been congruent with the Hygiene Hypothesis.

The availability of tap water has been associated with a reduced risk of developing IBD in some studies but not others [43, 44]. Among Asian participants of the ACCESS cohort, having a hot water tap and a flush toilet were associated with an increased risk of developing CD in unadjusted analyses (hot water tap: OR 1.48, 95% CI 1.03 to 2.13; flush toilet: OR 1.72, 95% CI 1.15 to 2.57) but neither association persisted when adjusting for sex, age, and country-level gross national income [39]. In contrast, having an in-home water tap, hot water tap, and flush toilet were associated with a decreased risk of UC (in-home water tap: OR 0.60, 95% CI 0.44 to 0.81; hot water tap: OR 0.58, 95% CI 0.43 to 0.78; flush toilet: 0.62, 95% CI 0.46 to 0.83); these associations persisted when adjusting for age, sex, and country-level income [39].

Exposure to animals at a young age may protect against later development of IBD. Growing up on a farm in Manitoba, Canada, was associated with a decreased risk of developing CD but not UC, with no differences noted by type of farm (cattle, pig, or poultry) [45]. This is consistent with another Canadian study demonstrating a strongly protective effect of early-life rural household (compared to growing up in a city) [46]. Having a household pet or exposures to other animals has generally been associated with a decreased risk of IBD [39, 45, 47–49]. Some differences have been noted across studies, with some describing an association that was specific to having a pet before age 5 [45] and the type of pet (e.g., pet dogs decreased the risk of CD but not UC, aquarium fish decreased the risk of UC but not CD) [39]. The association between household pets and risk of IBD appears to be consistent across geographic regions and ethnocultural groups.

Studies describing the associations between household crowding, family size, and birth order have been less conclusive. Inconsistent with the Hygiene Hypothesis, some studies have described an increased risk of IBD with bed sharing, while others have the described protective effects for bed sharing and other measures of household crowding congruent with the Hygiene Hypothesis [43, 47, 50, 51]. Large households, having older siblings, and having younger siblings have been shown to protect against the development of IBD, but this association has not been consistently reported in all studies [44, 45, 47, 49, 50, 52, 53].

Breastfeeding

Systematic reviews have consistently demonstrated a protective association between breastfeeding and pediatric-onset IBD [54, 55]. This decreased risk of IBD among those who are breastfed appears consistent across ethnicities and may exhibit a dose–response effect whereby longer durations of breastfeeding are associated with decreased risk [39]. The impact of breastfeeding is thought to influence IBD risk through modification of the intestinal microbiome. There are marked differences in the microbiome between children who are exclusively breastfed and those who are exclusively formula-fed; smaller differences have also been noted among infants who are exclusively and partially breastfed [56]. Perhaps the most remarkable difference between breastfed

and formula-fed infants is the time to maturity of the intestinal microbiome: the microbiome appears to reach maturity at three months of age among infants who are not breastfed, while maturity is not reached until 12 months of age in those who are continuously breastfed [56].

Cesarean Section

Babies delivered vaginally are exposed to their mother's microbiome at birth. Without this earliest exposure, babies born via cesarean section have an altered trajectory for the development of their microbiome from the time they are born. Consequently, it has been hypothesized that babies born via cesarean section may be at higher risk of developing IMIDs such as IBD. Studies on the association between mode of delivery and the risk of IBD have been inconclusive. Meta-analyses have failed to detect a significant association between cesarean delivery and the risk of IBD [57, 58]. However, the included studies were heterogenous in both study design and conclusions: Cesarean section delivery was associated with an increased risk of IBD in case–control studies relying on self-reported mode of delivery but not in population-based cohort studies relying on routinely collected health data [57]. A second meta-analysis described an increased risk of CD, but not UC, among individuals born via cesarean section delivery [58].

Infectious Diseases and Antibiotic Use

Antibiotic exposure alters the intestinal microbiome. While the microbiome of adults tends to revert to its pre-antibiotic state, the impact of early-life antibiotic exposure may have a long-lasting impact on the microbiome [59]. Accordingly, antibiotic exposure during childhood has been associated with an increased risk of IBD, with antibiotics during the first of life conferring the greatest risk on later development of IBD [39, 60–64]. In British Columbia, Canada, antibiotic usage and the incidence of childhood asthma have declined in parallel and the association between antibiotic use and asthma is mediated by the impact of antibiotics on the intestinal microbiome [65]. This same decline in IBD incidence in the era of declining antibiotic use has not been observed.

The impact of infections themselves on the subsequent risk of IBD is less clear. Infectious gastroenteritis and other infections (e.g., otitis media) have been associated with an increased risk of developing IBD in most studies evaluating the association [50, 51]. Other studies have reported that early-life infection protects against the development of IBD [47, 48, 66]. However, the relative contributions of the sequalae following infection and any antibiotics used to treat the infection in influencing this increased risk are not clear. In addition, the association between infections and IBD may be confounded by the presence of genetic polymorphisms conferring the risk of relative immunodeficiency, which may be more frequent in children with IBD [67].

Exposure to Cigarette Smoke

Cigarette smoking is the most consistently replicated environmental risk factor in IBD. Cigarette smoking is associated with an increased risk of developing CD; current smoking is associated with a decreased risk of developing UC, while former smoking is associated with an increased risk of developing UC [68]. Smoking is believed to impact the risk of IBD through several mechanisms, including alterations to the following: (1) mucus production, altering the physical barrier between the body and intestinal lumen; (2) innate immune response though altered macrophage functioning; (3) adaptive immune response through increased production of pro-inflammatory cytokines; (4) alterations to the gut microbiome; and (5) microvasculature of the intestines [69, 70]. The impact of cigarette smoking likely only occurs in someone who is genetically susceptible to developing IBD. Evidence from areas where IBD is emerging (e.g., Asia) suggests that the impact of smoking on the risk of developing IBD varies across ethnicities. For example, the ACCESS cohort demonstrated an increased risk of CD among smokers in Australia but not in Asia; former smoking still increased the risk of UC in this cohort [39]. It has been suggested that there is an interaction between *NOD2* and cigarette smoking, such that smokers who also carry a mutation in this gene are unexpectedly less likely to develop CD [71]. However, this interaction was likely driven by the differing penetrance of *NOD2* and cigarette smoking across the age spectrum [72]. Specifically, *NOD2* mutations are common in those diagnosed with CD as children but rare in those diagnosed as adults, while a history of cigarette smoking is very rare in children but common in adults. The impact of cigarette smoke on the risk of CD may be more pronounced in individuals with genetic variants involved in how the body metabolizes tobacco smoke [73], suggesting important differences in the causes of IBD across individuals.

The impact of smoking on the risk of childhood-onset IBD would most likely result from passive exposure to cigarette smoke—either through maternal smoking during pregnancy or exposure to second-hand smoke during childhood. However, a meta-analysis of 13 studies failed to identify an association between IBD and exposure to cigarette smoke, either in-utero or during early childhood [74].

Urban Environments, Air Pollution, and Residential Greenspace

A systematic review and meta-analysis described an increased risk of developing IBD among individuals living in urban areas but with a high degree of variability across studies [75]. Further study suggests the association between living in a urban area and the risk of IBD is highest for those diagnosed during childhood [46] and has been replicated in Asian countries with data from the ACCESS cohort [40]. One hypothesized mechanism for this association is through environmental exposures that are more common in urban environments: increased air pollution and reduced residential greenspace.

The association between air pollution and IBD has been inconsistently reported in the literature. In a study using a UK primary care database, high levels of exposure to NO_2 (a traffic-related pollutant) increased the risk of developing CD in those diagnosed ≤23 years of age (OR 2.31, 95% CI 1.25 to 4.28); there was a dose–response whereby the risk increased with increasing levels of NO_2 [76]. This same study found that SO_2 (a pollutant often found in industrial areas) exposure increased the risk of UC among those diagnosed ≤20 years (OR 2.62, 95% CI 1.15 to 6.00). These associations were specific to those who were young at diagnosis and there was either no significant association or a protective association between air pollution and IBD in those diagnosed later in life. A second study evaluating the association between NO_2 and childhood IBD reported no association [77]. Instead, this study reported a significant increased risk of pediatric IBD associated with the redox-weighted oxidant capacity of air pollutants (calculated using a combination of NO_2 and O_3 levels): HR 1.08 (95% CI 1.01 to 1.16). In a third study, high levels of traffic intensity on major roads (within a 100-m buffer) were associated with an increased risk of adult-onset IBD (adjusting for smoking, education, and NO_2 concentration OR 1.60, 95% CI 1.04–2.46) [78]. Higher exposure to particulate matter ($PM_{2.5}$ and PM_{10}) was associated with a decreased risk of adult-onset IBD in one study but not in the other two [76–78].

In Canada, children living in areas with more greenspace were less likely to develop IBD (HR 0.77, 95% CI 0.74 to 0.81) [79]. The association was consistent in both CD and UC and persisted after adjusting for air pollution (NO_2, $PM_{2.5}$, and O_3). The magnitude of the associations between childhood exposure to residential greenness was more pronounced when restricting to IBD diagnosed at ≤10 years of age (fully adjusted models for IBD: HR 0.70, 95% CI 0.69 to 0.72; CD: HR 0.70, 95% CI 0.68 to 0.72; UC: 0.71, 95% CI 0.69 to 0.73). This study also reported a dose–response relationship of residential greenspace and pediatric IBD. In-utero exposure to residential greenspace during pregnancy was not significantly associated with childhood-onset IBD after adjusting for NO_2, $PM_{2.5}$, and O_3 (HR 0.92, 95% CI 0.83 to 1.01).

Diet

The association between diet and the risk of IBD is challenging to study—and is likely to be influenced not only by individual food items (fats, proteins, processed food, fiber, micronutrients, preservatives, etc.) but also by the interaction between these food items, the intestinal microbiome, and the immune system [80]. Systematic reviews have summarized the literature between dietary factors and the risk of IBD. In general, these reviews have reported increased risk of IBD with diets high in animal protein/meat and fat (total fat, polyunsaturated fatty acids, and omega-6 fatty acids), and low in fiber [50, 80–82]. The mechanism through which this occurs involves the breakdown of dietary fiber by bacteria in the intestine into short-chain fatty acids which then play a role in the production of anti-inflammatory signaling molecules (e.g., butyrate) ultimately resulting in intestinal inflammation. Short-chain fatty acids also play a role in the maintenance of the mucosal barrier and tight junctions between intestinal epithelial cells—also important in the pathogenesis of IBD. When the diet is high in processed food (high fat, high sugar, high preservatives), there is decreased microbial diversity and decreased production of short-chain fatty acids which, in turn, decreases the body's natural defenses. This results in a breakdown of the mucosal barrier and a "leaky gut" allowing bacteria to cross the epithelial lining of the intestinal tract, triggering an inflammatory response. With increasing "Westernization," processed food diets become increasingly common. These dietary changes and subsequent impact on the microbiome, immune system, and the intestinal barrier function may be contributing to the emergence of IBD in regions where it was previously unknown [83].

Association vs. Causation

Solely studying the environmental risk factors described above using an epidemiologic lens does not allow us to conclude that these factors "cause" IBD. Instead, as with all non-interventional research studies, we are limited to interpreting these findings as associations. Sir Austin Bradford Hill proposed nine criteria for determining if environmental exposures truly cause disease (Table 6.2). [84] These criteria are not universally agreed upon as necessary or sufficient for determining causality. The most important criteria for establishing causality are arguably temporality and lack of confounding. Establishing a biological mechanism through which an exposure causes disease is also important in establishing a causal association.

Table 6.2 Hill criteria [84] for determining if an environmental exposure causes disease, including explanations and examples from the IBD literature to evaluate the application of the causal criteria

Criterion	Explanation	Example application from the IBD literature
Strength	Associations that are larger in magnitude are more likely to be causal. However, many causal relationships may be small in magnitude while many non-causal relationships may be large.	Many of the >200 IBD susceptibility genes confer a very small increase in the risk of IBD (i.e., ORs ranging from 1.05 to 1.4, with most less than 1.2) [133, 134].
Consistency	Repeated studies of a causal association reach the same conclusions, across populations, time, and study methodology. Since many environmental risk factors interact with an individual's genetics, microbiome, and other environmental exposures, a cause may not be replicable in all scenarios [135, 136].	Cigarette smoking is a well-established risk factor for CD. Yet, this association could not be replicated in Asia [39].
Specificity	A particular cause is only responsible for a single outcome or, alternatively, a particular outcome can only have one cause. However, it is unlikely for a single environmental exposure to cause a single disease [84].	The specificity criterion could imply that (1) cigarette smoking causes only CD or (2) the only cause of CD is cigarette smoking. Both are false: cigarette smoking causes many diseases and multiple factors play a role in CD pathogenesis.
Temporality *This is the only causal criterion that is necessary for causation, but it is not sufficient.*	An event (e.g., IBD diagnosis) must occur after the exposure that caused it.	Because subclinical inflammation can exist long before a formal IBD diagnosis is made, ensuring temporality can be challenging. In studies of early-life environmental factors (e.g., antibiotic use in the first year of life), exposure likely occurred prior to preclinical disease.
Biologic gradient	The greater the exposure, the greater the risk of the outcome (i.e., there is a dose response). However, the observed gradient may result from another exposure that increases in parallel with the exposure of interest.	Increasing levels of residential greenspace early in a child's life is associated with a decreasing risk of developing IBD [79] but this association may have resulted from another unknown factor that increases in parallel with greenspace.
Plausibility	There is a biological mechanism that explains how A causes B. This criterion is speculative, at best, and is subject to change as advances in knowledge contradict mechanisms that were previously hypothesized.	Evidence from basic and translational science suggests many ways through which cigarette smoke may cause CD, including altering: (1) mucus production; (2) innate and adaptive immune responses; (3) the gut microbiome; and (4) microvasculature of the intestines [69, 70].
Coherence	All evidence of a causal relationship is consistent, including from basic and translational science and epidemiology. Inconsistent findings may not mean that an association is not causal due to unmeasured confounding as the true cause (for example).	The relationship between cigarette smoking and CD is not coherent. The lack of association between smoking and CD in Asia does not mean this relationship is not causa. Instead, it likely results from underlying differences across populations.
Experiment	Hill's original explanation refers to the removal of an exposure (e.g., what happens after someone stops smoking?) [84]. Recent interpretations include evidence from randomized controlled trials and basic and translational experiments. However, experiments in humans are often unethical and findings from lab-based experiments may not extrapolate well to humans.	In addition to being an important risk factor for developing CD, cigarette smoking also worsens its prognosis [137]. The risk of negative outcomes in CD (e.g., the need for intestinal resection, disease flare) diminishes over time in people who quit smoking [138, 139].
Analogy	If X causes Y, then it is also possible for A to cause B (if X is similar to A and Y is similar to B). Criticisms often cite investigators' creativity as analogy's greatest limitation: creative individuals are often better at identifying analogous situations [135, 136].	If cigarette smoking causes CD, then it could be analogous for smoking to cause UC—as both diseases involve intestinal inflammation. However, the paradoxical impact of cigarette smoking on CD and UC contradicts this analogy.

Abbreviations: *CD* Crohn disease, *IBD* inflammatory bowel disease, *OR* odds ratio, *UC* ulcerative colitis.

Temporality requires that the proposed cause of disease occurs prior to the onset of disease. In studies of early-life environmental factors, temporality is less concerning than if studying long-term environmental factors where pre-symptomatic disease may have developed prior to exposure.

Confounding occurs when the described association between an environmental exposure and disease is due to a third variable that is associated with both the environmental exposure and the disease. An often-cited example is the association between birth order and Down syndrome. Having more older siblings is associated with an increased risk of Down syndrome; however, this association is confounded by maternal age. Determining the relative contribution of studied environmental factors and other, as of yet unknown, environmental factors is challenging without knowing the impact of confounding on these associations. For example, both childhood infections and early-life antibiotic exposure may be causally associated with IBD; however, understanding how each alters risk, independently and in combination, is not easy.

Lastly, the plausibility of an epidemiologic associations is substantially strengthened when there is a biological mechanism through which the environmental exposure results in disease. Many of the environmental factors described above are believed to influence the risk of IBD, in part, through their interaction with the intestinal microbiome. Causation can more convincingly be demonstrated by combining epidemiological associations with scientific experimentation, such as that using animal models of disease. The inclusion of particulate matter (PM_{10}) in mouse chow resulted in higher expression of inflammatory cytokines, pro-inflammatory changes to the intestinal microbiome, increased intestinal permeability, and changes in the immune response to microbes in mouse models of IBD [85, 86]. The impact of particulate matter in chow was most pronounced in young mice providing support for the epidemiologic evidence that the impact of air pollution on IBD may be more pronounced in children [85]. Using evidence from basic and translational science, air pollution is hypothesized to result in intestinal inflammation by altering the microbiome, then impacting the gut epithelial cells, resulting in increased intestinal permeability, and ultimately resulting in a dysregulated immune response [87]. This experimental evidence is an example of how epidemiology research findings can be used to shape scientific experiments to better understand the pathophysiology behind epidemiologic research.

Gaps in Knowledge and Challenges in Determining the Global Epidemiology of Pediatric Inflammatory Bowel Disease

Our knowledge of the global epidemiology of pediatric IBD has evolved greatly over the past decade. However, there remains a paucity of data on rates of IBD in children from many regions of the world. Our ability to understand global patterns, as well as to identify risk factors driving increases in pediatric IBD, shifts to younger ages at diagnosis, and ethnocultural differences depends on our ability to generate and study high-quality data. Studying the epidemiology of a disease can be even more challenging than studying factors that confer risk. Population-based estimates of incidence and prevalence require identification of all cases of disease within a specified geographic region. Without systematic strategies for population-based data generation, rates of disease are almost impossible to determine.

We are currently seeing exponential growth in research using routinely collected health data (e.g., electronic medical records and health administrative data)—including in regions where the current epidemiology of pediatric IBD remains unknown. As these systems are increasingly integrated into clinical practice and health system planning, the data they capture will facilitate research. As with all research, ensuring these data are of high quality—capturing all IBD cases in the region and confirming the accuracy of IBD diagnosis (e.g., through validation)—will be paramount [88–90]. Combining the increase in data availability with the continuing emergence of IBD in areas where the epidemiology has not previously been reported, we expect that our knowledge of the global epidemiology of pediatric-onset IBD will evolve rapidly. Initiatives are currently underway through the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) to enhance our understanding of the global epidemiology of adult-onset IBD, with future expansion planned for pediatric IBD. The emergence of these data will provide further opportunity to understanding the environmental exposures resulting in the rapid emergence of these diseases.

Conclusions

IBD is common in children in many parts of the world and becoming increasingly common in regions where it was previously unreported. Despite our growing knowledge of the global epidemiology of pediatric IBD, significant gaps in knowledge persist. As IBD continues to emerge and rates continue to rise, we are poised to be able to further understand environmental risk factors, including those specifically increasing the risk of IBD in children, and how these factors may differ across ethnocultural groups.

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The Natural History of Crohn Disease in Children

7

Benjamin Sahn and James Markowitz

Abbreviations

Anti-TNF	Antitumor necrosis factor-alpha
CD	Crohn disease
ECCDS	European Cooperative Crohn Disease Study
HRQOL	Health-related quality of life
IBD	Inflammatory bowel disease
NCCDS	National Cooperative Crohn Disease Study
SIR	Standardized Incidence Ratio

Introduction

Determining the natural history of Crohn disease (CD) involves the consideration of a number of different factors: the disease activity over time, the frequency of complications, the need for surgery, and the risk of disease recurrence following both medically induced and surgically induced remission. In children, evaluation of the natural history also must include the effects of CD on growth and development and on quality of life.

The true natural history of CD remains largely unknown, however, primarily because there are virtually no data describing the long-term course of untreated children or adults with this illness. The data that do exist arise from early clinical experience treating patients with corticosteroids and 5-aminosalicylate medications and from a small number of placebo-controlled treatment trials. These data document that the natural history of CD is associated with significant morbidity. As a consequence, one of the primary goals of current therapy includes improving the natural history of the disease. In the past decade, there has been a rapidly growing understanding of the roles that gene expression, proteomic, microbiome, and metabolomic factors play in the pathogenesis of disease and risk for complications over time. Capitalizing on this novel information is critical to understanding how to identify children at risk for complications and when to use therapies that may be able to alter these factors toward a more sustainable disease remission.

Disease Activity

The definitions of disease activity and remission are changing over time. The more historical body of literature defined remission clinically as the absence of symptoms. Today, we use clinical, biochemical, endoscopic, and histologic remission benchmarks to define treatment targets and successes. Scientific discovery may one day allow us to consider a patient in "genetic remission" via normalization of the gut microbiota and reversal of aberrant gene expression.

Spontaneous clinical remission in the absence of specific treatment can occur in Crohn disease. Two early adult trials, the National Cooperative Crohn Disease Study (NCCDS) [1] and the European Cooperative Crohn Disease Study (ECCDS) [2], included placebo treatment arms enrolling a total of less than 300 adult subjects. Among the 135 subjects with active symptoms at entry into the two trials, 26–42% achieved clinical remission after 3–4 months of placebo treatment, and 18% in both studies remained in clinical remission at 1 year [1, 2]. Prolonged spontaneous clinical remission, therefore, appears to occur in only a small number of adults with CD. However, in the NCCDS, among the subgroup of 20 subjects with active disease who achieved clinical remission by 17 weeks, 75% remained asymptomatic at 1 year, and 63% at 2 years [1]. Similarly, among the 153 subjects in the NCCDS and ECCDS who had the inactive disease when randomized into the placebo arms of a maintenance

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study, 52–64% remained asymptomatic at about 1 year and 35–40% at about 2 years [1, 2].

No comparable data from untreated or exclusively placebo-treated children exist. However, in children with moderate–severe disease activity who achieve remission after a course of prednisone, the likelihood of prolonged remission without ongoing therapy appears lower than in adults. Newly diagnosed children randomized to the control arm of a multicenter trial received prednisone for induction of remission and were then maintained only on a placebo [3]. One year following the course of corticosteroids, only 43% remained continuously asymptomatic. Similarly, 95% of a cohort of Italian children maintained on mesalamine following an 8-week course of corticosteroids relapsed by 1 year [4].

Whether specific genetic variants impact the likelihood of disease recurrence is only beginning to be investigated. In a study of 80 children with CD, the patients with homozygous ATG16L1 mutations had frequent relapses in the first year, while those with homozygous IRGM1 mutations had significantly fewer relapses in the first year [5].

Periods of active CD continue to be a problem beyond the first year after diagnosis. Disease activity over time has been described in a report derived from a large population-based inception cohort of patients with inflammatory bowel disease diagnosed and treated in Copenhagen County, Denmark, between 1962 and 1987 [6]. While useful, the data describing the course of pediatric CD in this study are based on observations of only 23 children. At diagnosis, 82.6% had disease activity characterized as moderate to severe. In each of the succeeding 9 years, only about 50% of the cohort was characterized as inactive during any given year, while roughly 20–35% had periods of high disease activity despite treatment [7] (Fig. 7.1).

Observations in the larger, primarily adult-onset cohort from the same geographic area revealed that individual patients had different patterns of clinical activity over time: some experienced frequent relapses, some only occasional relapses, and others had prolonged periods of disease quiescence [7]. In this cohort, relapse in any given year after diagnosis increased the risk of relapse in the following year. The relapse rate in the first year after diagnosis is also correlated with the relapse rate in the next 5–7 years. A review of North American experience revealed similar patterns of disease in adult CD patients treated prior to the widespread introduction of biologic therapy. Most experienced a chronic intermittent disease course, but 13% of patients had an unremitting disease course and only 10% experienced a prolonged clinical remission [8].

Increased disease activity is often seen in those with earlier disease-onset. In a study comparing the disease activity of 206 pediatric-onset patients with 412 adult-onset patients living in France between 1995 and 2007, a higher proportion of patient-years was marked by active disease in those with pediatric-onset (37%) compared to those with adult-onset CD (31%), ($p < 0.001$) [9]. In the study years 1999–2007, antitumor necrosis factor (anti-TNF) alpha therapy was required in 10.5% vs. 3.5% patient-years ($p < 0.001$), respectively. While many children have moderate to severe disease activity at diagnosis, a smaller subset of poorly studied children will have a quite mild disease activity. In a single-center retrospective study from Boston, MA, 29 of 1205 (2.4%) children with CD did not require any immunosuppressive therapy in the first 2 years after diagnosis. More of these children had isolated colonic disease, most had persistent colonic histologic disease activity on follow-up colonoscopy, and only 8/29 required escalation to immunosuppressive therapy in the follow-up period [10]. The long-term outcomes for children with the most mild inflammatory disease at diagnosis remain unclear.

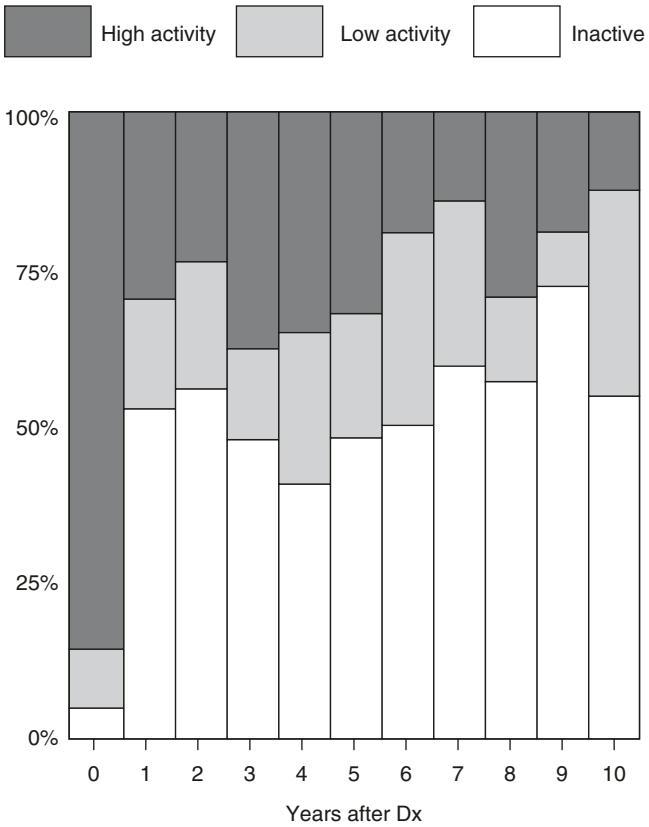

Fig. 7.1 Yearly Crohn disease activity over the first 10 years after diagnosis in a Danish population of children diagnosed prior to 15 years of age (Data from Langholz et al. [6])

Evolution of Disease Phenotype

Disease location is highly variable at diagnosis and is not fixed over time. Data from a large multicenter European registry found the initial disease location of 582 children with Crohn disease to be widely distributed according to the Paris classification [11], with disease location L1 in 16%, L2 in 28%, L3 in 53%, and isolated L4a + L4b in 4% [12]. In a report from Scotland, at diagnosis, extensive disease including the ileum, colon, and upper GI tract (disease location characterized as L3 + L4 by the Montreal classification [13]) was found in 31% of children [14]. However, among a subgroup of 149 children with a less extensive disease at diagnosis who were followed at least 2 years after diagnosis, the extension of CD was noted in 39% [14].

Disease behavior also evolves over time. At initial diagnosis, the vast majority of children have an inflammatory disease phenotype. However, as time goes on, an increasing proportion expresses a changing phenotype, characterized as either stricturing or penetrating. In a systematic review of the literature from years 1966 to 2010 evaluating 3505 pediatric-onset CD patients with at least 5 years of follow-up, development of stricture occurred in 24–43%, fistulae in 14–27%, and perianal disease in 25–30% of patients [15]. Similar disease behavior has also been documented clearly in data derived from the pooled observations from three multicenter North American pediatric IBD registries [16]. Among 796 children followed prospectively from diagnosis, 96 (12%) presented with a stricturing and/or penetrating CD phenotype. Among the 700 who had an inflammatory phenotype at presentation, 140 (20%) developed stricturing or penetrating disease after a mean of 32 months of follow-up [16], a finding strikingly similar to the 24% rate of complicated CD behavior described after 4 years in a pediatric study from Scotland [14]. Similar observations over extended periods of time have been reported in population-based studies in adults from both France [17] and New Zealand [18] (Fig. 7.2). In the latter study, a comparison of 630 subjects with adult-onset disease and 85 children diagnosed before age 17 years revealed no difference in the rate of progression from inflammatory to either stricturing or penetrating disease phenotype [18].

Racial differences may affect the frequency of complicated CD, as a study from Baltimore has demonstrated more frequent stricturing and penetrating disease in black children compared to white children seen in the same university-based practice [19]. The risk for phenotypic change may also be associated with the presence of specific genetic allelic variants. Earlier reports suggested an increased risk of fibrostenosis complications for patients with NOD2/CARD15 variants [20, 21], while those with abnormalities in the IBD5 gene may be more likely to develop perianal fistulae [22]. However, more recent studies only implicate NOD2/CARD15 mutation in risk of ileal disease location (which may be more likely to stricture compared to colonic disease) and not independently with increased risk of stricture [23, 24]. CD in children who are homozygous carriers of ATG16L1 mutation may have significantly increased stricturing behavior and have lower risk of perianal disease compared to wild-type patients [5]. In a small study of children and adults in Taiwan, a homozygous mutation in the risk candidate gene SLCO3A1 was significantly associated with perforating disease compared to those with wild type

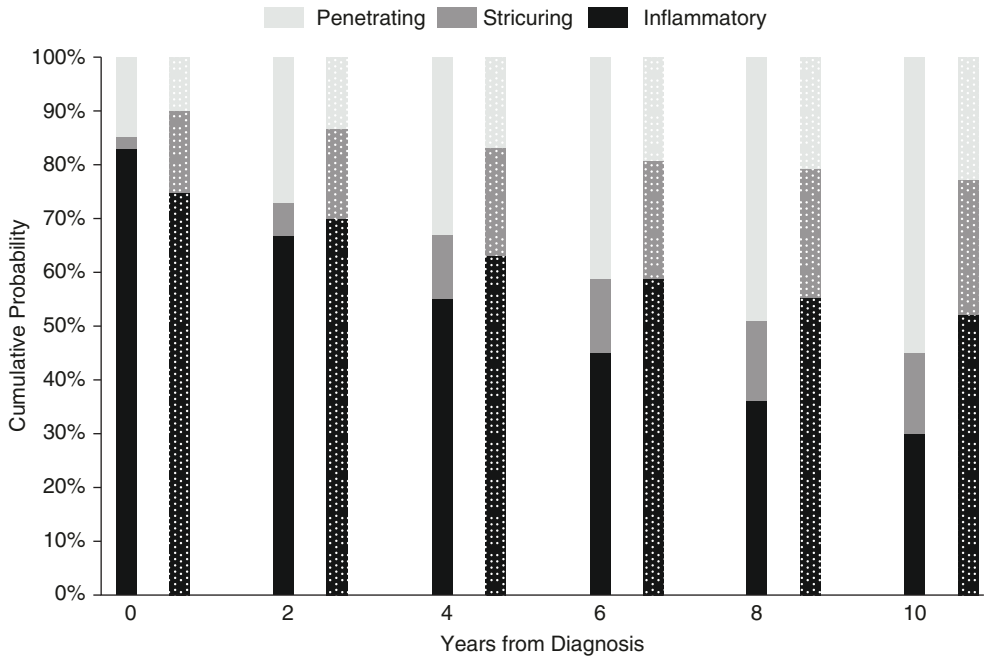

Fig. 7.2 Change in Crohn disease behavior over time (Adapted from Cosnes et al. [17] (*solid bars*) and Tarrant et al. [18] (*dotted bars*))

who had more inflammatory disease [25]. Children at risk for stricturing or internal penetrating complications have also been shown to be more likely to have increased immune responses to microbial antigens, characterized by the presence of high-titer antibodies such as anti-ompC, CBir1, and anti-I2 [16, 26].

The pediatric RISK trial [27]—a prospective multicenter inception cohort study of newly diagnosed children with CD—has provided a wealth of new information on factors that impact the evolution of CD over time. In 913 children from this cohort presenting with an inflammatory (B1) phenotype, the investigators found several genes from ileal tissue samples associated with the subsequent development of stricturing (B2) or penetrating (B3) complications, including a pronounced extracellular matrix gene signature in many who went on to develop fibrostenotic disease [27]. In a subset of these subjects with B1 disease at diagnosis, those with higher circulating levels of serum Extracellular Matrix Protein 1 at diagnosis were more likely to subsequently develop B2 behavior [28]. In the entire RISK cohort, early use of anti-TNF therapy markedly reduced the risk of progressing to fistulizing disease, but this same therapy did not appear to lessen the risk of developing a stricturing phenotype.

Microbial factors associated with progression to a complicated CD phenotype were also identified in the RISK cohort. Compared to children who remained B1 over 3 years of observation, baseline fecal and mucosal samples revealed increases in *Ruminococcus* and decreases in *Rothia* species in children developing stricturing disease, while those developing fistulizing disease were characterized by an increase in *Collinsella* and decrease in *Veillonella* species [27].

The RISK cohort has also been studied for environmental factors that may impact disease evolution. In one such study of early life environmental exposures, of 1119 pediatric CD patients, 15% developed B2 or B3 disease within 3 years of diagnosis. Infant breastfeeding was inversely related to the development of these complicated phenotypes, while maternal smoking was associated with an increased rate of CD-related hospitalization [29].

Growth

For a significant subgroup of children with CD, growth impairment is an important characteristic of the disease's natural history. While acute weight loss commonly is present in children with both ulcerative colitis and CD, impairment in linear growth is primarily a problem in the latter condition. Data derived from clinical observations in the 1970s and 1980s document that at the time of initial diagnosis, about a third of children with CD had already dropped two or more major growth channels from their pre-illness growth percentiles [30, 31]. More dramatically, 88% had delayed height velocity at diagnosis [32]. Over time, periods of significantly impaired growth can be seen in about 60% of children and adolescents [31]. While catch-up growth is often possible, 7–35% of children diagnosed during the 1970s and 1980s had final adult heights that were significantly shorter than expected [31]. As a group, young adults who develop CD as children have adult heights skewed toward the lowest percentiles. In reports from both Chicago and New York, ~50% of young adults with childhood-onset CD have final adult heights less than the 10% for the general population, and ~25% have adult heights less than the 5% [30, 31]. Therapies including enteral nutrition [33], methotrexate [34], and infliximab [35, 36] may improve growth parameters. Children diagnosed with CD at earlier pubertal Tanner stages (I-III) who achieve disease remission with anti-TNF therapy have improved linear velocity compared to those diagnosed in later puberty [37]. In the analysis of children with baseline growth impairment from the IMAgINE 1 trial, adalimumab therapy led to linear growth improvement or normalization at weeks 26 and 52 of treatment, with greater improvement in those who achieved remission after 4 weeks of induction [38].

Corticosteroid Dependence

An important characteristic of CD in children as well as adults is the tendency to develop corticosteroid (CS) dependence. Population-based studies in adults from both Olmstead County, Minnesota [39], and Copenhagen County, Denmark [40], demonstrate similar findings; acute response to CS therapy in adults with CD is reasonably good (complete remission in 48–58%, partial remission in 26–32%, and no response in 12–20%). However, long-term response is less optimal, with rates of CS dependence of 28–36% at 1 year reported from observations arising during the years before biologic therapies. [39, 40]

A similar risk for CS dependence is evident in children. As in adults, acute response to a course of corticosteroids is good. In data derived from a multicenter North American observational registry, among 109 newly diagnosed children with moderate–severe CD activity treated with corticosteroids, 60% had a complete and 24% a partial clinical response by 3 months after initiation of treatment [41]. However, despite the concomitant use of immunomodulators in many of these children, 31% were CS dependent at 1 year. In fact, without infliximab, only 46% of the children in this study maintained a CS-free remission to 1 year following an initial course of corticosteroids [41]. In a French population-based

cohort study of 535 CD patients diagnosed under the age of 17 years between 1988 and 2004 and followed for a median of 11.1 years, 42% were CS dependent and 15% were CS resistant at 1 year [42]. In an assessment of the impact of systemic corticosteroids on pediatric CD, Jakobsen and colleagues found ileal and ileocolonic disease location is a risk factor for CS dependency [43]. It is now evident that early anti-TNF therapy reduces CS dependency at 1 year from diagnosis. In 552 pediatric CD subjects in the RISK cohort, CS-free remission was achieved in 85% of those treated with early anti-TNF therapy, 61% treated with immunomodulators (IM), and 55% treated with neither anti-TNF nor IM [44]. When subjects were divided into propensity score-matched cohorts based on a variety of baseline characteristics, anti-TNF therapy remained significantly more likely to achieve CS-free remission.

Surgery

The need for surgery represents another important aspect of the natural history of CD in children. Table 7.1 summarizes published rates for surgery in children from a variety of different countries that were observed in the prebiological era. Data from Denmark estimate a mean yearly operation rate of approximately 13%. The cumulative probability of surgery in this Danish cohort at 20 years was estimated to be 47% [6]. A multicenter pediatric experience from the USA estimates the cumulative incidence of surgery to be 6% at 1 year, 17% at 5 years, and 28% at 10 years after diagnosis [49]. Similarly, a pediatric study from Scotland noted resection rates of 20% at 5 years and 34% at 10 years [14]. More recent data does not appear substantially different. In a more contemporary cohort of 852 children followed in a multicenter North American study between 2002 and 2008, the 1-year and 5-year risk of CD-related surgery was 4.8% and 17.7%, respectively [50]. Older age at diagnosis, increased disease severity, or complicated (stricturing or penetrating) disease behavior increased risk.

Table 7.1 Surgical frequency in Crohn disease

Author	No. of children observed (period studied)	% Operated	% Permanent stomas
Farmer [45] (USA)	522 (1955–1974)	67	??
Ferguson [46] (UK)	50 (1968–1983)	78	30
Griffiths [47] (Canada)	275 (1970–1987)	32	2
Besnard [48] (France)	119 (1975–1994)	30	2
Langholz [6] (Denmark)	23 (1962–1987)	43	??

The presence of variant NOD2/CARD15 [20, 21] and ATG16L1 [5] alleles appears to increase the risk for surgery, presumably due to the known association of these genetic polymorphisms with the development of fibrostenotic ileal disease. Beyond these well-described genes, our knowledge of genetic and serologic factors impacting surgical risk is expanding through genome-wide studies. For example, in a study performing a whole-genome analysis of 1115 adult and pediatric CD patients, the IL12B gene was independently associated with a need for surgery and early surgery [51]. The presence of anti-Saccharomyces cerevisiae antibodies and other serologic markers also appears to be associated with an increased risk for surgery [16, 49].

The effect of immunomodulatory therapy on the need for surgery remains an open question. An analysis from France evaluated a series of successive 5-year adult CD cohorts [52]. Although there was a significant increase in the use of immunomodulatory therapy over time, there was no associated change in the rate of surgery [52]. By contrast, multivariate analysis from a similar series of 5-year adult CD cohorts from the UK identified the early use of thiopurines (within 3 months of diagnosis) to be associated with a marked reduction in the rate of surgery [53, 54].

The studies evaluating infliximab therapy in decreasing surgical rates are also mixed. In a Spanish retrospective assessment of infliximab therapy used in a "step-up" fashion, no significant decrease in surgical rates could be identified in patients receiving infliximab compared to those not receiving the treatment [55]. However, other studies reach the opposite conclusion. For instance, in a study utilizing data from a combined Danish and Czech collaboration, surgical rates in adults 40 months after starting infliximab were 20–23% in infliximab responders compared to 76% in non-responders [56]. In the ACCENT I [57] and ACCENT II [58] trials of adults with moderate to severe CD, and fistulizing CD, respectively, response to maintenance infliximab was associated with decreased surgery. Similar findings in children have been reported, with surgical rates 50 months after starting infliximab of 10% in patients maintained on the biologic compared to 70% in infliximab failures [59]. Further, in children with a favorable initial response, development of antibodies to infliximab led to loss of response and increased risk of surgical resections [60]. In the data from the RISK inception cohort, 1 year post-diagnosis surgical risk in those treated with early anti-TNF was not different from those treated with immunomodulators [44]. A longer term analysis from the RISK cohort identified a significant reduction of penetrating disease but not fibrostenotic disease with early anti-TNF use [27], raising a possibility that early anti-TNF reduces surgical risk related to internal fistulas but not strictures.

Postoperative Recurrence

Following surgery, the natural history of CD is to recur both endoscopically and symptomatically. The natural progression of CD following ileocolonic resection has been previously described by Rutgeerts and colleagues, with five levels of disease severity (i0–i4) found endoscopically. Postoperatively, disease appears to evolve from normal mucosa (i0) to the initial appearance of a few aphthous ulcers (i1–i2), followed by progressively more and/or deeper ulcerations until an area of confluent inflammation, large ulcers, or stricturing develop (i3–i4) [61]. CD recurrence is defined by an endoscopic score of i2, i3, or i4, while postoperative remission is defined by a score of i0 or i1.

In retrospective adult studies, symptomatic recurrence of CD following the so-called curative resection (complete resection of all visibly evident disease) is reported to be 20–30% within the first year after surgery, with the increasing likelihood in each subsequent year [62]. One or more additional surgeries are required in 15–45% of adults within 3 years, 26–65% in 10 years, and 33–82% in 15 years [63]. Controlled trials document severe endoscopic recurrence after placebo treatment in 43–79% of adult subjects by 1 year after surgery and in 42–85% of subjects after 2 years [63–68].

In children, the overall rate of clinical recurrence is estimated to be 50% at 5 years after initial resection [47]. However, the site and extent of preoperative CD can affect the recurrence-free interval such that it is estimated that 50% of children with extensive ileocolitis recur within 1 year, compared to a 50% recurrence rate after 5 years in children with ileocecal disease and a 50% recurrence rate after 6 years if preoperative disease is confined to the small bowel [47]. In a more recent retrospective review of 81 children in the UK with a median age of 14.5 years and 7.7 years of follow-up, 52% had disease recurrence by end of follow-up, with younger age at first resection being a risk factor for clinical recurrence. The authors additionally identified colonic disease, as compared to more localized ileocecal disease, and post-operative complications as risk factors for requiring future intestinal resection [69]. Conversely, in a multicenter review of 122 children in the Netherlands undergoing ileocecectomy between 1990 and 2014, ileocecal disease location, along with positive histologic resection margins, was the risk factor for surgical recurrence [70]. Altering the natural history of postoperative CD and preventing recurrence has become an integral part of CD management. Use of mesalamine or thiopurines appears to have limited benefit [68, 71], while anti-TNF therapy may be effective in preventing CD recurrence [72–74].

Cancer Risk

Whether children with CD are at increased risk for malignancy over their lifetime is unknown. Limited but growing population data exists, and it can be difficult to isolate effects of CD from medications, or comorbid diseases, toward cancer risk from these reports. In a recent report from a Manitoba, Canada registry reviewing 947 people diagnosed with pediatric IBD followed for 14,938 person years, 17 post-IBD diagnosis cancers were identified. A diagnosis of CD had an increased risk of cancer with a hazard ratio of 2.47; the median age of cancer diagnosis was 37 years. Of note, there was no difference in exposure to thiopurine or anti-TNF medications between those who developed a cancer and those who did not [75]. Similarly, a large combined Finnish and Danish cohort that included 2921 cases of CD diagnosed in children between 1992 and 2014 found this group of people with CD had a 2.5-fold increase risk of cancer compared to the general population, a standardized incidence ratio (SIR) of 3.2 for lymphoproliferative diseases, and an SIR of 6.7 for skin cancer. The authors highlight that thiopurines are standard of care in these countries and the data could not determine the degree of risk related to this medication exposure [76].

One of the more comprehensive pediatric IBD malignancy risk studies to date comes from the DEVELOP registry—a multicenter, prospective, long-term registry of safety and outcomes data in pediatric IBD patients. The DEVELOP registry evaluated 5766 children including 4047 with CD, identifying 15 cancers and 5 cases of lymphoproliferative disease in >24,000 patient-years of follow-up from 2007 to 2016. Twelve of the 15 cancers occurred in patients with CD. Thiopurine exposure was found in all but 2 of these cancers. Malignancy incidence rates in this population were compared to the Surveillance, Epidemiology, and End Results (SEER) database to calculate the SIR to report differences in risk compared to the general population. The authors found SIRs of 2.88 for thiopurine exposed, and 1.3 for nonexposed individuals, suggesting in this cohort the risk of cancer is very low in those with pediatric IBD, particularly those not treated with thiopurine [77].

Studies in adults, however, suggest that patients with CD do have an excess of malignancies compared to the general population. In a population-based cohort from the Uppsala region of Sweden, there was an increased relative risk of colorectal cancer of 2.5 (95% confidence interval (CI) 1.3–4.3) in patients with CD [78]. Duration of illness and gender did not affect risk, but those subjects with colonic disease had a greater risk of colorectal cancer than those with only small bowel involvement. Of note, however,

among those subjects with any colonic involvement diagnosed with CD before the age of 30 years, the relative risk of colorectal cancer increased to 20.9 (95% CI 6.8–48.7) [78]. By contrast, a similar population-based study from Denmark identified a relative risk of colorectal cancer of only 1.1 (95% CI 0.6–1.9), and no risk differences were noted in different subgroups of patients [79]. A similar modest increase in colorectal cancer risk (1.9; 95% CI 0.7–4.1) was found in a population-based study from Olmstead County, Minnesota [80].

By contrast, the risk of small bowel cancer consistently appears to increase in patients with CD. In part, because the rate of small bowel cancer in the general population is very low (estimated to be 0.005% at 5 years and 0.03% at 25 years), there is a significantly elevated relative risk for small bowel cancers in patients with CD [80]. In the Danish study cited above, the relative increased risk for small bowel cancer was 17.9 (95% CI 4.8–42) [79]. In Olmstead County, the relative risk was found to be 40.6 (95% CI 4.4–118) [80]. Duration of CD did not appear to influence risk of developing small bowel cancer. Adenocarcinoma, carcinoid, leiomyosarcoma, and primary intestinal lymphoma have all been reported. The effect of age at CD onset on the risk of developing small bowel cancer has not been reported.

There may also be a slight increase in the risk of developing lymphoma, although data are mixed and not always controlled for risk associated with therapeutic agents. In a single-center, retrospective study between 1979 and 2008 that included 791 children with CD followed in Boston, MA, one non-Hodgkin's lymphoma occurred in a patient receiving thiopurines; the overall cohort lymphoma risk did not meet statistical significance [81]. In a large population-based retrospective study of adults living in the UK between 1988 and 1997, seven patients with lymphoma were reported among 6605 patients with CD, and 0/7 were exposed to thiopurines. The risk of lymphoma in this cohort was not increased compared to the control population (relative risk 1.39; 95% CI 0.50–3.40) [82]. The published data from the DEVELOP registry described above offers a stratified view of different patient cohorts based on medication exposure. Of cancer type described, 8/15 were leukemia or lymphomas. Importantly, the 763 non-biologic, non-thiopurine exposed patients, and 1146 biologic exposed, non-thiopurine exposed patients did not have a statistically increased cancer risk compared to the healthy matched SEER database reference population. This suggests cancer risk in the early years after CD diagnosis is based more on therapy than the intrinsic disease [77].

Quality of Life

In addition to imposing significant physical morbidity, CD in childhood imposes potentially dramatic psychosocial burdens as well. Health-related quality of life (HRQOL) scores, as measured by the IMPACT questionnaire (a validated, pediatric IBD health-related quality of life questionnaire) [83], correlate with physician's global assessment of disease severity, such that children with moderate–severe activity have the poorest HRQOL scores [84]. Pre-biologic era reports on quality of life have noted that children with CD frequently experience absences from school, require home tutoring, and express fears concerning everyday childhood activities, schooling, and ability to get a job [85–87]. Fifty-seven percent of a young–adult cohort was reported to have had an absence from school of at least 2 months duration and 8% were involuntarily unemployed. [88]

The past two decades have found improved quality of life measures correlating with greater ability to achieve disease remission [89, 90]. A recent study of 218 children in France found clinical remission status was the main independent factor determining IMPACT-III scores, with older age and the presence of comorbid psychological disorder associated with lower scores [91]. The psychological effect of IBD can also impact HRQOL separate from disease activity. De Carlo and colleagues found the degree of pain catastrophizing followed by generalized distress levels directly correlated with HRQOL in an Italian pediatric cohort [92].

One by-product of increased disease severity is increased parental stress. The effect of parental stress was found to partially contribute to lower HRQOL in children with active disease [93]. In a study of 100 children with IBD including 45 with CD, parental distress substantially correlated with patient HRQOL; in this study, parental distress was most affected by flares and disease activity [94].

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Natural History of Ulcerative Colitis in Children

8

Joelynn Dailey and Jeffrey S. Hyams

Introduction

We continue to strive to change the natural history of ulcerative colitis which is often marked by intermittent or continuous disease activity despite treatment with 5-aminosalicylates and corticosteroids. While the data presented in this chapter reflect the effect of our current therapies, we hope that management advances in the next decade will achieve greater disease control without increasing risk. This chapter will focus on natural history elements pertaining to clinical remission, endoscopic remission, and colectomy. Discussion of drugs will focus mainly on maintenance of remission. Lastly, new insights in predicting response to therapy and altering natural history will be addressed.

Overview

Clinical reports from the 1970s and 1980s describe a severe clinical course for children newly diagnosed with ulcerative colitis resulting in chronic activity, recurrent hospitalizations, frequent colectomy, and rare deaths [1, 2]. Subsequently, a report in 1996 of 171 subjects seen at two large pediatric inflammatory bowel disease centers in the Northeastern United States found that 43% of patients had mild disease and 57% moderate to severe disease at presentation. Forty three percent had pancolitis [3]. Over 80% had resolution of symptoms within 6 months of diagnosis, and during subsequent yearly follow-up intervals, 55% were symptom free, 38% had chronic intermittent symptoms, and 7% had continuous symptoms. Corticosteroid therapy was used in 27% of those with initially mild disease and 70% of those with moderate/severe disease by 1 year. Eleven percent of those with moderate/severe disease received additional immunomodulatory therapy (azathioprine/6-mercaptopurine or cyclosporine) during the first year. The colectomy rate during this time period of widespread immunomodulator use ranged from 1% to 8% at 1 year and 9% to 26% at 5 years, with initial disease severity and progression of disease greatly affecting colectomy rates [3–6].

More recent cohorts have encompassed populations that were diagnosed in the era of biologic agents. Much of our recent understanding of ulcerative colitis in children has been informed by the PROTECT Study: Predicting Response to Standardized Pediatric Colitis Therapy which was a 29 center North American inception cohort of children newly diagnosed with ulcerative colitis who were treated with standardized treatment protocols based on initial disease severity [7]. In this cohort of 428 children newly diagnosed with UC, 7% had proctosigmoiditis, 10% had left-sided colitis, and 83% had extensive colitis or pancolitis. Of the 400 patients who remained evaluable at 52 weeks, 25 (6%) had colectomy within that first year. The majority of the patients going on to colectomy had moderate to severe disease at diagnosis. A retrospective study from 25 centers across Europe and North America between 2009 and 2011 found that 83% of patients admitted for acute severe colitis, defined as PUCAI $\geq$ 65, had extensive colitis or pancolitis at diagnosis, versus 16% with left-sided disease [8]. In total, 16/141 (11.3%) of patients underwent a colectomy during their initial admission for acute severe colitis. Of those who had a colectomy, 82% had extensive colitis or pancolitis at diagnosis, while 18% had left-sided disease. Long-term follow-up showed colectomy rates of 28.7%, 33.6%, and 36.4% at 1, 3, and 5 years after initial acute severe colitis admission, respectively. A retrospective chart review of 110 patients from a center in Italy reported 29% of patients initially presenting with proctitis, 22% left-sided colitis, 15% extensive colitis, and 34% pancolitis [9]. Disease extension at follow-up was noted in 29% of patients and cumulative

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rates of colectomy were 9% and 14% at 2 and 5 years, respectively. A review of the published literature on population-based natural history studies of pediatric ulcerative colitis suggested an overall colectomy rate of between 4% and 17% at 1 year [7, 10, 11] and about 20% at 5 years follow-up [5]. All studies indicate that more severe disease at diagnosis correlates strongly with need for colectomy within the first several years after diagnosis.

Of course, the natural history of any disease is largely a function of the efficacy of medications used to treat it. Large-scale, blinded, placebo-controlled trials are generally lacking in the pediatric population, and much of what is done is extrapolated from adult studies.

Aminosalicylates

Data supporting the use of 5-aminosalicylate (5-ASA) compounds for the induction and maintenance therapy in adult ulcerative colitis (UC) are strong [12, 13]. Data in adults suggest that higher dose 5-ASA may be more effective in inducing remission (4.8 g mesalamine vs. 2.4 g mesalamine), but this added efficacy seemed limited to patients with moderate disease, and was not observed in those with mild disease [14].

One randomized, double-blind, controlled study of children with mild-to-moderately active ulcerative colitis compared the safety and efficacy of high-dose and low-dose oral, delayed-release mesalamine, and found that both doses were equally effective as short-term treatment, without a specific benefit or risk to using either dose [15]. Dosing was weight-dependent, with the low-dose group receiving 27–71 mg/kg/day and high-dose group receiving 53–118 mg/kg/day, within the constraints of using a 400 mg tablet. Twenty-three of 41 (56%) and 22 of 40 (55%) of patients achieved PUCAI-defined treatment success in the low- and high-dose groups, respectively ($P = 0.924$) after 6 weeks of treatment. No differences in efficacy, tolerability, or adverse reactions with either high- or low-dose mesalamine were noted but the large overlap in potential doses between the two groups makes interpretation of this study difficult.

In the PROTECT study mentioned previously, patient outcomes at one year from diagnosis were determined after the start of standardized treatment regimens based on initial disease severity. One-hundred fifty out of 400 (38%) patients achieved corticosteroid-free clinical remission (PUCAI<10) on mesalamine only at week 52 without the need for immunomodulators or biologics [7]. Of the initial cohort about two-thirds started therapy with corticosteroids (oral or intravenous) with an opportunity to transition to mesalamine maintenance if they responded to corticosteroids. Initial therapy used in this study was based on disease severity using Pediatric Ulcerative Colitis Activity Index (PUCAI) scores, as well as a joint decision by the prescribing physician, patient, and family. For patients with mild disease at diagnosis, mesalamine only was started with weight-based daily dosing given in two divided doses (range 50–75 mg/kg/day) to a maximum dose of 4 g/day. In this mild group, slightly less than half of all patients (48%) achieved PUCAI<10 with no other therapy at week 52. In PROTECT, about 5–7% of patients were intolerant of mesalamine and 1% developed pancreatitis.

The use of adjunctive rectal mesalamine therapy (suppositories, enemas) is often encouraged in those with limited distal disease or proctitis. However, many children and adolescents are unwilling to accept this type of therapy. When used, however, it is often quite helpful.

Corticosteroids

Corticosteroids remain the mainstay of induction therapy for moderate to severe ulcerative colitis, and therefore, understanding the course of disease following these medications is critical to understanding natural history. Corticosteroid use is more widespread in the treatment of pediatric ulcerative colitis compared with adults, with a rate of 79% reported in an observational registry [16]. Traditional corticosteroid therapy has usually meant prednisone for moderate to severe disease, though budesonide MMX has been used for mild to moderate disease [17]. There are minimal published data on budesonide for the treatment of pediatric UC.

In the PROTECT study, data are available on one-year outcomes in large groups of patients started on either oral prednisone or intravenous corticosteroids [7]. In this study, following standardized treatment guidelines, corticosteroids were used as initial therapy for moderate to severe disease (PUCAI score > 45), with goal of weaning steroid dosing and starting mesalamine based on response at 2 weeks. Prednisone was used at a dose of 1–1.5 mg/kg/day to a maximum dose of 40–60 mg in a single morning dose. For those hospitalized with severe disease at time of diagnosis, treatment with intravenous corticosteroids was started, with a suggested dose of 1–2 mg/kg/day of methylprednisolone to a maximum of 60 mg. Of the 400 patients who were followed to week 52, 140 (35%) were initially given oral corticosteroids and 135 (34%) initially received intravenous corticosteroids. If patients showed a response to corticosteroids at 2 weeks, defined by PUCAI decrease of at least 20 points with resulting PUCAI < 35, mesalamine was added, and the initial dose of oral corticosteroids was continued for one more week prior to tapering. Of the 275 patients initially treated with corticosteroids, at week 52 after diagnosis, 32% achieved corticosteroid-free remission on mesalamine only, 9% neither achieved corticosteroid-free remission nor required additional therapy, 22% required escalation to an immunomodulator only, and 37% required escalation to anti-TNFα therapy.

Optimal dosing regimens for corticosteroids have not been established though there appears to be little advantage to exceeding the equivalent of 40–60 mg/day in adults. An exhaustive description of the mechanisms underlying corticosteroid resistance is beyond the scope of this discussion and has been reviewed elsewhere [18]. In a study of 128 children hospitalized with ulcerative colitis (OSCI) and treated with intravenous corticosteroids, non-response to therapy was associated with overexpression of several genes involved in inflammatory pathways [19]. In vitro studies have identified the expression of certain microRNAs as potential mediators of glucocorticoid (GC) resistance [20], but few clinical studies have been published that support this relationship. One clinical study investigated a possible correlation between microRNA expression and variability in GC-resistant and GC-sensitive patients [21]. Assessing serum microRNA of patients with UC, it was noted that downregulated microRNAs had a significant correlation with several signal transduction pathways, including the PI3K-Akt and MAPK signal pathways, and to target genes, including HSP90B1, MAPK13, MAPK9, PIK3AP1, and TLR4, related to GC resistance. This study also found six specific microRNAs (miR-16-2-3p, miR-30e-3p, miR-32-5p, miR642a-5p, miR150-5p, and miR-224-5p) that were significantly downregulated in GC-resistant patients.

Immunomodulators

The use of immunomodulators, such as thiopurines, for the treatment of corticosteroid-dependent ulcerative colitis has greatly diminished with the emergence of more effective and perhaps safer biologic agents. A review of seven blinded, controlled trials of azathioprine in ulcerative colitis highlighted the methodological issues with many early studies of adults which left unanswered the question of whether this drug was useful in maintaining remission [22]. A review of the 30-year experience with azathioprine in a large cohort of adult patients in Oxford, England suggested significant utility of azathioprine in maintaining remission [23]. Almost two-thirds of patients maintained remission for up to 5 years, and median time to relapse upon stopping the drug was 18 months. The addition of the 5-aminosalicylate olsalazine to azathioprine did not improve the maintenance of remission rate compared to azathioprine alone in steroid-dependent adults with ulcerative colitis.

Pediatric data are more limited. One report detailed thiopurine use in 133 children from an inception registry cohort in North America [24]. Of these, 65 (49%) had CS-free inactive UC without rescue therapy at one year from thiopurine start. CS-free inactive disease at 1 year after initiating thiopurine was not affected by starting thiopurine $\leq$ 3 months versus >3 months from diagnosis, gender, age, or concomitant treatment with 5-aminosalicylates. Kaplan–Meier analysis showed that the likelihood of remaining free of rescue therapy (surgery, calcineurin inhibitors, or biologic therapy) in the thiopurine-treated patients was 73% at 1 year.

A more recent pediatric study looked to assess the efficacy of azathioprine comparing the outcomes of early (0–6 months) versus late (6–24 months) initiation of therapy from time of diagnosis with UC [25]. Of the 121 children, 76 (63%) started AZA between 0 and 6 months after diagnosis and 45 (37%) started between 6 and 24 months. By 6 months, 21 patients withdrew due to either lack of efficacy, adverse events, or lost to follow-up. Seventy-five percent of the early group received CS at diagnosis, with 30 (50%) achieving CS-free remission at one year. Fifty-three percent of the late group received CS at diagnosis, with 23 (57%) achieving CS-free remission at one year. Mucosal healing was also assessed at one and two years, with either endoscopy (49%) or fecal calprotectin (51%). Mucosal healing only occurred in 37% of patients at one year and 40% of patients at 2 years, with no difference between the early and late groups.

Overall, the use of thiopurines has increasingly fallen into disfavor among many pediatric gastroenterologists in North America because of concerns for malignancy, particularly hepatosplenic T-cell lymphoma, and hemophagocytic lymphohistiocytosis (HLH). Although quite rare, these devastating conditions have been linked to thiopurine therapy [26]. The reluctance to use thiopurines in UC is generally not shared in Europe as they remain part of standard treatment options [27].

The use of methotrexate as an immunomodulator for the treatment of ulcerative colitis remains controversial. A recently published study was the first randomized, placebo-controlled study comparing the efficacy of 25 mg parenteral methotrexate weekly compared to placebo in adults with UC who had previously responded to open-label methotrexate [28]. One hundred and seventy-nine patients with active UC based on Mayo score were first given open-label methotrexate for a 16-week induction period with a 12-week steroid taper. At week 16, 91 (51%) patients achieved steroid-free clinical response and 84 of these patients were randomly assigned to 32-week maintenance period with either 25 mg/week subcutaneous methotrexate (n = 44) versus placebo (n = 40) until week 48. Of the 84 patients, 25/40 (63%) and 27/44 (61%) were in steroid-free remission and 15/40 (37%) an 17/44 (39%) were in steroid-free response in the placebo and methotrexate groups, respectively. Sixty percent (24/40) and 66% (29/44) of patients in the placebo and methotrexate groups, respectively, discontinued their therapy before week 32 of the maintenance period, with lack of efficacy or relapse of UC being the main reason for discontinuation in 22 patients in each group. At week 48, 30% (12/40) of patients in the placebo group and 27% (12/44) of patients in the methotrexate group were in steroid-free clinical remission

without the need for additional therapies ($p = 0.91$). This study provided similar findings to the METEOR trial, with a large proportion of patients achieving steroid-free response and remission during open-label induction phase [29]. However, parenteral methotrexate monotherapy was not superior to placebo in maintaining steroid-free clinical response or remission and preventing relapse in patients with UC.

Although calcineurin inhibitors are widely accepted as effective therapy for inducing remission in severe ulcerative colitis [30–32], their use as maintenance therapy is uncommon. In children, there are limited data on the use of these agents and while short-term response averages about 80% the majority of treated children still require colectomy within 2–3 years of their use [33]. Additionally, because of their nephrotoxicity, increased susceptibility to infection, and other side-effects, the use of calcineurin inhibitors is generally limited to several months as a bridge to other immunomodulators, infliximab, vedolizumab, or surgery.

Biologics

There are ample data supporting the use of anti-TNF therapy in children with ulcerative colitis. In a formal clinical trial of 60 children and adolescents with active ulcerative colitis despite treatment with corticosteroids, immunomodulators, and 5-aminosalicylates, a response as defined by a decrease in Mayo score by ≥30% and ≥3 points was seen at 8 weeks in 73% of patients following a 3-dose induction of 5 mg/kg at 0, 2, and 6 weeks [34]. Clinical remission by Mayo score, as defined by a score ≤ 2 with no individual subscore > 1, was seen in 40% at 8 weeks. At 54 weeks, in those patients treated with this induction regimen followed by maintenance therapy every 8 weeks, remission was noted in 38% of subjects. Similar to the experience in adults, a direct relationship was found between serum infliximab levels and a positive therapeutic response [35].

It has been demonstrated that low-serum trough levels of infliximab as well as the development of antibodies to infliximab negatively affect response and durability [36]. One such retrospective chart review of 129 children with IBD treated at a tertiary care pediatric IBD center included 278 samples of infliximab levels and antibodies to infliximab, determined that for those who were treated with a dose of 5 mg/kg, 6 week dosing had significantly higher infliximab levels compared to 8 week dosing ($p = 0.009$) [37]. Out of the 129 patients, 48 (37.2%) demonstrated low infliximab levels (<3 μg/ml) and 24 of those 48 (50%) demonstrated antibodies to infliximab. Twenty-nine (22.5%) developed antibodies to infliximab, and low or undetectable serum infliximab levels were associated with the development of antibodies. This review was in line with prior studies [38, 39] showing the association that low infliximab levels have to the development of immunogenicity to infliximab as measured by antibodies to infliximab.

Therapeutic drug monitoring for IBD patients on anti-tumor necrosis factor (anti-TNF) therapy has become more common, though reactive versus proactive monitoring has not yet been standardized. A 2017 multicenter, retrospective study of 167 adults with Crohn disease and 97 with UC on infliximab maintenance therapy received either proactive ($n = 130$) or reactive ($n = 134$) monitoring and was followed to assess long-term outcomes including treatment failure, first IBD-related surgery or hospitalization, serious infusion reactions, and detection of antibodies to infliximab [40]. This study found that proactive drug monitoring was independently associated with reduced risk of treatment failure ($p < 0.001$), IBD-related surgery ($p = 0.017$), IBD-related hospitalization ($p < 0.001$), antibodies to infliximab ($p = 0.025$), and serious infusion reaction ($p = 0.023$) when compared to reactive monitoring. Rapid clearance of anti-TNF medications has been noted in patients with extensive disease and high C-reactive protein levels, likely through multiple mechanisms including the concept of a "large antigen-sink" of TNF, hypoalbuminemia, and loss in the stool [36, 41–43]. As rapid clearance can lead to loss of response or drug-related adverse events, the results of this study suggest that it is better to optimize infliximab therapy with use of proactive therapeutic drug monitoring rather than wait for these undesirable outcomes to occur before testing.

There are limited data on the use of adalimumab to treat pediatric ulcerative colitis. In a retrospective study assessing the effectiveness and safety of adalimumab in children with UC, all of whom were previously treated with infliximab, 32 patients received adalimumab, and at week 52, 13 (41%) were in corticosteroid-free remission, of whom 9 (28%) had mucosal healing [44]. 17 (53%), 15 (47%), and 13 (41%) were in steroid-free remission at 12, 30, and 52 weeks, respectively. Ten patients (31%) had a primary failure and 5 (15%) a loss of response to adalimumab. And, 12.5% of this study population required colectomy at 1-year follow-up, a rate that is consistent with previous data on disease course in UC. No serious side effects, including deaths or malignancies, were reported. Overall, adalimumab seemed to be effective in inducing clinical and endoscopic remission in children with UC who previously failed or were intolerant to infliximab therapy.

Golimumab is another humanized IgG1 antibody to TNFα, used in adults for the treatment of UC, as well as select other diseases. Although few pediatric studies have been performed, one multicenter, prospective, open-label study evaluated the safety, outcomes, and pharmacokinetics of golimumab in anti-TNF naïve children with moderate to severe active UC [45]. Thirty-five patients were enrolled in the study and received golimumab induction at weeks 0 and

2. Of the 35 participants, a total of 15 (43%) discontinued the medication prior to week 14; 3 after the 2 induction doses, 11 were not in Mayo clinical response at week 6 and medication was discontinued per study protocol, and 1 discontinued the medication prior to week 14 due to a disease flare. At week 6 following induction, Mayo clinical response was induced in 21 (60%) patients, Mayo clinical remission in 15 (43%), PUCAI clinical remission in 12 (34%), and mucosal healing (Mayo subscore 0/1) in 19 (54%), with 8 (23%) achieving complete mucosal healing (Mayo subscore 0). No malignancies, deaths, or serious infections were reported in this small cohort. Overall, the outcome data at week 6 of this study suggest that in pediatric patients with UC, golimumab offers generally comparable clinical benefits to the adult UC population.

Anti-integrin therapy has shown efficacy in the treatment of adults with ulcerative colitis [46], and published data in children are available. Vedolizumab is an α4β7 anti-integrin monoclonal antibody with gut specificity. A retrospective, multicenter review of 52 pediatric IBD patients (58% Crohn disease and 42% ulcerative colitis) receiving vedolizumab was performed to examine efficacy in pediatric IBD. Ninety percent of (47/52) patients had previously failed ≥ 1 anti-TNF agent. All patients received vedolizumab at 0, 2, and 6 weeks, then approximately every 8 weeks thereafter. At week six and week 14, 14/22 (63%) and 13/17 (76%) of UC patients were in clinical remission based on PUCAI score ≤ 10, respectively. Patients with UC were more likely to be in remission at week 14 compared to those with Crohn disease (76% vs. 42%, $P < 0.05$). Week 6 corticosteroid-free remission was associated with week 14 corticosteroid-free remission among both groups ($P < 0.0001$). At week 33, anti-TNF-naïve patients had a higher remission rate compared to TNF-exposed patients (100% vs. 45%, $P = 0.04$). This study also found that both pediatric Crohn disease and UC patients with colonic-only disease had higher rates of remission at multiple time points throughout the study. No infusion reactions or serious adverse events, including tuberculosis, meningitis, or progressive multifocal leukoencephalopathy were observed at last follow-up.

Ustekinumab is a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23 that is approved for use in the treatment of psoriasis, psoriatic arthritis, Crohn disease, and most recently ulcerative colitis in adults. The phase 3 UNITI trial recently evaluated 961 adults with moderate-to-severe ulcerative colitis in a randomized, double-blind, placebo-controlled study, with the primary end point being clinical remission at week 8 after induction and week 44 for the maintenance trial [47]. Nine-hundred and twelve (94.9%) patients completed the induction trial, either receiving approximately 6 mg/kg dose, 130 mg dose, or placebo intravenously, with 783 (81.5%) entering into the maintenance trial. Of these 783 patients, 523 underwent randomization into the maintenance population (primary population) receiving 90mg every 8 weeks, every 12 weeks, or placebo every 8 weeks subcutaneously; and 260 were placed in a nonrandomized maintenance population (157 receiving 90 mg every 8 weeks and 103 placebo). Histo-endoscopic mucosal healing, improvements in partial Mayo scores, and reductions in serum and fecal concentrations of inflammatory biomarkers were observed in inductions and sustained in maintenance by both doses of ustekinumab. Ustekinumab was found to be more effective in achieving induction of clinical remission at 8 weeks when compared to placebo, and for those who achieved response to induction and underwent second randomization into the maintenance population, the patients receiving ustekinumab were more likely to be in clinical remission at week 44 compared to those assigned to placebo.

Off-label use in the pediatric IBD population has been increasing, though no controlled clinical trials in this population have been performed. One observational cohort study followed 52 pediatric IBD (42 Crohn disease, 4 ulcerative colitis, and 6 IBD-unspecified) patients receiving ustekinumab for steroid-free remission at 52 weeks [48]. For this patient population, 81% had failed >1 anti-TNF, 37% failed anti-TNF and vedolizumab, and 10 patients were biologic-naïve. At week 52, 39 patients (75%) were still receiving ustekinumab (31 CD, 8 UC/IBDU), with 30 patients in steroid-free remission (25 CD, 5 UC/IBDU). No significant associations were round in respect to disease type or location and remission outcomes. At week 52, biologic-naïve patients (90%, $n = 9$) were significantly more likely to achieve steroid-free remission compared to biologic-exposed patients (50%, $n = 21$) ($P = 0.03$). With regard to safety, no serious infections or other serious adverse events were reported in this cohort.

Small Molecules

Due to a lack of universal response, risks of infections and neoplasia, parenteral administration, and risk of developing antidrug antibodies with use of immunomodulators and biologics, oral non-biologic small molecule therapies are now being investigated for the treatment of ulcerative colitis. The OCTAVE trials [49, 50] investigated tofacitinib, an oral small-molecule Janus kinase (JAK) inhibitor that inhibits all JAKs, but preferentially JAK1 and JAK3, for use of induction and maintenance therapy for adults with moderate to severely active ulcerative colitis. In the OCTAVE Induction 1 trial, remission at 8 weeks occurred in 18.5% (88 of 476) of patients receiving 10 mg tofacitinib twice daily versus 8.2% (10 of 122) in the placebo group ($P = 0.007$) and in OCTAVE Induction 2 trial, remission occurred at 16.6% (71 of 429) of the tofacitinib group versus 3.6% (4 of 112) in the placebo

group ($P < 0.001$). In the OCTAVE Sustain trial, 34.3% (68 of 198) of patients in the 5mg bid and 40.6% (80 of 197) of patients in the 10 mg tofacitinib bid groups achieved remission at 52 weeks compared to 11.1% (22 of 198) in the placebo group ($P < 0.001$ for both comparisons with placebo). In the OCTAVE Sustain trial, the rate of herpes zoster infections was higher among those treated with tofacitinib ($n = 13$; 3 receiving 5 mg and 10 receiving 10 mg) compared to placebo ($n = 1$). Across all three trials, non-melanoma skin cancer and cardiovascular events occurred in more patients who received tofacitinib ($n = 5$) compared to placebo ($n = 0$). Although no formal trials have yet been performed in the pediatric ulcerative colitis population, tofacitinib has started to be used off-label by some centers for children who have been refractory to biologics.

Ozanimod is the newest small molecule oral therapy showing promising outcomes for the treatment of ulcerative colitis in adults. Ozanimod is an oral agonist of the sphingosine-1-phosphate receptor subtypes 1 and 5, which induces peripheral lymphocyte sequestration, leading to potential decrease in the number of activated lymphocytes in the gastrointestinal tract. Preliminary data from phase 2 of the TOUCHSTONE trial [51], a double-blind, placebo-controlled trial of 197 adults with moderate-to-severe active ulcerative colitis, showed that daily use of 1 mg ozanimod resulted in a slightly higher rate of clinical remission, based on Mayo clinic scores (Mayo score ≤2, with no subscore >1) at week 8, compared to placebo. At week 8, clinical remission occurred in 16% who received 1mg dosing ($P = 0.048$) and 14% who received 0.5 mg dosing ($P = 0.14$), when compared to the placebo group, of which 6% achieved clinical remission. At week 32, exploratory outcome measures showed that those receiving 1mg of ozanimod daily continued to have higher rates of clinical remission, clinical response, mucosal healing, histologic remission, and lower Mayo scores compared to those with placebo. One limitation of this study was the use of 8 weeks at the timepoint for the primary outcome analysis, as this might not have been sufficiently long enough for ozanimod to target lymphocyte tracking.

Antibiotics

In recent years, there has been an increase in use of broad-spectrum antibiotics as salvage therapy in refractory colitis. In one small pediatric cohort of 15 children with moderate to severe refractory UC, almost half (7/15) entered complete clinical remission defined as PUCAI < 10 when treated with a 2–3 week oral broad-spectrum antibiotic regimen consisting of metronidazole, amoxicillin, doxycycline, or ciprofloxacin, and, in hospitalized patients only, the addition of vancomycin [52].

In a single-center retrospective study of 63 children with refractory UC, Crohn's colitis, or IBD-U given the same 3 or 4 antibiotic regimen, 40/63 (63.5%) experienced a clinical response, defined as PUCAI change ≥20 points, and 25/63 (39.7%) achieved clinical remission, defined as PUCAI < 10 [53]. The combination antibiotics led to a significant decrease in median PUCAI score from 55 (40–65) to 10 (0–40; $p < 0.0001$) over 3 ± 1 weeks after initiation of antibiotics. In a subset analysis of only patients with acute severe colitis ($n = 26$), the median PUCAI decreased from 65 (60–70) at baseline to 35 (10–65) at 3 ± 1 weeks after initiation of antibiotics ($p < 0.0001$).

In the first randomized controlled trial conducted in pediatric acute severe colitis (ASC), 28 hospitalized children with ASC were randomized to receive the quadruple oral antibiotic cocktail (amoxicillin, vancomycin, metronidazole, and doxycycline or ciprofloxacin) and intravenous corticosteroids ($n = 16$), or intravenous corticosteroids only for 14 days ($n = 12$). There was a significant difference in the mean day 5 PUCAI score, 25 ± 17 vs 40 ± 20, respectively ($p = 0.037$) [54]. Secondary endpoints of remission rate and calprotectin values were numerically better in the antibiotic + intravenous corticosteroid group, but did not reach statistical significance in this small study.

Can We Predict the Course of Disease?

The wide range in phenotypic expression of pediatric ulcerative colitis and its response to therapy has heretofore made prediction of disease course difficult. Clinical factors examined have included features such as severity of disease (i.e., fulminant features requiring hospitalization), endoscopic appearance, laboratory markers, and early response to therapy [55–57]. Specific laboratory markers present at diagnosis, including hypoalbuminemia [7], elevated CRP [58], and anemia [11, 59], have shown to be predictive of eventual colectomy. Clinical severity at diagnosis, the need for hospitalization at diagnosis, and the need for rapid rescue with immunomodulators or biologics remain the greatest risk factors for early colectomy.

Pediatric data of early outcomes following standardized therapy after initial diagnosis suggest that baseline PUCAI < 35, higher baseline albumin, and week 4 clinical remission are predictors of week 12 corticosteroid-free remission (PUCAI < 10) [60]. Following this same cohort of patients, predictors for achieving week 52 corticosteroid-free remission for all patients included PUCAI < 35 at diagnosis, higher baseline hemoglobin and albumin, and week 4 clinical remission [7]. Assessing for biological predictors of disease course, this study showed that patients with rectal eosinophil count < 32 per high power field before treatment and those with Vitamin D-25(OH) level <20 ng/mL were

more likely to escalate to anti-TNFα therapy during the first year. Using RNA sequencing to assess the pattern of rectal gene expression and fecal microbiota profiles, it was also found that lower levels of an antimicrobial peptide gene signature and *Sutterella* organisms, and a higher relative abundance of Ruminococcaceae were independently associated with week 52 corticosteroid-free remission. Specifically, it was found that the α-defensin antimicrobial peptide pathway showed a stronger negative association with week 52 corticosteroid-free remission, and that a greater number of α-defensin 5 positive cells were present in rectal biopsy samples from patients who did not achieve week 52 corticosteroid-fee remission, compared to those who did and healthy controls. Those with more severe disease in this same cohort of patients were found to have a significant increase in bacteria typically found in the oral cavity within their gut mucosa at both baseline and in follow-up [61].

Attempts have also been made to try to correlate disease course with genetic profiles. An association between severe and extensive disease and the major histocompatibility complex (MHC) genes DRB1*0103 and DRB1*15 has been identified in adults [62–64]. Human leukocyte antigen (HLA) DRB1*0103 has shown an association with both UC and colonic Crohn disease, strongly suggesting that this allele is critically involved in determining the colonic immune response to local flora [65, 66]. A genome-wide association study (GWAS) compared 324 adults with ulcerative colitis who required colectomy for refractory disease with 537 ulcerative colitis patients who did not [67]. A risk score determined from a combination of 46 single nucleotide polymorphisms (SNPs) associated with the medically refractory group accounted for a little less than 50% of the variance for the colectomy risk. Specifically, the known IBD susceptibility gene *TNFSF15 (TL1A)* on chromosome 9q32 was implicated in UC severity. The sensitivity and specificity of the risk score were over 90%.

Microarray of RNA isolated from colonic biopsy tissue has identified genes that may predict the response to infliximab in adults [68]. This panel of five genes (osteoprotegerin (OPG), stanniocalcin-1, prostaglandin-endoperoxide synthase 2 (COX2), interleukin 13 receptor alpha2 and interleukin 11) discriminated responders from non-responders with 95% sensitivity and 85% specificity. Another study of mucosal gene expression found a positive correlation between high IL-17 and IFN-γ expression and response to infliximab [69]. Variants of the IL-23R gene that increase susceptibility to UC seem to improve response to infliximab [70]. One study used a pharmacogenetics GWAS to evaluate infliximab non-response in a combined pediatric ulcerative colitis and Crohn disease group, finding BRWD1, TACR1, FAM19A4, and PHACTR3 to predict non-response [71].

In pediatric patients, elevated fecal levels of osteoprotegerin (OPG) are associated with failure to respond to intravenous corticosteroids in children with severe ulcerative colitis [72]. One study found that 41 genes, with statistical significance, were differentially expressed between IV corticosteroid responders and non-responders in children with severe ulcerative colitis [73]. Two of the genes, CEACAM1 and MMP8, are possibly inhibited by methylprednisolone through IL-8, and found to be over-expressed in corticosteroid non-responsive patients. The expression pattern of 10 out of the 41 genes were able to classify the treated patients with 80% sensitivity and specificity. Emerging areas of research into biologic molecules (e.g., metabolomics, proteomics, and epigenomics) have the potential to clarify disease phenotypes, behavior, and responsiveness to medications [74–76].

Summary

The optimal therapy for ulcerative colitis quickly induces and then effectively maintains remission with healing of the colonic mucosa and presents minimal toxicity to the patient. While 5-aminosalicylates are effective in inducing and maintaining remission in some patients, their efficacy in both aspects of therapy is limited for those with more severe disease. Nonetheless, 5-aminosalicylates should be the cornerstone of therapy if possible. Immunomodulators and anti-TNFα therapy are effective in many patients not maintained in remission on 5-aminosalicylates, but remission at one year is noted in less than half of patients treated with these agents, and disease flares are still common. Evidence suggests that the short-term impact of biological agents on disease course is positive, though it is still not clear that disease course is altered for those who present with fulminant disease. This group continues to exhibit a greater degree of treatment unresponsiveness and has an unacceptably high rate of colectomy. Long-term observations will be required to better understand the changing natural history of ulcerative colitis in children with the emergence of new therapies. Current research holds the promise of development of risk assessment (e.g., gene expression, microbiome, and genetics) promptly following diagnosis that will facilitate treatment design, decreasing the likelihood of treatment failure, and complications of ineffective treatments.

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Pediatric Inflammatory Bowel Disease: Unclassified

9

Brooke Boyer and Elana B. Mitchel

Abbreviations

CD	Crohn Disease
UC	Ulcerative Colitis
IBD	Inflammatory Bowel Disease
IBD-U	Inflammatory Bowel Disease-Unclassified

Introduction

A diagnosis of inflammatory bowel disease is made following a detailed clinical history in combination with biochemical, radiographic, endoscopic, and histologic evaluation. While for many pediatric patients, initial evaluation results in a clear diagnosis of either Crohn disease (CD) or ulcerative colitis (UC), the phenotype of IBD can be heterogeneous, existing across a spectrum. A subset of patients with colonic disease may present with atypical features that do not clearly fit the diagnostic criteria for UC or CD, resulting in a diagnosis of inflammatory bowel disease-unclassified (IBD-U).

A diagnosis of IBD-U can pose a challenge to providers as there have been varying definitions of this entity and less is known about the natural history, prognosis, or efficacy of treatment of the disease. Additionally, this diagnosis, even by its very name, can lead to confusion and a sense of uncertainty among patients and their caregivers. In this chapter, we will review the criteria used to establish a diagnosis of IBD-U, the epidemiology of IBD-U, diagnostic evaluation, as well as considerations for medical and surgical management.

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Definition

The term indeterminate colitis was first introduced in the 1970s as a diagnosis in IBD patients whose pathology after colectomy showed features consistent with both UC and CD [1]. This diagnosis has since evolved overtime. The Montreal classification, published in 2006, replaced the term indeterminate colitis with IBD-U to define the pre-surgical patient who has clinical, endoscopic, and biochemical features of IBD but no definitive features of UC or CD [2]. Since this time, with advances in diagnostic tools and disease detection, the uncertainty of IBD subtype classifications has increased and in the pediatric setting, several groups have worked to further define IBD-U [3, 4].

In 2014, the revised Porto criteria by the European Society for Pediatric Gastroenterology and Nutrition (ESPGHAN) were published, providing clinicians with a more defined framework for establishing a diagnosis of IBD-U. Certain features of IBD were divided into three distinct classes to help differentiate subgroups of pediatric IBD. Class 1 features were considered features incompatible with UC, making CD the definitive diagnosis. Class 2 features were more commonly found in CD but rarely found in UC (<5% of UC cases). Class 3 were features suggestive of CD but also found in UC (5–10% of UC cases). With increasing features from class 2 or 3, the likelihood of CD increased. The criteria stated that a diagnosis of IBD-U should be considered if a patient had at least one Class 2 feature such as rectal sparing, significant growth delay, transmural inflammation in the absence of severe colitis, duodenal or esophageal ulcers not explained by other causes, multiple aphthous ulcerations in the stomach not explained by other causes, or reverse gradient mucosal inflammation with more inflammation proximally rather than distally. IBD-U could also be diagnosed if a patient had at least 2 to 3 Class 3 features such as severe scalloping of the stomach or duodenum not explained by other etiologies, focal chronic duodenitis on multiple biopsies or marked scalloping of the duodenum not explained by other causes, focal active

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Table 9.1 Updated revised Porto Group classification system [6]

Class	Feature	Determination of IBD-type
Class 1		**CD diagnosis** If any class-1 features present If class-1 features absent, at least 1 class-2 feature and 4 or more class-3 features **UC diagnosis** If class-1 and class-2 features absent **Atypical UC** If class-1 and class-2 absent with 1-2 class-3 features **IBD-U** If class-1 features absent with at least 1 class-2 feature and up to 3 class-3 features
1	At least one well-formed granuloma anywhere in the GI tract, remote from ruptured crypt	
2	At least one of: deep ulcerations; cobblestoning; or stenosis anywhere in the small bowel or upper GI tract (excluding stomach)	
3	Fistulizing disease (internal or perianal)	
4	Large inflamed perianal skin tags	
5	Thickened jejunal or ileal bowel loops on radiology or other evidence of significant small bowel inflammation on capsule endoscopy not compatible with backwash ileitis	
6	Any ileal inflammation in the presence of normal cecum (incompatible with backwash ileitis)	
Class 2		
7	Macroscopically and microscopically normal appearing skip lesions in untreated patient (excluding rectal sparing and cecal patch)	
8	Complete (macroscopic and microscopic) rectal sparing	
9	Macroscopically normal colon in between inflamed mucosa but with microscopic inflammation (relative patchiness)	
10	Significant growth delay (height velocity <−2 SD), not explained by other causes	
11	Transmural inflammation in the colon in the absence of severe colitis	
12	Small and not deep ulcers (including aphthous ulcerations) anywhere in the small bowel, duodenum and esophagus (excluding stomach and colon) not explained by other causes	
13	Multiple (≥5) small and not deep ulcers (including aphthous ulcerations), in the stomach or colon (on the background of normal mucosa), not explained by other causes	
14	Ileitis, otherwise compatible with backwash ileitis, but in the presence of only mild inflammation in the cecum	
15	Positive ASCA in the presence of negative pANCA	
16	Reverse gradient of mucosal inflammation (proximal > distal [except rectal sparing])	
17	Severe scalloping of the stomach or duodenum, not explained by other causes	
18	Deep ulcerations (at least one) or severe cobblestoning of stomach not explained by other causes	
Class 3		
19	Focal chronic duodenitis on histology	
20	Focal active colitis on histology in more than one biopsy	
21	Several [<5] aphthous ulcerations in the colon or in the stomach	
22	Non-bloody diarrhea	
23	Focal enhanced gastritis on histology	

colitis, non-bloody diarrhea, or aphthous ulcerations in the colon or upper gastrointestinal tract [5].

In 2017, the Porto Group of ESPGHAN performed a retrospective longitudinal multicenter study to validate the classification system described above. The algorithm was slightly revised to allow for maximal diagnostic accuracy in over 500 IBD patients. The final classification system is listed in Table 9.1. IBD-U was defined if a patient had at least one Class 2 feature and/or up to three Class 3 features. This updated algorithm differentiated UC from CD and IBD-U with 80% sensitivity and 84% specificity and CD from IBD-U and UC with 78% sensitivity and 94% specificity [6]. Thus, while considerable progress has been made in defining IBD-U, there is still a need for further study.

Epidemiology

Estimating the incidence and prevalence of IBD-U is challenging due to variability in the classification of this disease phenotype, potential for labeling of this diagnosis when the work-up is incomplete, and the high likelihood of reclassification of this subtype.

The overall incidence of pediatric IBD is increasing [7]. Based on recent studies, the incidence of IBD-U in the pediatric population is also increasing [7–10]. The incidence is widely varied but in most pediatric studies ranges from 0.3 to 1.2 per 100,000 person years [7–14]. The highest annual incidence reported is 2.1 per 100,000 persons in North America and 3.6 per 100,000 person years in Europe [15, 16].

The proportion of patients with IBD who receive the diagnosis of IBD-U varies widely across studies and is more likely to be changed to CD or UC overtime. In the RISK study, a multicenter inception cohort of pediatric IBD patients, 136 of 1411 (9.6%) patients were diagnosed with IBD-U at enrollment. Within 2 years after diagnosis, only 60% of patients remained with the diagnosis of IBD-U, 26% were reclassified as UC and 14% as CD. Of those requiring reclassification, the ratio of change to UC versus CD was 2:1 [17]. In another large inception cohort from Canada, 8% of pediatric patients were classified as IBD-U at diagnosis. Within the first year after diagnosis, 39 (44%) were reclassified to UC, 11 (12%) were switched to a diagnosis of CD and only 39 (44%) continued to hold a diagnosis of IBD-U [18]. In one tertiary care center registry of 250 children with IBD, retrospectively 74 (29.6%) were diagnosed with IBD-U and only 49 (66.2%) remained with the diagnosis of IBD-U after a mean follow-up time of 6 years. In another retrospective single-center study, 78 (22%) children and adolescents were diagnosed with IBD-U over a 25-year period with a significant proportion undergoing reclassification during follow-up [19]. These studies also illustrate that study design impacts the estimate of IBD-U, with higher estimated proportions found in retrospective as compared to prospective studies [20].

Age at diagnosis plays a major role in the diagnosis of IBD-U. IBD-U is more commonly diagnosed in pediatric patients as compared to adults. In one meta-analysis, 13% of children as compared to 6% of adults were given the diagnosis of IBD-U [20]. In a large cohort study, 18% of pediatric as compared to 11% of adult patients were diagnosed with IBD-U [21]. This difference is likely related to the fact that pediatric patients are more likely to present with colonic CD as compared to adults and adult UC is more likely to present with left-sided disease or proctitis [5, 22]. However, even within pediatric populations, IBD-U is more commonly applied to younger children, present in 13% of children <10 years old and 7% of children ≥10 years old ($p < 0.001$). In another study, early presentation before age 10 was seen in 31% patients with IBD-U as compared to 17% CD and 20% UC [14]. This finding may be related to the different phenotype that many very-early onset (VEO) IBD patients display and may be compounded by difficulty completing the diagnostic work-up in young children.

Finally, when considering the epidemiology of IBD-U, the importance of pursuing a complete diagnostic work-up in pediatric and adolescent patients is underlined by a study using the EuroKIDS Registry. IBD-U was made as the initial diagnosis in 7.7% of children (265 out of 3461). However, about half of these children had not undergone complete diagnostic work-up. Upon reinvestigation with endoscopy and imaging, 12% had a change in diagnosis from IBD-U to CD and 20% to UC over a median of 5.7 years of follow-up. After reinvestigation, IBD-U diagnosis was only in 5.6% of pediatric patients [23]. Furthermore, IBD-U epidemiology may be impacted by the subspecialist and the diagnostic capabilities of the pediatric center under which the patient is being cared for.

Diagnosis

A complete diagnostic work-up including endoscopy and small bowel imaging is essential in making the diagnosis of IBD-U or reclassifying patients to a diagnosis of CD or UC. Additionally, throughout the disease course and during periods of exacerbation, patients given a diagnosis of IBD-U should undergo complete endoscopic and radiographic evaluation in order to assess disease distribution and potential progression which may result in reclassification [4].

Clinical Features

There are no definitive clinical or histological features that are diagnostic of IBD-U. There have been few studies that have looked to further define clinical features suggestive of IBD-U. Patients with IBD-U typically display a more UC phenotype with the most common symptoms at presentation being diarrhea and rectal bleeding [24]. In one large pediatric study of 3991 children and adolescents with IBD, initial diagnostic symptoms were compared across IBD subtypes. Blood in the stool was reported most commonly in UC and IBD-U as compared to CD. In addition, diarrhea was less common in CD patients. Abdominal pain was present in all three subtypes (59.2% UC, 77.3% CD, and 57.9% IBD-U) [25].

Endoscopic Evaluation

Upper endoscopy and ileocolonoscopy are essential to the diagnostic evaluation of IBD-U. Studies have shown that IBD-U and UC share similar endoscopic findings [23, 24]. In one study evaluating 158 IBD-U patients, 58% presented with pancolitis, 17% with ulcerative proctitis, 7.6% with left-sided colitis, and 7.0% with extensive colitis [23]. In another recent pediatric study, 61% of patients with IBD-U had pancolitis on diagnostic endoscopy [6]. Interestingly, Rinawi et al., in a retrospective study of over 700 patients with pediatric IBD, found that patients with IBD-U had more extensive colonic involvement than those with pediatric-onset UC at diagnosis (70% vs. 45%, $p = 0.02$) suggesting that IBD-U may have more extensive and aggressive features at the time of presentation [26].

Studies have also shown the wide-spread and heterogenous endoscopic findings in IBD-U patients, including involvement of the esophagus, stomach, duodenum, and ileum [27]. In one study, 23% of pediatric patients with IBD-U were found to have visual inflammation in the stomach, duodenum, or both [23]. Therefore, it is important, even if a diagnosis of IBD-U or UC is suspected, that full endoscopic evaluation be performed to understand extent.

Small Bowel Imaging

Comprehensive evaluation of the gastrointestinal tract at the time of diagnosis must include small bowel evaluation to further differentiate IBD subtype and potentially confirm the diagnosis of IBD-U. Imaging in the pediatric population requires multiple considerations including the patient's ability to tolerate the study with attention to duration of the study, need for sedation, ingestion of contrast, and radiation exposure. Imaging studies and capsule endoscopy can provide important diagnostic information.

Radiologic Studies: Several imaging modalities exist to evaluate the gastrointestinal tract. Previous fluoroscopic barium studies including small bowel follow through and contrast enema have been largely replaced by cross-sectional imaging with either magnetic resonance enterography (MRE) or computed tomography enterography (CTE). Both MRE and CTE, through the use of intravenous and enteral contrast, are able to detect luminal, transmural, and extraintestinal inflammation [28]. Both studies are similar in their detection of active inflammation; however, MRE is more sensitive in identifying fibrosis [28, 29]. In many pediatric centers, MRE has become the preferred imaging modality of choice given its high specificity and sensitivity in detecting inflammatory changes in the intestinal wall as well as other disease complications. In addition, MRE has no associated ionizing radiation exposure [30, 31]. However, due to the long study duration, issues related to claustrophobia and tolerance of enteral contrast may pose a challenge, particularly in young children and those with developmental delay. This is important to consider especially in IBD-U, a subtype that favors the pediatric population, particularly a younger cohort. In cases where MRE is not feasible, CTE or alternatively ultrasound should be pursued. Contrast-enhanced ultrasound (CEUS), an emerging imaging modality in pediatric IBD, is a complementary or alternative means to assess for bowel inflammation in addition to extramural complications such as abscess or inflammatory mass [32, 33].

In general, IBD-U patients seem to be less likely to undergo a complete diagnostic study as compared to CD and UC, respectively (48% vs. 60% vs. 64%, $p < 0.001$) [23]. One pediatric study found that patients diagnosed with IBD-U were less likely to have small bowel imaging performed as compared to CD patients (73% vs. 62%, $p < 0.001$). A wide variety of small bowel imaging in IBD-U patients was also used in this study [34].

Video Capsule Endoscopy: Video capsule endoscopy (VCE) allows for complete visual examination of the small intestine. In pediatric patients, swallowing a capsule may be difficult, and in these instances, endoscopic placement should be pursued. Limitations to capsule endoscopy include capsule retention as well as poor bowel preparation which can obscure visualization. The greatest risk for capsule retention is a known diagnosis of IBD (5.2% risk) [35]. In patients with higher clinical suspicion of CD with small bowel involvement, patency capsule should be considered prior to capsule endoscopy.

VCE has been shown to be helpful in defining IBD subtype and may be particularly helpful in the IBD-U cohort. In one retrospective study, the impact of VCE on decision-making and diagnostic accuracy was evaluated in 66 pediatric IBD patients. Use of VCE allowed for clarification of the diagnosis where 50% of patients with a diagnosis of IBD-U or UC were changed to CD with this additional information [36]. In an adult study, 36 patients with IBD-U underwent VCE. After VCE, about 25% of patients had reclassification to a diagnosis of CD and in about 44%, a diagnosis change to UC. Twenty-eight percent maintained a diagnosis of IBD-U based on the VCE results [37].

Medical Management

Patients with IBD-U are often excluded from randomized clinical trials or, when included, are often grouped with UC. As such, there are no medications approved specifically for the treatment of IBD-U. This cohort of patients is heterogenous and therapy should be guided by clinical presentation in addition to disease phenotype. Patients with IBD-U are treated with the same classes of medications as children with CD or UC, including aminosalicylates, immunomodulators, and biologic agents.

In 2017, the Porto Group of ESPGHAN published results from a retrospective multicenter study reviewing therapeutic management of patients with a diagnosis of IBD-U. A total of 797 children were included in the study, 260 patients diagnosed with IBD-U, of which 23% had extensive colitis at the time of diagnosis. Patients with IBD-U had a statistically significant lower use of corticosteroids and higher use of exclusive enteral nutrition compared to those with UC. In comparison to patients with CD, patients with IBD-U received more aminosalicylates and were less likely to be treated with EEN or immunomodulators. Biologic therapy use was higher in patients with CD (34%) versus UC (17%) and IBD-U (12%) [6]. More work is needed to better understand this population and to better define therapeutic algorithms.

Surgical Management

Surgical intervention is taken very seriously in IBD-U patients due to the uncertainty of the diagnosis and the potential for later reclassification. IBD-U patients are less likely to undergo surgery as compared to patients with UC and CD [38]. In those with IBD-U who do undergo surgery, a diagnosis reclassification is more likely to occur [23].

One surgical option for this group of patients is ileal diversion. This procedure can be a helpful temporizing measure in patients with IBD-U who are ill but in whom the IBD phenotype is unclear. In one pediatric retrospective study at a single tertiary care center, patients who underwent surgical diversion had significant improvement in height and weight velocities, height velocity *z*-score, blood transfusion requirement, hemoglobin, and hospitalization rates. Fifty-four percent of the patients who underwent diversion had the diagnosis of IBD-U at the time of diversion. About half of these IBD-U patients had reclassification of their disease after diversion. Thus, in these patients, diversion allowed for the time needed to determine the diagnosis [39].

Ileal pouch-anal anastomosis (IPAA) is another common surgical approach in patients with IBD-U. Multiple studies have shown that patients with IBD-U have similar retention of the pouch, pouch function, and favorable quality of life scores after IPAA as compared to those with UC [35, 40–42]. Failure rates are also similar to patients with UC [42]. However, IBD-U patients have higher rate of pouch fistula, perianal fistulae, and pelvic abscesses; thus the risks and benefits of this procedure must be weighed [35, 40, 41].

Conclusion

The IBD phenotype can be heterogeneous and exists across a spectrum, not always distinctly categorized as UC or CD. The diagnosis of IBD-U is made in patients with colonic disease but with atypical features that do not fit clearly into a diagnosis of UC or CD. While there is less known about the natural history, prognosis, and efficacy of treatment in patients with IBD-U, there has been recent work to better define this entity. IBD-U is increasing in incidence and is more prevalent in the pediatric population, particularly in younger patients. A complete diagnostic work-up including endoscopy and small bowel imaging is essential to solidifying the diagnosis of IBD-U or reclassifying patients to a diagnosis of CD or UC. Additionally, throughout their disease course and during periods of exacerbation, patients given a diagnosis of IBD-U should undergo complete endoscopic and radiographic evaluation in order to assess disease distribution and potential progression which may result in reclassification. Once a diagnosis is made, medical management is similar to that in CD and UC; however, there is little evidence in efficacy of therapies as IBD-U patients are often excluded from drug trials. Medical management should be guided by the patient's clinical presentation in addition to their disease phenotype. Surgical intervention can be helpful in the treatment of IBD-U but must be approached with extreme caution given the uncertainty tied to the diagnosis of IBD-U and potential later reclassification. Future research in this patient population is extremely important to better define the pathogenesis, diagnostic accuracy, and medical and surgical management.

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Extraintestinal Manifestations of Pediatric Inflammatory Bowel Disease

10

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Introduction

Inflammatory bowel disease (IBD) is not just a disorder of one organ system, but rather a multi-systemic disease. In addition to the more typical gastrointestinal involvement which can present with symptoms such as abdominal pain, chronic diarrhea, or bloody stools, several other organs can be involved as well, including the eyes, skin, joints, kidneys, and liver. In fact, these extraintestinal manifestations (EIMs) may be the presenting symptom and become the predominant source of morbidity for a given patient.

EIMs are frequently encountered in pediatric IBD. The incidence of developing any EIM is estimated to be as high as 40% in predominately adult studies and it can be the presenting symptom in one out of four patients with IBD [1, 2]. Pediatric studies have shown similar or even higher rates. In a retrospective study of over 1600 children with IBD, the incidence of EIMs was 29% at 15 years post-diagnosis [3]. These complications were more common in older patients and 6% of the patients had extraintestinal symptoms prior to diagnosis. In another prospective study of over 1000 pediatric IBD patients, the incidence of EIMs was 28% with the majority (87%) occurring in the first year after diagnosis [4]. More recent studies have shown higher rates of EIMs in pediatric patients than adult counterparts especially at disease onset. The Pediatric IBD Swiss Cohort reported EIM in 8.5% of children at disease onset compared to 5.0% of adults [5]. Prior to IBD onset, EIMs were present in over 27% of the patients in this study [5]. EIMs appear more common in Crohn disease than ulcerative colitis and have been reported as a surrogate maker of more severe disease as defined by increased need for biologics, surgery, or increased flares [6, 7]. Interestingly, patients with abnormal biomarkers and more severe disease had a higher likelihood of having an EIM [6, 8]. Further, the presence of one extraintestinal manifestation confers a risk to develop other manifestations [2].

EIMs have been classified into various ways such as their relationship with the presence or degree of inflammation of the underlying bowel disease or by the location of the bowel disease, for example, colonic versus small intestinal [9]. They can also be divided by whether or not they are a consequence of the IBD itself. EIMs effecting the joints, skin, hepatobiliary system, and eye can be differentiated from those that are complications of the disease such as malabsorption leading to osteoporosis, growth issues, kidney stones, etc.

The pathogenesis of the extraintestinal manifestations, like the etiology of IBD, is unknown. However, possible hypotheses include abnormal self-recognition, antibody production against specific extraintestinal organs that cross-react with gastrointestinal antigens, and/or genetic susceptibility. It is postulated that the inflammatory response in patients with IBD leads to the inability of the intestine to act as a selective barrier. Hence, the uptake of bacterial products or dietary antigens can induce circulating immune complexes or a systemic inflammatory response [10]. Another theory involves the cross-reaction with a bacterial epitope leading to autoimmunity directed against an antigen shared among the intestine, skin, synovium, eye, and biliary system [11]. An autoimmune reaction to an isoform of tropomyosin which is expressed in the eye (non-pigmented ciliary epithelium), skin (keratinocytes), joints (chondrocytes), biliary epithelium, and the gut is speculated as the focal point for this theory [12]. Similarly, extraintestinal manifestations may share a common pathway with the bowel disease in that recruitment of mucosal memory and/or effector T-cells to various tissues via the expression of endothelial adhesion molecules that are usually restricted to the gut may lead to destruction from the influx of inflammatory cells [13]. One

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Table 10.1 Common extraintestinal manifestations of IBD in children and their relative prevalence

Extraintestinal manifestation	Prevalence
Growth failure	++++
Sacroiliitis	++++
Osteoporosis/Osteopenia	+++
Peripheral joint inflammation	+++
Aphthous ulcers	+++
Primary sclerosing cholangitis	++
Granulomatous skin lesion	++
Erythema nodosum	++
Pyoderma gangrenosum	+
Uveitis/Episcleritis	+
Ankylosing spondylitis	+

mechanism does not explain all of the different extraintestinal symptoms described in IBD patients. This is supported by the lack of uniform response to treatment. For example, half of patients with Crohn disease had complete resolution of their extraintestinal manifestations with adalimumab treatment. There was a significant reduction in arthralgias, arthritis, oral aphthous ulcers, and erythema nodosum but not ankylosing spondylitis, iritis, or uveitis [14].

There is a strong genetic influence on EIMs with reports of 70% concordance between parent–child pairs and 83% concordance between siblings [15]. The human leukocytes antigens (HLA) system is postulated as a link between IBD and certain extraintestinal manifestations, especially ocular and articular manifestations [15]. HLA-A2, -DR1, and -DQw5 are more commonly associated with extraintestinal co-morbidities in Crohn disease. On the other hand, genotypes HLA-DRB1, -B27, and -B58 are linked with EIMs of ulcerative colitis. Primary sclerosing cholangitis as well as other autoimmune disorders (e.g., celiac disease, autoimmune hepatitis, and myasthenia gravis) have been associated with IBD patients with haplotype HLA B8/DR3, while HLA B27 is reported in 50–80% of IBD patients with ankylosing spondylitis [12].

Many EIMs have been reported in the literature associated with IBD, and although fortunately most of these are rare, there are multiple excellent comprehensive reviews available on this topic [16–23]. This chapter will focus on the more common EIMs found in the pediatric population and present them by the affected system and descending order of prevalence (Table 10.1).

Growth Failure

A discussion of EIMs in pediatric IBD patients cannot be presented without first mentioning growth failure, which is estimated to occur in 30% of children with Crohn disease and in 5–10% with ulcerative colitis [1]. Children can present with an obvious lack of growth such as a height below the fifth percentile for age, or growth changes can be more subtle with a gradual flattening of the child's height velocity that is only evident upon plotting of multiple height measurements on a growth chart and comparing to mid-parental height. Some children can have delays in bone maturation and pubertal development. It is important to not merely assume that growth failure is a consequence of gastrointestinal manifestations as decreases in weight and height velocities can precede any clinical evidence of bowel disease [24]. Thus, the concept of viewing growth failure as an independent manifestation of IBD will help clinical providers develop a higher index of suspicion for the diagnosis of IBD in children presenting in this manner, even if they do not have gastrointestinal complaints.

IBD-associated growth failure could be secondary to deficient nutrient intake, poor digestion, and absorption as well as increased metabolic demands; however, the most likely etiology remains chronic caloric insufficiency [25]. Unfortunately, treatment for the IBD, especially with chronic corticosteroids, can have deleterious effects on overall growth and this needs to be weighed against the detrimental effects of the inflammatory process on growth. In addition to consideration of immunomodulator (such as 6-mercaptopurine/azathioprine or methotrexate) and tumor necrosis factor-alpha (TNF-α) antagonists earlier in the disease course of pediatric patients, administration of oral or enteral formula feedings should be considered to rehabilitate the growth-stunted patient. A more extensive review can be found in the chapter devoted to growth issues in pediatric IBD.

Joint Manifestations

Joint inflammation is a commonly seen EIM of IBD in both adults and children with arthritis or joint pain occurring in 16–33% of children with IBD [1, 26]. Similar to most other EIMs, symptoms of joint inflammation may occur before or after the development of bowel disease. Besides joint inflammation, one in five pediatric patients report enthesitis, inflammation at the bony insertion sites of ligaments, tendons, and fascia [27]. Joint manifestations can be divided into an axial form (involvement of the axial spine and sacroiliac joints) and a peripheral form (involvement of larger joints such as the knees, ankles, hips, wrists, and elbows).

The axial form of joint involvement which includes ankylosing spondylitis and sacroiliitis, is less common than peripheral arthropathies with reported incidence of 3–25% [23]. These axial forms of joint involvement are demonstrable on magnetic resonance imaging enterography (MRE), although further dedicated imaging may be necessary [28]. Ankylosing spondylitis, which is associated with the HLA-B27 antigen, occurs in less than 2% of IBD patients. Symptoms include back stiffness, pain, and eventually

stooped posture as well as peripheral arthralgias. Almost all of these patients will have involvement in their sacroiliac joints. On the other hand, asymptomatic sacroiliitis is more common with an estimated incidence of 10–52% [15]. Isolated sacroiliitis seems not to be associated with HLA-B27; however, there appears to be striking racial disparity in occurrence rates [12, 29]. African Americans have a fourfold adjusted odds of sacroiliitis compared to Caucasian cohorts [29]. Asymptomatic HLA-B27-negative patients with normal spinal mobility do not require specific treatment. Physical therapy and an exercise program to stop the progression of any disability and deformation in addition to nonsteroidal anti-inflammatory drugs (NSAIDs) remain a mainstay of treatment. However, there is concern of IBD relapse with the latter and hence some emerging literature supporting coxibs in IBD patients. Glucocorticoid injections are an option as well but there is a risk of long-term complications [29, 30]. Although ankylosing spondylitis has been shown to respond to sulfasalazine in multiple double-blind studies, none of the studies addressed ankylosing spondylitis in IBD patients [31]. Small studies have demonstrated a role of TNFα antagonist therapy in patients with IBD and ankylosing spondylitis [29, 30]. There are case reports of response to ustekinumab and vedolizumab, although these are best used primarily to control the intestinal disease [29, 30, 32].

Peripheral joint inflammation is most frequently reported with Crohn disease and is most typically associated with colonic inflammation although it can also be associated with small bowel disease [15]. The patient usually presents with erythema, swelling, and decrease range of motion in an asymmetric pauciarticular pattern. Fortunately, joint deformity is uncommon. The arthritis tends to worsen during times of increasing bowel disease and there is an association with other EIMs such as those of the skin, mouth, and ocular systems. In fact, patients with involvement of these systems can share serologic markers such as elevations in antibody levels against exocrine pancreas compared to other IBD and non-IBD patients [33].

Primary treatment of the bowel inflammation with 5-aminosalicylate medications, corticosteroids, immunomodulator, or biologic is the first course of action for peripheral joint inflammation [1]. Often resolution is achieved with this approach in less than 8 weeks [26]. Methotrexate and intraarticular corticosteroid injections should be considered in refractory cases. Studies have shown that TNF-alpha and Il12/23 antagonists are efficacious in the treatment of spondyloarthropathies such as the articular and musculoskeletal findings in IBD [15, 29, 30]. Similar to the treatment of the axial joint EIM, treatment with NSAIDs and cyclooxygenase-2-inhibitors may need to be limited due to the potential for gastrointestinal mucosal injury.

Bone Disease

There has been increasing interest in identifying osteopenia and osteoporosis in patients with IBD especially given that IBD commonly presents during adolescence and young adulthood when bone mass is being rapidly attained. In adult populations, the overall prevalence of osteoporosis in IBD is estimated between 4 and 40% with increasing prevalence in older patients [12]. A large population-based adult study reported an osteoporosis prevalence of 15% and relative risk of 1.4 for fractures in IBD patients compared to the general population [34]. Prevalence of osteopenia and osteoporosis in the pediatric population is estimated between 8 and 30% based on several smaller studies [35]. The increased risk of eventually developing osteoporosis in IBD patients, especially those with Crohn disease, is secondary to multiple factors including inadequate intake or malabsorption of calcium and vitamin D, corticosteroid use, low estrogen states in females, and negative effects of circulating proinflammatory cytokines [36]. This osteoporosis can make the patients prone to bone fracture, bone deformities, and chronic pain.

Diagnosis of osteopenia/osteoporosis is made with dual-energy X-ray absorptiometry (DEXA) which measures bone mineral density in the spine, femoral neck, or other bones rapidly and with low amounts of radiation. Treatment with calcium and vitamin D may prevent further deterioration of bone but not necessarily help in recovery of lost bone density. However, some pediatric studies have suggested bone recovery in children with IBD on treatments. Prevention has not been well studied in IBD patients, but it would be prudent to ensure intake of at least the recommended daily requirement for age of calcium and vitamin D, proper exercise, and minimization of corticosteroid usage to maximize the pediatric patient's potential in achieving an appropriate peak bone mass. The role of bone protecting agents in IBD, especially pediatrics, is unknown so far.

Other bone complications in IBD patients include osteonecrosis of the femoral head, hypertrophic osteoarthropathy, and chronic recurrent multifocal osteomyelitis (CRMO). Osteonecrosis of the femoral head is usually associated with patients who have received chronic steroids and have complaints of hip or knee pain. Clubbing or hypertrophic osteoarthropathy is another bone manifestation associated with IBD especially with small intestinal Crohn disease. The etiology, though unknown, is postulated to involve increased blood flow to the fingers and hence increased connective tissue growth secondary to circulating cytokine production [1]. Chronic recurrent multifocal osteomyelitis (CRMO), rarely described in children with IBD, is an aseptic inflammatory bone disease that typically affects the long bones and clavicles [37].

Oral Lesions

Oral lesions can arise at any time in patients with IBD and at any age. Although the incidence can vary, the highest report rate was 50% in a pediatric age group study [38, 39]. More common in males and Crohn disease patients, oral lesions can be asymptomatic and precede intestinal involvement in up to 20% of patients [38, 39]. Oral manifestation of IBD can be specific such as cobblestoning of the mucosa, granulomatous cheilitis (Fig. 10.1), pyostomatitis vegetans, or nonspecific such as ulcers (Fig. 10.2) including aphthous, lichen planus, and cheilitis angularis. Nonspecific lesions can be due to malnutrition or drug effect. Recurrent aphthous ulcers are the most common oral lesions associated with IBD with a reported incidence of approximately 8–14% in pediatric IBD patients with higher rates in Crohn disease compared to ulcerative colitis. Aphthous lesions, shallow round ulcers surrounded by an erythematous halo with a central fibrin membrane, tend to parallel intestinal disease though they often can predate intestinal symptoms and can correlate 40–70% of the time with active intestinal disease [38]. Other oral lesions can consist of lip swelling, fissures, and gingivitis which can demonstrate granulomas on histology [40]. Angular cheilitis, sores in the corner of the mouth, often occurs due to anemia or secondary to a fungal or bacterial infection [39]. Orofacial granulomatosis is a rare syndrome with chronic swelling of the lips and lower half of the face combined with oral ulcerations and hyperplastic gingivitis that has been reported in three dozen Crohn's cases [41]. Orofacial granulomatosis can be seen in other disorders such as foreign body reaction, tuberculosis, sarcoidosis, and idiopathic causes which share similar histopathologic features. Another rare disorder seen in association with ulcerative colitis patients is pyostomatitis vegetans which can present with oral and cutaneous findings in the axillae, genital areas, and scalp. The oral lesions consist of multiple neutrophil and eosinophil-filled pustules on erythematous bases which can erode and fuse to form shallow ulcers that have been described as being "snail track" configuration [42]. Lichen planus, a chronic inflammatory dermatosis, has also been seen as a suspected drug reaction to sulfasalazine and mesalamine [39]. Oral lesions in IBD patients could also be a result of nutritional deficiencies, specifically low levels of zinc, folic acid, niacin, and vitamin B12 [38, 39].

Treatment of oral lesions is usually reserved for those causing significant discomfort and may involve topical, intralesional or systemic corticosteroids, dapsone, or preparations directed at the bowel disease including immunomodulators, biologics, and thalidomide [39, 43].

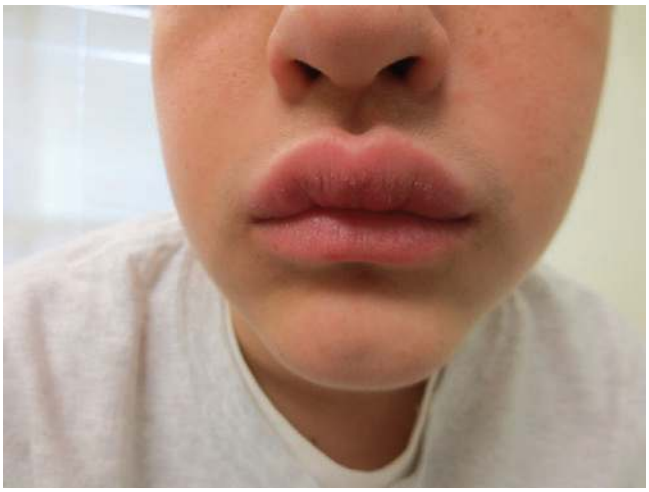

Fig. 10.1 Granulomatous cheilitis , Courtesy of Dr. Anna L. Grossberg, Johns Hopkins University

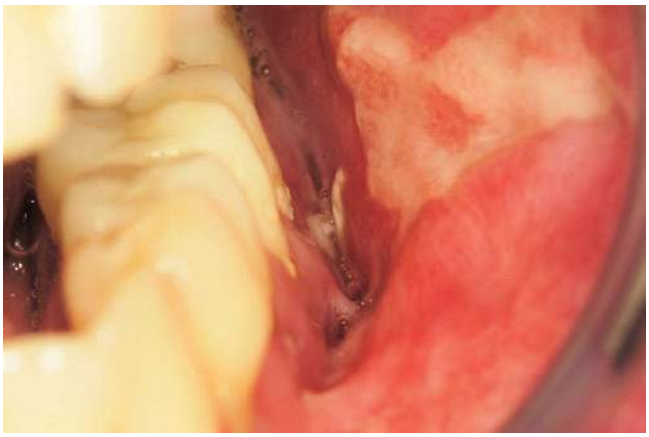

Fig. 10.2 Oral ulcer, Courtesy of Dr. James J. Sciubba, Johns Hopkins University

Skin Lesions

Cutaneous manifestations of IBD can be classified into three principal groups: granulomatous, reactive, and secondary to nutritional deficiency. Granulomatous skin manifestations have the same histological features as the bowel disease and can include perianal and peristomal ulcers and fistulas, oral granulomatous ulcers, epidermolysis bullosa acquisita, and metastatic Crohn disease. The latter is a rare complication that manifests as subcutaneous nodules or ulcers mainly in the lower extremities and on occasion can occur in the genital areas. The lesions have a heterogenous presentation including erythematous and violaceous plaques, nodules, ulcerations, crusts, and erosions including the knife-cut sign describing linear ones [44]. It appears unrelated to bowel activity and can be treated successfully with corticosteroids, antibiotics, azathioprine, methotrexate, and biologics [15]. Epidermolysis bullosa acquisita is seen mostly in Crohn's patients and secondary to antibodies against tyle VII colla-

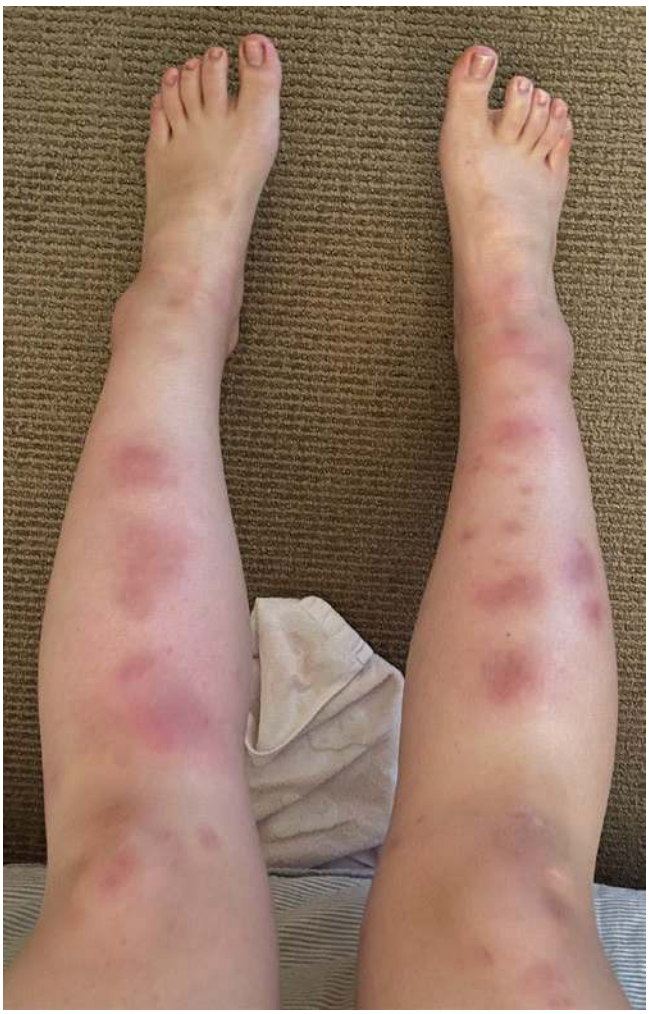

Fig. 10.3 Erythema nodosum

Fig. 10.4 Pyoderma gangrenosum, Courtesy of Dr. Anna L. Grossberg, Johns Hopkins University

gen. Patients have skin fragility, blister formation, and scarring. The antibodies may be related to bowel inflammation and hence treatment involves improvement in the active intestinal disease [45].

Of all the skin manifestations associated with IBD, erythema nodosum (Fig. 10.3) and pyoderma gangrenosum (Fig. 10.4) are the most common. However, in the pediatric patient, erythema nodosum, which is more commonly associated with Crohn disease than with ulcerative colitis, is encountered more frequently [1]. Erythema nodosum presents as tender, subcutaneous, erythematous nodules, usually on the extremities, especially the lower legs and the majority of patients with this skin manifestation will have associated joint pain or develop arthritis. Children may appear systemically ill with fever. Over days to weeks, the nodules will flatten, turn brown, or gray and can be mistaken for bruises. Histologically, erythema nodosum is a septal panniculitis consisting of a lymphohistiocytic infiltrate. The prevalence in all IBD patients, adult and pediatric, is estimated between 3% and 15% [34]. Erythema nodosum appears more significantly in women and Hispanics who have an adjusted odds ratio of 3 and 3.3, respectively, compared to Caucasian counterparts [29]. Exacerbations of erythema nodosum correlate most often with increased intestinal inflammation; hence, treatment toward the bowels is considered a primary form of management. Recent reports in children have shown good response to infliximab [29].

Pyoderma gangrenosum is an ulcerating lesion often correlating with exacerbations of the bowel disease; however, it can persist for long periods, while the intestinal inflammation is clinically quiescent. Fortunately, it is relatively rarely associated with IBD with a reported incidence of 2% in UC patients and a smaller number in Crohn's patients [45]. The lesions are often painful and located on the lower extremities. Histopathology reveals endothelial injury with fibrinoid necrosis of blood vessels and marked neutrophilic and lymphocytic infiltrates. Treatment is difficult and patients may require large doses of systemic corticosteroids or immunomodulators as well as topical ulcer care. Infliximab and other TNF antagonists have been shown to be effective in refractory cases; however, some extreme cases might require grafting [30, 46]. There are scant reports of response to vedolizumab,

ustekinumab, and tofacitinib, the latter especially as there may be upregulation of the JAK-STAT pathway in both erythema nodosum and pyoderma gangrenosum [30, 32].

Sweet's syndrome is another very rare reactive cutaneous disorder associated with IBD. It is a neutrophilic dermatosis presenting with painful erythematous plaques or nodules often associated with fever and leukocytosis. Usually, there is a good response to corticosteroids and a study has demonstrated the benefit of cyclophosphamide in steroid refractory patients [47].

Psoriasis can be seen commonly (7–11%) in patients with IBD [45]. The link and therapeutic overlap suggests common inflammatory pathway, genetics, and pathogenesis. Therapy-related psoriasiform skin lesions have also been reported in patients undergoing TNFα antagonist therapy. Anti-IL-12/IL-23 therapy may have a role in treatment of these patients from an intestinal and skin standpoint [45].

Nutritional issues, such as trace mineral and vitamin deficiencies, can be common in children with IBD, especially Crohn disease; however, skin disorders secondary to these are unusual. There are rare reported cases of acrodermatitis enteropathica, pellagra, and scurvy secondary to zinc, niacin, and vitamin C deficiency, respectively.

Vulvar lesions have also been associated with IBD with patients presenting with vulvar ulcers, labial swelling, exophytic lesions, condylomatous lesions, and abnormalities on pap smear. Most often the histopathology demonstrates non-caseating vulvar granulomas, but dysplasia and carcinoma have also been reported [48].

Eye Lesions

Eye manifestations in IBD patients can be classified into inflammatory and vascular disorders [49]. Inflammatory conditions include uveitis, episcleritis, orbital myositis/pseudotumor, optic neuritis, and dacryoadenitis. Vascular disorders usually result from an inflammatory etiology, possibly retinal vasculitis leading to reported conditions of retinal artery or vein occlusion. There is a reported lower prevalence of ocular involvement in children (0.6–1.8%) with IBD than in adults with IBD [49]. The most common eye manifestation of IBD is episcleritis [15]. Episcleritis (Fig. 10.5), inflammation of the blood-rich episclera, may parallel bowel activity and is often confused with conjunctivitis as the patients present with eye redness and burning. It is the most common ocular manifestation. Episcleritis does not impair vision and usually responds clinically to cool compress, lubricant eye drops, topical non-steroidal anti-inflammatory medications, and topical corticosteroids. If visual impairment or pain is present, the possibility of scleritis, which can occur with protracted intestinal disease, needs to be considered and an emergent evaluation by an ophthalmologist is required to evaluate for retinal detachment or optic nerve swelling. Scleritis needs systemic treatment with steroids or immunosuppressants [50].

Fig. 10.5 Episcleritis, Courtesy of Dr. Rachel Nussbaum, Johns Hopkins University

Uveitis is defined as inflammation of the uveal tract or middle layer of the eye which includes the iris, ciliary body, and choroid. Its prevalence seems to increase with time post-IBD diagnosis and is unrelated to the patient's age of disease onset [49]. An evaluation of 147 children with IBD who had no ophthalmologic complaints revealed a prevalence of uveitis of 6.1% in those with Crohn disease [51]. African Americans have a 5.5-fold adjusted odds ratio compared to Caucasian counterparts [29]. Uveitis, is often associated with other EIMs, especially arthritis and erythema nodosum and likely does not correlate with intestinal disease activity [50]. Symptoms can include acute or subacute eye pain, headache, photophobia, and blurred vision or occasionally decreased vision; however, many patients may be asymptomatic. Recognition and appropriate treatment can help prevent complications which can be serious and include iris atrophy, synechiae, pigment deposits, glaucoma, cataracts, and permanent visual deficits. Attention must be paid for early signs of uveitis which can include a cellular or proteinaceous exudate of inflammatory cells in the anterior chamber of the eye. Like scleritis, acute anterior uveitis is an ophthalmologic emergency. Treatment involves covering the eye to reduce pain and photophobia, pupillary dilatation, and use of topical for milder cases. More aggressive disease can require systemic corticosteroids, as well as immunomodulator and biologic regimens, with more data for TNF antagonists [30].

Liver Disease

Liver pathology, including hepatitis, fatty liver, cholelithiasis, amyloidosis, and primary sclerosing cholangitis, is found in less than 5–10% of patients with IBD [1]. Screening with periodic checks of serum aminotransferases, alkaline phosphatase, gamma-glutamyl transferase, and direct bilirubin is necessary as many of the children with liver disease are asymptomatic. A more extensive review of this EIM can be found in another chapter devoted to liver disease in pediatric IBD.

Other Extraintestinal Manifestations

Many other systems, listed below, have had reported involvement in IBD but they have been reported to occur in less than 1% of pediatric IBD patients [1].

Hematologic Abnormalities

Anemia, thrombocytosis, and leukocytosis are common hematologic abnormalities in IBD patients and can be seen in up to half the patients with active disease [1]. Usually, the anemia is secondary to iron, vitamin B12, and folic acid deficiency as well as anemia of chronic disease. The thrombocytosis is postulated to result from circulating inflammatory cytokines that stimulate platelet production. Similarly, leukocytosis can occur as a result of generalized inflammation. On the other hand, patients should be monitored for leucopenia with certain therapies such as use of thiopurine immunomodulators (e.g., 6-mercatopurine or azathioprine).

Vascular

Patients with IBD have been reported to have a threefold increased risk of venous thrombosis compared to matched controls [52]. Interestingly, this increased risk is specific for IBD as it is not seen with other inflammatory conditions such as rheumatoid arthritis or other bowel disorders such as celiac disease. Deep venous thrombosis and pulmonary embolism are the most common complications resulting from an overall increased coagulation. Coagulation factors may be elevated as part of an acute phase response. Factor V Leiden, a genetic disorder characterized by an impaired anticoagulant response to protein C leading to a prothrombotic state, may be increased in Crohn's patients [53]. Furthermore, IBD patients might have higher levels of homocysteine, which can be a potential cause of thrombosis [53]. Awareness of the risk of thrombosis is even more important with the approval of tofacitinib for ulcerative colitis in adults given the recent link of this medication with certain vascular side effects. Another vascular complication, arteritis of small or large vessels, has been reported in children with IBD [54].

Pancreatitis

The incidence of pancreatic involvement in IBD varies but estimated to be 0.7–1.6% in children [55]. The most likely etiologies are medications, anatomic, immunologic, or gallstones secondary to ileal disease. Although patients with IBD appear to have a small increased risk for idiopathic pancreatitis, the most common cause of pancreatitis in IBD appears to be associated with medications such as 5-aminosalicylate preparations or 6-mercaptopurine. As this is presumed to be an idiosyncratic reaction, discontinuation of the medication is indicated. Although pancreatic autoantibodies have been found been found in up to 40% of Crohn's patients, their significance remains unclear. In one series, patients with Crohn disease who were pancreatic antibody positive had a higher rate of pancreatic exocrine insufficiency than those who were antibody negative [12]. Furthermore, chronic pancreatitis has also been reported in a series of six adult IBD patients, five of whom had changes on pancreatic pathology samples [56]. Autoimmune pancreatitis, some with elevations in IgG4, has been rarely reported in children and adults with IBD [57].

Renal

Children with IBD appear to be at risk for kidney abnormalities. A small study of pediatric IBD patients reported that 25% of patients had either previously reported kidney disease or ultrasound signs of chronic kidney disease [58]. IBD patients, especially those with extensive ileal disease or ileal resection with significant fat malabsorption or fluid losses, are at risk for developing calcium oxalate and uric acid stones. Although uncommon in children, nephrolithiasis is reported in 12–28% of adults with IBD compared to 5% of the general population [59]. Tubular injury and tubulointerstitial nephritis, unrelated to medications, can be seen as an EIM in IBD as well. Patients typically recover fully post-treatment of their IBD. Glomerulonephritis with immune complex deposition can also be seen which can progress to severe renal disease. The most common type is IgA nephropathy which is associated with HLA-DR1 [59]. Treatment is focused on controlling IBD inflammation though specific renal treatment may be needed in some patients. Other renal diseases, described in children with IBD, include renal artery stenosis, amyloidosis leading to renal failure, ureteral compression, and perinephritic abscesses secondary to abscesses or inflammation surrounding the terminal ileum [60]. Most IBD treatments have nephrotoxic adverse effects. Nephritis (tubulointerstitial or interstitial) has been reported with aminosalicylates, thiopurines, and vedolizumab. TNF antagonist medications, especially infliximab, have been linked to glomerulonephritis in a small subset of patients.

Pulmonary

Pulmonary manifestations associated with IBD are reported less frequently in children than adults, although the scope of disorders is similar. Nearly 10% of children with IBD reported respiratory related quality of life issues on a ques-

tionnaire [61]. Reactive airway disease, bronchitis, bronchiectasis, tracheal obstruction, granulomatous lung disease, interstitial or hypersensitivity pneumonitis, and bronchiolitis obliterans are being reported at an increasing frequency [12, 15, 62–64]. However, the latter two have been associated with 5-aminosalicylate products and methotrexate treatment [12, 64]. Similar to other extraintestinal manifestations, pulmonary disease can predate the bowel disease by months or years. Most pulmonary manifestations respond to corticosteroids via an inhaled, oral, or intravenous route.

Neurologic

Peripheral nerve disorders, cardiovascular disorders, myopathy, multiple sclerosis, optic neuritis, and epilepsy have been described in IBD patients [65]. Peripheral neuropathies are the most common neurologic disorder reported, while cardiovascular disorders with neurologic morbidities have been documented in up to 4% of patients [66]. A retrospective cross-sectional study of adult patients with IBD reported an odds ratio of 1.67 for developing multiple sclerosis, optic neuritis, or a demyelinating disorder [12]. An interesting future focus will center around the role of medication treatments for IBD and neurologic adverse events especially given the risk of progressive multifocal leukoencephalopathy related to anti-alpha 4 integrin antibody, natalizumab.

Cardiac

Rarely children with IBD can develop myopericarditis and pleuropericarditis with symptoms of chest pain and dyspnea. Cardiac manifestations are not necessarily associated with active bowel disease and respond to corticosteroids and nonsteroidal anti-inflammatory agents, which need to be used with caution in IBD patients. An active area of research is the risk of cardiovascular events in patients with IBD. A recent study showed an increase in incidence in coronary artery disease in adults with IBD [67]. Interestingly, the IBD patients had significantly lower rates of traditional coronary artery disease risk factors such as hypertension, diabetes, obesity, and dyslipidemia. Further work will help determine the effect of various treatments on decreasing risk of cardiac disease.

Summary

Given that Crohn disease and ulcerative colitis are associated with numerous EIMs, it is clearly evident that IBD is a multisystemic disease that stretches beyond the gastrointestinal tract. Knowledge about EIMs is critical as patients can present with these instead of more classic bowel symptoms. Furthermore, the EIMs associated with IBD can be a cause of major morbidity in patients and need to be considered and addressed at all points of care.

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Liver Disease in Pediatric Inflammatory Bowel Disease

11

Rebecca Little, Binita M. Kamath, and Amanda Ricciuto

Introduction

Diseases involving the hepatobiliary system are among the most common extraintestinal manifestations of inflammatory bowel disease (IBD). They can be classified into a few broad categories: (1) liver diseases that may share a common pathogenic mechanism with IBD, such as primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), and PSC/AIH overlap, also known as autoimmune sclerosing cholangitis (ASC); (2) liver diseases that reflect the pathophysiology of IBD, such as cholelithiasis and portal vein thrombosis; and (3) liver diseases that result from the adverse effects of IBD therapy, such as drug-induced hepatitis [1]. In addition, an association has been noted between a number of other less common hepatobiliary diseases and IBD, including IgG4-associated cholangitis (IAC). Some of the conditions listed above are observed more frequently in Crohn disease (CD) or ulcerative colitis (UC), while others occur at similar rates in both types of IBD (Table 11.1). Liver enzyme abnormalities are common in IBD and, while often transient and inconsequential, deranged hepatic biochemistry may herald serious underlying liver disease, such as PSC. The challenge lies in determining which patients merit further work-up versus observation. No standardized algorithm exists to guide clinicians in this decision-making process, particularly in children, in whom there is a relative paucity of data. This chapter strives to facilitate this task by providing an overview of liver disease occurring in association with pediatric IBD.

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Table 11.1 Hepatobiliary diseases associated with pediatric IBD

Hepatobiliary disease	Ulcerative colitis	Crohn disease
Primary sclerosing cholangitis (PSC)	++	+
Autoimmune hepatitis (AIH)	++	++
Autoimmune sclerosing cholangitis (ASC)	++	+
IgG4-associated cholangitis (IAC)	++	+
Cholelithiasis	–	++
Portal vein thrombosis and hepatic abscess	+	++
Drug-induced hepatitis	++	++
Hepatitis B reactivation (anti-TNFα)	++	++
Hepatosplenic T-cell lymphoma	+/–	+
Fatty liver	++	++
Hepatic amyloidosis	–	++
Granulomatous hepatitis	–	++
Primary biliary cholangitis (PBC)	++	–

Abnormal Liver Chemistry

Abnormal liver chemistry is common in IBD. Liver enzyme abnormalities (any value exceeding the upper limit of normal (ULN)) have been reported in 15–40% of adults with IBD over 1–5 years of follow-up [2–4], with more marked elevations (>2× the ULN) occurring in 5% [2]. Abnormal liver biochemistry appears to be similarly frequent in pediatric IBD. Nemeth described "pathological liver function tests" in 52% of his 46-patient cohort in 1990 [5], and similar findings have since been reproduced by two large retrospective pediatric studies, in which at least one liver enzyme elevation was observed in 40–60% of children with IBD over 3 years [6, 7], even after excluding patients with PSC/ASC. No differences were observed between patients with CD and UC. Liver enzyme elevations >2× the ULN occur in a smaller proportion of children, roughly 15–30% [7, 8]. The pattern of biochemical injury is typically hepatocellular, but can be mixed or, less commonly, cholestatic [4, 6]. ALT is the most frequently abnormal test [7], with the caveat that ALT also

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tends to be measured more often than other tests, like GGT. The majority of these biochemical abnormalities are mild, transient, and benign in nature [4, 6–8]. The degree of transaminase elevation appears to correlate with the likelihood of identifying underlying liver disease; in one study, 95% of children with peak ALT <2× ULN were found to have no specific liver disease [6], and conversely, in another study, 93% of children with PSC or ASC had liver enzymes 2× the ULN or greater, sustained for 30–90 days [7]. In this latter study, GGT was found to be particularly useful for identifying PSC/ASC, with a value of 252 U/L having a sensitivity of 99% and specificity of 77% for PSC or ASC [7].

Well-defined chronic liver disease (PSC/ASC and AIH) accounts for only 1.4–6% of elevated liver enzymes in pediatric IBD, whereas a majority of cases remain idiopathic [6, 7, 9]. The most common etiology, when one is identified, is drug toxicity [2, 6, 8]. In children, steroids, antibiotics, methotrexate, anti-tumor necrosis factor-α (anti-TNFα), as well as exclusive enteral nutrition, have been associated with liver enzyme abnormalities [7]. Conversely, liver enzyme abnormalities appear to be less frequent in children taking 5-ASA and sulfasalazine, although these agents may simply be surrogates for milder IBD [3, 7]. Other less common causes of deranged hepatic biochemistry in pediatric IBD include infection (particularly CMV and EBV), nonalcoholic fatty liver disease (NAFLD), cholelithiasis, and vascular abnormalities [6]. Active IBD has also been proposed as a cause of abnormal liver enzymes, but the evidence is conflicting; several studies lend support to this hypothesis [4, 8, 10], while others refute it. One such study in adults found a higher prevalence of liver enzyme abnormalities in patients in remission compared to those with active IBD [3]. In children, biochemical abnormalities do not appear to be associated with IBD duration or extent [5, 6, 9]. With regard to prognosis, death was found to be 4.8 times higher in adults with abnormal liver biochemistry, even after excluding those with any diagnosis of liver disease [3]. No equivalent pediatric data exist.

In summary, abnormal liver biochemistry is common in children with IBD. Most cases are mild and resolve spontaneously, and such cases tend to be associated with undefined etiologies. However, a small subset of patients with more severe, prolonged derangements have serious disease or medication adverse effects. Given this, it seems reasonable to adopt a period of watchful waiting in patients with mild elevations (<2× the ULN) unless there are overt signs of underlying liver disease. More marked or persistent (>1 month) abnormalities may warrant further investigation. We suggest obtaining a liver biochemical panel, including ALT and GGT, in all newly diagnosed IBD patients and repeating this at least every 6–12 months for surveillance.

Primary Sclerosing Cholangitis

Epidemiology and Pathogenesis

Primary sclerosing cholangitis (PSC) is a chronic, progressive, cholestatic liver disease characterized by inflammation and obliterative fibrosis of the intrahepatic and/or extrahepatic biliary tree, resulting in multifocal strictures and dilatation. It is a rare disease, with an incidence and prevalence of 0.1–0.2 and 1.5 per 100,000 children, respectively, which is substantially lower than in adults [11–13]. Pediatric PSC typically presents in the second decade of life and has a modest male predominance, as in adults [12, 14–16]. The link between PSC and IBD has been known for greater than five decades [17]. As many as 60–80% of adults with PSC in North America and Northern Europe have IBD, primarily ulcerative colitis (UC) [18, 19]. The prevalence of IBD in children with PSC is also very high, >50% in most series and up to 97% in a recent population-based study [12, 14, 16, 20, 21]. Conversely, only a minority of children with colitis, <10% in most series, have or develop concurrent PSC [7, 12, 21, 22]. A Norwegian study highlighted that screening MRCP performed in 322 patients with established IBD identified PSC-like lesions in 7.5% of patients, of whom only 2.2% were known to have PSC [23]. Adjusting for missed diagnoses and small duct disease, the overall incidence is 8.1%, around threefold higher than initially detected based on symptoms [23]. Subclinical PSC associated with IBD was detected on MRCP in sixty-five percent of patients in the absence of biochemical abnormalities and mild disease [23].

Most patients are found to have PSC within a year of their IBD diagnosis [12], but the two can occur years apart. PSC can manifest first, in which case a full colonoscopy is recommended at PSC diagnosis to screen for IBD [24].

The pathogenesis of PSC remains incompletely understood. Genome-wide association studies have identified a number of HLA and non-HLA risk loci [25, 26], some of which are shared with IBD, and a hallmark paper in 2004 reported an accumulation of gut-homing CCR9-positive T-cells in explanted human livers of patients with PSC [27], findings that point to both a genetic and immunological basis for PSC. In addition, there is growing evidence for the role of the "gut-liver" axis in the pathogenesis of PSC. Several animal models and human tissue-based translational studies support that enteric microbial products/dysbiosis can lead to PSC-like hepatobiliary inflammation [28]. Mucosal biopsy cultures have identified enriched taxa levels of several organisms including *Pseudomonas, Streptococcus,* and *Haemophilus* species as well as alterations in beta diversity in patients with PSC-IBD compared with healthy controls and conventional UC [29–33]. Similarly, enriched fecal microbiota levels of *Veillonella* and *Enterococcus* species

have been reported [34, 35]. *Klebsiella pneumoniae* strains derived from gnotobiotic mice transplanted with PSC-IBD microbiota were found to induce pore formation in human intestinal epithelial cells and enhanced Th17 response thus adding credence to the role of heightened immune response to enteric dysbiosis in PSC-IBD pathogenesis [36]. The gut microbiota in PSC/PSC-IBD patients may further exert a pathogenic influence through their role in bile acid synthesis. Deconjugation of the primary bile acids (BA), cholic acid (CA), and chenodeoxycholic acid (CDCA), by gut microbes produces secondary Bas, predominantly lithocholic acid (LCA) and deoxycholic acid (DCA). Secondary Bas function as signaling molecules via their interaction with the nuclear receptor Farnesoid X receptor (FXR) and the membrane-bound G protein-coupled bile acid receptor-1 TGR5 [37]. Agonism of these receptors exerts important cholangioprotective and anti-inflammatory effects. Two recent small studies of fecal BA profiles in patients with PSC-IBD compared to conventional IBD have identified a significant reduction in total BA pool, more conjugated Bas, lower DCA/CA ratio, and a lower relative abundance of bacteria known to be actively involved in BA synthesis (12% in PSC-IBD compared with 0.4% IBD) [38, 39]. A recent pilot study evaluating microbial metagenomic alterations in PSC-IBD versus UC and differentially expressed genes between these two groups implicated dysregulation of bile acid (BA) metabolism in PSC-IBD [30]. Multi-omics integration identified upregulated networks involved in bile acid homeostasis and cancer pathway regulation.

Primary Sclerosing Cholangitis and IBD

There is growing evidence that the intestinal inflammation in individuals with PSC and colitis constitutes a distinct IBD phenotype, termed PSC-IBD. This phenotype has been well characterized in adults as extensive colonic involvement, often worse on the right, and relatively frequent "backwash ileitis," rectal sparing, and an increased rate of pouchitis post colectomy [40, 41]. Figure 11.1 highlights the apparent disconnect between the extensive disease distribution and the mild clinical course of PSC-IBD. Crohn disease (CD) is uncommon in the setting of PSC, but, when it does occur, it too tends to have an extensive colonic distribution; isolated small bowel, perianal, and fistulizing disease are very uncommon [42]. Despite the extensive nature of the colonic inflammation, PSC-IBD tends to have a relatively mild clinical course with a paucity of overt clinical symptoms [43, 44].

Findings analogous to those in adults have been reported in a large retrospective pediatric series in which 74 children with PSC-UC/IBD-unclassified (IBD-U) were compared to colitis controls [45]. This study identified growth impair-

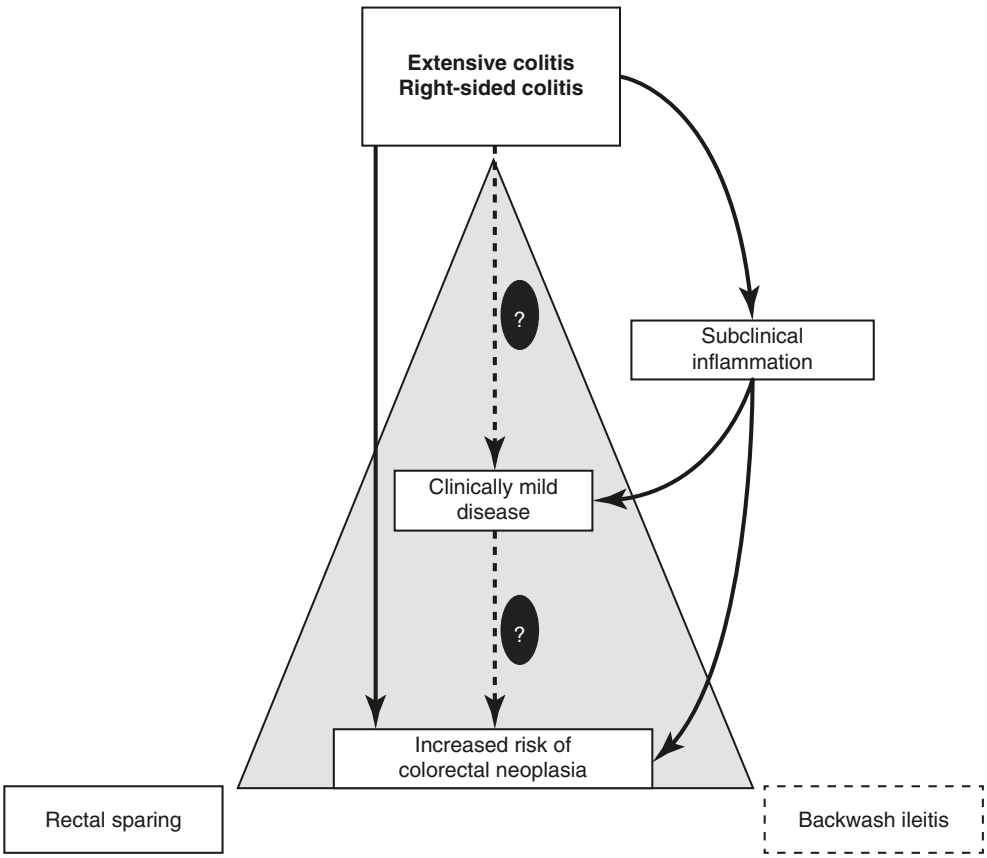

Fig. 11.1 The IBD phenotype of PSC-IBD, highlighting the apparent disconnect between the extensive disease distribution/increased risk of colorectal cancer and mild clinical course, and the way in which subclinical inflammation might bridge these inconsistencies [52]. Reprinted with permission from Springer Nature

ment as a novel pediatric-specific phenotypic feature of PSC-IBD compared to conventional UC. In a separate prospective study from the same center, subclinical inflammation (active endoscopic disease in the absence of significant symptoms) was found to be much more common in children with PSC-IBD compared to those with UC without PSC [46]. Unlike symptom report, fecal calprotectin, a stool biomarker of intestinal inflammation, was found to be highly accurate for endoscopic healing in this pediatric PSC-IBD cohort.

The interplay between IBD and PSC remains to be elucidated. Interestingly, adults with severe PSC requiring liver transplant (LT) have been found to have milder UC than patients with less severe liver disease [47]. Studies have also suggested that IBD activity may worsen following LT for PSC, despite heightened immunosuppression [48]. Furthermore, while it has long been maintained that PSC and IBD progress independently, as supported by older studies indicating that the natural history of PSC is unaffected by colectomy [49], more recent findings suggest that colectomy may reduce the risk of PSC recurrence post-LT [50]. In line with this, studies have suggested that moderate to severe active IBD post-LT constitutes a risk factor for recurrent PSC [51]. The interaction between PSC and IBD, including the effect of ongoing colonic inflammation on PSC progression, if any, requires further clarification.

Diagnosis

The diagnosis of PSC in a child is based on a compatible clinical presentation and biochemistry, with characteristic changes on cholangiography and/or liver biopsy, after excluding secondary causes of sclerosing cholangitis [53]. The most common presenting symptoms and signs are hepatomegaly and abdominal pain, followed by diarrhea, splenomegaly, fatigue, pruritus, weight loss, impaired growth, and jaundice. The presenting features may also, uncommonly, be those of advanced liver disease, such as gastrointestinal bleeding and cholangitis, or those of associated colitis, especially bloody diarrhea [53]. A substantial subset of children with PSC is asymptomatic at presentation and come to medical attention solely due to deranged liver biochemistry. Transaminases are often modestly elevated, with a predominantly cholestatic pattern. GGT is more reliable in children as ALP elevations may reflect bone growth. The odds of PSC are 660-fold greater in children with ALT and GGT elevations >50 U/L within 3 months of IBD diagnosis compared to children whose values remain <50 U/L [9]. INR, albumin, and conjugated bilirubin, which reflect synthetic function, are generally normal at presentation. Elevated conjugated bilirubin may signal a stricture, cholangitis, or a mass, and warrants further work-up. Serum immunoglobulin G (IgG) levels may be elevated, and a variety of autoantibodies may be present, the most common of which is antineutrophil cytoplasmic antibody (ANCA), usually with an atypical perinuclear ("p") pattern, which is found in up to 80% of patients. None of these are specific to PSC, however [12, 24]. Serum IgG4 should be measured at least once in children with PSC. An elevated IgG4 may denote IgG4-associated cholangitis (IAC), which has important implications, given its favorable response to corticosteroids [53].

Ultrasound is a reasonable initial imaging modality; it may reveal bile duct wall thickening, focal bile duct dilatation, and/or gallbladder changes, including wall thickening, enlargement, cholecystitis, and mass lesions. It is also useful for ruling out alternate etiologies. However, none of these findings are diagnostic, and ultrasound may be normal in the setting of PSC [24]. Cholangiography, preferably by magnetic resonance cholangiopancreatography (MRCP), which has supplanted endoscopic retrograde cholangiopancreatography (ERCP) as the first-line diagnostic imaging modality due its less invasive nature and lower cost, is a vital component of the PSC diagnostic work-up [23, 54, 55]. Characteristic cholangiographic findings include multifocal, short strictures alternating with normal or dilated segments, producing a "beaded" appearance (Fig. 11.2) [24]. The gallbladder, cystic duct, and pancreatic duct may also be abnormal [56]. Contrary to adult practice, a liver biopsy is often performed in a child with suspected PSC given the more frequent occurrence of autoimmune sclerosing cholangitis (ASC), which is typically treated with immunosuppressive therapy (although definitive evidence that this is associated with improved outcomes is lacking). A liver biopsy is also useful to diagnose small-duct PSC, a label applied to cases

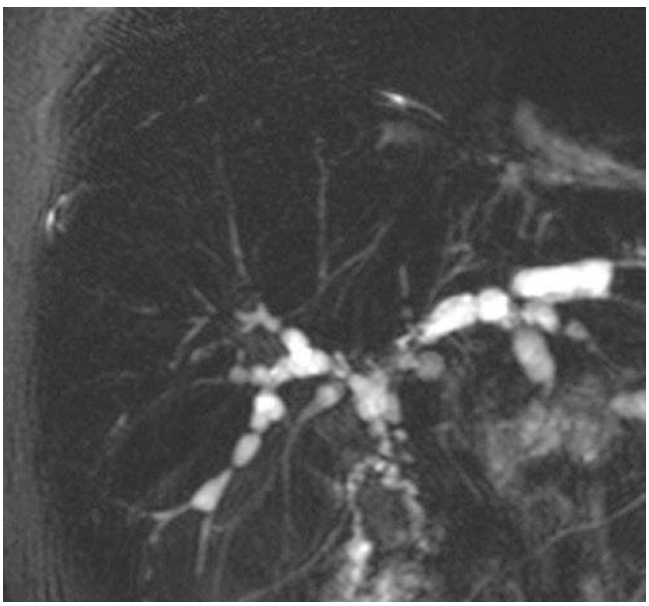

Fig. 11.2 Cholangiographic appearance of PSC with typical "beading"

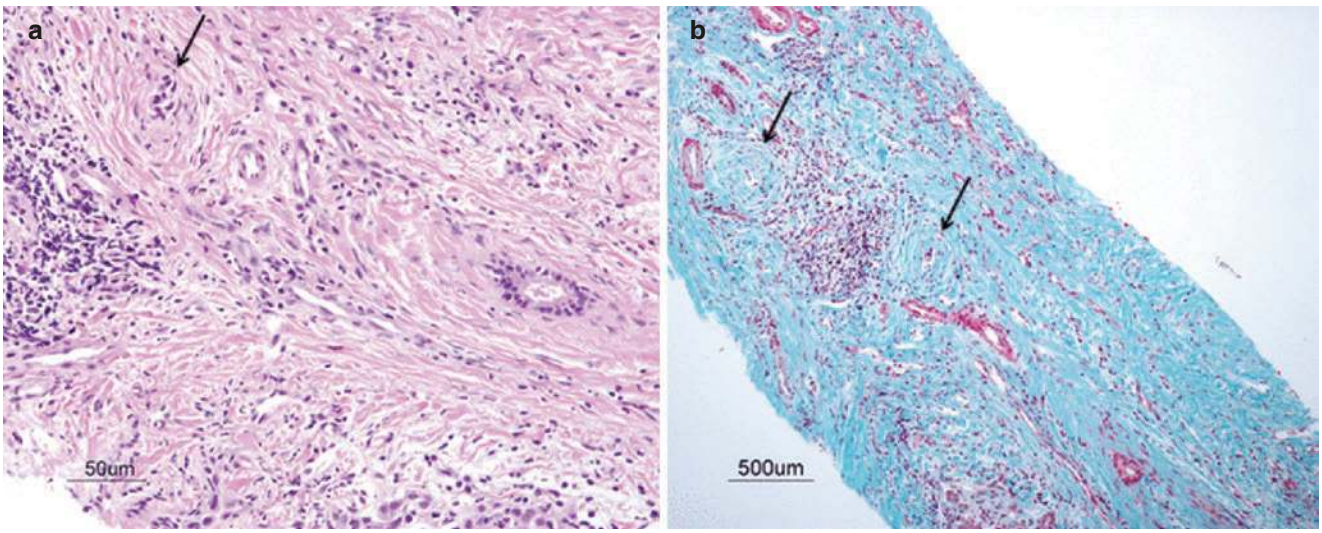

Fig. 11.3 Liver biopsy showing typical histological changes of PSC, including periductular concentric fibrosis denoted by the arrows with (**a**) H&E and (**b**) trichrome staining

with compatible histological changes but without cholangiographic abnormalities, and to stage the degree of fibrosis. Periductular concentric fibrosis, or "onion-skinning" (Fig. 11.3), is pathognomonic for PSC, but not always observed. Other, nonspecific findings may include ductular proliferation or periductular inflammation, with variable types of portal inflammation and fibrosis. Liver biopsy may also be normal in PSC given its patchy nature. The diagnostic work-up for suspected PSC in children is illustrated in Fig. 11.4.

Outcomes

PSC is one of the most important sources of morbidity and mortality in IBD, but few studies have examined its natural history in children. In 2017, the Pediatric PSC consortium published a large multi-center, retrospective international study of long-term outcomes in 781 children with PSC [57] with time to event analysis across key outcomes, including portal hypertension, biliary complications, cholangiocarcinoma, liver transplant, and death. In this study, the development of portal hypertension and biliary complications marked pivotal points in the natural history of pediatric PSC and occurred in 38% and 25% of patients, respectively, over 10 years of follow-up. The median survival with native liver (SNL), once portal hypertension and biliary complications occurred, was 2.8 and 3.5 years, respectively [57]. Overall event-free survival was 70% at 5 years and 53% at 10 years of follow-up [57]. Fourteen percent of children underwent LT at a median age of 15 years, a median of 4 years following PSC diagnosis. Long-term outcome data for pediatric-onset PSC into adulthood are lacking. Unfortunately, recurrence post-LT occurs in about 10–25% of cases [13, 58, 59]. Survival is significantly shorter in children with PSC compared to age- and sex-matched children, although absolute mortality rates are low during the pediatric period, 1.4% in the Pediatric PSC Consortium [57]. Lower platelet count, high bilirubin, higher GGT, splenomegaly, and older age at diagnosis are associated with shorter survival [57]. GGT nor-

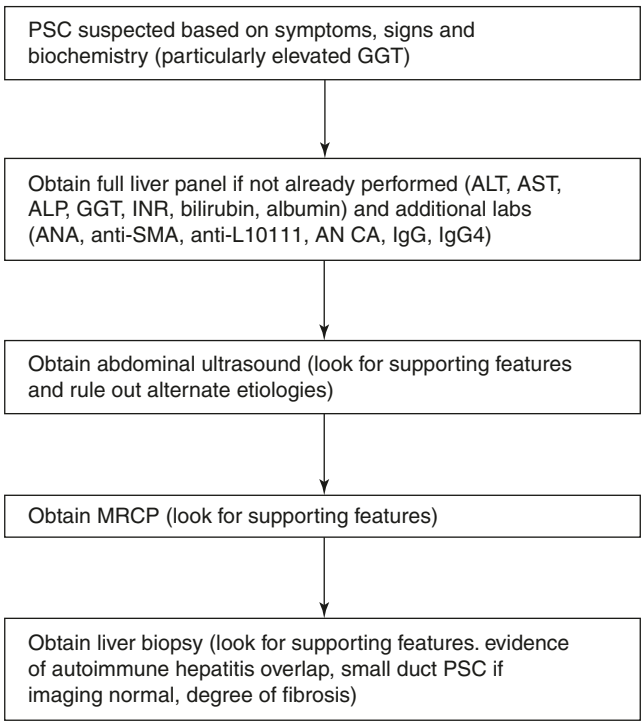

Fig. 11.4 Diagnostic work-up for suspected pediatric PSC. *ANA* antinuclear antibody, *ANCA* antineutrophil cytoplasmic antibody, *LKM1* liver kidney microsomal type 1, *MRCP* magnetic resonance cholangiopancreatography, *PSC* primary sclerosing cholangitis, *SMA* smooth muscle antibody

malization at one year, on the other hand, has been associated with favorable outcomes, regardless of ursodeoxycholic acid use [60].

Adults with UC and PSC have an almost five times greater risk of colorectal neoplasia compared to adults with UC alone [61]. While data on the risk of colorectal neoplasia in PSC-IBD during the pediatric period are sparse, the absolute event rates appear to be low, particularly before puberty. In the Pediatric PSC Consortium, there were eight cases of colorectal dysplasia/carcinoma among 509 children (1.6%) with PSC-IBD, including three discovered incidentally on colectomy for medically refractory IBD [62]. Surveillance colonoscopies every 1–2 years from the time of diagnosis are recommended in adults [24]. No equivalent pediatric guidelines exist, but it seems reasonable for similar screening practices to be applied to older children and teenagers. There is a markedly increased risk of cholangiocarcinoma (7–9%) in adults with PSC [63–65], but this malignancy is exceedingly rare (1%) in children [57]. Nevertheless, a handful of cases have been reported in older teenagers [66]. While adult guidelines suggest consideration be given to screening for cholangiocarcinoma with regular cross-sectional imaging and CA 19–9, this is not routinely recommended in children [24, 54]. However, based on clinical experience and expert opinion, the authors suggest an ultrasound yearly, an MRI every 2 years, and CA 19–9 levels yearly in children with PSC to screen for cholangiocarcinoma.

Small-duct PSC may have a more favorable prognosis than classic PSC. It has been associated with a longer transplant-free survival in adults, and there have been no reports of cholangiocarcinoma occurring with small-duct PSC. However, small-duct PSC can progress to classic PSC with cholangiographic abnormalities over time, and it can recur post-LT [67]. It is unclear whether small-duct PSC represents an early stage of classic PSC or a distinct entity. The Pediatric PSC Consortium recently developed a clinical risk score, termed the SCOPE index (which includes total bilirubin, albumin, platelets, GGT and large duct involvement), for use specifically in pediatric PSC [68]. The tool demonstrates excellent predictive ability for adverse events at 1 and 5 years and correlates strongly with biopsy-proven liver fibrosis. It also outperforms other tools developed in adult populations, such as the Mayo Risk Score.

Treatment

Data pertaining to the medical management of PSC in children are scarce, and current practices largely derive from adult studies. No medical therapy currently exists to reverse or halt the progression of PSC liver disease. As such, treatment is mainly supportive. Although numerous aspects of PSC invoke an autoimmune basis for the disease, thus far, no single immunosuppressive or immune-modulating agent has been found to be efficacious [69].

Ursodeoxycholic acid (UDCA) is widely used in adults and children with cholestatic liver disease, including PSC. Although biochemical improvement has been demonstrated in children, a beneficial effect on the natural history of PSC, as reflected by a decrease in mortality and/or LT rates, has never been shown [14, 70, 71]. Similarly, adult studies have documented improvements in biochemistry, but not in hard outcomes [72]. Furthermore, the use of high-dose UDCA >28 mg/kg has been associated with a twofold increased risk of death/transplant [73] and a fourfold increased risk of colorectal cancer in adults [74, 75]. There is no consensus regarding the use of UDCA in adults with PSC, with one expert group advising against its use entirely [76] and another merely recommending against the use of high doses [54]. In light of this, it appears prudent to avoid high-dose UDCA in children with PSC, but continued use of low-to-moderate doses, not exceeding 20 mg/kg/day, is reasonable.

There has been substantial interest in the use of oral vancomycin therapy (OVT) for treating pediatric PSC [71, 77–82]. Oral vancomycin's therapeutic effect may occur through immunomodulation, by increasing transforming growth factor-β (TGF-β) and peripheral levels of regulatory T-cells [81, 83]. However, most studies (excluding small uncontrolled case reports/case series) have shown only biochemical benefit [82]. In an open label study of OVT, with a median treatment duration of 2.7 years, 96%, 81%, and 95% of patients experienced reduction of GGT, ALP, and ALT, respectively [82]. Yet, when OVT was compared to UDCA or observation alone in a propensity score-matched analysis from the Pediatric PSC Consortium, OVT was not associated with superior outcomes [71]. Limited data in the form of case series suggest possible benefit of OVT for the IBD in PSC-IBD [84]. Overall, more rigorous, clinical trial data are needed to ascertain the role of OVT in treating PSC and PSC-IBD. Metronidazole and minocycline, but not rifaximin, have also been associated with improved liver biochemistry in adults with PSC [85–87]. At the current time, the use of oral antibiotics for pediatric PSC remains experimental, as a benefit beyond biochemical improvements has yet to be confirmed. The role of fecal microbial transplant (FMT) to modulate the dysbiosis seen in PSC has garnered much interest recently following the publication of a pilot study of 10 PSC-IBD patients where 30% of FMT recipients displayed an ALP reduction of at least 50% [88]. FMT also resulted in an increase in bacterial diversity with no adverse safety events reported. Larger prospective studies are required.

BA-targeting therapies for PSC currently under study include FXR agonists such as obeticholic acid (OCA) [89] and cilofexor [90], and Apical Sodium Dependent Bile Acid Transport (ASBT) inhibitors [73]. A phase 2 trial of 5–10 mg OCA demonstrated significant reductions in serum ALP at week 24 of treatment compared to placebo with no

significant effect on total bilirubin [89]. The main limitation of OCA is tolerability, especially pruritus. Cilofexor has been shown to reduce serum ALP by 21%, GGT by 30%, and ALT by 49% compared to placebo after 12 weeks of therapy [90]. Significant pruritus also emerged as a predominant adverse event with cilofexor, but with much lower rates compared to OCA. ASBT inhibitors A4250 and LUM001 (lopixibat) which act to interrupt the enterohepatic circulation of bile acids are currently under investigation for PSC treatment [91].

Dominant strictures are less common in children than adults, but should, when identified in association with symptoms or signs such as cholangitis, jaundice, pruritus, right upper quadrant pain, or worsening biochemistry, be managed with ERCP and balloon dilatation, often with sphincterotomy, with or without stent placement [24]. This may prolong symptom-free intervals prior to LT [92]. Although cholangiocarcinoma is rare in pediatrics, brush cytology in the setting of a dominant stricture remains important. ERCP should be performed by a physician who is adequately experienced with the procedure, which often requires collaboration with an adult gastroenterologist.

Vedolizumab, an IBD therapy, is a selective monoclonal antibody directed against the $\alpha_4\beta_7$ integrin expressed on lymphocytes. It interferes with the interaction of $\alpha_4\beta_7$ with mucosal cellular adhesion molecule-1 (MAdCAM-1) expressed on gut endothelial cells, thereby preventing lymphocyte trafficking to the gut. Although MAdCAM-1 is not expressed in normal liver tissue, it is expressed on portal vein and sinusoidal endothelial in chronically inflamed human liver, including in PSC [93, 94]. As such, the introduction of vedolizumab stimulated excitement as a potential biological treatment for PSC. Disappointingly, this has not been upheld by clinical studies thus far, although these have all been retrospective [95, 96]. A multicenter cohort study by the French GETAID group reported that vedolizumab therapy failed to result in liver biochemical improvements even when followed out to 30 and 54 weeks [96]. These findings were echoed by two additional adult [95, 97], and one small pediatric study [98]. On the other hand, vedolizumab appears to display similar efficacy for treating IBD in PSC-IBD, as in non-PSC IBD populations [95].

LT remains the only definitive treatment for PSC and should be considered for children with decompensated cirrhosis, recurrent or chronic cholangitis refractory to ERCP, hilar cholangiocarcinoma, and intractable pruritus [24, 99]. PSC accounts for 2.6% of pediatric transplants [100]. The median age at transplant is 15 years [57]. Patient and graft survival after LT for PSC are comparable to that for non-PSC pediatric indications, with 1-year and 5-year patient and graft survival rates of 99% and 97%, and 93% and 76%, respectively. However, a diagnosis of IBD prior to LT is associated with an increased risk of death post-LT. Intrahepatic biliary strictures and cholangitis are more common in the first 6 months post-LT in children with PSC compared to other liver diseases [101]. Furthermore, PSC recurs in 10–25% of pediatric patients by 5 years post-LT [57]. A diagnosis of IBD and younger age have been linked with an increased risk of PSC recurrence [101, 102]. As mentioned above, colectomy prior to or during LT may decrease the risk of PSC recurrence [50].

Other Autoimmune Liver Diseases

Autoimmune Hepatitis

Epidemiology and Pathogenesis

Autoimmune hepatitis (AIH) is an idiopathic, progressive, inflammatory liver disease characterized by elevated transaminases, interface hepatitis on biopsy, hypergammaglobulinemia, and autoantibody positivity. It is the most common pediatric autoimmune liver disease, with an incidence and prevalence of 0.23–0.4 and 3 per 100,000 children, respectively [12, 103]. The prevalence of IBD in children with AIH, which approaches 20% [103–105], exceeds that in the general pediatric population, but the magnitude of the association between AIH and IBD is less than that between PSC and IBD as demonstrated in Fig. 11.5. Only 0.3–0.6% of children with IBD develop AIH and, unlike in PSC, this proportion does not differ substantially between children with UC and CD [12]. Two main types of AIH are recognized: AIH type 1 (AIH-1), which accounts for the majority (60–87%) of cases, is characterized by positive antinuclear (ANA) and/or

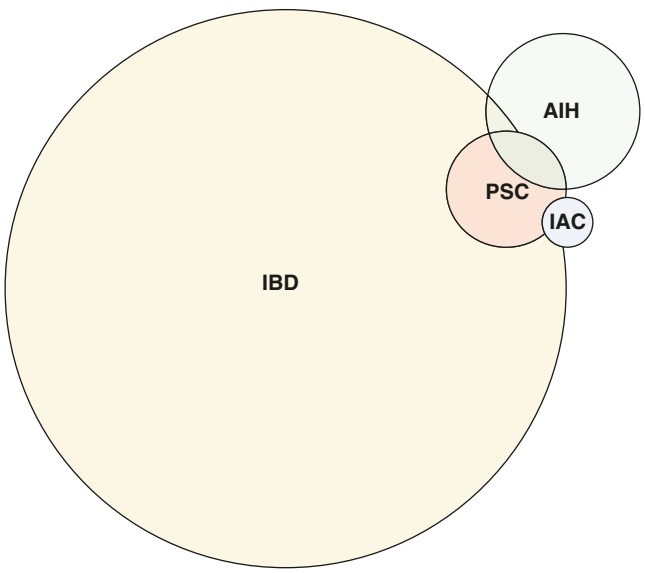

Fig. 11.5 The relationship between autoimmune liver disease and IBD. *AIH* autoimmune hepatitis, *IAC* IgG4-associated cholangitis, *IBD* inflammatory bowel disease, *PSC* primary sclerosing cholangitis

anti-smooth muscle (SMA) autoantibodies, whereas AIH-2 is distinguished by positive anti-liver kidney microsomal type 1 (LKM-1) and/or anti-liver cytosol type 1 (LC-1) autoantibodies. Of note, lower antibody titers are considered significant in children, namely, 1:20 for ANA and SMA, and 1:10 for LKM1 and LC-1, compared to a threshold of 1:40 in adults [106]. Both types of AIH have a female predominance [103], although it is not clear whether this is also true of cases associated with IBD [103, 104, 107]. The pathogenesis of AIH is unknown, but is likely multifactorial, involving genetic susceptibility and immune dysregulation, modified by environmental factors. An aberrant immune response targeting liver autoantigens has been implicated [108].

Diagnosis

Pediatric AIH can present in a highly variable manner, ranging from nonspecific insidious symptoms to fulminant liver failure. The most common presenting symptoms are fatigue, jaundice, and abdominal pain, which occur in about half of patients. Hepatomegaly and splenomegaly are the most frequently observed abnormalities on physical exam [103]. In the context of IBD, however, AIH typically comes to light as a result of elevated transaminases, which can fluctuate over time. The pattern of injury is predominantly hepatocellular, with AST and ALT values typically in the several hundred range which are comparatively higher than the levels seen in PSC and ASC [109]. Conjugated bilirubin may be normal or elevated, and GGT and ALP levels may be modestly elevated [109]. Serum IgG is elevated in 80% of cases, but a normal result does not rule out AIH. Although none of the autoantibodies listed above are entirely specific to AIH, the presence of high-titer autoantibodies, in combination with compatible clinical features and histological findings, strongly supports a diagnosis of AIH. A liver biopsy is typically performed to confirm a diagnosis of AIH and to establish the severity of liver damage. Characteristic findings include interface hepatitis, lymphoplasmacytic infiltrates, and rosetting of hepatocytes. Biliary changes, such as ductular proliferation, can be seen, as well as fibrosis. Cirrhosis is observed in 20–80% of children at presentation and is more common in AIH-1 [103, 110, 111]. Of note, the distinction between AIH and drug-induced liver injury, which is particularly relevant in children with IBD, can be very challenging. In addition to the AIH work-up presented above, it is recommended that all children with IBD with presumed AIH undergo cholangiography to investigate for ASC or PSC.

Outcomes and Treatment

Although a significant fraction of children with AIH present with cirrhosis, when treatment is instituted promptly, outcomes are usually favorable. Conventional treatment is with prednisone 1–2 mg/kg/day (maximum 60 mg/day) to induce remission, decreased over 4–8 weeks, and then continued at a lower dose (0.1–0.2 mg/kg/day, or 2.5–5 mg/day) as maintenance, often with azathioprine [112]. Azathioprine is generally started at a dose of 1–2 mg/kg/day and increased to a maximum of 2–2.5 mg/kg/day until remission is achieved [112–114]. Thiopurine methyltransferase (TMPT) activity may be verified prior to initiating azathioprine to identify patients at heightened risk of myelosuppression [108]. This treatment regimen is associated with biochemical remission (normalization of liver enzymes and IgG) rates >80% in children with AIH, although this can take several months, and relapses requiring temporary increases in immunosuppression are common [103, 107]. In patients who have had sustained biochemical remission for 2–3 years, a liver biopsy may be performed and, if resolution of histological inflammation has occurred, treatment withdrawal may be attempted [112, 114].

Children with AIH have an approximately 15% probability of developing liver cirrhosis and portal hypertension in the 5 years post diagnosis [12]. Transplant rates for AIH are variable but range from 5 to 10% in recent studies [12, 103, 115]. AIH can recur post-transplant with recurrence rates varying between 12 and 46% [115, 116]. It is therefore recommended that steroid-based immunosuppression be maintained at a higher dose than that used for non-AIH transplants [117]. At the current time, it is unclear whether the disease course of AIH occurring in association with IBD differs from that in children without IBD [57]. However, it has been recognized that flares of pre-existing UC can occur following liver transplantation for AIH with the resulting IBD activity taking a more aggressive course than previous and up to 9% of patients require colectomy post-transplant [118–120].

Autoimmune Sclerosing Cholangitis

Epidemiology and Pathogenesis

Autoimmune sclerosing cholangitis (ASC) is an overlap condition between AIH and PSC, characterized by the combination of autoimmune features, namely, positive autoantibodies (especially ANA and SMA), hypergammaglobulinemia and interface hepatitis on liver biopsy, and cholangiopathy, as demonstrated by an abnormal cholangiogram or histological evidence of ductal involvement [105]. However, there are no clear diagnostic criteria for ASC. The International Autoimmune Hepatitis Group (IAIHG) suggests that conditions with overlapping features between autoimmune liver diseases not be considered separate diagnostic entities [121]. Rather, ASC may exist along a continuum of pathological changes between AIH and PSC. Given the lack of established diagnostic criteria, the epidemiology of ASC is difficult to ascertain. However, a recent population-based study reported

an incidence and prevalence of 0.1 and 0.6 per 100,000 children, respectively [12]. ASC appears to occur predominantly in children and young adults: a quarter to a third of children with sclerosing cholangitis have autoimmune overlap features [14–16, 57], compared to only 1.4–17% of adults [24]. Similar to PSC, ASC is typically diagnosed in the first half of the second decade of life, but, unlike PSC, it tends to affect both sexes more equally [12, 15, 104]. A definite association exists between ASC and IBD, the magnitude of which appears to be intermediate between that of PSC and AIH. Up to 75% of children with ASC have IBD [122]. Conversely, 1.5–1.7% of children with IBD, mostly UC, have ASC [7, 12]. Given this, all children with ASC should undergo an evaluation for IBD, even if asymptomatic.

Diagnosis

The clinical presentation of ASC in children is similar to that described above. Biochemistry can provide some guidance in distinguishing ASC from AIH and PSC. Although ALP and GGT levels may be normal or only mildly elevated in the early stages of ASC [122], compared to AIH, ASC is typically associated with a higher ALP to AST ratio (around 4), and p-ANCA positivity is more common (74% compared to 36% of cases). Anti-LKM1, on the other hand, is more specific to AIH [105]. Clues of a possible diagnosis of ASC rather than PSC include higher transaminases, elevated serum IgG, and high-titer ANA and SMA autoantibodies. However, none of these biochemical parameters is sufficiently specific to make a diagnosis of ASC. The ability to firmly diagnose ASC and to differentiate it from AIH and PSC requires both cholangiography and liver biopsy. This is particularly relevant in children with IBD given the known association between ASC and IBD. It is noteworthy that despite having abnormal cholangiograms up to one quarter of children with ASC have no histological evidence of bile duct involvement and, conversely, 27% of patients with AIH have histological evidence of bile duct damage, chronic cholangitis, and biliary periportal hepatitis [104, 123].

Outcomes and Treatment

An accurate diagnosis of ASC is important as it may have prognostic and therapeutic implications. While the authors feel that a trial of corticosteroids with or without azathioprine is generally warranted in the setting of ASC [124, 125], whether this alters disease natural history (beyond improving biochemistry) remains unclear. There are data to support that the biliary disease in ASC typically progresses despite treatment [104]. UDCA is often used at doses of 15–20 mg/kg/day to address the biliary component of the disease, but, as with PSC, there is no evidence that biochemical improvement translates into a positive effect on natural history [112, 126]. Twenty-five percent of children with ASC develop liver cirrhosis and portal hypertension within 5 years of diagnosis, a rate that is intermediate between that for PSC and AIH [12]. Given the lack of well-defined diagnostic criteria, it is difficult to comment on precise LT and mortality outcomes in children with ASC and studies to date have yielded conflicting results. An older series reported a 65% 10-year survival with native liver, distinctly worse than the 100% survival in children with AIH [104], whereas a more recent study found a 90% 5-year survival with native liver, comparable to the rate observed in children with AIH. Overall, it is believed that transplant rates in ASC are similar to those in PSC, around 20% [105, 109]. As with PSC and AIH, ASC can recur post-LT [116]. Uncontrolled intestinal inflammation in patients with IBD may be a risk factor for ASC recurrence [105].

IgG4-Associated Cholangitis

IgG4-associated cholangitis (IAC) is a rare inflammatory disorder of the biliary tree, characterized by elevated serum IgG4 levels and infiltration of IgG4+ plasma cells in the bile duct walls, causing thickening and stenoses. IAC is often associated with type 1 autoimmune pancreatitis (AIP), the pancreatic manifestation of IgG4-related disease (IgG4-RD), a systemic multiorgan disorder only defined during the last decade [127]. The typical IAC/IgG4-RD patient profile is that of an elderly man with obstructive jaundice, weight loss, and abdominal discomfort. However, IAC occurring in association with UC has been reported, including in children [128]. The clinical and cholangiographic presentation of IAC is often indistinguishable from that of PSC. Furthermore, 9–36% of patients with PSC have elevated serum IgG4 levels (although usually lower than in IAC) [129, 130], and IgG4+ plasma cells have been documented on liver biopsy in PSC patients [131], further blurring the relationship between the two. However, PSC and IAC appear to be distinct entities, as evidenced by their vastly different response to corticosteroids; in contrast to PSC, IAC typically shows excellent response to immunosuppressive treatment, including resolution of strictures. However, relapse is common after tapering immunosuppression; long-term low-dose therapy with corticosteroids/azathioprine is often needed, analogous to the management of autoimmune hepatitis [132]. Diagnostic criteria have been proposed for IAC; these combine biochemical, radiographic, and histopathological characteristics with the multiorgan involvement of IgG4-RD and responsiveness to immunosuppressive treatment [133].

Figure 11.5 graphically depicts the relationship between autoimmune liver diseases and IBD.

Table 11.2 Differential diagnosis of clinical syndromes associated with IBD drugs causing liver injury

Syndrome	Drug
Acute hypersensitivity reaction	Sulfasalazine, mesalamine, thiopurines
Acute granulomatous hepatitis	Sulfasalazine, mesalamine
Autoimmune hepatitis-like	Anti-TNFα
Noncirrhotic portal hypertension	Thiopurines
Fibrosis/cirrhosis	Methotrexate
Cholestatic jaundice	Sulfasalazine, mesalamine, thiopurines, anti-TNFα
Sinusoidal obstruction syndrome	Thiopurines
Hepatic rupture	Thiopurines (peliosis)
Hepatic mass on imaging	Thiopurines (peliosis), anti-TNFα/ thiopurines (HSTCL)
Hepatitis B reactivation	Anti-TNFα

HSTCL hepatosplenic T-cell lymphoma

Drug Hepatotoxicity (Table 11.2)

Methotrexate

A recent systematic review and meta-analysis examining 32 randomized controlled trials, including a total of 13,177 adults primarily with rheumatological indications for treatment, demonstrated an increased risk of liver enzyme abnormalities in patients treated with methotrexate compared to a comparator agent, but no difference in the risk of liver failure, cirrhosis, or death [134]. The results of two adult IBD studies, in which fairly large numbers of liver biopsies were performed, also found very low rates of hepatic fibrosis in patients receiving methotrexate [135, 136], indicating that hepatic fibrosis is not as commonly observed in methotrexate users as suggested by older studies.

Pediatric IBD studies have found varying rates of biochemical liver abnormalities in children treated with methotrexate, ranging from 10% in a systematic review to 39% in a multicenter retrospective comparison of oral and subcutaneous methotrexate [137]. Most resolved spontaneously or with dosage adjustment; medication discontinuation was required in only a minority (<5%) [138–141]. These studies are limited, however, by their retrospective nature, the inability to correlate biochemistry with histopathology, and the inability to definitively ascribe the biochemical abnormalities to methotrexate given the absence of documented normal laboratories prior to medication initiation in most cases. Conflicting data exist regarding whether higher methotrexate doses and parenteral versus oral administration are associated with a greater risk of hepatotoxicity [135, 139, 142]. The risk of hepatotoxicity may be higher in the immediate period after starting methotrexate [143]. Importantly, abnormal liver biochemistry does not reliably identify methotrexate-associated fibrosis.

Based on the available evidence, when initiating methotrexate in children with IBD, the authors recommend obtaining liver biochemistry at baseline, weekly for the first month and every 2–3 months thereafter. In cases of persistent moderate enzyme elevations (up to 2–3× ULN), the dose of methotrexate can be adjusted, whereas, when faced with more marked elevations (>5× ULN), methotrexate should be entirely held, at least temporarily. A liver biopsy should be performed in cases in which liver enzymes remain abnormal despite medication cessation, or when methotrexate discontinuation would be deleterious to IBD management. The use of methotrexate in patients with underlying liver disease, such as PSC, should generally be avoided, if possible.

Thiopurines

Azathioprine (AZA) is a prodrug for 6-mercaptopurine (6-MP), which is, in turn, converted to 6-thioguanine (6-TG), the final effector metabolite. The enzyme thiopurine methyltransferase (TPMT) catalyzes the formation of 6-methylmercaptopurine (6-MMP) and 6-methylmercaptopurine ribonucleotides (6-MMPR) [144]. A systematic review, including 34 mostly adult IBD studies, found a mean prevalence of AZA/6-MP-induced "liver disorder" of 3.4% and a mean annual rate of abnormal liver tests (up to 2× ULN) per patient-year of 1.4%, suggesting that thiopurine-associated hepatotoxicity is relatively uncommon. However, most studies did not provide definitions for "liver disorder" and were retrospective in design [145]. Two large pediatric studies examining the use of thiopurines in IBD also found fairly low rates of hepatotoxicity, namely, 4.6% and < 3%, respectively [146, 147].

Thiopurine-induced hepatotoxicity can be grouped into four syndromes: [1] hypersensitivity reactions; [2] idiosyncratic cholestatic reactions; [3] endothelial cell injury including sinusoidal obstruction syndrome (SOS or veno-occlusive disease); and [4] nodular regenerative hyperplasia (NRH) [148]. Hypersensitivity reactions occur in 5–15% of patients and usually have their onset within 2–3 weeks. Non-allergic cholestatic injuries are characterized by increased serum bilirubin and ALP, with or without moderate aminotransferase elevations, and typically occur within 2–5 months of therapy initiation. Variable parenchymal cell necrosis is typically seen on liver biopsy. Jaundice regression is not universal upon medication cessation [145]. Peliosis hepatis, sinusoidal dilatation, SOS, and NRH are felt to be dose dependent. The inciting injury in this group of vascular pathology is at the level of the endothelial cells lining the sinusoids and terminal hepatic venules and tends to occur

between 3 months and 3 years of treatment [148, 149]. IBD patients treated with AZA have a cumulative incidence of NRH of approximately 0.6 and 1.3% at 5 and 10 years, respectively [150]. Patients with NRH may be asymptomatic with normal or only mild elevations in liver function tests or isolated thrombocytopenia, or may present with clinically evident portal hypertension (PH). NRH can be detected on liver biopsy, which demonstrates diffuse transformation of normal hepatic parenchyma into small, regenerative nodules with little or no fibrosis [151], and on MRI, which shows multiple fine, non-enhancing nodules [152]. The course is usually indolent, but, rarely, NRH may progress to end-stage liver disease requiring LT [153]. Thiopurine cessation in patients with NRH is generally followed by biochemical normalization, but patients with PH have a variable course, with resolution of PH in some, but persistence in others. Peliosis hepatis results in multiple cystic blood-filled spaces in the liver, spleen, lymph nodes, and other organs, which can lead to hepatic hematomas and, rarely, hepatic rupture [154]. SOS typically presents with a Budd-Chiari-like picture, with the triad of rapid-onset ascites, painful hepatomegaly, and jaundice.

A reasonable monitoring strategy when initiating thiopurine therapy might include liver biochemistry at baseline, weekly for the first month, biweekly for the second and third months, and monthly thereafter. 6-MMP levels >5700 pmol/8 × 10^8 red blood cells have been linked with liver toxicity in children [155], but this finding has not been consistent across all studies [156]. If available, metabolite levels may be used to complement liver enzyme monitoring, and TPMT genotype or activity may be determined prior to initiating therapy, but this remains controversial. Mild liver enzyme abnormalities in children on thiopurine therapy may be observed with repeat blood work, but the authors suggest that the dose of thiopurine be reduced by about 50% in patients with more marked derangements. If this does not result in biochemical normalization after several weeks to months, therapy should be withdrawn entirely. Immediate thiopurine discontinuation should be the approach in any patient with clinically overt jaundice. Liver biopsy should be considered if liver tests fail to normalize after medication withdrawal or if there is any suggestion of PH, even in patients with normal laboratory parameters.

Antitumor Necrosis Factor-α (Anti-TNFα)

Based on post-marketing surveillance, the Food and Drug Administration (FDA) has issued warnings about the potential risk of serious liver injury with the use of anti-TNFα antibodies [157]. TNFα plays an important role in many aspects of immune response regulation. The association between anti-TNFα use and the development of autoantibodies is well known, although the pathological role of these antibodies remains unclear [158]. Anti-TNFα-related hepatotoxicity does not appear to be dose-dependent, but instead idiosyncratic. The release and presentation of hepatic autoantigens by immune cells may be involved [159].

Infliximab (IFX) and adalimumab (ADA) have been implicated in drug-induced liver injury (DILI) in both rheumatology and IBD populations. The median latency period is 13–18 weeks, but is hugely variable; DILI may have its onset after a single infusion/injection, but 20% of cases occur more than 6 months into therapy [160, 161]. DILI seems to occur more frequently with IFX than ADA; the rate of DILI has been found to be 1/120 IFX-treated patients compared to 1/270 ADA-treated patients [162]. This is in keeping with the findings of a large retrospective review of adult IBD patients, in which IFX accounted for a disproportionate fraction of the 2.7% of patients who developed significant liver enzyme elevations felt to be secondary to anti-TNFα therapy [161]. The most common presentation is an autoimmune phenotype with primarily hepatocellular injury, high rates of autoantibody (especially ANA) positivity, and histological findings compatible with autoimmune hepatitis. However, mixed non-autoimmune and predominantly cholestatic patterns also occur. Cases with autoimmune features may have a longer latency and higher peak ALT [160]. Autoantibody positivity prior to anti-TNFα initiation does not appear to predict the risk of DILI [162]. Cases of DILI with AIH features should be managed with anti-TNFα discontinuation, in which case the prognosis is favorable. Some patients benefit from treatment with corticosteroids [160]. Anti-TNFα-associated DILI does not seem to be a class effect, and switching to a different anti-TNFα, with close observation, appears safe. Milder cases of hepatotoxicity without overt autoimmune features often resolve spontaneously without anti-TNFα discontinuation [161]. Pediatric data exploring abnormal liver enzymes in children receiving anti-TNFα therapy are scarcer. In a study of 195 pediatric IBD patients on infliximab, liver biochemical abnormalities were common; AST was elevated in 27% and ALT in 25% of patients [163]. A retrospective study of 659 children with IBD who initiated anti-TNFα therapy revealed that 7.7% experienced a hepatocellular pattern of liver injury with new ALT elevations at least 2x the ULN [164]. Ninety-three percent had normalization of ALT and only 8% required cessation of anti-TNFα therapy [164].

Another concern with anti-TNFα agents is the risk of viral reactivation, in patients with chronic hepatitis B (HBV) infection, particularly those who are HBsAg-positive. Approximately, one-third of HBsAg-positive IBD patients were observed to develop liver dysfunction while receiving immunosuppressive therapy, including anti-TNFα [165]. Treatment with anti-TNFα in IBD patients with hepatitis C (HCV) appears to be less of a concern and is generally well

tolerated, with most patients displaying either unchanged or even improved biochemistry while receiving anti-TNF therapy [166]. Notably, no pediatric data exist regarding the outcomes of children with IBD and HBV or HCV receiving anti-TNFα. Strong consideration should be given to treating chronic HBV infection in children who are to commence anti-TNF therapy, whereas this may not be necessary in children with HCV. Regardless, routine surveillance with liver enzymes and viral loads should be performed regularly in such children.

A child's immunization history should be carefully reviewed at the time of IBD diagnosis, and viral serologies, including HBsAb, HBsAg, anti-HBc, and anti-HCV, should be verified. Although it is preferable to vaccinate for hepatitis A (HAV) prior to anti-TNFα initiation, seroconversion is still likely once on therapy and should be attempted regardless [167]. Patients with IBD who have nonimmune HBsAb levels (<10 mI U/mL) should be revaccinated with the routine three-dose regimen.

Other Biologics and Small Molecules

Licensed non-anti-TNFα biologics (vedolizumab, ustekinumab) and small molecules (tofacitinib) have not consistently been linked to significant risk of hepatotoxicity.

Sulfasalazine and Mesalamine

Sulfasalazine causes two main forms of hepatic injury. First, acute hepatocellular damage may develop as part of a generalized hypersensitivity reaction. This reaction, sometimes referred to as DRESS (drug rash with eosinophilia and systemic symptoms), is characterized by fever, rash, hepatomegaly, lymphadenopathy, atypical lymphocytosis, and eosinophilia, and is thought to be due to the sulfapyridine moiety [168]. The injury typically manifests within 2 months of starting therapy, with a shorter latency upon re-exposure [169]. This reaction is uncommon with data from the UK suggesting an incidence of 0.4% [170]. Prompt sulfasalazine discontinuation is critical, and corticosteroids may be helpful. However, progression to acute liver failure and death has been reported [170, 171]. Second, acute granulomatous hepatitis, characterized by fever, malaise, right upper quadrant pain, variable transaminases, and ALP and non-caseating granulomas on biopsy, may also occur [172]. In addition, cholestatic injury has been described with sulfasalazine use [173]. Mesalamine-induced hepatotoxicity is rare. A UK audit reported an incidence of 3.2 cases per million prescriptions, which was not statistically different from the six cases per million for sulfasalazine [174]. Cholestatic injury, with or without granulomatous hepatitis, resolving upon mesalamine discontinuation, has been reported [175–177]. An apparent cross-reactive hypersensitivity reaction with mesalamine after a reaction to sulfasalazine [178] and a case of chronic hepatitis with autoimmune features have also been described [179].

Glucocorticoids

It is postulated that glucocorticoid-related alterations in hepatic lipid metabolism may lead to hepatic steatosis. Steroid use has been identified as an independent risk factor for nonalcoholic fatty liver disease (NAFLD) identified by abdominal imaging in IBD patients [180–182].

Hepatosplenic T-Cell Lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is a rare, aggressive, and almost uniformly fatal extranodal lymphoma. The usual presentation includes fever, fatigue, abnormal liver tests, hepatosplenomegaly, and pancytopenia. As of 2020, 62 cases of HSTCL have been identified in IBD patients with a median age of 28 years (range 12–81); 83.6% were male, 84.7% had Crohn disease [183]. At the time of HSTCL diagnosis, 57 of 62 patients had current or previous exposure to thiopurines, 38 had exposure to anti-TNFα therapy, 27 were on combination therapy and 3 patients had exposure to natalizumab, vedolizumab or ustekinumab (of which all 3 also had anti-TNF and azathioprine exposure) [183]. The absolute risk of HSTCL in all patients receiving thiopurines has been estimated to be 1:45,000 compared to 1:7404 in men <35 years old, whereas the absolute risk for all patients receiving concomitant thiopurine and anti-TNF has been estimated to be slightly less than 1:22,000 compared to approximately 1:3534 in men <35 years [184]. In keeping with this, in a case–control study, anti-TNF combined with thiopurine therapy was associated with a higher risk of HSTCL compared to infliximab alone [185]. At the current time, the role of anti-TNFα agents in the development of HSTCL is uncertain [186], but the risk appears to be greater with combination therapy [187, 188]. A high degree of suspicion must be maintained for this diagnosis, especially in young males.

Other Liver Diseases and IBD

Cholelithiasis

The incidence and prevalence of cholelithiasis in CD patients are 14.35 per 1000 person-years and 11–34%, respectively, compared to 7.75 per 1000 person-years and 5.5–15%,

respectively, in controls [189, 190]. Overall, the odds of gallstones are 2.1-fold higher in CD patients compared to the general population. In contrast, definite evidence of an association between UC and cholelithiasis is lacking [189]. Although gallstones are relatively unusual in pediatric populations, 2.3% of children with IBD in an American consortium developed cholelithiasis [22], which significantly exceeds the population prevalence of 0.88–0.99% in individuals <30 years [191]. Previous intestinal resection is the strongest risk factor for gallstone disease in patients with CD, with an ileal resection >30 cm increasing the odds of cholelithiasis sevenfold. Other risk factors include ileal location, disease duration, age, number of clinical recurrences and hospitalizations, total parenteral nutrition, prolonged hospitalization, and female sex. Symptomatic cholelithiasis should prompt a referral to a pediatric surgeon. Children may also present with cholecystitis, which should be managed with broad-spectrum antibiotics and a general surgery consultation to guide eventual cholecystectomy.

Liver Abscess

Liver abscess is a rare complication of IBD. The incidence of pyogenic liver abscess is higher in IBD patients (6.72 per 10,000 person-years) compared with healthy controls (4.06 per 10,000 person-years) [192]. It is more common in CD and in males and tends to occur in the setting of active disease. There is a tendency to develop multiple abscesses, which almost invariably involve the right lobe. The presentation is similar to that in non-IBD patients, but the diagnosis can be challenging and is often overlooked. Investigations, when suspected, should include an ultrasound and blood cultures, which are positive in 50% of cases. Compared to hepatic abscesses in the general population, which are usually polymicrobial, a single pathogen, often *Streptococcus milleri*, is frequently isolated in patients with IBD. Treatment is with prolonged parenteral antibiotics (commonly 4–8 weeks) with or without drainage, preferably percutaneously. An intra-abdominal source should be ruled out. Risk factors for liver abscess in IBD include intra-abdominal abscesses, fistulizing disease, intestinal perforation, abdominal surgery, and malnutrition [189, 193].

Portal Vein Thrombosis and Budd-Chiari Syndrome

Adult and pediatric patients with CD and UC are at increased risk of thromboembolism (TE). To date, the mechanism behind this prothrombotic state is not fully understood, but it is likely multifactorial and related to the inflammatory state. The potential etiologies for increased thrombosis in IBD include thrombocytosis/platelet activation, hyperhomocysteinemia, increased fibrinogen, impaired fibrinolysis, increased procoagulation factors, decreased anticoagulation factors, and procoagulation mutations. The extent of IBD has also been shown to correlate with the risk of TE, but TE can occur in patients with UC even after proctocolectomy [194].

Portal vein thrombosis (PVT) appears to occur at higher rates in the IBD population, particularly postoperatively. Most studies suggest it is a rare complication, with a prevalence of 0.1–1% in IBD [195]. The incidence specifically in pediatric IBD patients has been reported to be 9 per 10,000 hospitalizations, with sixfold increased odds compared to non-IBD controls [194]. Overall, the precise epidemiology of the condition is difficult to ascertain as most patients are asymptomatic. Intra-abdominal surgery, IBD flare, and intra-abdominal infection have been identified as key risk factors [196]. The diagnosis may be made at the chronic stage, at which time cavernomatous transformation of the portal vein may be evident on imaging. A variety of imaging modalities can be used to make the diagnosis, including ultrasound with Doppler, contrast-enhanced CT, and MR angiography. Treatment is generally with anticoagulation for 3–9 months depending on the particular anticoagulant agent chosen [196]. While older studies suggested high mortality rates with this complication, more recent publications indicate a more benign natural history [195].

Budd–Chiari syndrome is a rare complication of UC, mostly in adults, but has been reported in a small number of children as well, with an incidence of 2.1 per 10,000 hospitalized pediatric IBD patients [194, 197–199]. It typically presents with hepatomegaly, right upper quadrant pain, and rapid-onset ascites with abnormal liver tests, but 25% can be asymptomatic. Diagnosis is supported by imaging and/or liver biopsy. Therapy may include thrombolysis, anticoagulation, angioplasty, or vascular stents. More definitive treatment, such as porto−/mesocaval shunts, or even liver transplant, may be required in medically refractory cases. Symptomatic treatment of ascites is with diuretics and paracentesis. While outcomes have often been poor in adults, the pediatric cases reported to date have had a favorable evolution, with anticoagulation or even spontaneously.

Non-Alcoholic Fatty Liver Disease

The prevalence of nonalcoholic fatty liver disease (NAFLD) in IBD has varied widely across different studies, ranging from 13 to 100% [1], depending on the diagnostic modality employed and the indication for screening/testing. According to a systematic review, the mean prevalence of fatty liver disease in adults is 23% in UC and 1.5–39.5% in CD, in comparison to 20% in the general population [189]. The prevalence of NAFLD in pediatric IBD patients has never

been specifically examined. Overall, it would appear that fatty liver is common in the IBD population, but definitive evidence that the prevalence of NALFD in IBD exceeds that in the general population is lacking. Adult studies point to an increased risk of NAFLD in male patients with IBD [200] and those who develop IBD at a younger age, [201] but these risk factors have not been demonstrated in pediatric IBD cohorts. Patients with metabolic risk factors, such as obesity and hypertension, are at increased risk, but these risk factors are not universally present in IBD patients with NAFLD. Indeed, IBD patients with NAFLD have a significantly lower weight and BMI than patients with NAFLD alone, pointing to a unique NAFLD phenotype [202]. Coupled with the asymptomatic nature of NAFLD, a high degree of suspicion must be maintained, particularly in the setting of raised liver enzymes. Since IBD patients can have multiple possible etiologies for elevated liver enzymes (medications, obesity, immune-mediated liver disease), liver biopsy is often required.

Management includes attaining adequate IBD control, withdrawing therapies that may be associated with hepatic steatosis (such as steroids), if possible, and working toward a healthy BMI in patients who are overweight, in conjunction with a pediatric dietitian.

Granulomatous Hepatitis

Granulomatous hepatitis is estimated to occur in <1% of IBD patients, primarily those with CD. It tends to present as unexplained hepatic masses on routine imaging or asymptomatic elevations of cholestatic liver enzymes, especially ALP. The diagnosis is confirmed by visualizing granulomas on liver biopsy. The most common cause in the setting of IBD is medications, especially mesalamine and sulfasalazine, but granulomatous hepatitis can also be an extraintestinal manifestation of IBD and can be associated with malignancy or infections [172, 175, 203]. Corticosteroids and immunosuppressive agents have been used as treatment [1].

Hepatic Amyloidosis

Amyloidosis is a rare but serious complication of IBD, especially CD. It has a prevalence of 0.5% in IBD, more specifically 0.9–3% in CD, and 0–0.07% in UC [204–206]. The pathogenesis remains unclear. Patients are usually male with extensive, long-standing disease, although amyloidosis may be present at the time of, or even prior to, the diagnosis of IBD. Fistulae and/or abscesses, as well as other extraintestinal manifestations, are common. Amyloidosis is predominantly a disease of the kidneys, but hepatic involvement has been described in a small subset of patients, including in children [206]. Signs and symptoms of hepatic amyloidosis are few, and liver tests are generally normal. The diagnosis is established by biopsy, and, often, only comes to light at the time of autopsy. Management in hepatic amyloidosis focuses on achieving control of underlying IBD in an effort to modulate release of serum amyloid A, an acute phase reactant [182]. Mortality is closely tied to the renal disease, but hepatic involvement is associated with a reduced likelihood of survival [207].

A Clinical Approach to Children with IBD and Liver Abnormalities

Children with IBD who develop abnormal liver biochemistry or physical stigmata of liver disease may have a wide range of potential underlying diagnoses, as reviewed in this chapter. Based on the available but limited evidence presented, the authors suggest the following approach to liver disease in pediatric IBD (Fig. 11.6). All children with IBD should have routine liver biochemistry with ALT, AST, GGT, ALP, fractionated bilirubin, and albumin measured every 6–12 months when the child is well. The frequency of blood work can be increased if the child is unwell or receiving medications with known potential hepatotoxicity, as detailed above. If low-grade abnormalities are detected, liver tests should be repeated in 2 weeks to ensure they are not rising acutely and subsequently followed for the first few months. With more marked elevations, or clinically overt evidence of liver disease, such as hepatosplenomegaly or jaundice, further investigations should be considered, including autoantibodies (ANA, SMA, LKM1, ANCA), serum IgG, viral hepatitis serologies, celiac serology, ceruloplasmin, and alpha-1 antitrypsin level, along with abdominal ultrasound. Depending on the clinical context, MRCP and/or liver biopsy may also be indicated. If medications are felt to be a potential contributor, a trial of reducing the dose or holding the medication entirely (if this is not felt to be detrimental to the child's IBD care) should be performed. The distinction between "low" and "high-grade" elevations is controversial. The authors propose that elevations >2–3× ULN are significant and require further investigation. Additional studies in pediatric IBD populations are required to construct truly evidence-based algorithms to guide the work-up and management of abnormal liver biochemistry and liver disease in children with IBD.

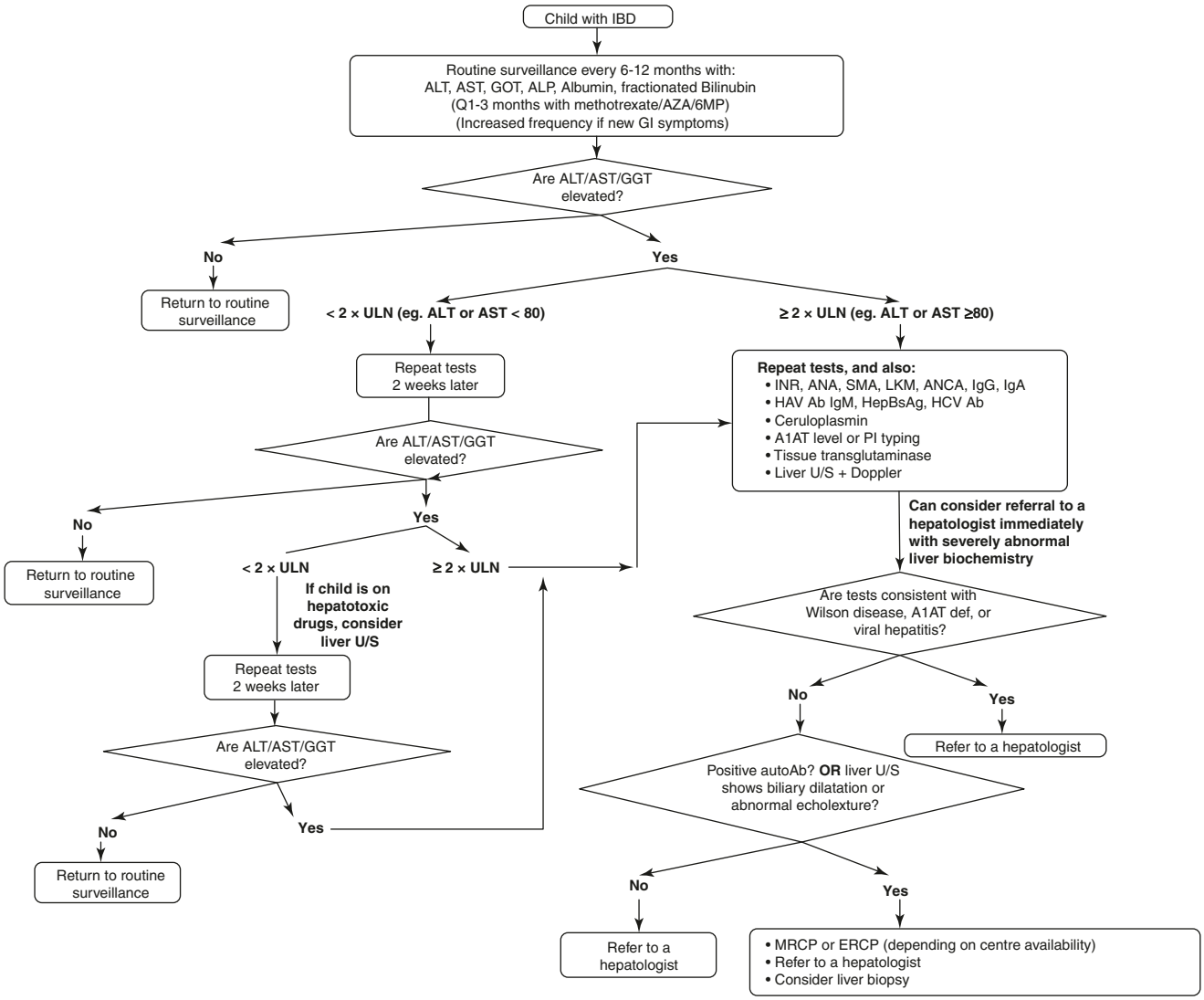

Fig. 11.6 Suggested approach to liver disease in pediatric IBD

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Growth Impairment in Pediatric Inflammatory Bowel Disease

12

James Huang and Thomas D. Walters

Normal Growth and Pubertal Development

"Normal" children grow at very different rates. Patterns of growth and pubertal progression in young patients with IBD can only be accurately recognized as pathologic, if the variations in the normal development of healthy children and adolescents are first appreciated [1, 2]. A child's growth is the result of both genes and environment; it appears principally mediated by hormones and nutrition [3]. Linear growth can be represented by stature (attained height) or by the rate of growth (height velocity). A child's attained height represents the culmination of growth in all preceding years; height velocity reflects growth status at a particular point in time.

Normal Growth Patterns

Growth can be conceptualized as the product of three overlapping biological phases: infancy, childhood, and puberty. Final height represents the sum of each of the individual components.

Linear growth velocity decreases from birth onwards, punctuated by a short period of growth acceleration (the "adolescent growth spurt") just prior to the completion of growth. As the rapid growth of infancy tails off, the steady growth of childhood predominates. Healthy children grow at a consistent rate in the range of 4–6 cm annually from 6 years of age until the onset of puberty [4].

At puberty, there is a rapid alteration in body size, shape, and composition; for a year or more, height velocity approximately doubles. Puberty depends on a healthy hypothalamic-pituitary-gonadal (HPG) axis and is marked by the return of gonadotropin-releasing hormone (GnRH) secretion. GnRH stimulates the secretion of luteinizing and follicle-stimulating hormones, which then stimulate gonadal maturation and sex-steroid production [5]. Although much is known about the components of the HPG axis, the factors that trigger pubertal onset remain elusive [5]. The age of onset of puberty, and hence of the pubertal growth spurt, varies among normal individuals and between ethnic populations. Puberty begins earlier in girls than in boys; moreover, the pubertal growth spurt occurs in mid-puberty (prior to menarche) in girls but in late puberty (after Tanner stage 4) in boys [4]. There is hence quite consistently a two-year difference in the timing of peak height velocity (PHV) in girls compared to boys [4]. In North American females, PHV occurs at a mean age of 11.5 years, but in males not until 13.5 years (2SD = 1.8 years) [4]. The occurrence of menarche is an indication that linear growth is nearing completion; usually, girls gain only 5–8 cm more in height within the two subsequent years [4].

Normal Growth Physiology

To understand the mechanisms by which growth is inhibited in children with IBD, and to thoughtfully consider solutions by which it might be corrected, it is necessary to understand the normal physiology and regulation of growth. The growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis plays a pivotal role in normal postnatal growth. Thyroxine, cortisol, and the sex steroids are also implicated in the maintenance of normal linear growth.

The GH/IGF-1 Axis

The Somatomedin Hypothesis

In 1956 Daughaday and Salmon proposed that an intermediate hormone they termed "Somatomedin C" mediated all the growth-promoting effects of Growth hormone (GH). This hormone was subsequently purified and named "Insulin-like Growth Factor-1" (IGF-1) [6–8] and found to act in both an "endocrine" fashion, via its hepatic generation and subsequent release into the circulation, as well as in an "autocrine/paracrine" fashion, through its local generation within target

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organs [9, 10]. More recent work has determined that, by acting on different cell types, both hormones (GH and IGF-1) can directly stimulate longitudinal growth: GH induces differentiation of epiphyseal growth plate precursor cells toward chondrocytes, which in turn become responsive to IGF-1, while IGF-1 stimulates the clonal expansion of differentiated chondrocytes [10, 11] (Fig. 12.1).

Growth Hormone and IGF-1

The precise mechanism by which GH is released and subsequently stimulates the release of IGF-1 is now well established [12–16] (Fig. 12.2). In humans, the majority of circulating IGF-1 is synthesized in the liver, although a low level of GH-dependent and GH-independent IGF-1 expression does occur in extrahepatic tissues.

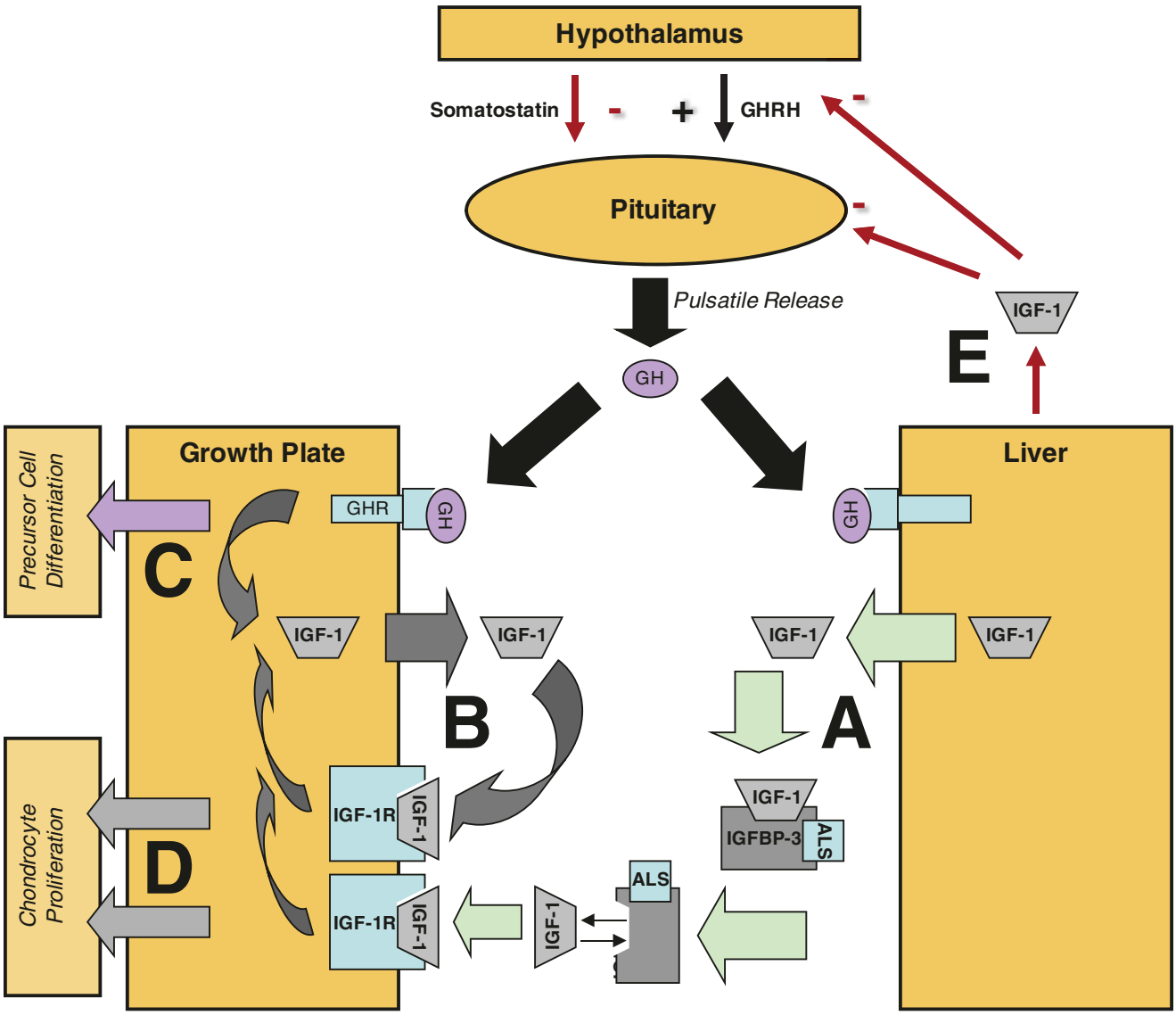

Fig. 12.1 The GH/IGF-1 Axis and its role in linear growth. The hypothalamic release of Growth Hormone-Releasing Hormone (GHRH) stimulates the pulsatile release of Growth Hormone (GH) from the pituitary. The GH cell surface receptor (GHR) is widely expressed throughout the body. GH binds to the extracellular domain of GHR, inducing the upregulation of various anabolic target genes including Insulin-like Growth Factor 1 (IGF-1). The majority of circulating IGF-1 forms a ternary complex with acid-labile subunit (ALS) and Insulin-like Growth Factor Binding Protein-3 (IGFBP-3). IGF-1 acts in both an "endocrine fashion" (process **a**) and "autocrine/paracrine" fashion (process **b**). In addition to up-regulating IGF-1 production, GH contributes directly to linear growth by inducing differentiation of the precursor cells within the growth plate toward chondrocytes (**c**). IGF-1 stimulates mitosis of epiphyseal chondrocytes (**d**) and also mediates the negative feedback of GH (**e**)

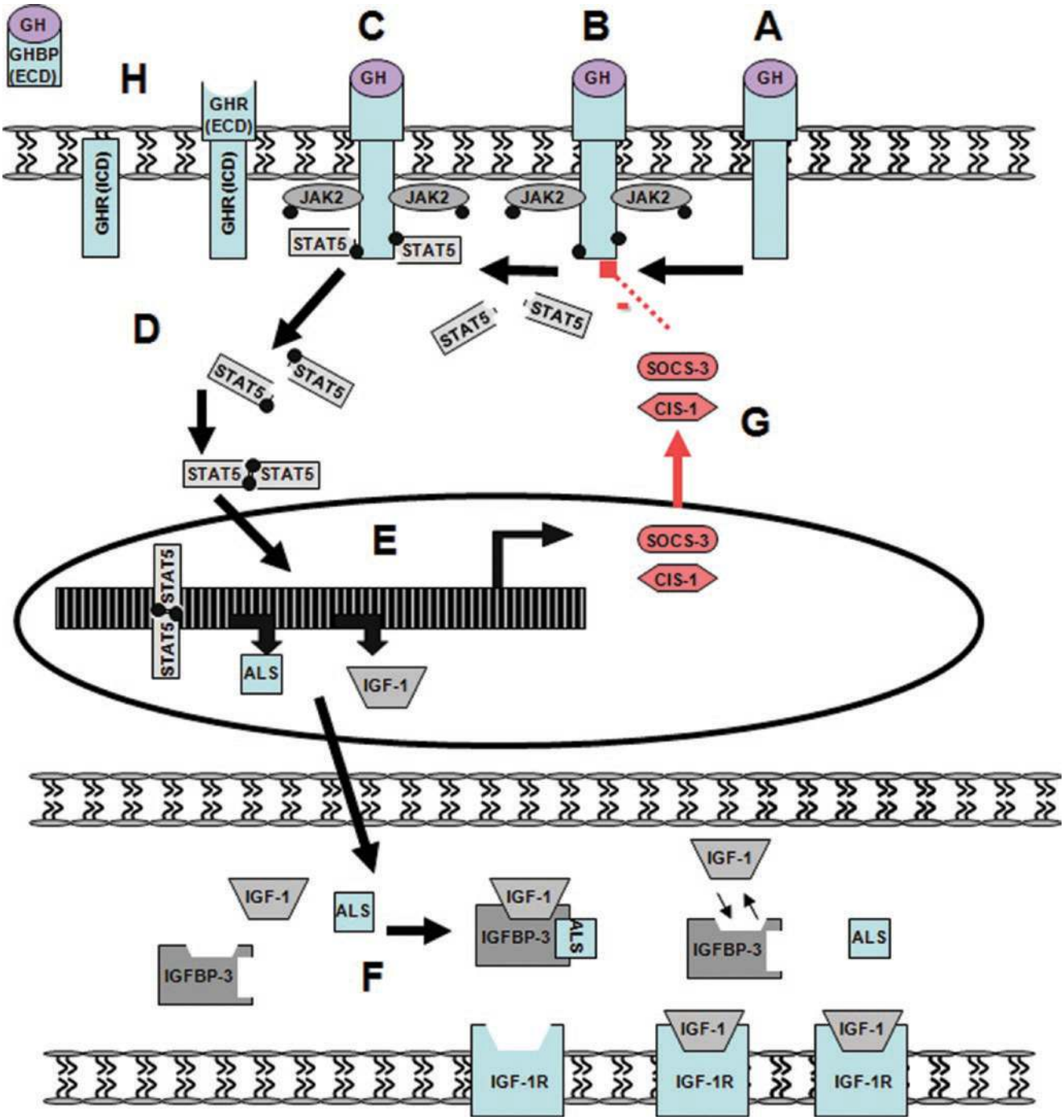

Fig. 12.2 The Growth Hormone Receptor and JAK2/STAT5 signaling pathway. (**a**) Within its various target tissues, GH binds to the extracellular domain of the Growth Hormone Receptor (GHR), (**b**) inducing the intracellular auto-phosphorylation of Janus kinase 2 (JAK2). (**c**) In turn, phosphorylated JAK2, in association with activated GHR, leads to the phosphorylation of signal transducer and activator of transcription protein 5 (STAT5). (**d**) Activated STAT5 dimerizes and then (**e**) translocates to the nucleus, resulting in the upregulation of various anabolic target genes including IGF-1 and acid labile subunit (ALS) [13–15]. (**f**) IGF-1 and ALS pass to the circulation and form ternary complexes with Insulin-like Growth Factor-Binding Protein (IGFBP), about 75% as a 150 kDa complex with IGFBP-3. (**g**) Suppressors of cytokine signaling (SOCS) proteins are post-receptor inhibitors of cell signaling that mediate their effect via the JAK/STAT pathway [16]. GH rapidly and prominently induces expression of SOCS-3 and cytokine-inducible SH2-containing protein-1 (CIS-1) within the liver as part of a negative feedback loop that functions by blocking the phosphorylation of STAT5. SOCS-3 inhibits JAK2 by a mechanism requiring GHR. (**h**) The GHR has both an intra- and extracellular domain (ICD and ECD). Growth Hormone Receptor-Binding Protein (GHBP), present within the circulation, is produced by the inducible metalloproteolytic cleavage of the GHR's extracellular domain. Serum concentrations of this protein are thought to reflect GHR density [215]

Gender Differences in the GH/IGF-1 Pathway

GH is released in a pulsatile pattern that is gender-specific, with males experiencing higher peaks and deeper troughs compared to females [17]. Interestingly, STAT5 exists in two genetically distinct, although highly homologous, forms (STAT5A and STAT5B) [18] which are known to differ somewhat in their tissue distribution [19]. Of note, while STAT5A and STAT5B are both required for normal GH-dependent growth, STAT5B is responsive to pulsatile GH, whereas STAT5A is not. Indeed, STAT5B-deficient male mice have pronounced growth impairment, and tend to grow at a rate similar to normal females. Thus, the complex regulation of sexually dimorphic growth appears to be mediated, at least in part, by STAT5B "interpreting" the differing GH pulsatile secretion patterns of males versus females [18]. Given this, it seems plausible that any interference within the GH/STAT5B/IGF-1 pathway is likely to have a more pronounced effect on growth patterns in males than in females.

Insulin-Like Growth Factor Binding Proteins (IGFBPs)

The bioavailability of IGF-1 depends on its unbound or "free" fraction. Six specific high-affinity IGF-1-binding proteins (IGFBP-1 to IGFBP-6) are present within the circulation and can each bind IGF-1 with an affinity at least equal to the binding of IGF-1 to the IGF receptor [20]. The IGFBPs are each regulated by specific proteases that dramatically reduce their IGF-1-binding affinity. The specific function and structure of the six IGFBPs differ significantly [21]. IGFBP-1,-2,-4, and -6 primarily inhibit IGF-1 by tightly binding to it and preventing it from binding to its receptor [20, 22, 23]. Conversely, IGFBP-3 potentiates the action of IGF-1 by "loosely" binding to it, thus prolonging the time it is available within the circulation to interact with its receptor. About 75% of IGF-1 circulates as a 150 kDa ternary complex composed of IGF-1, acid-labile subunit (ALS), and IGFBP- 3 [20]. This large complex, which cannot cross the endothelial barrier [24] significantly increases the half-life of IGF-1 from less than 10 min to greater than 16 h [20]. Caloric and protein restriction can cause a reduction in the levels of IGFBP-3 [25, 26].

Growth Plate Proliferation, Senescence, and Fusion

The normal age-dependent decline in growth rate is due primarily to a senescent decline in the rate of growth plate chondrocyte proliferation[27, 28] referred to as "growth plate senescence" [29–31]. The proliferative capacity of the "stem-like" cells within the resting zone of the growth plate is finite. Thus, "senescence" is not a function of time per se, but of proliferative cycle number. Given this, it becomes apparent that interventions that slow the proliferation rate of growth plate chondrocytes, such as glucocorticoid exposure, will also slow the rate of growth plate senescence [30, 32]. That is to say, following transient growth inhibition, growth plates are "less senescent," retaining a greater proliferative capacity than expected for age. Thus, in the "post inhibitory period," the growth plate will show a greater growth rate than expected for age, resulting in "catch-up growth," the apparently "accelerated" linear growth that occurs after resolution of a growth-inhibiting condition [31, 33].

The pubertal growth spurt is primarily induced by estrogen, which acts to increase the activity of the GH/IGF-1 axis [34, 35]. In addition, the sex steroids, especially the androgens, appear to stimulate growth by a direct effect on growth plate chondrocytes [36–38]. Estrogen is also known to be the key hormone that promotes epiphyseal fusion [29].

Monitoring and Assessment of Growth

Standardized charts are available for graphically recording height, weight and height velocity such that an individual child's growth can be compared to normative values [39–41]. Wherever possible, reference data most appropriate to the child being monitored should be utilized. An individual child's growth measurement can be represented as a percentile or as a standard deviation score, a quantitative expression of distance from the reference population mean (50th percentile) for the same age and gender [42]. Healthy children grow steadily along the same height percentile and hence maintain the same standard deviation score for height from early childhood through until adulthood. Combined parental heights can be used to estimate a child's potential height [42]. Some temporary deviation from the usual growth channel may occur if the pubertal growth spurt occurs particularly early (temporary increase in height velocity and height centiles) or late (temporary decrease in height velocity and height centiles).

Definitions of Impaired Growth

Within a large patient group, skewing of standard deviation scores (SDS) for height below population reference values is evidence of disease-associated growth impairment. Mean height SDS of a population characterized by normal growth approximates zero. Growth disturbance in an individual child is indicated by an abnormal growth rate [42]. A definition in terms of static height measurement, although sometimes used, may be misleading, since it is so influenced by parental heights. An individual child may be normally short; conversely a previously tall child may Not have increased his height in two years, but still be of average stature. A shift from higher to lower centiles on a growth chart of height attained more sensibly signifies growth faltering. Height velocity, expressed either as a centile or as a standard devia-

tion score for age and gender, is the most sensitive parameter by which to recognize impaired growth. In the absence of historical linear growth information, the identification of linear growth impairment is challenging. In this scenario, referencing a patient's predicted or "target" height can be helpful. Target heights and their corresponding centiles/*Z*-scores can be calculated from an individual's parental heights using the mid-parental height formula [43]. Impaired growth can then be defined by the difference between current and target centiles. This definition would take into account an individual's genetically predetermined growth pattern as a predictor for current as well as ultimate adult stature.

Growth in Pediatric IBD

Prevalence of Growth Impairment in IBD

Inflammatory disease occurring during early adolescence is likely to have a major impact on nutritional status and growth because of the very rapid accumulation of lean body mass that normally occurs at this time. Further, boys are more vulnerable to disturbances in growth than girls because their growth spurt comes later and is ultimately longer and greater [4, 44].

Crohn Disease

Several studies have characterized the growth of children with Crohn disease (CD) as treated in the 1980s and into the 1990s [1, 45–50]. These studies are important as a benchmark of outcomes with traditional therapy. It is to be hoped that the now better understanding of the pathogenesis of growth impairment, together with the greater efficacy of current therapeutic regimens in healing intestinal inflammation, may lead to enhanced growth of young patients diagnosed now.

As summarized in Table 12.1, the estimated percentage of patients with Crohn disease, whose growth is affected, varies with the time of assessment, the definition of growth impairment and with the nature of the population under study (tertiary referral center versus population-based) [1, 45–55]. It has nevertheless been consistently observed that impairment of linear growth is common prior to recognition of Crohn disease as well as during the subsequent years, and that height at maturity has often been compromised [1, 45–54, 56, 57]. More recent data from the UK, Sweden, and USA suggest that the degree of deficit at maturity may be slowly reducing [57–59]. It is also apparent that these problems are, and remain, more frequent among males than females, independent of disease location or severity [1, 55, 56, 60–63]. The basis of this observed gender difference is yet to be fully elucidated. Interestingly, as the incidence of CD increases in geographic regions where it was previously rare, reports demonstrate that similar patterns of impaired growth are being observed [64, 65].

At the time of diagnosis mean standard deviation score (SDS) for height is reduced among children with Crohn disease as a group compared to reference populations (Table 12.2), an indication of the growth retardation occurring prior to recognition and treatment of intestinal inflammation [1, 46, 47, 50–52]. During the decade 1990–1999 in Toronto, mean SDS for height at time of diagnosis among 161 Tanner stage 1 or 2 children was −0.74 ± 1.2 [50], indicating overall lesser growth delay in comparison to the earlier decade [1]. Nevertheless, the percentage of children with height less than the fifth centile (SDS score <−1.8), based on Center for Disease Control 2000 data, was still 22% [50]. Mean SDS for height among 333 patients aged less than 16 years was −0.54 (95% CI -0.67 to −0.41) in a 1998–1999 population-based surveillance study of incident IBD in the United Kingdom [51]. Thirteen percent were below the third centile (SDS < −1.96) for height based on data from Child Growth Foundation, London [51]. In Israel, SDS for height at diagnosis among a cohort of 93 patients aged less than 18 years was −0.56 ± 1.16, but 20% had SDS score <−2.0 [52]. Taken together, these data confirm that growth delay prior to diagnosis remains a challenge [50–52]. Reassuringly, data from a more recent Canadian inception cohort of children diagnosed with Crohn disease between 2014 and 2017 demonstrated a more modest reduction in mean height *Z*-scores (−0.30 [95% CI: −0.39 to −0.20], with no significant differences noted across the age spectrum or gender [66]. The basis of these epidemiological differences in linear growth outcomes compared to earlier studies is unclear. While it may be possible that this is related to an underlying change in the relative proportions of specific disease phenotypes, it is more likely attributed to reduced diagnostic delay in the recent decade. Indeed, a single center study in Toronto of 111 children diagnosed with IBD found that diagnostic delay was longer among Crohn disease than ulcerative colitis (median 6.8 vs 2.4 months) and height impairment was independently associated with diagnostic delay (odds ratio 0.59 for height-for-age *Z*-score) with height impairment persisting 1 year after initial presentation [67]. This reaffirms the importance of a prompt diagnosis of IBD with regard to growth outcomes. Given the frequency of linear growth impairment in Crohn disease, growth failure was introduced as a key phenotypic component in the Paris modification for the Montreal disease classification system in pediatric Crohn disease in 2011 [68].

Delay in epiphyseal closure allows growth to continue longer than normal. Hence SDS for height may improve over the course of treatment, if chronic inflammation can be controlled [1, 47, 50]. Additionally, due to the delay of epiphyseal closure, improvement of linear growth may be protracted beyond the typical chronological age of linear growth cessation.

Table 12.1 Prevalence of linear growth impairment in pediatric Crohn disease. Varying definitions and times of assessment (at the time of diagnosis and during follow-up) are applied

Study details (ref)	Time of assessment	Patients studied	*n*	Definition of linear growth impairment	Percentage with growth impairment (%)
Baltimore, USA 1961 to 1985 [46]	At diagnosis	Prepubertal (Tanner I or II)	50	Decrease in height velocity prior to diagnosis	88
Toronto, Canada 1980 to 1988 [1]	During follow-up	Prepubertal (Tanner I or II)	100	Height velocity ≤2 SD for age for ≥2 years	49
Sweden 1983 to 1987 [47]	During follow-up	Population-based cohort <16 years at Dx	46	Height velocity ≤2 SD for age for 1 year	65
New York, USA 1979 to 1989 [48]	At maturity	Children in tertiary care	38	Failure to reach predicted adult height	37
Toronto, Canada 1990 to 1999 [50]	During follow-up	Prepubertal (Tanner I or II)	161	Height velocity ≤2 SD for age for ≥2 years	54
United Kingdom 1998 to 1999 [51]	At diagnosis	Population-based cohort <16 years at Dx	338	Height SDS < −1.96	13
Israel 1991 to 2003 [52]	At diagnosis	Children in tertiary care	93	Height SDS < −2.0	20
France 1988 to 2004 [55]	At diagnosis	Population-based cohort <17 years at Dx	261	Height SDS < −2.0	9.5

Table 12.2 Mean height standard deviation scores for height in children diagnosed with Crohn disease prior to or in early puberty (Tanner stage I or II)

Study (ref)	Patients studied	*n*	Mean height SDS (SD)	
			At diagnosis	At maturity
Baltimore, USA 1961 to 1985 [46]	Prepubertal (Tanner I or II)	50	−0.48	Not assessed
Toronto, Canada 1980 to 1988 [1]	Prepubertal (Tanner I or II)	100	−1.1 (1.3)	−0.82 (1.1)
Sweden 1983 to 1987 [47]	Population-based cohort <16 years at Dx	46	−0.5 (1.4)	−0.4 (1.1)
Toronto, Canada 1990 to 1999 [50]	Prepubertal (Tanner I or II)	161	−0.74 (1.2)	−0.70 (1.2)
United Kingdom 1998 to 1999 [51]	Population-based cohort <16 years at Dx	338	−0.54	Not assessed
Israel 1991 to 2003 [52]	Children in tertiary care	93	−0.56 (1.16)	Not assessed
Leiden, The Netherlands Reported in 2002 [54]	Children in tertiary care	64	Not reported	−0.9 (1.2)
London, UK 1996 to 2002 [53]	Prepubertal children in tertiary care	20	Not reported	−0.57 (0.3)
Finland 1987 to 2003 [56]	Population-based cohort <17 years at Dx	128	Not reported	Male: −0.56 Female: −0.24
Canada 2014 to 2017 [66]	Children in tertiary care at Dx	698	−0.30 (1.23)	–

Indeed, a large retrospective cohort study of 3007 pediatric IBD patients showed continued linear growth beyond the time of expected growth plate closure in the majority (80%) of the cohort, with median height gain greater in those with Crohn disease than with ulcerative colitis [69]. A separate subcohort of patients within the same study diagnosed with IBD *after* the expected age of growth plate closure also exhibited continued statural growth. While the authors acknowledge the lack of baseline bone age assessment as a study limitation, the findings do verify a high prevalence of delayed bone maturation among childhood IBD patients, especially those with Crohn disease [70]. As children with IBD do have the potential for catch-up growth beyond the expected point of bone maturity, linear growth should continue to be a therapeutic target even after the point of transition to adult care.

No population-based cohort studies have compared pre-illness height centiles with final adult stature in order to determine how often catch-up growth is complete. In spite of gains, past and current reports suggest that the mean adult height of patients with prepubertal onset of disease remains reduced compared to population reference data [1, 47, 50, 53, 54, 56–58]. Studies suggesting otherwise have included patients with post-pubertal onset of disease, and therefore not at risk for growth impairment [71]. There are in general few population-based studies of final adult stature in childhood IBD patients. Varying results between such studies, as alluded to above, could be explained by differing proportions of patients with pre-pubertal onset IBD. A recent large population-based Swedish study of final adult heights in childhood Crohn disease patients demonstrated a modest adjusted mean height difference of −1.3 cm (equivalent approximately to a *Z*-score of −0.2) compared to their matched healthy peers and a similar pattern of height difference was also significantly observed relative to their healthy siblings. Compared to their healthy peers, patients with prepubertal disease onset had a more marked adjusted mean difference in final adult height: −1.6 cm compared to −0.8 cm in those with disease onset during or after puberty [59]. Another population-based cross-sectional study examined the linear growth of 2372 Jewish Israeli adolescents with childhood-onset IBD. Although showing no overall difference in heights at late adolescence, subanalysis showed Crohn disease patients with onset of disease earlier than 14 years of age were significantly shorter (male: 172.7 cm vs 174.0 cm, female: 160.6 cm vs 162.0 cm) [72]. These results suggest that the effects of chronic inflammation on growth in the pre-pubertal phase may not be completely irreversible. Further studies are required to determine whether better access to newer therapeutic modalities in IBD would be able to ameliorate the deleterious effects on long-term growth outcomes in these patient subgroups.

Ulcerative Colitis

Cohort data are sparse in comparison to Crohn disease, but in general at diagnosis no significant reduction is observed in height-for-age standard deviation scores among young patients with ulcerative colitis compared to the reference population [47, 49, 51]. As an example, SDS for height was not reduced (mean −0.12, 95%CI −0.30 to 0.05) in 143 children and adolescents with incident UC in the British pediatric surveillance study [51]. A Canadian inception cohort of 392 children with UC/IBD-U diagnosed between 2014 and 2017 similarly described heights measured as comparable to age- and gender-matched standard populations (mean height

Z-score 0.11 [95% CI −0.01 to +0.22]) [66]. As such, linear growth impairment in UC at diagnosis is considered a rare presenting feature (<5%) and should prompt consideration of an alternative diagnostic label [73, 74]. Growth delay thus does not feature as a key phenotypic component in the Paris modification of the Montreal disease classification system for UC unlike CD [68].

In follow-up, growth impairment remains a less frequent complication, although relatively few studies have carefully described linear growth in ulcerative colitis as compared to the abundance of studies in Crohn disease. Hildebrand et al. observed that 11 (24%) of 45 children had a height velocity <−2.0 SD during at least one year [47]. Final attained mean height was comparable to reference population data in this study [47]. In a recent large population-based study of 4201 childhood IBD patients in Sweden, there was a modest reduction in the adjusted mean height difference (AMHD) among UC patients (−0.6 cm) relative to their matched reference peers, although there was a stronger association with lower adult mean height in CD patients (AMHD: −1.3 cm) [59]. This is the first population-based study to demonstrate childhood UC patients attaining a slightly shorter final adult height, a finding which the authors attribute to the much larger number of patients compared to earlier studies. However, drug prescription data could only be retrieved from 2005 and thus steroid exposure status could be determined in less than one-third of the UC patients. Hence it is not certain to what extent steroid dependence could have contributed to the slight growth deficit witnessed in the Swedish UC subgroup. Gupta and colleagues similarly noted in a cohort study of 3007 patients from the ImproveCareNow database registry, a surprisingly high proportion of UC patients (75%) having continued statural growth beyond the expected age of growth plate closure [69]. This suggests that delayed bone maturation could also be a prevalent problem in UC, although it is also not certain whether iatrogenic steroid exposure was the main etiologic factor rather than the disease phenotype itself.

Interestingly, Ricciuto and colleagues observed in a retrospective study of 74 children with primary sclerosing cholangitis (PSC) and colonic-type IBD (UC or IBD-unclassified) that these patients had significantly lower height-for-age and weight-for-age *Z*-scores at presentation compared to matched UC/IBD-U controls. The male gender was associated with higher height-for-age Z scores over time, contrary to the male predilection for poorer growth outcomes in CD [75]. These findings suggest a unique disease phenotype in PSC-IBD distinct from non-PSC UC/IBD-U and correspondingly differing influences on growth outcomes. A plausible mechanistic explanation could be a hepatic-related impairment of the GH/IGF-1 axis, which has been described in other forms of chronic liver disease such as non-alcoholic fatty liver disease and liver cirrhosis [76].

Why linear growth impairment is less common in ulcerative colitis than in Crohn disease is not entirely clear. Certainly, the interval between symptom onset and diagnosis correlates with the degree of growth impairment [51, 58, 77]. The usual colitis symptom of bloody diarrhea in ulcerative colitis is more promptly investigated than the often subtle presenting symptoms of Crohn disease, particularly the non-specific abdominal pain and anorexia associated with small bowel Crohn Disease, and the resulting difference in time to presentation may account at least in part for the lesser effect on growth prior to diagnosis. Underlying disease-related differences in cytokine production are likely also important. Notably, pubertal delay can contribute to growth impairment, and Crohn disease is more frequently associated with delayed puberty [44, 78, 79].

Sex Differences in Linear Growth Impairment

As mentioned, growth impairment is both more frequent and more severe in boys compared to girls with Crohn disease [1, 63]. These differences persist post diagnosis [56]. Gupta and colleagues found in a large retrospective cohort study of 3007 childhood IBD patients that continued linear growth beyond predefined chronological ages of expected growth plate closure occurred in 79% of male CD patients versus 83% of female CD patients ($p = 0.012$). The median final adult height was greater in males with UC than CD but did not statistically differ in females with UC compared to females with CD [69].This further supports the current body of evidence that male CD patients continue to have worse linear growth outcomes than female patients with CD .

Pathophysiology of Growth Impairment in IBD

As summarized in Table 12.3, several interrelated factors contribute to linear growth impairment in children with IBD. The fundamental mechanisms have recently been comprehensively reviewed [80].

Table 12.3 Factors contributing to growth impairment in children with Crohn disease

Factor	Explanation
Pro-inflammatory cytokines	Direct interference with IGF-1 mediation of linear growth
Decreased food intake	Cytokine-mediated anorexia, fear of worsening gastrointestinal symptoms
Stool losses	Mucosal damage leading to protein-losing enteropathy; diffuse small intestinal disease or resection leading to steatorrhea
Increased nutritional needs	Fever; required catch-up growth
Corticosteroid treatment	Interference with growth hormone and insulin-like growth factor-1

Chronic Caloric Insufficiency

Growth requires energy. Chronic undernutrition has long been implicated and remains an important and remediable cause of growth retardation [81]. Multiple factors contribute to malnutrition [82]. However, reduced intake, rather than excessive loss or increased need, is generally the major cause of the caloric insufficiency [83, 84]. Kirschner et al. reported caloric intakes of growth-impaired patients to average 54% of that recommended for children of similar height age [85]. Food restriction may be deliberate to avoid symptoms. More importantly, cytokine-mediated disease-related anorexia may be profound. Work in a rat model of colitis suggests that tumor necrosis factor alpha (TNFα) and interleukin-1 interact with hypothalamic appetite pathways via serotonin receptors [86, 87]. Human studies have demonstrated an association between inflammatory cytokines and alterations in gut hormones related to appetite such as ghrelin [88] and polypeptide YY [89]. While clinical studies have demonstrated that significant intestinal fat malabsorption is uncommon [90], leakage of protein is frequent [91]. However, neither have been shown to be common causes of undernutrition in Crohn disease. In general, resting energy expenditure (REE) does not differ from normal in patients with inactive disease, but can exceed predicted rates in the presence of fever and sepsis [92].Moreover, malnourished adolescents with CD fail to reduce their REE as efficiently as comparably malnourished patients with anorexia nervosa [92]. Reduction in REE is a normal biologic response to conserve energy. This relative failure of a compensatory mechanism has, again, been attributed to the effects of pro-inflammatory cytokines.

Direct Cytokine Effects

A simple nutritional hypothesis, where adequate caloric delivery would remediate any growth impairment, fails to explain all the observations related to growth patterns among children with IBD. To date, a variety of cytokines have been implicated in the pathogenesis of IBD including tumor necrosis factor-alpha (TNF-alpha), interferon-gamma (IFN-gamma), and multiple interleukins (including IL-6, IL-12, IL-17, and IL-23). The direct growth-inhibiting effects of pro-inflammatory cytokines released from the inflamed intestine have been increasingly recognized [93–96].

Disruption of the GH/IGF-1 Axis

As described above, IGF-1, produced by the liver in response to GH stimulation, is the key mediator of GH effects at the growth plate of bones. An association between impaired growth in children with Crohn disease and low IGF-1 levels is well recognized [97]. However, GH production in this setting has been shown to be normal [98]. The molecular mechanisms by which cytokines induce this state of "GH resistance" have not yet been completely elucidated. Conceptually, they could involve downregulation of the GH receptor (GHR), upregulation of post-receptor inhibitory proteins, reduced protein synthesis, and/or increased protein degradation. Information from both animal models and/or human studies supports each of these potential mechanisms [15, 16, 93, 95, 99–112] (Fig. 12.3).

IGF-1 Independent Mechanisms

Inflammatory cytokines inhibit linear growth through pathways other than IGF-1 production [113–116]. Animal experiments have shown that TNF-α and interleukin-1 (IL-1) increase chondrocyte death, and thus may have a deleterious effect on growth [95]. In an organ culture model of fetal rat parietal bone, marked impairment in osteoblast function and bone growth was observed with the addition of serum from children with CD, but not from children with ulcerative colitis, nor from healthy controls [96]. Finally, cytokines appear to impair end-organ responsiveness to circulating testosterone, thereby compounding the effects of under-nutrition in delaying progression through puberty [107].

The Role of IL-6 in Growth Impairment

As with a number of chronic inflammatory conditions, IL-6 is known to be elevated in the serum of pediatric patients with active CD, and predictive of clinical relapse [117]. IL-6 activates STAT3 via the glycoprotein 130 signaling receptor (gp130); a process that is negatively regulated by SOCS-3 [118–120]. SOCS-3 is also a negative regulator of GH signaling. Very recently, it was confirmed that IL-6:STAT3 activation correlates with mucosal inflammation in active pediatric-onset CD [121, 122].

Transgenic mice with defective growth have been found to overexpress interleukin-6 (IL-6). Antibody to IL-6 partially corrected the growth defect, whereas administration of IL-6 led to a decrease in IGF-1 before food intake was affected [93]. Similar to CD, children with juvenile idiopathic arthritis (JIA) also present with linear growth failure [123, 124]. Of note, IGF-1 levels are negatively correlated with IL-6 among this patient group [93]. The exact mechanism underpinning this observation, however, is not completely clear. While these, and other data [125] suggest an IL-6-mediated decrease in IGF-1 *production* [93]; work by DeBenedetti et al. suggests that the primary mechanism is a reduction in IGFBP-3 levels due to reduced production and/or increased proteolysis of this binding protein [106]. Previously, low levels of IGFBP-3 have been associated with accelerated clearance, and hence low levels, of IGF-1 [106].

Studies in both of these pediatric patient groups have demonstrated a significant "uncoupling" of osteoblast and osteoclast activities [108, 126–128]. Concurrent mouse and human studies have shown that chronic IL-6 exposure promotes osteoclast maturation and activation, affects osteoblasts, is associated with osteoclast/osteoblast uncoupling

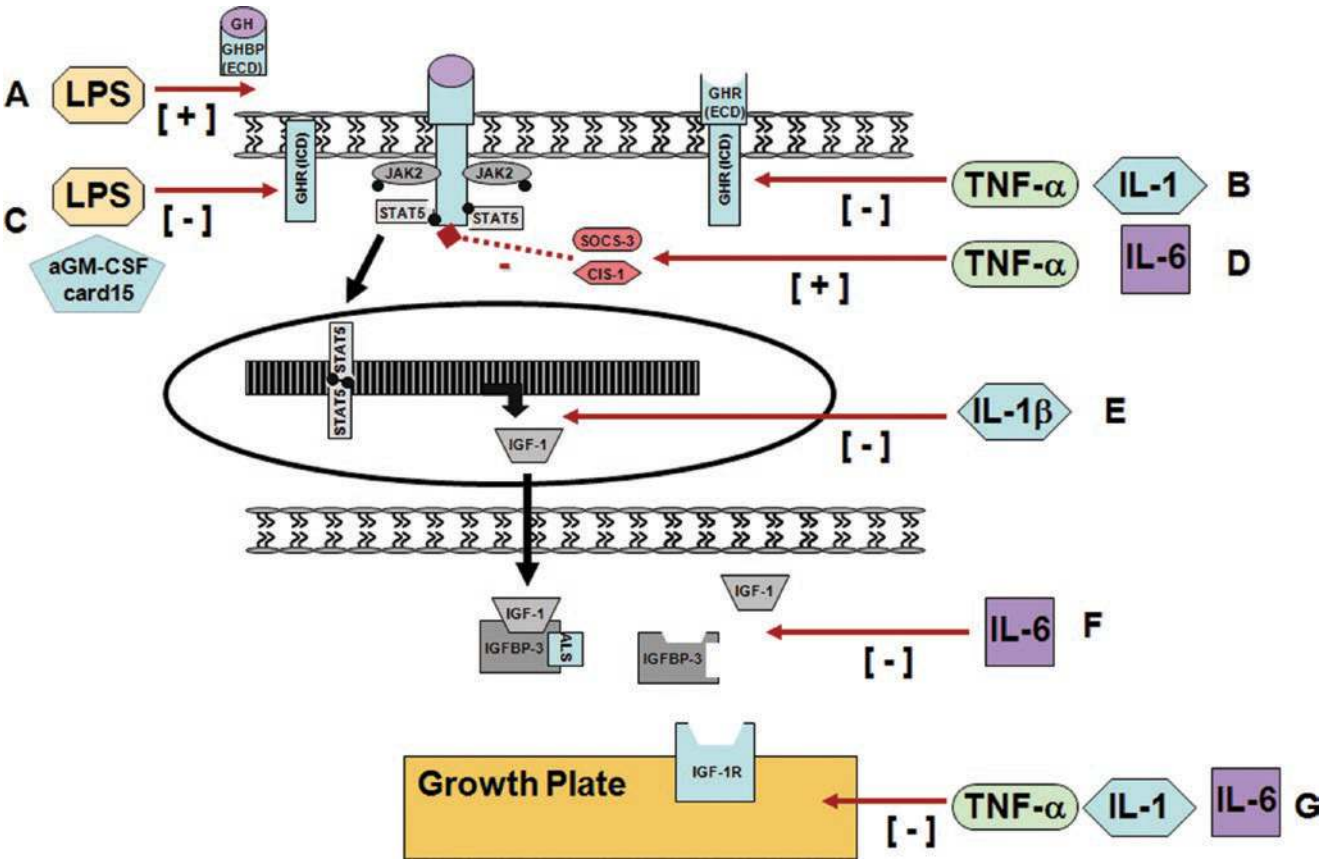

Fig. 12.3 Confirmed and potential molecular mechanisms that underpin the development of GH resistance in Crohn Disease: *At the Growth Hormone Receptor*: (**a**) Endotoxin exposure, specifically Lipopolysaccharide (LPS), reduces GHR density by inducing GHR proteolysis and increasing the shedding of GHBP [99] (mechanism not yet ascertained). (**b**) TNF alpha has been demonstrated to downregulate GHR formation via inhibition of Sp1/Sp3's ability to transactivate the GHR gene [100]. Il-1 suppresses GHR promoter activity [100]. (**c**) LPS can directly inhibit GHR gene expression via a cytokine-independent mechanism through the TLR-4/MD2 signaling pathway that results in a cytokine response, significant reduction in GHR promoter activity. Importantly, the addition of anti-TNF-alpha antibody failed to abrogate this effect [101]. Innate immune pathways associated with granulocyte-macrophage colony stimulating factor autoantibodies and card15 deficiency can also reduce GHR expression [112]. *Via post-receptor inhibitory proteins*: (**d**) IL-6 and TNF-alpha can upregulate the expression of SOCS-3 and cytokine-inducible SH2-containing protein (CIS)1 [15, 102]. Both of these proteins have, in turn, been shown to inhibit GH signaling by blocking the phosphorylation of STAT5 [16, 103, 104]. *Via reduced protein synthesis*: (**e**) IL-1β has been shown to reduce IGF-1 mRNA levels. The mechanism is yet to be elucidated, but does not appear to be via upregulation of SOCS nor by impairment of JAK2/STAT5 signaling [105]. *Via increased protein clearance*: (**f**) IL-6 has been implicated in a reduction in IGFBP-3 levels due to either reduced production and/or increased proteolysis [106]. Previously, low levels of IGFBP-3 have been associated with accelerated clearance, and hence lower levels, of IGF-1 [106]. *Via IGF-1 independent mechanisms*: (**g**) Animal experiments have shown that TNF-α and interleukin-1 (IL-1) increase chondrocyte death and thus may have a deleterious effect on growth [95]. Cytokines appear to impair end-organ responsiveness to circulating testosterone [107]. IL-6 exposure promotes osteoclast maturation and activation, affects osteoblasts, is associated with osteoclast/osteoblast uncoupling and results in thinning of the growth plate [93, 108–111]. Although the mechanism is yet to be determined, laboratory evidence suggests that it is independent of IGF-1 [108]

and results in thinning of the growth plate [93, 108–111]. Again, while the mechanism is yet to be determined, laboratory evidence suggests that it is independent of IGF-1 [108].

Taken together, these data suggest that increased IL-6 may represent a major generalized mechanism by which chronic inflammation affects the developing skeleton. This would imply that anti-IL6 therapeutic approaches, which have shown promising anti-inflammatory efficacy in CD, rheumatoid arthritis, and systemic JIA [129–132], may also specifically address the problem of growth impairment. Notably, in a rat model with TNBS-induced colitis and poor growth, treatment with an anti-IL6 antibody enhanced IGF-1 expression and growth without reducing intestinal inflammation [125].

The Interplay Between Nutrition And Cytokines

Thus, inflammation may have a direct effect on linear growth, via the mechanisms described above, as well as an indirect effect via its effect on the appetite centers of the brain and subsequent reduction in caloric intake. The relative contribu-

tions of malnutrition and inflammation to linear growth delay were explored by Ballinger et al. using a rat model of TNBS colitis [94]. Two control groups were used: healthy controls with free access to food, and a pair-fed group comprised of healthy animals with daily food intake restricted to match that of colitic rats [94]. In the colitic rats, IGF-1 levels were reduced to 35% of control values. Comparison with the healthy but undernourished pair-fed rats suggested that malnutrition accounted for 53% of the total depression of IGF-1 in colitic rats, with the remaining 47% directly attributable to inflammation [94].

Disruption of the GH/IGF-1 Axis by Cytokine-Independent Molecular Pathways

Impaired intestinal barrier function is a recognized feature in some patients with CD, and may predispose them to chronic, subclinical, endotoxin exposure, specifically lipopolysaccharide (LPS)[133]. Various groups are currently investigating whether LPS directly interferes with the GH/IGF-1 axis via cytokine-independent mechanisms. To date, in-vivo data from a mouse model have demonstrated that LPS exposure reduces GHR density by inducing GHR proteolysis, probably via the metalloprotease cleavage site, resulting in the increased shedding of GHBP [99]. More recent in-vitro data demonstrate that LPS can directly inhibit GHR promoter activity and subsequent expression through an effect on the TLR-4 signaling pathway[101]. Both mechanisms are seemingly independent of the inflammatory cytokine cascade and the addition of anti-TNF-alpha antibody failed to abrogate the effect [101]. Although intriguing, the clinical significance of these findings and their relative importance in the setting of growth impairment and CD are yet to be determined.

Interaction Between the Gut Microbiome and the GH/IGF-1 Axis

The interaction between the gut microbiome in inflammatory bowel disease, the GH/IGF-1 axis, and bone health could account for another mechanistic explanation for linear growth impairment in IBD. The anti-inflammatory properties of microbial metabolites, short-chain fatty acids (SCFAs), are of particular interest as potential therapeutic targets. Gut microbial dysbiosis with the reduction of SCFA-producing bacteria and consequently reduction in key SCFA concentrations such as butyrate, have been postulated mechanisms in the pathogenesis of inflammatory bowel diseases [113, 114]. There has been emerging research on the influence of the gut microbiome and the role of short chain fatty acids, on bone metabolism. Jing and colleagues report the induction of IGF-1 through colonization of germ-free mice with pathogen-free gut microbiota resulting in an increase in longitudinal and radial bone growth. Antibiotic treatment reduced IGF-1 production and bone formation in a mouse model, and SCFA supplementation of these antibiotic-treated mice restored IGF-1 levels and bone mass [115, 116]. Modulation of the gut microbiome could form the basis of future therapeutic targets for improving bone health and linear growth in IBD.

Corticosteroid Suppression of Linear Growth

The growth suppressive effects of glucocorticoids are multifactorial, and can occur at virtually any point along the growth axis (Table 12.4) [134]. In general, exogenous corticosteroids are considered to create a state of functional GH deficiency [78]. Dose, preparation, and timing of glucocorticoids all influence the degree of growth suppression observed. It appears that concentrations of glucocorticoids required to exert direct suppression on the growth plate may be lower than those required to suppress GH secretion. Growth, particularly in prepubertal children, can be impaired by relatively modest daily doses of prednisone (3–5 mg/m^2) [134]. This effect may be reduced, but is not necessarily eliminated, by alternate-day therapy. Selectively eliminating evening administration may avoid blunting of both nocturnal

Table 12.4 The effects of exogenous glucocorticoid therapy related to linear growth [134]

GH/IGF-1 axis
Inhibit endogenous GH secretion
Reduce pulsatile release of GH Increase somatostatin
Interference with the GHR
Reduce GHR expression Reduce GHR binding Uncouple GHR from signal transduction components
Reduce IGF-1 activity levels
Reduced activation of STAT5b Increased levels of IGFBP-3
Skeletal system
Growth plate
Inhibit chondrocyte mitosis Inhibit IGF-1 induced chondrocyte proliferation Inhibit epiphyseal maturation
Skeletal matrix
Diminish activity of enzymes required for post-translational procollagen chain modification Inhibit collagen synthesis Increase collagen degradation Inhibit osteoblast function
Peripheral tissues
Calcium balance
Decrease intestinal calcium absorption Increase urinary calcium excretion
Body composition
Increase protein catabolism Decrease lipid oxidation
Inhibit secretion of adrenal sex steroids
Reduce direct growth stimulatory effect of sex steroids Reduce usual augmentation of GH release

Adapted from Allen D.B., *Acta Paediatrica,* 1998 [134]

GH secretion and/or ACTH induced adrenal androgen production [134]. Catch-up growth, following the cessation of glucocorticoid therapy, does not always fully compensate for growth deficits, particularly when treatment occurs during puberty. Although chronic daily dosing and frequent induction courses of steroids have been shown to lead to bone demineralization, at present, there is *not* good evidence that short-term use of steroids for the induction of remission in CD is detrimental to long-term growth.

The Pathogenesis of Pubertal Delay and Its Influence on Growth Impairment

Puberty is frequently delayed in young patients with CD [78]. It not only results in linear growth impairment, but also decreases bone mineralization and can significantly impact a patient's quality of life and psychological health [79]. In girls with Crohn disease, a delay in menarche is closely related to delays in skeletal maturity [135]. Pubertal delay is defined as the absence of testicular enlargement in boys or breast development in girls at an age that is 2–2.5 standard deviations later than the population mean [5]. Traditionally, the mean age has been 14 years in boys and 13 years in girls; however, with recent downward trends in pubertal timing in many countries, some observers are advocating for younger age cut-offs [5, 136, 137].

As alluded to earlier, the factors that trigger normal pubertal onset remain elusive [5], thus impeding our comprehension and complete understanding of the mechanisms that underlie pubertal delay in CD. Similar to linear growth impairment, although undernutrition has been frequently considered the main reason for delayed puberty in children with CD, there is a group of patients with persistently active disease who do not enter puberty despite the provision of adequate energy [138]. Experimental colitis models demonstrate that inflammatory mediators potentiate the puberty-delaying effects of undernutrition [78, 139–141] via alterations in gonadotropin-releasing hormone (GnRH) secretion patterns, although which specific inflammatory cytokines impact on puberty are yet to be determined. However, both human and experimental data suggest that there is also an element of gonadotropin resistance in pubertal delay, and in vitro studies implicate TNF-alpha in the downregulation of androgen gene expression [142]. Although Cushing's disease has been associated with pubertal delay [143, 144], it is not known whether the doses of corticosteroid used in the management of CD are sufficient to delay either the onset or progression of puberty [78].

Influence of Genetic Factors

A number of genetic polymorphisms have been implicated in CD susceptibility and pathogenesis, the most prominent of which are within the NOD2 gene. While some investigators [145, 146] have suggested that CD-associated NOD2 polymorphisms may be determinants of growth impairment, neither analysis controlled for disease location. A subsequent careful analysis of growth prior to and following diagnosis found no such association [52]. Scottish pediatric data suggest an association between polymorphisms in the IBD5 susceptibility locus and low anthropometric centiles at diagnosis [147]. Similarly, data from Boston examining 14 different CD susceptibility genes highlight a potential association with the CD susceptibility allele within ATG16L1 [148].

It is feasible that common genetic polymorphisms which alter cytokine expression may contribute to growth impairment but not influence overall susceptibility to CD. A recent study of Israeli patients suggests that relatively common variations in the promoter region for TNFα may have an independent effect on linear growth outcomes [149]. Similarly, data from Sawczenko et al. demonstrate a potential causal relationship between variation in the promoter region for Il-6, subsequent IL-6 expression, and a differential in linear growth impairment during active inflammation [125]. Confirmation of these and similar findings is awaited and may help better elucidate the complex molecular interactions pertinent to the pathophysiology of growth impairment.

Facilitation of Normal Growth in IBD

The Importance of Prompt Recognition of IBD

The clinical presentation of childhood Crohn disease may be subtle and varied. Impairment of linear growth and concomitant delay in sexual maturation may precede the development of intestinal symptoms and dominate the presentation. Prompt diagnosis is important in avoiding a long period of growth retardation. The greater the height deficit at diagnosis, the greater is the demand for catch-up growth.

The Importance of Monitoring Growth

In caring for children with IBD, it is important to obtain pre-illness and parental heights [57], so that the impact of the chronic intestinal inflammation can be fully appreciated. Following diagnosis and institution of treatment, regular measurement and charting of height, together with calculation of height velocity, are central to management. A properly calibrated wall-mounted stadiometer is required for accurate and reproducible serial measurements.

Part of the assessment of response to therapy in children with IBD is a regular analysis of whether rate of growth is normal for age and pubertal stage and whether catch-up growth to pre-illness centiles is being achieved. Height velocity should be appraised in the context of current puber-

tal stage, because of the variation in normal rates of growth before puberty, during puberty and near the end of puberty. If growth and puberty appear either delayed or very advanced, radiologic determination of bone age can be used to indicate the remaining growth potential. Delayed radiological bone age suggests greater potential for catch-up growth than may be anticipated for the subject's chronologic age. Conversely, in the subject with growth failure and a normal bone age, the potential window to achieve any growth catch-up may be very small.

One of the difficulties in evaluating growth in response to a therapy is the relatively long interval of time required for valid assessment. Published normal standards for height velocity throughout childhood are based on height increments during 12-month periods [150]. When growth velocity is calculated over short time periods, small errors in individual measurements are significantly magnified, and the normal seasonal variation in growth is overlooked. The consensus from pediatric endocrinologists is that height velocity should be calculated over intervals no shorter than six months [150]. On a research basis, efforts to reflect growth changes over intervals shorter than six months have focused on measuring changes in lower leg length by knemometry and on determination of circulating levels of markers of bone and collagen metabolism [150–152]. The clinical utility of routine serial assessment of the GH/IGF-1 axis is yet to be ascertained [153]. A valid indicator of contemporaneous linear growth would allow for a more timely change in therapy. A summary of techniques that should be employed to clinically assess and monitor linear growth through to adulthood, based on Heuschkel and colleagues management guideline, are presented in Table 12.5 [154].

Table 12.5 Techniques to assess and monitor linear growth in children with CD

Initial evaluation
Accurate measurement of the patient's height and weight by trained staff using reliable equipment
Accurate pubertal assessment
Accurate measurement of the biological parents' heights and calculation of mid-parental height (MPH) *Formula to estimate a subject's potential adult height* Male: MPH plus 6.5 cm; Female: MPH minus 6.5 cm
Obtain pre-illness anthropologic (height, weight) data on the patient
Radiological bone age estimation
Dietetic assessment of caloric, Ca, Vitamin D, and micronutrient intake
Ongoing monitoring
Accurate height and weight measurements by trained staff using reliable equipment
Calculate height velocity
Calculate *Z*-score for height, weight and height velocity data and/or plot sequentially on gender specific, ethnically appropriate reference curve
Accurate pubertal assessment
Consider repeat bone age estimation
Endeavour to follow until adult height achieved (Tanner stage 5 and <0.5 cm linear growth annually)

Psychosocial Impact of Impaired Growth

Growth impairment and accompanying pubertal delay have a significant psychosocial impact on adolescents, as the physical differences between them and healthy peers become progressively more obvious. In the development process of a disease-specific health-related quality of life instrument for pediatric IBD, body image issues including height and weight were among the concerns most frequently cited by adolescents with Crohn disease [155].

General Principles of Management

Prior to recognition of the direct influences of pro-inflammatory cytokines on linear growth, management of growth-impaired children focused on nutritional restitution [81, 85]. Improved growth following supplementary enteral or parenteral nutrition is well documented [156–158]. Decreases in inflammatory parameters and increases in IGF-1 occur very early during exclusive enteral nutrition and precede changes in nutritional parameters [159], highlighting that nutrition and inflammation constitute a bidirectional pathway [160]. Nevertheless, a subset of patients fail to grow despite nutritional repletion, presumably because intestinal inflammation remains chronically active. Hence, in the management or prevention of growth impairment, attention needs to focus on providing adequate nutritional support, as well as treating inflammatory disease using the most appropriate pharmacologic, nutritional, or surgical intervention available [154, 161] (Table 12.6). A comprehensive management guideline is available for children with IBD-related growth failure [154].

Anti-Inflammatory Treatments and Effects on Growth

Few interventions have been tested in the randomized controlled trial setting in children, and hence the effects of therapies on growth have seldom been rigorously assessed. The one exception is enteral nutrition as primary therapy of pediatric Crohn disease. For most other therapies, until recently, growth outcomes have been reported only in observational/retrospective studies. However, given the importance of persistent inflammation in the pathogenesis of growth impairment, it is intuitive that therapies which achieve mucosal healing are more likely to facilitate normal

Table 12.6 Strategies for managing growth failure in children with CD

Initial evaluation
Detailed assessment of disease activity and distribution
Ensure optimal nutrition (supplement energy and/or substrates as required)
Induction of remission
Aim for the rapid induction of a complete remission
Endeavor to avoid/minimize steroid usage (enteral therapy)
Consider surgical resection, especially in cases of limited localized ileal/ileocecal disease
Use biological therapies when other medical options have failed and surgery is not appropriate
Monitor closely and ensure remission is achieved in a timely fashion
Maintenance of remission
Aim for a prolonged, ongoing continuous remission
Consider the early introduction of immunomodulator therapy
Ensure optimal nutrition (supplement energy and/or substrates as required)
Monitor closely to ensure the persistence of remission and the timely re-induction of remission in the event of disease relapse
Persistent growth failure in the setting of clinically quiescent CD
Ensure optimal nutrition (supplement energy and/or substrates as required)
Detailed re-assessment of disease activity and distribution
Consider alternative causes of poor growth (including endocrinological and psychosocial)

growth. When assessing the available evidence of any treatment's impact on linear growth, two important questions need to be considered: were the population of patients being studied growth impaired prior to commencing therapy (recognizing that linear growth impairment is not a universal feature of all young patients with active CD); did the population being studied still have enough remaining "growth potential" for any therapeutic impact to be measurable. Below, treatments of pediatric IBD will be briefly discussed with respect to their potential effects on growth. A detailed Cochrane review by Newby and colleagues is available [162] for reference.

Enteral Nutrition

Prior to the availability of biologic therapies, acute treatment options for moderately to severely active Crohn disease were limited. "Exclusive enteral nutrition" (EEN) refers to the administration of formulated food as sole source nutrition. It has been shown to decrease mucosal cytokine production and induce endoscopic healing [163] . The appeal of EEN among pediatric patients primarily relates to avoidance of steroid therapy [161]. Amino acid-based and peptide-based formulae are administered by nocturnal nasogastric infusion, but more palatable polymeric formulae can be consumed orally, and appear comparably efficacious [164]. Some have argued that active Crohn disease occurring in children is more responsive than that occurring in adults, where corticosteroid therapy more often induces clinical remission [165, 166]. It seems likely, however, that other factors, such as small bowel localization and recent onset of Crohn disease, rather than young age per se, influence responsiveness of intestinal inflammation to exclusive enteral nutrition [167, 168]. Nevertheless, enteral nutrition does seem to be more feasible in pediatric patients. Children quickly become adept at swallowing the silastic catheter required for nasogastric feeding regimens and can remove it each morning before school.

If enteral nutrition is to facilitate growth, remission must be maintained. One of the limitations of liquid diet therapy has been the observed tendency for symptoms to recur promptly following its cessation [169]. Chronic intermittent bowel rest with nocturnal infusion of an elemental diet one month out of four has been reported as a means of sustaining remission and facilitating growth [157]. Another nutritional strategy, continuation of nocturnal nasogastric feeding four to five times weekly as supplement to an unrestricted ad lib daytime diet was also associated with prolonged disease quiescence and improved growth in a historical cohort study [158]. Maintenance EEN, however, is not always well tolerated by patients.

A recent multicenter Canadian inception cohort study of 377 pediatric CD patients from the CIDsCaNN[1] registry network compared long-term growth outcomes at 18 months post-diagnosis between patients receiving EEN induction versus those receiving corticosteroid(CS) induction stratified by baseline linear growth status [170]. Notably, within the subgroup of patients with no evidence of growth impairment at diagnosis (73% of the cohort), there was no detectable change in growth pattern by 18 months regardless of therapy group. In the smaller subgroup with baseline growth impairment (27%), while both treatment arms showed evidence of improved linear growth, the degree of improvement at 18 months was significantly greater in the EEN group compared to the CS group. Consistent with this finding, a propensity matched analysis of 111 patients in a single Canadian center similarly showed that while EEN-treated patients had a significantly greater linear growth recovery than CS patients at the 1-year follow-up (Δ Height *Z*-score 0.09 vs −0.14), this effect was not sustained over the 6-year follow-up period of the study [171]. These results suggest an initial advantage of EEN over CS in facilitating early catch-up growth in a selected subset of CD patients with baseline growth impairment. The apparent absence of any longer term linear growth advantage based on initial therapy choice is likely explained by current ongoing treatment paradigms that discourage recurrent steroid use and favor the early introduction of effective steroid-sparing therapies such as anti-TNF agents [170].

[1]CIDsCaNN: Canadian Children Inflammatory Bowel Disease Network

Corticosteroids

Conventional corticosteroids are still the most commonly used drug to treat acute disease exacerbations of pediatric Crohn disease and ulcerative colitis. Resolution of inflammation, if sustained following a short course of steroids, will be associated with normal linear growth. Chronic daily administration of corticosteroids to control intestinal inflammation is clearly contraindicated in pediatric IBD because of the interference with linear growth in addition to the other unwanted long-term adverse effects common to children and adults. Children with moderate symptoms of active Crohn disease localized to the ileum and/or right colon may respond to short-term treatment with controlled ileal release budesonide. Cosmetic effects of steroids are spared in this context, even if efficacy is overall less than with conventional corticosteroids[172, 173]. Studies in adults demonstrate little benefit in comparison to placebo in maintaining remission. Limited clinical experience with maintenance budesonide in children raised concern that linear growth was impaired during therapy in spite of good weight gain [174].

Immunomodulatory Drugs

The steroid-sparing roles of immunomodulatory drugs, azathioprine, 6-mercaptopurine, and methotrexate, are well documented [175, 176]. In a multi-center trial, newly diagnosed children with moderately severe Crohn disease treated with an initial course of prednisone were randomized to receive either concomitant 6-mercaptopurine or placebo [175]. A beneficial effect on linear growth was not clearly apparent in this study in spite of the steroid-sparing effect and improved control of intestinal inflammation, perhaps a function of sample size and difficulties inherent in comparing growth rates among patients of varying ages and pubertal stages [150]. Retrospective data have shown enhancement of linear growth, when methotrexate was given to young CD patients intolerant of or refractory to thiopurine therapy [176], a finding replicated in a recent prospective observational cohort [177].

Anti-Tumor Necrosis Factor-Alpha (Anti-TNFα)

The development of anti-cytokine therapies, such as infliximab and adalimumab, with the potential to achieve mucosal healing, even in otherwise treatment refractory patients constitutes a tremendous advance. The efficacy of anti-TNF agents in pediatric as well as adult patients is well established [178]. Considering the role cytokines, including TNFα, play in growth impairment, and the ability of anti-TNFα antibodies to achieve mucosal healing, it is of little surprise that both observational [177, 179–188] and clinical trial [189–191] data demonstrate a beneficial effect on linear growth, if treatment is undertaken early enough prior to or during puberty in children demonstrating evidence of linear growth impairment. Data from a clinical trial of adalimumab in pediatric Crohn Disease patients demonstrated a significant and rapid improvement in median height velocity *Z*-scores among those with baseline growth retardation (baseline −3.25 to −0.34) by week 26 and normalization (0.21) by week 52, but no such effect was seen in patients without growth delay [192]. Complementary data have demonstrated a restoration of hepatic GH signaling and improved anabolic metabolism in the setting of TNFα blockade [193]. Furthermore, and consistent with our evolving mechanistic understanding of IBD-related growth impairment, improvement in height velocity with the use of TNFα therapy has been correlated with increases in IGF-1 and IGFBP-3 levels with no accompanying change in serum GH levels [194]. These observations are cause for optimism that the medical therapy for Crohn disease available in the present decade will reduce the prevalence of sustained growth impairment in pediatric patients. As alluded to earlier in the chapter, the deleterious effects of uncontrolled chronic inflammation on growth during or prior to puberty may be partially irreversible, thus a "top-down" approach with anti-TNF therapy as primary induction should be strongly considered in patients who already present with severe growth retardation at diagnosis [195].

Surgery

Optimal management of young patients with IBD includes appropriate and timely referral for intestinal resection. Sustained steroid-dependency and associated impairment of linear growth should not be tolerated in children with ulcerative colitis, where colectomy cures the disease and restores growth [196]. For some children with Crohn disease, notably those with localized internal penetrating or stricturing disease, timely surgical intervention is a very attractive therapeutic option. Despite the almost inevitable endoscopic and subsequent clinical recurrence of CD, the significant period of post-operative remission that can be anticipated in many patients allows important catch-up growth in patients undergoing operation prior to or during early puberty [197–199].

Hormonal Interventions

The potential therapeutic role of GH and IGF-1 in pediatric IBD patients with persistent growth impairment is an alluring prospect. There have been increasing pediatric data exploring this over the last several decades [200–203] culminating in three small randomized trials [204–206]. These data have been recently reviewed by Vortia and colleagues [207]. The rationale for pursuing GH therapy (GHT) in growth impaired IBD patients is strengthened by the improved growth that has been recently observed following GHT in children with juvenile idiopathic arthritis [208] and cystic fibrosis [209] To date, while demonstrating that GHT

can improve short-term linear growth in select CD patients, it should be emphasized that there are no data yet available to suggest that GHT will alter the final adult height of children with IBD associated growth disturbance. There is a small experience with the supplemental use of GH during ongoing steroid therapy in a number of pediatric conditions [107] including steroid-dependent CD [210], again without evidence that final adult height is impacted.

Beyond its "anti-glucocorticoid" effects, it is possible that GHT has a direct anti-inflammatory effect in IBD. A randomized controlled clinical trial by Slonim in 2000 demonstrated a possible positive effect of GHT on disease activity in adults with Crohn disease [211]. Recent experimental data support this finding; wherein GHT was demonstrated to reduce mucosal inflammation in an experimental colitis via an IGF-1-independent mechanism that downregulated IL-6/STAT3 [212] but did not reverse local inflammatory resistance to the GH up-regulation of IGF-1 [212]. However, clinical data in pediatrics are scant and the observations conflicting [205, 206] Despite the possible benefits, GHT may also introduce a variety of risks and complications. Described adverse systemic effects of GHT include altered carbohydrate metabolism with glucose intolerance, a transient increase in total body fluid, hypertension, cardiac disease, stimulation of autoimmune disease, and increased malignancy risk. Given the variety of potential risks and complications, GHT, as either an adjunct to support linear growth or as a form of anti-inflammatory therapy, should be considered experimental in the setting of IBD, and is still best limited to formal investigative study settings.

Studies on the utility of recombinant IGF-1 on growth in CD have not been described to date. This is likely due to the theoretical risk of colon cancer with high circulating levels of IGF-1. A model has recently been formulated that allows for the calculation of a dose in children with active CD that would maintain IGF-1 levels within normal limits [213]. It remains to be seen whether future studies determine this to be any more effective than GH therapy.

Although there are no controlled clinical studies, three to six months of testosterone therapy, carefully supervised by pediatric endocrinologists, has been used in boys with extreme delay of puberty and has been associated with a significant growth spurt [78, 214].

It must be emphasized, however, that children requiring consideration of these adjunctive hormonal therapies should be encountered increasingly less commonly. Treatment of intestinal inflammation and assurance of adequate nutrition are of much greater importance. However, targeted therapies based on our current understanding of the GH-IGF-1 axis may be important for patients with significant linear growth impairment whose inflammation remains refractory to best current anti-inflammatory therapies.

Summary

Increased understanding of the mechanisms of linear growth impairment associated with chronic inflammatory disease points the way toward better management. Early recognition of Crohn disease remains an important challenge. Following diagnosis of IBD, restoration and maintenance of a child's pre-illness growth pattern indicate success of therapy. Current treatment regimens limit the use of corticosteroids, via optimization of immunomodulatory drugs, use of enteral nutrition in Crohn disease, and, if necessary, surgery for ulcerative colitis and for intestinal complications of localized Crohn disease. Biologic agents with the potential for mucosal healing hold promise of growth enhancement even among patients with otherwise refractory disease, whose growth was previously compromised. For all interventions, there is a window of opportunity, which must be taken advantage of before puberty is too advanced.

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Inflammatory Bowel Diseases and Skeletal Health

13

Francisco Sylvester

Introduction

The skeleton is a scaffold for soft tissue but is also the largest calcium reservoir in the body. Bone marrow harbors and interacts with hematopoietic precursors. In addition, bone tissue is metabolically active and susceptible to regulation by local and systemic signals, including those generated during active intestinal inflammation. Moreover, mechanical strain exerted by skeletal muscle is anabolic to bone. Since muscle mass is frequently decreased in inflammatory bowel disease (IBD), anabolic strain by striated muscle can be weakened. In addition, children with IBD can have deficiencies in macro- and micronutrients that impact the availability of protein to synthesize bone matrix and calcium and phosphate to mineralize it. Consequently, the integrity of the skeleton is vulnerable to the effects of IBD on bone cell function and muscle mass. In addition, IBD may influence bone indirectly, by inhibiting key endocrine axes, such as insulin-like growth factor-1 (IGF-1) and sex steroids, which are critical for bone formation and maintenance of skeletal mass.

Childhood is characterized by active bone metabolism and growth in size and width due to the combined activities of bone cells and the growth plate. In the 2 years before and 2 years after the growth spurt in height, children gain about 33% of adult total bone mass [1, 2]. Since IBD typically strikes at this time in children, the skeleton is susceptible to the effects of IBD on bone mass and structure.

Bone modeling is the process responsible for bone tissue expansion in childhood until skeletal maturity is reached. Bone modeling involves bone-forming osteoblasts, bone-resorbing osteoclasts, and osteocytes. All three cell types are active *at the same time* on different bone surfaces, resulting in bone mass gains (Fig. 13.1) [3]. Osteoblasts, osteoclasts, osteocytes, and chondrocytes may be sensitive to disease and treatment effects in children with IBD, impairing bone formation and linear growth [4]. *Bone remodeling* is, on the other hand, a slower process that aims to repair and maintain existing bone mass and architecture. It involves the *sequential* activities of osteoclasts and osteoblasts under the direction of osteocytes on the same bone surface. Osteoclasts first dissolve stressed or microfractured bone. Osteoblasts then lay down bone matrix formation to fill the resorbed cavity. This process is orchestrated by osteocytes embedded in the bone matrix [5]. In children with active IBD, both bone metabolic activity and linear growth are impaired [6]. Both modeling and remodeling may be affected by multiple influences, including malnutrition, inflammation, inactivity, hypogonadism, and medications such as corticosteroids [4]. In this chapter, we will review current clinical and experimental evidence of the effects of IBD on the pediatric skeleton.

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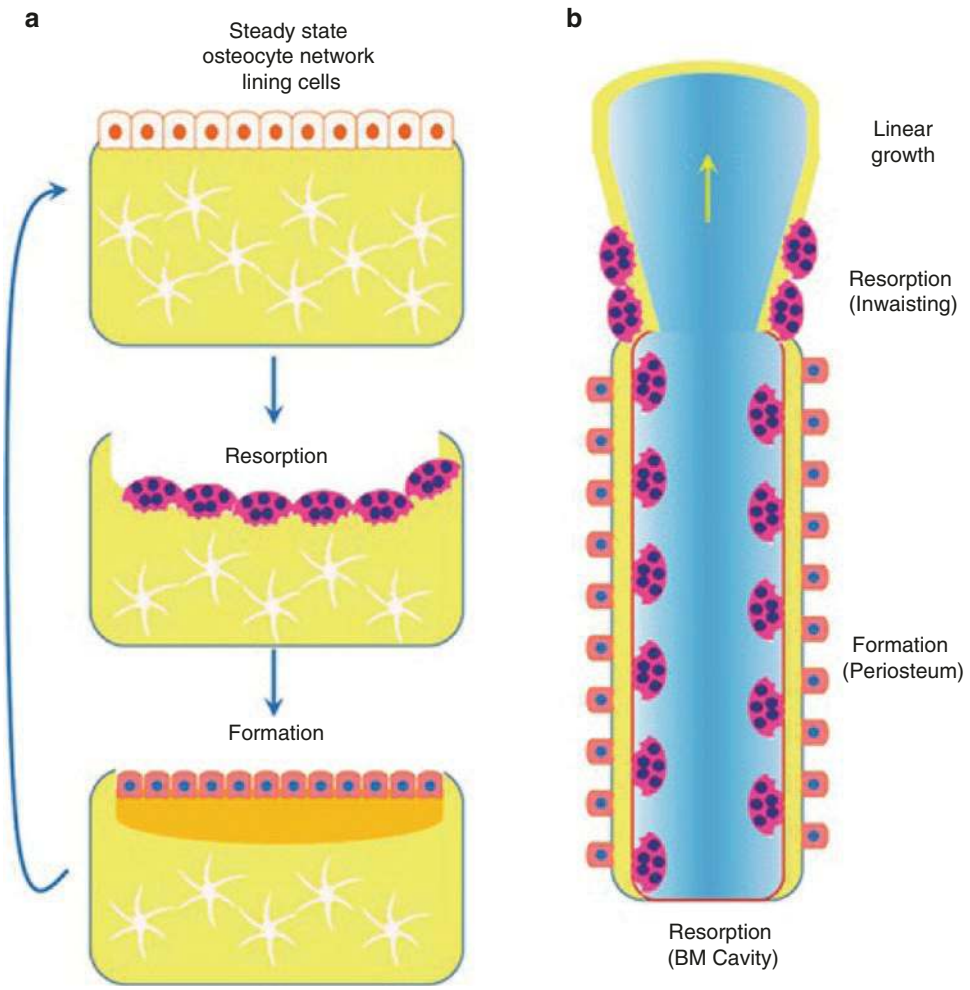

Fig. 13.1 Bone modeling and remodeling. (**a**) Bone remodeling takes place in both adults and children. It can occur in either trabecular or cortical bone as a consequence of microfractures, mechanical stress, or triggered to replace old bone. Small amounts of bone are dissolved by osteoclasts, which are followed by a wave of bone-forming osteoblasts. The protein matrix secreted by osteoblasts then becomes calcified, restoring the original bone mass. (**b**) Bone modeling occurs uniquely in children and results from the combined activities of osteoblasts, osteoclasts, osteocytes, and growth plate cells. As a result, bone grows in length and width and is reshaped. Compared to remodeling, bone modeling is a fast process in which all bone surfaces are active and osteoblasts and osteoclasts work at the same time

Growth and Bone Modeling and Remodeling

Childhood is a time of active skeletal growth and maturation. After rapid growth in the third trimester of gestation and in the early neonatal period, bone growth velocity falls sharply until puberty. Sexual maturation during puberty is associated with a dramatic acceleration in longitudinal bone growth. Liner bone growth ceases when growth plates closed. On average, growth plates close in girls between 14 and 15 years of age and in boys between 16 and 17 years of age. The structure of bone changes during growth, with expansion of the medullary cavity and thickening of the cortical shell and of existing bone trabeculae. Consequently, the mechanical properties of bone evolve rapidly during adolescence. Bone mineralization lags behind linear growth, resulting in a relative structural weakness that increases fracture risk during puberty [7]. After growth plate closure, bone mass gains continue. Peak bone mass that is achieved is usually achieved at the end of the second decade of life in females and at the beginning of the third decade of life in males [8]. After a period of stability that lasts for about two decades after the achievement of peak bone mass, bone loss occurs and is accelerated with aging in both males and females after menopause in women. In adults, loss of mineral mass is accompanied by deterioration of bone microarchitecture and increased propensity to fractures with age, leading to osteoporosis [9]. Bone deterioration may be enhanced by IBD in adults, but the effects of IBD in children may be unique due to their skeletal biology.

Bone mass is maintained by bone remodeling, characterized by the formation of a functional unit that consists of osteoclasts and osteoblasts, under the direction of osteocytes (the bone-remodeling unit) (Fig. 13.1) [5]. In response to damage or mechanical strain, osteoclasts resorb bone and form resorption pits. Ostecytes respond by decreasing the secretion of sclerostin [10], which removes a break for bone formation. As a consequence, osteoblasts differentiate locally and fill the resorptive cavity with osteoid (bone matrix), composed primarily of type I collagen. Osteoid becomes mineralized by deposition of hydroxyapatite, a calcium and phosphate crystal. Some osteoblasts then undergo apoptosis, while others become embedded in the newly

formed bone matrix and become osteocytes. Ostecytes are the most abundant cell type in bone and are long lived [11]. Osteocytes form a network interconnected by dendrites, which sense mechanical strain, and direct the cells of the bone-remodeling unit with mediators such as sclerostin, receptor activator of nuclear factor kappa-B ligand (RANKL) [12], osteoprotegerin (OPG), tumor necrosis factor-α (TNFα), interleukin (IL)-1β, IL-6, FGF23, DKK1, MEPE, PHEX, prostaglandins, nitric oxide, ATPs, and IGF-1 [11, 13]. The process of remodeling typically takes several months and generates small amounts of bone per remodeling cycle. In bone remodeling, the activities of osteoblasts and osteoclasts are coordinated and sequential. Only about 20% of bone surfaces in the body are actively engaged in bone remodeling at any given time. Bone remodeling occurs in adults and children and takes place in cortical and trabecular bone [14]. Importantly, bone cells involved in remodeling cross talk with bone marrow cells [15]. The bone marrow harbors T-cells that may be generated in the inflamed intestine. Colitogenic $CD4^+$ T central memory cells and T effector memory cells have been reported in the bone marrow of mouse models of colitis [16, 17]. Interleukin-7 (IL-7) produced by bone marrow stromal cells is required to maintain these cells [18]. In the IL-$2^{-/-}$ model of colitis, activated T-cells accumulate in the bone marrow and produce receptor activator of nuclear factor κB ligand (RANKL), which activated bone resorption [19]. T regulatory cells also exist in the bone marrow [20, 21]. Therefore, it is possible that T-cells that migrate from the inflamed gut to the bone marrow influence bone remodeling in mice and humans.

Gains in bone mass in childhood are largely due a combination of the action of the growth plate and bone modeling, which occurs predominantly in children (Fig. 13.1). Bone modeling can be compared to the process of erecting a skyscraper, which requires a large amount of new materials and connecting diverse structural elements. Bone remodeling, on the other hand, is akin to maintain the building's structural integrity over time by scheduled and unscheduled repairs (prompted by damage).

Longitudinal growth is triggered by hormonal signals and involves the production of a cartilaginous scaffold by the growth plate that is calcified, remodeled by osteoclasts, and turned into trabecular bone by osteoblasts. Trabeculae act as struts, plates, and joists to distribute mechanical load from the epiphysis to the compact bone shaft, which carries the majority of the load. Linear growth and bone modeling occur simultaneously, with osteoblasts laying down new osteoid in the periosteal surface, while osteoclasts reshape the bone by resorbing endosteal and metaphyseal bone (resulting in the expansion of the medullary cavity and metaphyseal inwaisting, respectively). Bone modeling occurs in 100% of bone surfaces, with both osteoclasts and osteoblasts active at the same time, and is faster than bone remodeling [22].

These significant physiological differences between pediatric and adult bone have important implications for children with IBD. Disease and treatment factors influence bone modeling and remodeling, but the major impact in children is likely to be on growth plate cells and bone modeling, the two most active processes in bone during growth. Moreover, IBD in children is associated with significant deficits in muscle mass, leading to a decrease in mechanical strain on bone and a consequent reduction in bone modeling. Moreover, weight loss associated with IBD decreases anabolic gravitational forces on the skeleton.

Measurement of Bone Mass

Dual X-ray absorptiometry (DXA) is a precise and accurate method commonly used to assess bone mass. DXA measures bone mineral content, which is divided by bone area (e.g., DXA "density" is expressed as g/cm^2, or "areal" bone density, not a true volumetric density). DXA produces a two-dimensional projection of the three-dimensional skeleton, so larger bones with equal density than smaller bones will appear "denser" in DXA. Therefore, diseases like IBD that can affect linear growth, and bone size may affect DXA measurements by underestimating bone mass in smaller children. This requires correction of DXA readings for patient's size, sex, and sexual maturation [23, 24]. The measurement of true volumetric bone density with peripheral computed tomography is available in some centers (please see Chap. 24 "Bone Health Assessment in Pediatric Inflammatory Bowel Disease" for more information).

Bone Cells and Inflammation

Osteocytes

Osteocytes are the most abundant bone cell. Osteocytes have a critical role in the regulation of osteoblast and osteclast activity. They originate from osteoblasts that become embedded in new bone after a bone-remodeling cycle. Osteocytes have an average half-life of 25 years, and their senescence affects bone cell function [11, 25]. Osteocytes form a mechanosensory network interconnected by cellular dendrites. Osteocytes are influenced by local and systemic factors. In turn, osteocytes secrete modulators of bone cell activity like RANKL, sclerostin, Notch, and DKK1. In addition, osteocytes can also secrete cytokines, including TNF-α and IL-6, which can affect osteoblast and osteoclast development and function [26]. In a rodent model of IBD, osteocytes increased their cytokine output [27]. This suggests that osteocytes not only respond to systemic cytokines but could also amplify the effect of inflammation on bone cells in IBD.

Osteoclasts and the *RANKL/OPG* System

Bone remodeling and modeling involve the activity of osteoclasts and osteoblasts. Osteoclasts secrete enzymes (e.g., cathepsin K) and acid that dissolve bone mineral and degrade the bone matrix. Osteoclast activity generates collagen-split products and growth factors (such as transforming growth factor-β) embedded in the bone matrix that stimulate osteoblast differentiation to fill the resorption site with bone matrix. Osteoclasts are cells from the macrophage/monocyte (myeloid) lineage, which are regulated by cytokines [26]. Osteoclasts are formed primarily by stimulation of hematopoietic precursors with RANKL in the presence of macrophage stimulating factor (M-CSF) (Fig. 13.2). RANKL, a member of the tumor necrosis factor receptor superfamily, is produced by osteocytes, osteoblasts, stromal cells, fibroblasts, and activated T-cells [28], and stimulates osteoclast differentiation, activation, and survival. A complex network of cytokines and immune receptors regulates osteoclast formation and activity either directly or indirectly via RANKL [26, 29, 30]. RANKL-deficient mice have hyperdense bones secondary to lack of osteoclasts [31]. RANKL has been implicated as a key factor in the pathogenesis of bone loss associated with increased resorption, including postmenopausal osteoporosis and rheumatoid arthritis. A monoclonal antibody to RANKL, denosumab, is used to treat postmenopausal osteoporosis and bone loss associated with rheumatoid arthritis [32, 33].

Osteoprotegerin (OPG) is a soluble decoy receptor for RANKL produced by osteoblasts and stromal cells [34]. OPG is a potent inhibitor of osteoclast development. OPG transgenic mice have hyperdense bones. Systemic administration of OPG also increases bone mass in normal mice. OPG-null mice, on the other hand, are profoundly osteopenic due to unopposed osteoclast activity [35, 36]. Besides OPG, another control switch in osteoclast development is interferon (IFN)-β, which is induced by RANKL binding to its receptor RANK on osteoclast precursors [37]. IFN-β interferes with the activity of c-fos, a transcription factor that is essential for osteoclast formation. Other factors,

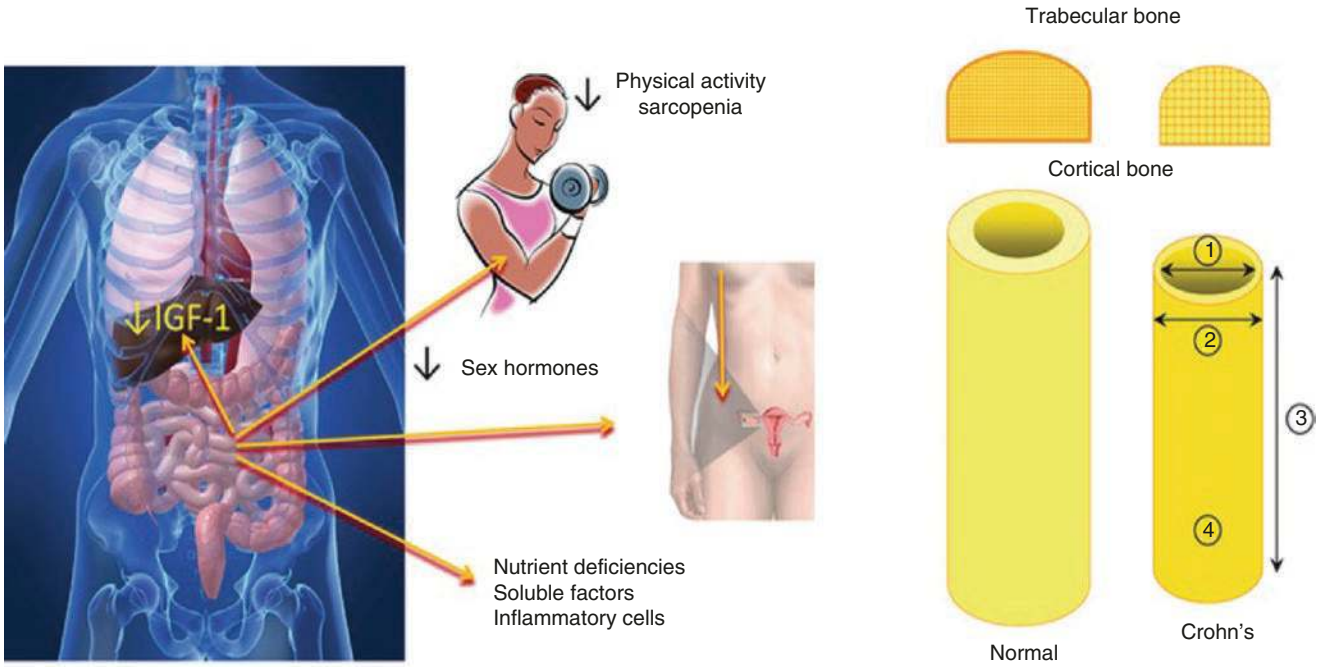

Fig. 13.2 Effects of IBD on the muscle-bone unit. (**a**) Active inflammation in IBD can affect the skeleton by multiple mechanisms, including blocking the formation of IGF-1 in the liver, delaying puberty, and affecting bone cell function via immune cells and cytokines. A decrease in muscle mass (sarcopenia) can impair bone development. Active IBD can also cause fatigue and decreased weight-bearing activity. Corticosteroids to treat IBD can primarily impair bone formation and secondarily increase bone resorption. Malnutrition can affect the availability of protein, calcium, and vitamin D; they are essential for normal bone formation. Therefore, IBD constitutes a multipronged attack on the integrity of the muscle-bone unit and puts at risk the acquisition of genetically programmed peak bone mass. (**b**) At diagnosis, children with Crohn disease have significant bone mass deficits and alterations in bone geometry. In cortical bone, these include ① increased endosteal surface probably due to increased bone resorption, ② decreased periosteal circumference secondary to decreased bone formation, ③ reduced bone length due to growth plate inactivity, and ④ increased cortical bone density, likely a result of reduced bone remodeling. Trabecular bone is less dense ⑤. Some of these abnormalities can be partially reversible with anti-inflammatory therapy (resulting in reduction in endosteal surface, improved bone length, increased trabecular bone density, and decreased cortical bone density), but periosteal circumference can remain lower than normal

such as transforming growth factor-β (TGF-β) and Wnt, inhibit osteoclastogenesis by upregulating the production of OPG by osteoblasts [38]. Wnt also directly represses RANKL expression via the Wnt canonical pathway [39, 40], while Wnt5a, a typical non-canonical Wnt ligand, enhances the expression of RANK in osteoclast precursors [41]. In addition, several cytokines relevant to the pathogenesis of IBD inhibit osteoclast differentiation, including interferon-γ (IFN-γ) [42], IL-10 [43, 44], IL-12 [45, 46], and IL-17 [47, 48]. Moreover, osteoclast differentiation involves transcription factors such as NFκB, AP-1, and NFATc1, as well as co-stimulation via immunoglobulin-like receptors and activation of the phosphatase calcineurin, which can be regulated by inflammation [47, 49–51]. Therefore, osteoclast formation is subject to multiple regulatory controls by cytokines, transcription factors, and enzymes that play key roles in IBD. In addition, osteoclasts interact closely with the hematopoietic stem cells niche [52, 53]. These pathways are an example of the close physiological ties between the immune system and bone cells. However, it is not yet known whether these mechanisms are engaged in regulating bone mass in children with IBD.

The RANKL/OPG system also plays important roles outside of bone. This is evidenced by the lack of peripheral lymph nodes and impaired development of lactating mammary glands in RANKL or RANK-null mice [54]. In addition, RANKL/OPG may be involved in the formation of calcified atherosclerotic plaques, and serum OPG is emerging as a marker of cardiovascular mortality [55, 56]. The balance between RANKL and OPG may affect the severity of bone metastases of several cancers [28]. RANKL contributes to normal dendritic cell function and survival and the early development of B- and T-cells [31, 57]. In addition, RANKL/RANK may play a role in intestinal mucosal tolerance [58]. OPG also has a role in the regulation of the immune response. Both B cells and dendritic cells secrete OPG, and this secretion is regulated by the CD40 receptor [59]. Also, dendritic cells isolated from $OPG^{-/-}$ mice more efficiently present antigen in vitro and secrete more inflammatory cytokines when stimulated with bacterial products or soluble RANKL in vitro [60]. In mice, M cells express OPG, which suppresses the differentiation of adjacent follicle adjacent epithelial cells into M cells. OPG deficiency ameliorates symptoms of experimental colitis, but OPG-deficient mice are highly susceptible to Salmonella infection [61]. Thus, OPG-dependent self-regulation of M cell differentiation is essential for the balance between the infectious risk and the ability to perform immunosurveillance at the mucosal surface. Collectively, this evidence suggests that RANKL/RANK/OPG plays an important role in the regulation of the immune response and in pathways involving the mobilization of calcium [62].

A role for the RANKL/OPG system is emerging in IBD. Circulating OPG levels are elevated in patients with IBD [63], and expression of OPG and RANKL is increased in colonic macrophages, dendritic cells, and epithelial cells [64, 65]. High-fecal OPG (which probably comes from the inflamed colonic epithelium or from activated vascular endothelium) predicts resistance to corticosteroids and to infliximab in patients with IBD [66, 67]. In addition, fecal OPG decreases in children with IBD in remission [68]. Currently, it is not clear whether circulating OPG in patients with IBD represents spillover from intestinal inflammatory activity or it comes from bone or other tissues (e.g., the endothelium or the liver). The function of RANKL/OPG in the pathogenesis of intestinal inflammation deserves further study.

Osteoclast differentiation is also regulated by Notch. There are four types of Notch, of which Notches 1–3 are expressed in skeletal cells. The effects of Notch on osteoclasts are complex and depend on the type of Notch. Notch1 inhibits osteoclastogenesis, whereas Notch2 enhances osteoclast differentiation and function by direct and indirect mechanisms. Notch3 induces the expression of RANKL in osteoblasts and osteocytes and as a result induces [69] osteoclast differentiation [70].

Osteoblasts

Osteoblasts are cells from mesenchymal origin that lay down bone matrix that is rich in type 1 collagen (osteoid). Several factors and hormones regulate osteoblast formation, both systemic and in the bone microenvironment [71]. Among the most important, there are factors secreted by osteocytes including sclerostin and Dkk1, which inhibit osteoblast differentiation and function, and Wnt and Notch, which stimulate osteoblast development [5, 40, 72]. The concentration of Wnt, Dkk1, and sclerostin is affected in mice with experimental colitis [27]. Insulin-like growth factor-1 (IGF-1) is secreted by the liver in response to stimulation by growth hormone from the pituitary gland. IGF-1 enhances the expression of the mature osteoblast phenotype [73]. Serum IGF-1 is frequently reduced in children with active IBD due to growth hormone insensitivity in the liver and malnutrition [74]. Consequently, relative IGF-1 deficiency in children with IBD may negatively affect osteoblast differentiation and function. Tumor necrosis factor-α (TNF-α), an important cytokine in the pathogenesis of IBD, inhibits osteoblast development by inducing the degradation of Runx2 [75], a critical transcription factor in osteoblast development and suppression of osteogenic factor signaling including Wnt [76] and bone morphogenetic protein-2 [77, 78]. TNF-α also regulates a number of inflammatory chemokines and cytokines, inflammatory genes, transcriptional regulators, bone-remodeling genes, signal transducers, cytoskeletal genes,

and genes involved in apoptosis in pre-osteoblasts [79]. TNF-α and colitis decrease the expression of *Phex* in osteoblasts which affects their mineralization function [80, 81]. TNF-α induces cAMP response element-binding protein H (CREBH), which blocks the anabolic effects of bone morphogenetic protein-2 on osteoblast precursors by inducing the Smurf1-mediated degradation of Smad1 [82]. In children, TNF-α blockade leads to a brisk increase in biomarkers of bone formation and significant linear growth, suggesting an activation of bone modeling [83, 84]. However, the effects of infliximab may be a product of improved disease control and not specific effects of this drug on bone metabolism in these patients.

T-Cells and Bone Loss

T-cells are emerging as important regulators of bone cell function [85]. Activated T-cells can regulate osteoclast formation and activity by several mechanisms, both RANKL dependent and independent. Activated T-cells secrete RANKL and consequently can promote osteoclast differentiation and survival. Both soluble and membrane-bound RANKL are produced by activated $CD4^+$ and $CD8^+$ T-cells [86]. T-cell-induced bone resorption has been implicated in tissue injury in animal models of arthritis and periodontal disease [87]. $CD4^+$ Th17 T-cells may be the most pro-resorptive T-cell in the bone marrow [47] probably due to their ability to secrete cytokines that stimulate osteoclast formation and activity [88], upregulation of RANK in osteoclast precursors [89], and increased expression of RANKL in osteocytes [90]. This is significant given the importance of Th17 cells in the pathogenesis of IBD [91]. However, γδ T-cells produce IL-17A, which promotes bone formation after fractures [92]. T-cells may also play an important role in bone loss associated with estrogen deficiency, where osteoclast activity is upregulated. This is suggested by experiments performed in ovariectomized mice, where the absence of T-cells prevents bone loss [69]. In this model, the expansion of a TNF-α-producing T-cell pool appears to be essential and may occur as a result of upregulation of antigen presentation. The nature of the activating antigen(s) is not yet known, but it is possible that both self and foreign epitopes (including intestinal bacterial products) may play a role [93]. The concept that T-cells activated by bacterial antigens may regulate bone cell function is intriguing in the setting of IBD, due to the defects in microbial recognition and processing that have been identified in this condition [94]. In IBD, it is possible that activated T-cells and T-cell memory cells may serve as "inflammatory shuttles" between the intestine and bone, since circulating T-cells produce cytokines that can regulate both osteoblasts and osteoclasts [95, 96]. Ciucci et al. have shown that bone marrow IL-17/TNF-α-producing $CD4^+$ T-cells from IL-$10^{-/-}$ mice with colitis (but not from IL-$10^{-/-}$ without colitis or wild-type mice) induce osteoclast formation in vitro without addition of RANKL/M-CSF. These cells express membrane-bound RANKL and secrete M-CSF [17]. In addition, it is possible that circulating antigens may trigger immune responses via T-cell memory cells in the bone marrow that affect bone cell function. The activation state of T-cells may also be important in their interaction with osteoclasts, since resting T-cells inhibit osteoclastogenesis [97]. T regulatory cells (Treg) are present in the bone marrow and are potent inhibitors of bone resorption [98] probably due to their secretion of IL-4, IL-10, and TGF-β. In addition, T-cells may also regulate bone formation by osteoblasts. For example, bone marrow $CD8^+$ T-cells stimulated by intermittent parathyroid hormone administration activate anabolic canonical Wnt signaling in pre-osteoblasts by $CD8^+$ T-cells [99]. Moreover, bone cells can influence T-cell differentiation and activity. Osteoclasts affect the differentiation and activity of γδ T-cells from peripheral blood in vitro via soluble factors and cell-to-cell contact [100]. Osteoclasts can function as antigen-presenting cells and direct the formation of effector $CD4^+$ and $CD8^+$ cells [101] and induce FoxP3 expression in $CD8^+$ cells [102]. Osteoclasts can also induce the formation of anti-resorptive $CD8^+$ Treg [103], in a process that involves permissive levels of RANKL [104]. Moreover, the effects of T-cells in the skeleton may be site specific [105]. Lastly, microbial metabolites generated in the gut may affect bone cells function via regulation of T-cells [106]. Examining these complex mechanisms in the context of IBD awaits additional research.

Novel Pathogenic Pathways in IBD: Osteoimmune Connections

Genome-wide association studies have identified a number of unsuspected pathogenic pathways in IBD. Among them, there are endoplasmic reticulum (ER) stress, the unfolded protein response (UPR), and autophagy [107]. These pathways regulate the function of highly secretory cells such as Paneth cells and goblet cells in the intestinal lining and innate immune cells in the intestinal lamina propria [108]. When there is an overabundance of unfolded and misfolded proteins in the ER, the ER becomes stressed. The UPR is triggered, involving the activation of inositol-requiring kinase 1 α (IRE1α), pancreatic ER eIF2α kinase (PERK), and activating transcription factor 6α (ATF6α) [109]. Each pathway leads to separate and distinct transcriptional events. The UPR aims to restore homeostasis to the ER by decreasing transcription and protein synthesis, degradation of proteins inside the ER, and shuttling of proteins away from the ER with chaperones. When ER stress is chronic and homeostasis cannot be achieved by the UPR, the cell goes into

apoptosis. Osteoblasts secrete large amounts of collagen (osteoid, the bone matrix) and other factors and might be affected by defects in ER stress and the UPR found in IBD [110, 111]. Bone morphogenetic protein-2 (BMP-2, a stimulator of osteoblast development and activity) induces the expression of ER stress transducers, such as old astrocyte specifically induced substance [112] and ATF [113]. The inositol-requiring protein 1α (IRE1α) and its target transcription factor X-box-binding protein 1 (XBP1) are essential for BMP-2-induced osteoblast differentiation [114]. The BMP-2-signaling pathway also activates the UPR during osteogenesis [113, 114], which induces the synthesis of RANKL and osteoclastogenesis. To date, it is not known whether defects in the UPR that occur in IBD affect osteoblast function. Mature osteoclasts actively secrete acid and proteolytic enzymes such as cathepsin K to degrade the bone matrix and are also sensitive to ER stress. The IRE1α/XBP1-mediated branch is important in osteoclast development [114] and is involved in parathyroid hormone-induced osteoclast formation. RANKL, which induces osteoclast differentiation and activity, is upregulated by the UPR in in cultures of primary osteoblastic cells and in osteoblast and osteocyte cell lines [115]. Therefore, defects in the UPR and ER stress present in IBD may affect the development and activity of both osteoblasts and osteoclasts.

Autophagy is a process by which cells recycle old proteins, damaged organelles, and other cellular debris. These elements are encircled by double-membrane vesicles called the autophagosomes, which fuse with lysosomes to become autolysosomes. Their content is recycled and returned back to the cell. Autophagy also plays a role in bacterial digestion after phagocytosis. The mammalian target of rapamycin (mTOR) is an important regulator of autophagy. In addition to controlling cell growth and metabolism, mTOR negatively regulates autophagy when nutrients and growth factors are abundant [116]. Autophagy has a role in bone cell development and function [117]. In IBD autophagy can be deficient, leading to persistence of bacteria inside of cells. It is possible that defects in autophagy in IBD may affect bone cell function [118]. Induction of autophagy in osteoclasts decreases bone resorption [119]. On the other hand, autophagy induces osteoclast formation during hypoxia [120] and microgravity [121]. Autophagy is important for osteoblast differentiation [122, 123] and bone mineralization [124]. A mouse model of conditional deletion of ATG7 (autophagy related 7) exhibits a reduced bone mass, indicating that autophagy may be important for normal bone formation [125]. Therefore, it is possible that altered autophagy in IBD impairs normal osteoid mineralization by osteoblasts. Moreover, GWAS suggests that genes involved in autophagy regulate bone mineral density in humans [126].

Cytokines produced by the inflamed intestine can regulate bone cell activity. IL-6, IL-17, and TNF-α induce osteoclast formation in vitro [17, 127, 128]. TNF-α induces osteocyte expression of RANKL, thus, promoting osteoclast formation and activity [129]. Cytokine effects on osteoclasts may also occur indirectly through osteoblasts. For example, IL-17 stimulates osteoblasts to secrete GM-CSF in the presence of vitamin D, resulting in inhibition of osteoclast formation in vitro [130]. IL-17 can also induce mesenchymal stromal cells and osteoblasts to secrete RANKL, which would stimulate osteoclastogenesis and bone resorption [47, 131]. In a mouse model of colitis, Th17 cells in the bone marrow that produce TNF-α and RANKL increase osteoclast formation; this effect can be blocked by an anti-IL-17 antibody, suggesting that IL-17 is an important pathogenic factor that reduces bone mass in this model [132]. Oncostatin M (OSM), a cytokine of the IL-6 family, is a major coupling factor produced by activated circulating CD14+ or bone marrow CD11b + monocytes/macrophages upon activation of toll-like receptors (TLRs) by lipopolysaccharide or endogenous ligands that induce osteoblast differentiation and matrix mineralization from human mesenchymal stem cells [133].

Notch plays complex roles in osteoblast and osteoclast differentiation. The effects of Notch on bone cells depends on context, cell type, and stage of development. As a consequence, Notch may either stimulate or suppress osteoblasts and osteocytes [134]. Isoforms of Notch 1–3 regulate osteoclasts differently [70]. In a TNF transgenic mouse model, Notch inhibitors increased bone mass [135], suggesting that the negative effects of TNF-α on bone formation may be blocked by Notch inhibitors. These findings open an avenue to explore the effects of Notch in IBD.

Innate immune responses can be activated by toll-like receptors (TLRs). The mechanism of pathogen-induced bone disease includes activation of TLRs in immune cells by pathogen-derived molecules [136]. This activation results in synthesis and release of inflammatory cytokines that are capable of stimulating osteoclastic bone resorption, thus, causing bone loss. Osteoclasts express functional TLRs. TLR ligands (CpG-ODN, LPS, Poly(I:C)) exert dual effect on osteoclast precursors. They inhibit the activity of the physiological osteoclast differentiation factor, RANKL, in early precursors, but strongly increase osteoclastogenesis in RANKL-pretreated osteoclast precursors [137–139].

The Gut Microbiome and Bone Health

The gut microbiome probably plays an important role in the pathogenesis of IBD, and IBD affects the microbiome [94]. The intestinal microbiota and their products may have effects on bone development and homeostasis. A recent study that compared estimated heel bone mineral density in 1126 twin pairs and their gut microbial genes suggested a causal relationship between specific microbial taxa and bone develop-

ment [140]. A report by Sjogren et al. suggests that gut bacteria are essential for normal postnatal bone remodeling [141]. Britton et al. showed that a strain of *Lactobacillus reuteri* can reverse osteoporosis caused by ovariectomy in mice [142]. The same group has treated bone loss associated by experimental type 1 diabetes in mice [143]. Glucocorticoid-induced osteoporosis in mice was prevented by an antibiotic cocktail, and treatment of mice exposed to glucocorticoids with *L. reuteri* prevented bone loss. Fecal microbial transfer from mice treated with glucocorticoids into untreated wild-type mice induced bone loss [144]. Collectively, this evidence offers proof of principle that enteric organisms have the potential to regulate bone mass. More research is needed in this important area that is very relevant to human IBD.

Effects of Intestinal Inflammation on Bone

Animal Models

IBD is a complex clinical entity, where multiple disease and treatment factors contribute to affect bone cell biology and ultimately skeletal health. In an effort to study mechanistic questions, animal models of intestinal inflammation have been used by several groups. A brief description of their observations follows.

Studies in rat and mouse models suggest that intestinal inflammation can decrease bone mass by impairing bone formation. Lin et al. induced colitis in rats by rectal instillation of TNBS [145] to study its effects on bone mass, assessed by quantitative histomorphometry. After 3 weeks, rats with colitis had a 33% loss of trabecular bone loss in the tibia compared with age-matched, pair-fed control animals. This was associated with a marked suppression of the trabecular bone formation rate. As the colitis healed, bone formation became more active and bone mass normalized after 12 weeks. In IL-10$^{-/-}$ mice with colitis, Dresner-Pollak et al. performed bone densitometry, ash weight, histomorphometry analysis, and mechanical fragility testing [146]. They observed that bone mass decreased secondary to decreased bone formation in 8- and 12-week-old mice; bone resorption was not increased in mice with colitis compared to wild-type controls. Long bones were more fragile in IL-10$^{-/-}$ with colitis, and ash weight was reduced. However, since these studies did not include IL-10$^{-/-}$ mice without colitis, it was not clear if at least, some of the observations in the skeleton of IL-10$^{-/-}$ mice were due to the IL-10 deficiency. More recently, Ciucci et al. addressed this gap and reported significant decreases in trabecular thickness, trabecular number, trabecular bone surface density, and trabecular bone volume per tissue volume in IL-10$^{-/-}$ mice with colitis, but not in IL-10$^{-/-}$ mice without colitis [17], suggesting that in this model, bone effects are due to colitis and not IL-10 deficiency. IL-10$^{-/-}$ mice with colitis harbor in their bone marrow IL-17/TNF-α-producing CD4^{+} T-cells that attract osteoclast precursors. In addition, bone marrow mesenchymal stromal cells produce chemokines that may attract additional osteoclast precursors in this model [17]. Harris et al. have demonstrated that the inhibition of bone formation and bone modeling is reversible with healing of colitis in mice [147].

In the dextran sodium sulfate (DSS) model of colitis in mice, bone formation is reduced [148] and the number of osteoclasts precursors and osteoclasts attached to bone surfaces is increased [149]. Interestingly, growth plate thickness and hypertrophic chondrocyte matrix components (collagen X) are reduced. Bone mass is reduced even when mice do not lose weight and their colitis is mild, suggesting that inflammation per se is responsible for suppressing bone formation [148]. In addition, sarcopenia associated with inflammation may also reduce anabolic muscle strain on the skeleton [150]. In the DSS model, an antagonist of IL-15 prevents bone loss [149].

Three reports using adoptive transfer models of colitis suggest that bone mass decreases secondary to increased bone resorption. In the first paper, Ashcroft et al. studied IL-2$^{-/-}$ mice with colitis at 4, 7, and 9 weeks of age and compared X-ray and histomorphometry with IL-2$^{-/+}$ and wild-type mice. IL-2$^{-/-}$ mice develop colitis and also have splenomegaly, anemia, and other signs of systemic inflammation [19]. They observed a decrease in trabecular bone volume in IL-2$^{-/-}$ with colitis compared with the other two groups of mice at 7 and 9 weeks of age. C57BL/6-Rag1$^{-/-}$ mice transplanted with CD3^{+} cells from IL-2$^{-/-}$ had significantly lower femoral BMD and % trabecular volume 6–8 weeks post-grafting. Serum OPG and osteoclast number were significantly higher in mice engrafted with T cells from IL-2$^{-/-}$ mice compared to IL-2$^{+/+}$. In this model, treatment with OPG was associated with both improved bone mass and decreased intestinal inflammation. These results point to a possible role of T-cells in bone loss in the context of intestinal inflammation and suggest a possible anti-inflammatory role for OPG. In the second study, Byrne et al. transferred CD4^{+}CD45RB^{Hi} or CD4^{+}CD45RB^{Lo} from CB6F1 mice to C.B.17 *scid/scid* mice [151]. CD4^{+}CD45RB^{Hi}, but not CD4^{+}CD45RB^{Lo}, caused colitis in recipient mice, and mice with colitis had lower bone mineral density in the femur/tibia. To treat bone loss, mice received Fc-OPG 3.4–5 mg/kg SC three times weekly for 34 days. OPG had no effect on the severity of colitis but significantly improved BMD. However, this may be a nonspecific effect of OPG on normally active osteoclasts and by itself does not establish that increased bone resorption is responsible for bone loss in rodent models of colitis. It is interesting that in the CD4^{+}CD45RB^{Hi} model, there is an inflammatory infiltrate in the bone marrow containing TNF-α-producing cells [151]. This provides proof of principle that intestinal inflammation is associated with the

presence of activated T-cells in the bone marrow that secrete pro-inflammatory cytokines which may influence the function of bone cells. In the third study, Ciucci et al. reported $CD4^+$T-cells in the bone marrow of mice with colitis that produce IL-17 and TNF-α, capable of stimulating osteoclastogenesis in vitro [17].

Collectively, these observations suggest that intestinal inflammation can directly affect bone mass in rodents. Mechanisms may include decreased bone formation or increased bone resorption, depending on the model. Calcium and phosphate homeostasis by the kidney may also be impaired by inflammation [152]. Additional studies are needed to further elucidate pathogenic mechanisms.

Human Studies

Many studies have measured bone mineral density in children with IBD, both in incident and in prevalent cohorts. The studies, which have been either longitudinal or cross-sectional and have used primarily DXA or pQCT to image bone, suggest that decreased bone mineral density is common in children with Crohn disease at the time of diagnosis, especially in patients with delays in growth and sexual maturation, active disease, and those with decreased lean tissue mass [6, 153–155]. Studies performed in incident cohorts of treatment-naïve patients suggest that disease factors can affect bone mass in children with IBD prior to the initiation of treatment. Collectively, this work suggests that children with Crohn disease are at greater risk for decreased bone mass than children with ulcerative colitis, probably because Crohn disease is more likely to affect linear growth and may be diagnosed less promptly than ulcerative colitis. Patients with low body mass index, low serum albumin, and active severe IBD appear to be at particular risk for decreased BMD. The role of corticosteroids on BMD in pediatric Crohn disease, however, is not clear. The attainment of peak bone mass in Crohn disease is at risk, which may affect fracture risk later in life [156].

According to the guidelines by the International Society for Clinical Densitometry (ISCD), children with IBD should have DXA of the whole body (less head) and the lumbar spine if in the clinician's judgment, the measurement may influence the patients' management [157]. The updated recommendations offer guidance concerning DXA at the distal forearm, proximal hip, and lateral distal femur in children who need additional information for clinical decision making, or in whom spine or whole body DXA scans cannot be obtained [157]. Pediatric Bone Mineral Accrual *Z*-Score data are available to help interpret DXA results [2], as well as equations to correct DXA BMD data for height *Z*-score [158]. Vertebral fracture assessment (VFA) can be performed in children by DXA images [157]. The annual rates of change for BMD in early-stage and late-stage adolescents are approximately 10% and 3%, respectively [159]. Therefore, follow-up DXA should be obtained at minimum intervals of 6–12 months to observe clinically meaningful changes.

In addition to measuring bone mass, body composition data provided by DXA may be helpful in guiding the nutritional rehabilitation of these patients. It is important to DXA BMD measurements to patient size, gender, and sexual maturation, because in any given patient with IBD, the challenge is to distinguish between small, normally mineralized bones and abnormally thin and weak bones [160]. Taken together, these studies indicate that the observed reduction of BMD in children with IBD can be attributed in part to decreased bone size due to growth delay. However, it is important to note that smaller bones may be weaker, and their physical properties may not be normal. It is not yet known whether smaller bone size leads to increased fracture risk in children with IBD. Conversely, increases in height track with significant improvements in BMD, especially in trabecular bone.

Indirect markers of bone cell function, including osteocalcin and bone alkaline phosphatase for osteoblasts and products of type I collagen degradation for osteoclasts, can be used to infer bone-remodeling activity in adults. In children, however, bone biomarkers cannot distinguish between bone modeling, bone remodeling, and bone growth. Nonetheless, significant reductions in the concentration of bone metabolic activity markers suggest that children with Crohn disease have decreased bone turnover at diagnosis [6]. This indicates that the observed reduction in BMD in children with IBD is probably secondary to a combination of decreased net bone formation and linear growth. A study reported the results of histomorphometry in transiliac bone biopsies of 20 children with newly diagnosed Crohn disease and confirmed that bone formation and resorption are reduced at diagnosis; in addition, there was cortical thinning, but trabecular thickness and number were unaffected [161]. Longitudinal studies of incident cohorts of children with Crohn disease have revealed significant alterations in bone geometry of long bones, including decreased periosteal circumference (due to reduced bone formation), expanded endosteal surface (due to increased bone resorption), and increases in cortical bone density (probably due to decreased cortical bone remodeling) [154, 162]. Treatment with anti-TNF-α antibodies for 12 months was associated with improved bone length, reduction of the endosteal surface, and decreased cortical bone density (likely due to increased bone cell activity and rapid growth, respectively), but not a significant increase in periosteal circumference compared to normal controls [84]. Periosteal circumference may be responsive to gains in muscle mass that occur as a result of sustained disease remission.

Laboratory observations suggest that systemic factors impair bone formation in human IBD. For example, serum

from newly diagnosed children demonstrates decreased markers of osteoblastic activity in bone explants [163] and in osteoblasts [164], while indicators of bone resorption are not increased. IL-6, a pro-inflammatory cytokine, appears to play an important role in these effects, in cooperation with other factors present in intact bone. Consequently, IBD may have systemic effects on linear growth and direct effects on bone cells in children, thereby decreasing bone mass. Although globally both bone formation and bone resorption appear lower in children with IBD at diagnosis, it is possible that in some regions of the skeleton, bone resorption may be increased, resulting in thinner bone cortices and mechanical fragility.

While systemic and local humoral factors can directly influence bone cell function in IBD, other influences, albeit indirect, may also be significant. For example, an important stimulus for bone formation is mechanical loading by the expanding muscle forces during puberty [165]. Muscle volume (lean body mass) normally expands during sexual maturation, and its expansion precedes gains in bone mass. Children with IBD often present with malnutrition, with significant losses in both the fat and lean tissue compartments and decreased body mass index. With treatment and clinical improvement, children gain weight but deficits in lean body mass persist [155, 166, 167]. This may result in decreased mechanical loading on bone and be a reason for decreased bone formation in children. In addition, children with IBD may be less active than their peers when they do not feel well, which may also affect gains in muscle and bone mass over time.

Nutritional factors can also negatively impact bone mass. For example, vitamin D is essential for normal calcium absorption and may have immunoregulatory effects in the gut [168, 169]. Vitamin D deficiency may be common in children with IBD, especially in high latitudes [170] and in African-American and Hispanic children [171]. Patients with IBD may spend more time indoors during disease exacerbations, affecting their exposure to sunlight and cutaneous synthesis of vitamin D. Their intake of dairy products fortified with vitamin D may be limited due to secondary lactase deficiency. Vitamin K deficiency is prevalent in children with IBD [172] and may compromise the normal γ-carboxylation of osteocalcin, a mineralization factor [173].

Osteoporosis and Fractures in Pediatric IBD

The ISCD in 2013 recommended the following diagnostic criteria for osteoporosis in pediatrics: (a) the presence of one or more vertebral compression fractures in the absence of local disease or high-energy trauma or (b) the presence of a clinically significant fracture history and BMD Z-score of ≤ -2.0. An abnormal BMD *Z*-score by DXA is insufficient by itself to make the diagnosis of pediatric osteoporosis. A clinically significant fracture history was defined as two or more long-bone fractures by the age of 10 years or ≥ 3 long-bone fractures at any age up to age 19 years [24].

More recent approaches to determine clinically significant fractures rely less on BMD *Z*-score cut-offs. The diagnosis of pediatric osteoporosis incorporates the presence of a family history of osteoporosis and osteogenesis imperfecta, ruling out rickets, and searching for signs of a genetic disorder that affects the skeleton (i.e., blue sclera, Wormian bones, joint hypermobility, etc.) [174]. Ascertaining the affected bone(s), and circumstances and mechanism of injury are essential to determine if a fracture is clinically significant for the diagnosis of osteoporosis. Stress fractures are not considered fragility fractures and should not be considered to count toward the diagnostic criteria for osteoporosis [174].

It is not clear whether children with IBD are at increased risk of fractures. One important confounder is that long-bone fractures are very common in children (mostly of the upper extremities). Consequently, demonstrating that IBD caused a in children may be very difficult. Moreover, children with IBD may have comorbidities such as rickets that are responsible for fractures. Nonetheless, fractures of the femur and vertebrae should be investigated thoroughly for underlying skeletal fragility. Population-based studies in adults with IBD suggest that the risk of clinically apparent fractures appears to be modestly increased [175] or not elevated [176]. Two pediatric studies examining the prevalence of long-bone fractures, one by a questionnaire and the other an analysis of an administrative database, found no increase in the frequency of fractures in children with IBD [177, 178]. However, a study of vertebral fracture assessment in adults with Crohn disease indicated high prevalence of asymptomatic vertebral fractures, even in patients with normal bone density by DXA [179]. Vertebral fractures have been reported in children as well [180]. Children who report back pain, have pain upon palpation of the spinal processes, or have a reduction in height should have spine films to screen for vertebral fractures.

Treatment

In all children with IBD, disease and treatment factors that can impair the acquisition of bone mineral should be identified and corrected when possible. These include active inflammation, malnutrition, specific nutrient deficiencies (calcium, vitamin D, and vitamin K), and corticosteroid exposure [181]. High doses of vitamin D may be required to replenish vitamin D stores [182, 183]. Weight-bearing physical activity should be encouraged [184]. Treatment modalities such as exclusive enteral nutrition and anti-TNF-α

antibodies have positive effects on linear growth and BMD [84, 185, 186] and should be considered in children with IBD with very low BMD.

In children with "clinically significant fractures" (see previous section) with or without low BMD, it is important to evaluate for primary bone disease in addition to establishing measures to optimize nutrition, reduce inflammation with corticosteroid-spearing strategies, and improve physical activity. The growing skeleton is highly capable of healing if the primary disease is adequately treated. Therefore, children with IBD and osteoporosis may not need to be treated with bone-specific therapy. If bone-active agents are being considered, it is important to partner with a pediatric endocrinologist with knowledge and experience in these therapies [187].

Conclusions

Inflammatory bowel disease can negatively affect bone development in children through multiple mechanisms. Due to differences in bone metabolism in children and adults, IBD impacts bone metabolism differently in these two age groups. In children, decreased BMD is probably the result of impaired growth, a primary decrease in osteoblast function, and reduced mechanical strain on bone. Current therapies, including corticosteroids and immunomodulators, may not be optimal for promoting normal body composition and skeletal health in children with IBD. Preliminary data indicate that TNF-α blockade may be more effective in this regard. In children, careful attention to disease control, nutrition (including calcium and vitamin D), and activity level is probably appropriate to improve skeletal mass. Anti-resorptive agents such as bisphosphonates may be helpful in selected children (e.g., those with fragility fractures, especially if they have growth potential) but should not be started in children without input from experts in pediatric metabolic bone diseases.

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Puberty and Pediatric-Onset Inflammatory Bowel Disease

14

Jacquelyn Hatch-Stein

The Pubertal Process in Healthy Children and Adolescents

Puberty is the stage of growth during which sequential biological processes occur that ultimately lead to sexual maturity and reproductive capacity [1]. The onset of puberty is initiated following increased synthesis and secretion of gonadotropin-releasing hormone (GnRH) in the hypothalamus and its transport to gonadotrophs within the anterior pituitary. In response to pulsatile GnRH, the gonadotrophs secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn regulate ovarian and testicular functions. Activation of the gonads by LH and FSH is termed gonadarche (see Table 14.1). Pituitary sensitivity to GnRH varies throughout life but increases prior to the onset of puberty. Around this time, LH is secreted in a pulsatile manner, primarily during sleep, but subsequently changes to a pulsatile pattern throughout the day as puberty progresses [2]. In females, LH stimulates theca cells in the ovary to produce androgens which diffuse to granulosa cells for conversion into estrogens. FSH causes growth of granulosa cells in the ovarian follicle and estrogen production (estrone or E1 and estradiol or E2), which leads to feminization in girls. In males, LH stimulates testosterone production by Leydig cells in the testis. Testosterone subsequently undergoes 5α-reduction to dihydrotestosterone, which induces secondary sex characteristics. FSH acts on Sertoli cells in the seminiferous tubules of the testes to stimulate sperm production and testicular enlargement.

Adrenarche, which frequently begins before gonadarche, is defined by a detectable increase in the secretion of adrenal androgens. Adrenarche most often occurs between 6 and 9 years of age [3] and results in the first appearance of pubic hair, often termed pubarche. Adrenarche is typically temporally related to pubertal maturation of the hypothalamic–pituitary–gonadal (HPG) axis and gonadarche but is not causally related to maturation of this axis. While adrenal androgen production is a minor component of the midpubertal male testosterone level, the adrenal gland contributes about half the total testosterone produced in the female. Since adrenal androgen production is ACTH dependent, this synthesis is subject to suppression with exogenous glucocorticoid therapy. In normal maturation, the adrenal androgen dehydroepiandrosteroine sulfate (DHEAS) is the most abundant circulating adrenal steroid after the onset of adrenarche and often reflects endogenous glucocorticoid secretory capacity. [4].

Table 14.1 Definitions of pubertal events

Gonadarche	Activation and maturation of the gonads in both sexes
Adrenarche	Maturation of the adrenal gland with detectable increase in adrenal androgen secretion
Pubarche	Pubic hair development
Thelarche	Breast bud development in females
Spermarche	Development of mature sperm in males
Menarche	Onset of first menstrual period

Since in early puberty, increased gonadotropin pulse amplitude increases first during sleep, gonadal steroid secretion at this point of development is maximal in the very early morning hours and may wane to low, prepubertal levels by 0900. Thus, it is important to assay gonadotropin and sex steroid levels in the early morning. In addition, it is important to perform these assays in a specialty laboratory with sensitive pediatric assays (as opposed to standard adult assays) to detect the normally low prepubertal and early pubertal levels. The adrenal steroid DHEAS does not follow this pattern because of its long plasma half-life, and a meaningful level may be determined throughout the day. A summary of normal hormone levels as they vary in puberty is seen in Table 14.2.

The factors in the brain that trigger the onset of the pulsatile GnRH secretion at the time of puberty are still not completely understood. Leptin is a peptide hormone expressed predominantly in adipocytes that regulates food intake and

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Table 14.2 Hormone levels in puberty

Hormone	Stage/age	Male	Female
Dehydroepiandrosterone sulfate (DHEAS) (mcg/dL)	Tanner I	<89	<46
	Tanner II	<81	15–113
	Tanner III	22–126	42–162
	Tanner IV	33–117	42–241
	Tanner V	110–510	45–320
Luteinizing hormone (LH) pediatric (IU/L)	3–7 years	<0.26	<0.26
	8–9 years	<0.46	<0.69
	10–11 years	<3.31	<4.38
	12–14 years	0.23–4.41	0.04–10.8
	15–17 years	0.29–4.77	0.97–14.7
Follicle stimulating hormone (FSH) pediatric (IU/L)	5–9 years	0.21–4.33	0.72–5.33
	10–13 years	0.53–4.92	0.87–9.16
	14–17 years	0.85–8.74	0.64–10.98
Estradiol (E2) Pediatric (pg/mL)	Prepubertal	<4	<16
	10–11 years	<12	<65
	12–14 years	<24	<142
	15–17 years	<31	<283
Testosterone (Te) (ng/dL)	Tanner I	<5	<8
	Tanner II	<167	<24
	Tanner III	21–719	<28
	Tanner IV	25–912	<31
	Tanner V	110–975	<33
IGF-1 (ng/mL)	Tanner I	96–341	105–359
	Tanner II	101–478	99–451
	Tanner III	101–478	197–642
	Tanner IV	318–765	330–776
	Tanner V	318–765	330–776

Modified from Nakamoto and Mason [80], and Quest Diagnostics Reference Ranges, Quest Diagnostics Inc., San Juan Capistrano CA
Caution is suggested in differentiating puberty from prepuberty, especially with regard to LH, FSH, E2, and Te. The assays must be sufficiently specific as well as sensitive for the normally low prepubertal and early pubertal levels. In addition, these hormones are secreted episodically with short half-lives in the blood. Early morning testing is recommended

energy expenditure at the hypothalamic level [5]. Serum leptin levels have been shown to correlate closely with body fat content. Leptin is thought to be an important link between nutrition and the attainment and maintenance of reproductive function, as patients with leptin deficiency have been shown to not only be obese but to also have gonadotropin deficiency [6]. However, while leptin levels normally rise throughout childhood and puberty, a rise in leptin is not required to trigger puberty. Thus, leptin likely functions as a permissive factor rather than a trigger in the onset of human puberty. In late 2003, loss of function mutations of GPR54 (a G-protein-coupled receptor) was described in patients with hypogonadotropic hypogonadism [7]. This discovery led to the finding that GPR54 and its ligand (kisspeptin) act as a signal for pubertal GnRH release. Further research suggests that kisspeptin influences the timing of puberty and the integration of nutritional and energy status, likely indirectly through leptin expression. However, what controls the regulation of kisspeptin expression at the time of puberty is not completely known. Neuropeptide Y (NPY), a potent appetite-stimulating agent found in the hypothalamus, may also mediate the effects of leptin on puberty. Based on studies in prepubertal rats, Pralong et al. suggested that NPY may inhibit GnRH secretion and delay sexual maturation [8]. In a limited study, girls with constitutional delay in puberty were found to have higher levels of NPY than those with a normal course of puberty [9].

Physical changes associated with puberty are described by one of five Tanner stages. The onset of puberty is associated with Tanner stage II early-breast bud development in girls and testicular enlargement to a volume of 4 mL or length of 2.6 cm in boys [10, 11]. The current best estimates for the mean age of onset of puberty in healthy children in the United States are 10.2 years for girls and 11.5 years for boys [10]. The mean age of menarche is 12.6 years in Caucasian girls, 12.3 years in Mexican-American girls, and 12.1 years in African-American girls of normal weight. Adiposity is associated with earlier pubertal development [12]. The mean age for spermarche in boys is between 13.5 and 14.5 years [13]. The average duration of puberty in girls is 4 years (range 1.5–8 years) and for boys 3 years (range 2–5 years) [13]. The typical pubertal growth acceleration begins in girls at the start of puberty, and in boys in mid-puberty [14]. See Fig. 14.1 for a summary of the sequence of pubertal events in both males and females.

The standard deviation for all pubertal milestones is about 1 year [16, 17]. Thus, early or precocious puberty is defined

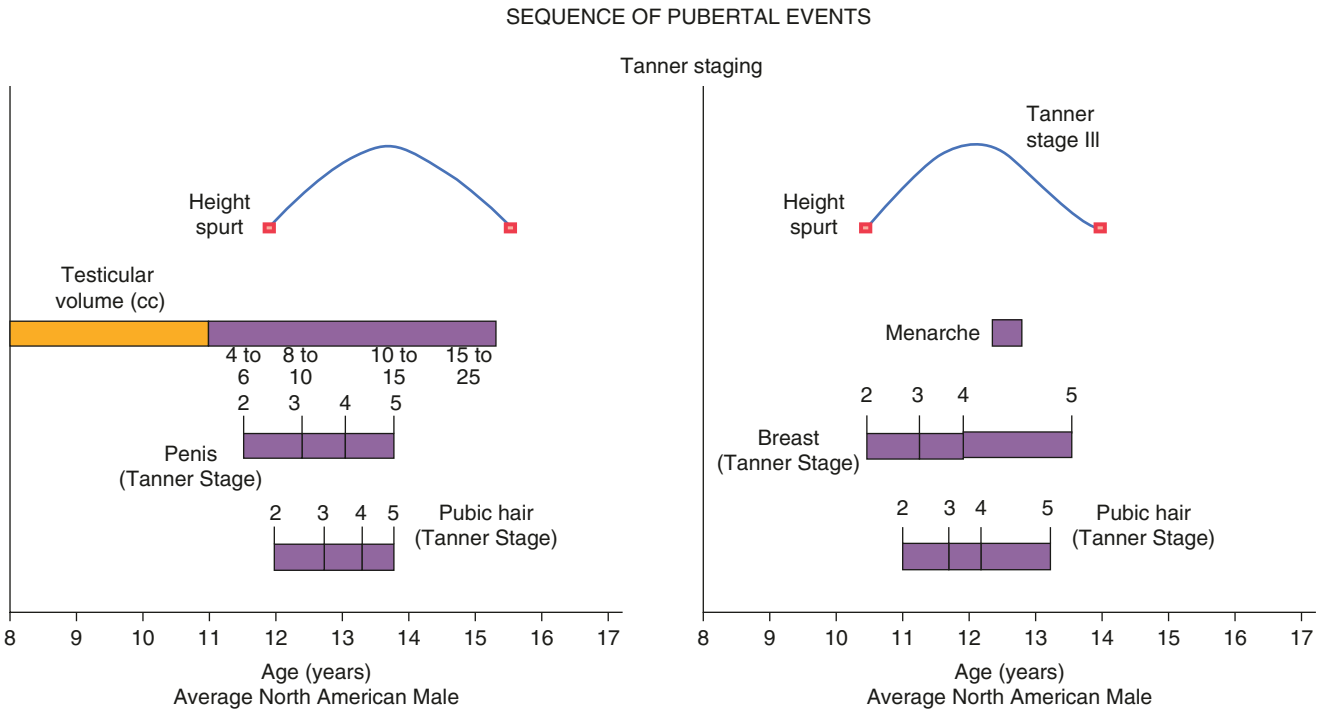

Fig. 14.1 Sequence of pubertal development in males and females. Reprinted from Radovick and Misra [15], Figure 26.4, page 593, with permission

as physical development prior to age 8 years in girls, and 9 years in boys, though these cut-offs do not necessarily account for racial differences. A diagnosis of delayed puberty applies to girls older than 13 years without evidence of breast development and boys older than 14 years without evidence of testicular enlargement . The most common cause of delayed puberty in otherwise healthy children is an extreme variant of normal known as constitutional delay of growth and puberty (CDGP). Children with CDGP are often referred to as "late-bloomers." This occurs due to an unexplained delayed activation of the hypothalamic–pituitary–gonadal axis. A family history of delayed puberty is common and a delay in skeletal age as visualized by bone age X-ray is expected. In a large case series, CDGP was found to be the cause of delayed puberty in 53% of the subjects (approximately 63% of boys and 30% of girls) [18]. The second most common cause of delayed puberty in the case series was functional gonadotropin deficiency, which affected 19% of subjects. Functional gonadotropin deficiency can be seen in chronic illness, especially in conditions that are also associated with decreased body fat (such as IBD). Other less common causes of delayed puberty include primary gonadal failure and gonadotropin deficiency.

The standards of Tanner staging are used for distinguishing different phases of pubertal development in both males and females [19–21] (see Table 14.3). In girls, palpation of breast tissue is more accurate than visualization for confirmation of attainment of true breast buds, as it can be difficult to distinguish adipose versus true glandular tissue. In similar fashion, measurement of testicular size in boys with a tool such as the Prader orchidometer is more accurate than visualization alone [22]. Most reports in the pediatric gastroen-

Table 14.3 Staging of Pubertal Development (Tanner) [14]

Staging—girls	Breasts	Pubic hair
1	Prepubertal	No pigmented hair
2	Palpable budding	Sparse hair along the labia
3	Enlargement of the breast mound beyond the areola	Coarser, with spread of hair over mons
4	Secondary mound of areola	Adult hair but does not spread to thigh
5	Fully mature	Full adult distribution

Staging—boys	Genital size	Pubic hair	Prader orchidometer (mL)
1	Prepubertal	No pigmented hair	1–3
2	Early testicular, penile, and scrotal growth	Sparse hair at base of penis	3–6
3	Increased penile length and width	Coarser, with spread of hair above penis	8–12
4	Further increase in penis size	Adult hair but does not spread to thigh	12–15
5	Fully mature	Full adult distribution	>15

terology literature have used Tanner stages which rely on visual observation of the progression of pubic hair character and distribution, breast size and contour, and testicular size [23]. In certain clinical scenarios, these visual observations may be an acceptable alternative when more accurate measures are not possible. Schall et al. studied the validity of self-assessment of sexual maturity in 100 patients with Crohn disease (CD) age 8–18 years [24]. Patients' self-assessments were compared with those of a designated pediatrician. Agreement varied between 74% and 85%, depending on the sex and sexual maturity status, with younger children and overweight boys tending to overestimate their sexual maturity status (SMS). Rapkin et al. also noted that self-staging of Tanner stage did correlate with circulating estradiol and FSH measurements in 124 healthy girls, aged 8–18 years [25]. However, caution must be taken when Tanner staging by visualization alone, and when clinically indicated more accurate measures should be considered.

Thus, puberty involves a change in the balance of inhibitory and stimulatory signals that impact the GnRH neuron. Genetic factors, ethnicity, nutrition, and environmental chemicals are important in the pubertal process. However, the mechanisms by which neuroendocrine and genetic factors control pubertal development are yet to be fully elucidated.

The Influence of IBD on Puberty

Delayed puberty and poor growth often complicate the clinical course of children diagnosed with IBD, especially children diagnosed with CD. In fact, some children with IBD, moreso in CD, may present with a slowdown of growth velocity and delayed puberty as the first sign of the onset of IBD [26]. As progression through puberty and increased growth velocity are intricately linked, most studies that look at the effects of IBD on puberty examine both growth and pubertal progress. Normal prepubertal growth velocity after 3 years of age averages about 5–6.5 cm/year. The pubertal growth spurt provides an additional 15–25 cm of growth [9, 12, 13, 16]. Delayed puberty is often associated with lower peak height velocity (PHV).

Hildebrand et al. [27] sought to assess the effect of IBD on puberty and obtained height and weight data from birth through final adult height in 46 patients with childhood-onset CD and 60 patients with childhood-onset ulcerative colitis (UC) in Sweden. In this study, the age at PHV was stated to represent the middle of puberty. The PHV for healthy children in Sweden was reported to be 12.05 ± 0.88 years for girls and 14.15 ± 0.98 for boys. Delayed puberty was defined as a delayed age at PHV of >2.0 SDS. No significant delay was noted in children with UC with age at PHV 11.9 ± 1.1 years for girls and 14.0 ± 1.2 years for boys. However, mean age at PHV was later in patients with CD: 12.7 ± 1.4 years for girls and 14.9 ± 1.2 years for boys, and 23% of these children with CD had a delayed age of PHV of >2.0 SDS. A retrospective study by Mason et al. analyzing serial height measurements in adolescents with IBD supports these findings, with the observation that an altered pubertal growth spurt is not uncommon in this age group, perhaps even moreso in boys. They also observed that the delay in PHV frequently depends on disease activity and adequate nutrition, in this case measured as erythrocyte sedimentation rate and body mass index [28].

Brain et al. also observed several alterations in the pattern of puberty among pediatric patients with IBD [11]. The mean age of onset of puberty was delayed for both female and male patients when compared to healthy controls: 12.6 years versus 11.1 years in girls and 13.2 years versus 12.4 years in boys. In addition, the duration of puberty was prolonged, especially in adolescents with frequent disease relapses during puberty [11]. Some patients with IBD took up to 4 years to progress from Tanner stage II to stage IV. Peak height velocities during puberty reached rates >12 cm/year in patients who remained in remission in contrast to as little as 1–2 cm/year in those with relapsing disease. When surgical resection was performed in 11 prepubertal children with CD, puberty started within 1 year of resection. The authors postulated that if the onset of puberty was delayed beyond 14 years, then the final height may be "irreparably compromised." The data from Kirschner et al. support that statement, as they observed that there is a strong correlation between age at menarche and height gain [29]. In this study, when menarche occurred at <13 years of age, the mean increment in height was 10 cm compared with only 3.0 cm in those aged >15 years at menarche. Homer et al. also noted that catch-up growth, even in prepubertal patients, occurred only in those with sustained clinical remission [30].

More recently, Gupta et al. compared the age at menarche in 34 patients with CD with that of 545 controls, using data from the National Health and Nutrition Examination Survey (NHANES) [31]. The authors found that the median chronological age at menarche (13.9 years) in CD was older than that in the NHANES sample (12.0 years). In CD patients, the cumulative incidence of menarche was 10% at chronological age 12 years, 51% at chronological age 14 years, and 100% at chronological age 16 years. Menarche occurred earliest in South Asians, followed by East Asians, and then Caucasians. They suggested if menarche has not occurred by bone age >14 years, endocrinology referral should be considered.

To determine if steroid sparing agents lead to improvements in growth and normal advancement in puberty in CD, Pfefferkorn et al. analyzed growth outcomes in children with

newly diagnosed CD [32]. They found that despite improvements in disease activity, mean height SDS scores did not change significantly, and pubertal progression remained slow. Children diagnosed with CD prior to 9 years of age had a higher mean growth velocity 2 years after diagnosis, as compared to children diagnosed after 9 years of age. Children who required prolonged corticosteroid therapy (longer than 6 months) had poorer growth outcomes. These data suggest that despite advances in nutritional and anti-inflammatory therapies for CD, growth and pubertal delays continue to persist in these children with CD.

In contrast, a study by Malik et al. suggested that children who had a clinical response to infliximab therapy had improvement in their linear growth that was independent of their pubertal progression [33]. In addition, children who had not been exposed to exogenous glucocorticoids also exhibited better growth with infliximab therapy, suggesting that the effect on growth was not simply related to a decrease in glucocorticoid use. In a more recent study, Cameron et al. also sought to examine whether antitumor necrosis factor (anti-TNF-α) therapy improves growth in pediatric IBD. This was a retrospective review of Scottish children with all subtypes of IBD on infliximab or adalimumab, with height measurements 12 months prior to anti-TNF-α initiation, at the start of anti-TNF-α therapy, and 12 months after the start of the therapy. In general, anti-TNF-α therapy was associated with improved linear growth. However, anti-TNF-α use was most likely to be associated with growth improvement when used at earlier stages of puberty, Greater disease control was the biggest factor influencing improvement in growth, with no improvement in growth seen in those who did not achieve remission [34].

Potential Causes of Pubertal Delay in IBD

Pubertal delay in IBD can have many etiologies. Poor nutritional status is often thought to be the major cause, as optimal nutrition is necessary for the initiation and maintenance of reproductive function. GnRH secretion is blunted in the malnourished state which leads to pubertal arrest, and secretion of GnRH normalizes with weight gain [35]. However, the delay of puberty in IBD presents a more complex issue, with weight not the sole independent variable. Stress and inflammation likely also have important roles. The complex interactions between severity of disease, fluctuations in inflammatory cytokines, and their effect on nutritional status and hormonal profile make it difficult to determine how individual factors influence the onset and progression of puberty in pediatric patients with IBD. As a consequence, while nutritional deficits are well described in patients, other aspects such as the potential role of inflammatory cytokines on puberty are often extrapolated from animal models [36].

Nutritional Causes of Pubertal Delay

In otherwise healthy children, undernutrition may cause a delay in sexual maturation and menarche. Important studies done by Frisch and colleagues demonstrated that the age of pubertal growth and menarche in girls correlated more closely to weight than to chronological age [37–39]. During the adolescent growth spurt prior to menarche, girls had a continuous decline in the percent body water and increase in body fat, resulting in a change in the ratio of lean body weight from 5:1 to 3:1 and a mean percent body fat at menarche of 22% [37–39]. The investigators noted that the mean weight at menarche in girls in the United States was 47.8 ± 0.5 kg [37–39]. A possible relationship between body fat and menarche was suggested by adipose tissue being a significant extragonadal site of estrogen production through conversion of androgen into estrogen. She postulated that the decrease in age at menarche (approximately 3–4 months each decade over the past 100 years) is due to girls reaching the "critical" weight earlier, secondary to improved nutrition. In girls with primary amenorrhea due to undernutrition, a minimal equivalent of 17% body fat may be necessary for menarche to occur [37–39]. For girls experiencing secondary amenorrhea, resumption of menses usually occurred when weight gain was 10% higher than the weight at menarche.

Dreizen et al. compared the age at menarche of 30 girls with "chronic undernutrition" with 30 "well-nourished" girls living in north central Alabama [40]. The average age at menarche was 14.5 years in the former group and 12.4 years in the latter group. Interestingly, standing heights that had differed by 9.2 cm at 12.5 years decreased to a difference of only 3.5 cm at 14.5 years and were not significantly different (1.1 cm) at 17 years. Similarly, skeletal age was delayed in the undernourished group, but at the time of menarche, the bone age in the undernourished girls was only 3.8 months more advanced than the well-nourished group. Complete fusion of the epiphyses was delayed in the malnourished group to 17.6 years versus 15.9 years for healthy controls. Therefore, although the timing of the adolescent growth spurt was delayed by undernutrition, final height (in the absence of underlying disease) was not significantly reduced. An earlier study by the same authors in undernourished boys also showed delayed epiphyseal fusion to 18.7 years versus 17.0 years and a mean difference in height between the groups of 2.68 inches at 16 years [41]. Unfortunately, final adult heights were not reported.

Similar delays in menarche (with onset averaging 15.1 ± 0.5 years) are seen in ballet dancers, swimmers, and runners whose training and low calorie intakes begin prior to menarche [38, 39]. Frisch postulated that these females have a raised lean/fat ratio. Both increased nutrition and reduction in the intensity of training may restore menses. Athletic amenorrhea is a hypothalamic reversion to a more immature

pattern in GnRH response. Normalization may occur with reduction in exercise and/or other stress without the weight change estimated by Frisch.

Reduction in calorie intake has been documented in many studies of pediatric-onset IBD, especially CD [42–44]. Kirschner et al. found that weight loss could be associated with prepubertal levels of circulating sex hormones despite previous physical signs of pubertal progression [45]. Thus, undernutrition is likely to be one of the contributing factors leading to delay in the onset and progression of puberty. Similarly, secondary amenorrhea seen in female patients with IBD may be caused by weight loss, a frequent complication of IBD in adolescents.

Sentongo et al. used dual-energy X-ray absorptiometry (DEXA) and anthropometric measures to compare fat mass (FM) and fat-free mass (FFM) in 132 pediatric patients with IBD and 66 healthy controls [46]. They found that patients had normal fat stores but reduced FFM, consistent with "inflammatory cachexia" [46]. They cited data suggesting that proinflammatory muscle-active cytokines may impair accretion of lean tissue.

Burnham et al. compared 104 North American patients with CD to 233 healthy control subjects and found delayed sexual maturation in the CD group [47]. Patients within Tanner stages II–IV averaged 1.4–1.5 years older than control subjects at the same pubertal stages. Lean mass was reduced by 8% in the patient CD group. Thus, the role of undernutrition in both growth failure and sexual maturation may be underestimated if these complications are compared only with documented weight loss. Failure to gain weight (without a history of weight loss) may also adversely affect the timing of menarche and the progression of puberty.

Advancement in puberty may also be related to excess weight gain [12, 48]. Early adrenarche appears to be related to excess weight gain and may be accompanied by skeletal advancement and possibly earlier true puberty. This may be related to peripheral aromatization of adrenal androgens to estrogens in fat.

Endocrine Aspects of Pubertal Delay

Most studies of endocrine function in children and adolescents with IBD have been performed to investigate the causes of growth failure rather than the onset and progression of puberty [42–44, 49–52]. An intact growth hormone (GH)/insulin-like growth factor I (IGF-I) axis is necessary for normal postnatal growth. Thyroid hormone and cortisol are also important, as are the sex steroids at the time of puberty. IGF-I is produced in the liver under the stimulation of GH and is thought to be the key mediator of the growth-promoting effects of GH. Reports in growth-impaired patients with IBD have generally demonstrated normal GH secretion, thyroid function, cortisol response to hypoglycemia, and gonadotropin response to GnRH. What changes were observed such as reduced amplitude of the GH pulse or increase in reverse triiodothyronine (rT3) were not associated with reduced growth velocity [51]. IGF-1 levels have been shown to be reduced in children and adolescents with IBD [36, 45, 53, 54]. This usually occurs despite the presence of adequate circulating levels of GH and is known as "growth hormone resistance." Since IGF-1 is modulated by both GH and nutritional status, it is not clear whether the reduction of IGF-1 seen in this population is secondary to active disease or to the decrease in calorie intake (or both). An increase in IGF-1 does occur following nutritional restitution in children with IBD [36, 45]. Corkins et al. also noted that the major binding protein for IGF-1 (IGFBP-3) was reduced at diagnosis in children with IBD which would result in a reduced half-life for circulating IGF-1 [53]. The use of IGF-1 as a potential therapeutic agent to enhance growth in childhood IBD is hampered by concerns regarding a potential increased risk for colon cancer and other malignancies in this population [55].

In a trinitrobenzene sulfonate (TNBS) model of experimental colitis in rats, Azooz et al. noted that puberty was delayed but plasma concentrations of gonadotropins were similar to healthy controls [56]. Interestingly, delayed puberty and reduced levels of plasma testosterone and 17β-estriol levels were present in both colitic and noncolitic pair-fed rats, compared to healthy controls, emphasizing the importance of caloric sufficiency. However, the frequency of delayed puberty was less in the food-restricted rats (28%) versus the colitis rats (57%), suggesting an independent role for inflammation in this process. The authors demonstrated that the administration of testosterone subcutaneously on a daily basis to the colitis rats normalized the onset of puberty. Similar results were recently reported by DeBoer and colleagues comparing pubertal progression in dextran sodium sulfate (DSS)-induced colitis, food-restricted mice, and free-feeding control mice. For both sexes, puberty was more delayed in the colitis model than the food-restricted animals, despite similar leptin levels [57, 58].

Proinflammatory Cytokines–Endocrine Interactions

Several in vitro studies have elucidated ways in which proinflammatory cytokines (such as TNF-α, interleukin-6 (IL-6), and interleukin-1β (IL-1 β)), elevated in patients with IBD, affect endocrine function. Elevations of these cytokines have been shown to lead to altered gonadal function and reduced sex steroid synthesis [59]. Several of these findings may be applicable to explaining pubertal delay in patients with chronic inflammatory bowel disease.

TNF-α has inhibitory effects on GH and sex hormone function. Transgenic mice overexpressing TNF-α (or IL-6) are growth-impaired and have low IGF-1 levels despite normal GH because of inhibition of GH signaling within hepatocytes [60]. Denson et al. showed that TNF-α suppressed GH receptor expression by inhibiting Sp1/Sp3 transactivators [61]. IL-6 inhibits hepatic GH signaling by inducing a suppressor of cytokine-inducible signaling (SOCS-3) and reduces the half-life of IGF-1 by increasing the catabolism of its binding protein, IGFBP-3. TNF-α and IL-6 also reduce IGF-1 action by inhibiting insulin receptor substrate 1 which influences IGF-1 binding to its receptors and interleukin-1β (IL-1 β). TNF-α and IL-1β have also been shown to induce anorexia. It has been suggested that GH therapy may overcome hepatic GH resistance induced by IL-6 [62].

TNF-α has also been shown to decrease androgen receptor protein as well as dihydrotestosterone activation. TNF-α, IL-6, and IL-1 β reduce testosterone synthesis in Leydig cells and steroidogenesis in cells in the ovary. DeBoer et al. reported partial normalization of puberty in female mice with dextran sodium sulfate (DSS) colitis treated with anti-TNF-α, when compared to a placebo-treated group. The authors utilized the day of life of the vaginal opening as the validated measure of puberty in female mice and found pubertal onset at day 30 in controls, day 31 in DSS colitis with anti-TNF-α, and day 33 or later in DSS and placebo. The DSS colitis mice controls and those treated with anti-TNF-α maintained similar weights throughout the study.[63].

Psychosocial Issues and Puberty

There is extensive literature describing dynamic changes in the psychosocial interests and concerns of adolescents. Shafer and Irwin addressed these issues and emphasized how they develop and are different among adolescents during early adolescence (ages 10–13 years), middle adolescence (ages 14–16 years), and late adolescence (ages 17–21 years) [13]. Nottelmann et al. studied the relationship between adolescent psychosocial adjustment and chronological age, pubertal status, and serum hormone levels [64]. In boys, adjustment problems were associated with low sex hormones or lower pubertal stage in conjunction with higher chronological age. These included sadness/anxiety and problems with body and self-image. In girls, adjustment problems in social relationships were also associated with lower pubertal stage and higher age. Both groups had elevated levels of androstenedione, an adrenal hormone responsive to stress, which the authors suggested may be due to self-comparison with same-age peers. They speculated that boys may be more sensitive to hormonal influences and girls to environmental influences.

Delayed sexual maturation may have significant adverse effects on self-esteem and socialization, as the child with delayed puberty looks younger than their chronological age and often is treated as such [65]. Thus, an adolescent with IBD must cope not only with the impact of having a chronic disease, but also with the psychological issues of delayed puberty.

In addition to the psychological response to pubertal delay, stress itself may interfere with the functioning of the brain–pituitary–gonadal axis. Evidence suggests that this may be mediated by elevated cortisol levels over a protracted period of time. Consten et al. noted that cortisol administration to male carp caused delayed testicular development, reduced testosterone levels, and impaired maturation of pituitary gonadotrophs [66].

Therapeutic Approach to Addressing Pubertal Issues in IBD

The observations and studies described above suggest that prolonged control of active inflammation and providing adequate nutrient intake are both essential in promoting normal puberty. Alperstein et al. reported that it took 2.5–10 years for five of nine children with growth delay who were in Tanner stage I to attain their pre-illness height percentile following surgery for CD [67]. Thus, optimal control of IBD and optimization of nutritional status are paramount in adolescents with IBD and delayed puberty.

When growth and puberty concerns persist in children with IBD, whether the disease is controlled or not, referral to pediatric endocrinology may be warranted. For the pediatric gastroenterologist, timely referrals regarding growth and puberty concerns to an endocrinologist are of great importance, as a delayed referral will potentially limit the time window in which limited treatment options may be considered.

While early puberty is not a known complication of IBD in children, it certainly can occur as it does in otherwise healthy children. Early puberty would be critical to identify in IBD, as treatment considerations would be warranted in the context of potential implications on final adult height, both from the disease and the early puberty. Thus, most girls with breast bud development prior to age 8 years and all boys with testicular enlargement prior to age 9 years should be referred to endocrinology for discussion of further work up and potential treatment options. Current treatment typically includes the use of GnRH agonists to temporarily halt puberty, which come in both injection (leuprolide) and implantable (histrelin acetate) formulations. Typically these medications are not used to halt puberty at older ages just for height related concerns, though some small studies have sought to investigate this use [68]. Most evidence does not

support the use of GnRH agonists for this indication, though some reports indicate potentially some effect on adult height when used in combination with GH. Potential downsides of the use of GnRH agonists outside of a central precocious puberty diagnosis could include deleterious effects on bone health [68, 69].

Of course, children with IBD are referred to endocrinology for linear growth concerns more commonly than puberty-specific concerns. Treatment options for short stature in IBD are limited, but when indicated GH therapy can be a consideration. Although experience with GH treatment in pediatric patients with IBD is limited, improvement of growth velocity may be observed when there is reasonable disease control with reduced corticosteroid exposure. Furthermore, steroid-related growth effects may be in part ameliorated with GH treatment [70–72]. Growth-related treatments in IBD are more fully described elsewhere in this book. However, it is important to note that response to GH in children with IBD may be related to pubertal staging. In one study, a trend was observed that improved growth velocity was greater in Tanner stage I and II patients who received GH as compared to those who were in the later stages of puberty [72].

When GH treatment is unavailable, or feared to be insufficient for optimal height outcomes, some pediatric endocrinologists consider the off-label use of aromatase inhibitors (such as letrozole and anastrozole) to augment final adult height in boys. Aromatase inhibitors are typically considered when there is concern that the eventual progression of puberty itself could limit the window of growth and ultimately negatively impact final adult height. Since estradiol (converted from testosterone) is primarily responsible for growth plate closure in late puberty, the goal of aromatase inhibitor use is to delay growth plate closure by slowing testosterone to estradiol conversion, potentially leading to an increased final adult height. The limited evidence on this use shows variable efficacy, and no known studies have looked specifically at the use of this in adolescents with IBD. The greatest effect of aromatase inhibitors on height outcomes seems to be when used in combination with GH [73].

For those children with delayed puberty secondary to the IBD disease process, pubertal induction may be considered. However, especially in children with IBD, final height preservation may be at odds with the child's desire to proceed through puberty. Artificial induction of puberty with estrogen or testosterone runs the risk of skeletal advancement without commensurate growth. An anabolic steroid such as oxandrolone, which does not advance bone maturation as much as testosterone in modest dose, might be of some small value. Mason et al. described a retrospective study of eight boys with IBD (seven of whom were prepubertal at 13.6–15.6 years of age) who received testosterone therapy for pubertal induction [74]. Testosterone dose and route of administration were either monthly injections of testosterone enanthate 50 mg (five patients) or transdermal testosterone patch 2.5 mg daily (two patients) or 5.0 mg daily (one patient). Following 6 months of treatment, seven out of eight boys progressed in puberty to Tanner stage II–IV, and the median height velocity increased from 1.6 to 6.9 cm/year. There was noted a negative correlation between C-reactive protein levels and height velocity, and so response to treatment was likely still quite dependant on disease control [74].

Ballinger et al. describe their approach to pubertal induction in IBD as including a 3- to 6-month course of 100–125 mg/month of intramuscular testosterone ester (enanthate or cypionate) in boys and ethynyl estradiol 4–6 mcg/day orally for the same length of time in girls [75]. Another approach to pubertal induction in selected male patients with delayed puberty consists of a 6-month course of 50 mg/m^2 intramuscular testosterone ester. For girls with either functional gonadotropin deficiency or constitutional delay of puberty, it is reasonable to offer a 6-month course of either a low dose of IM depot estradiol (0.2–0.4 mg monthly), or a low-dose estrogen patch (applying a 25 mcg patch twice weekly for 1 week out of the month) for pubertal induction [76]. As opposed to boys, there are few studies that report the outcome of a brief exposure to sex steroid therapy for girls with delayed puberty. The response to this approach in pediatric patients with IBD has not been studied.

The relationship between puberty and its effects on bone density in children with IBD has not been addressed in this chapter as the topic is discussed in depth elsewhere in this text. Although pubertal delay has been associated with reduced BMD in adult men, its impact on peak bone mass in pediatric patients with IBD has not been determined [77, 78]. Bernstein et al. compared BMD T scores of the lumbar spine, femoral neck, total hip, and total body in a series of 70 adult women with IBD, who were <45 years of age. They observed no significant differences between 12 patients with disease onset before puberty compared with 58 whose disease was diagnosed after puberty [79]. More long-range data are needed on the relationship between pubertal delay and bone mineralization in adulthood.

Delayed growth and sexual maturation are a frequently described potential consequence of IBD in children and adolescents. For the reasons stated above, assessment of pubertal staging should be an integral part of the monitoring of pediatric patients with IBD. Reasons to refer to a pediatric endocrinologist are many, but certainly should be considered in boys who have reached 14 years and girls who have reached 13 years without evidence of any physical changes of puberty. However, an earlier referral may be necessary in a child with early or normally timed puberty, if there is concern for a history of poor growth that may ultimately be affected further by pubertal timing and ultimate closure of growth plates.

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Classification of Pediatric Inflammatory Bowel Disease

15

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Introduction

Inflammatory bowel disease (IBD) comprises a group of disorders characterized by chronic inflammation of the gastrointestinal tract, with symptoms beginning during childhood or adolescence in about 25% of patients [1]. Although the labels ulcerative colitis (UC) and Crohn disease (CD) are applied to differentiate the two major phenotypic forms, it is recognized that both, and particularly CD, comprise a spectrum of chronic intestinal inflammation, with tremendous variation in phenotypic characteristics such as disease location and extent, behavior (inflammatory, stricturing, or penetrating), severity, responsiveness to therapies, and associations with extraintestinal manifestations [1, 2]. Between 5% and 13% of patients have colitis with clinical or histological features that make it difficult to assign a diagnosis of either CD or UC, and a diagnosis of inflammatory bowel disease-type unclassified *(IBD-U)* is assigned [3–5]. Rates of IBD-U may be higher in very young children, with one study describing this phenotype at diagnosis in 12 of 54 (22%) children presenting prior to 6 years of age [6]. Over time, the true type of IBD may become more evident, and the patient can be re-categorized as having either CD or UC [7]. The EUROKIDS registry, which prospectively collects data on newly diagnosed pediatric patients with IBD in Europe and Israel, found the rate of IBD-U decreased from 7.7% (265/3461) at diagnosis to 5.6% over the course of follow-up or when further diagnostic workup was complete [4].

The first question for the physician is whether the patient has inflammatory bowel disease or if the presentation represents an acute, self-limiting colitis, secondary to infection, ischemia, or other pathology. Increasingly we are recognizing a primary immune dysfunction or deficiency as a cause for the "IBD phenotype" in very young children presenting with IBD-like symptoms. This is an important group to recognize, as immunosuppressive medications may be harmful in this setting and patients may benefit from a more targeted treatment approach, and in some cases, bone marrow transplantation [8, 9].

IBD is confirmed using a combination of clinical, biochemical, endoscopic, and radiologic assessments (described in detail in other chapters in this book), and the patient is given a diagnostic label of CD, UC, or IBD-U. Where possible, the physician should strive to assign a diagnosis of either CD or UC, as this may have therapeutic implications, and is particularly important if a surgical intervention is being considered [2]. Deciding on the type of IBD can be challenging unless features which are diagnostic of CD are present, such as stenosing or penetrating disease behavior, macroscopic skip lesions or small intestinal disease, perianal disease, and granulomata (well formed, and remote from a ruptured crypt) on histology [10]. In addition, there are a number of features such as relative or absolute rectal sparing, peri-appendiceal inflammation (the "cecal patch"), backwash ileitis, and the presence of upper GI tract findings that can make determining the type of IBD challenging. These features are discussed in more detail later in this chapter.

Within each diagnostic category, of either CD or UC, phenotypic classification systems aim to delineate disease location and behavior in CD and disease extent and severity in UC. While classification systems were initially developed with adult patients in mind, a pediatric IBD classification system (the Paris modification of the Montreal classification, hereafter referred to as the Paris classification) was developed and is now in widespread use in both the clinical and research setting [10].

In 2007, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, led by Dr. Athos Bousvaros (author of an earlier edition of this chapter), developed a detailed document that provided recommendations for assisting pediatric gastroenterologists in distinguishing CD from UC and provided detailed evidence-based directions for gray areas. The authors of this chapter would like to direct readers to this publication as well as the

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Paris classification and the revised Porto criteria, all of which contributed to the drafting of this chapter [2, 10, 11].

The first part of the chapter will review the historical perspective, as well as the development and refinement of the IBD phenotypic classifications. The second part of the chapter will describe the challenges of assigning a diagnosis of UC or CD and the use of the IBD classes system to assist in the process.

Phenotypic Classification of IBD: A Historical Perspective

For decades, CD was considered a relatively homogeneous condition, without attempts to further subclassify the phenotype. In 1975, Farmer et al. hypothesized that sites of inflammation influenced outcomes and disease behavior. The group categorized CD into [1] ileocolonic, [2] small intestinal, [3] isolated colonic, and [4] isolated anorectal disease [12]. The authors attempted to correlate clinical symptoms at presentation with disease location. They also described the evolution of disease over time, including the development of rectal and internal intestinal fistulae, growth impairment, intestinal obstruction, and need for surgery. By using categories of disease location, the authors provide some of the earliest data on the potential relationship between phenotype and clinical outcomes and recognized that such correlations might facilitate therapeutic decisions for these patients. Even now, we use disease location to explain the constellation of symptoms (and biochemical marker abnormalities) that occur at diagnosis.

Further consideration toward a phenotypic classification of CD came from Greenstein et al. in 1988 who described two disease behavior patterns, perforating and non-perforating, using a cohort of 770 patients undergoing surgery. Site of inflammation, categorized as ileitis, colitis, or ileocolitis, was associated with type of surgery. Patients with ileal disease were more likely to require surgery for obstructive symptoms in comparison to those with ileocolonic disease, where fistulizing disease was the main surgical indication [13].

These observations that disease location and behavior influence outcomes became the basis of the more rigorously developed Vienna, Montreal, and Paris classifications for IBD [10, 14, 15].

The Vienna Classification [14]

Between 1996 and 1998, an international working group was established to develop and validate a phenotypic classification for CD [14]. The final categories were age at diagnosis (<40 or ≥40 years), disease location (terminal ileum, colonic, ileocolonic, or involvement of the upper GI tract), and disease behavior (non-stricturing non-penetrating, stricturing, or penetrating). While great efforts were made to develop a reproducible and validated phenotypic classification, there were some limitations. The Vienna classification could not distinguish disease location when disease was present in both the upper GI tract along with other intestinal regions or when it occurred in isolation. Likewise, perianal disease was not considered a separate category; rather it was categorized as "perforating" disease behavior, making it impossible to distinguish whether a patient had perianal disease, intestinal fistulizing disease, or both.

The Montreal Classification [15]

The Montreal classification was developed to provide a uniform system of designating subgroups of patients with IBD, with the aim of facilitating multicenter genotype–phenotype correlation studies. It remains the most used classification for adult patients. Unlike earlier classification systems, the Montreal classification includes a phenotypic classification for UC and makes recommendations for assigning the diagnostic label of "inflammatory bowel disease-type unclassified" (IBD-U).

For CD, modifications to the Vienna classification [1] include an additional category to classify children diagnosed at ≤16 years of age, [2] allow for upper GI tract disease to be classified independently of ileocolonic and colonic involvement, and [3] classify perianal disease as a category independent of the "penetrating disease behavior" category.

The group recommends that the maximal disease extent prior to first resection (in those undergoing surgery) is used when considering "disease location." Given the propensity for disease behavior to evolve over time [16], the recommendation of the working group is to wait a minimum of 5 years before definitively assigning a disease behavior for the non-stricturing, non-penetrating category, particularly when data are used as part of research studies.

For UC, the group proposed that patients be classified according to maximal extent of inflammation at any time during follow-up. Maximal disease extent is E3, which denotes any disease extending proximal to the splenic flexure.

When a principal diagnosis of UC or CD cannot be established, the group recommends that the term colonic "IBD-type unclassified (IBD-U)" be assigned. The term "indeterminate colitis" should be reserved for use only after colectomy has been performed, when features of both CD and UC coexist.

The Paris Modification of the Montreal Classification for Pediatric IBD [10]

In 2009, an international group of pediatric IBD experts took on the task of modifying the Montreal classification, to capture aspects of disease phenotype that are pertinent to pediatric patients. Following an extensive literature review, with attention focused on pediatric data, where available, and including recommendations from expert opinion and narrative review, the Paris classification of pediatric inflammatory bowel diseases was published in 2011. The committee also reviewed, and agreed with, the 2007 paper put forward by NASPGHAN and the Crohn and Colitis Foundation of America (CCFA), which provided recommendations for differentiating UC from CD [2].

Novel Features of the Paris Classification

1. *Age*: A new age category, differentiating between patients presenting prior to or after their 10th birthday, was introduced. The new classification proposed that children presenting prior to 10 years of age are designated to the age category A1a, and those presenting between 10 and 17 years are assigned to the category A1b. Disease location in CD at diagnosis appears to be different in these two age groups with the younger group being more likely to have isolated colonic disease rather than ileal involvement. In the older age group, ileal disease (whether isolated or in conjunction with disease in other locations) is more common [6, 17–20]. Phenotypic differences according to patient age are also evident in ulcerative colitis, with a Canadian population-based study finding lower colectomy rates in children diagnosed prior to 10 years of age [21].
2. *Upper GI tract*: The Paris group recognized that the Montreal classification did not optimally describe disease location, particularly regarding the Montreal upper GI tract category (L4), which is unable to distinguish between disease of the small intestine and disease proximal to the ligament of Treitz. The Paris classification recommends that the presence of upper GI tract disease only is assigned in the presence of macroscopic disease, as there is no literature to suggest that histologic involvement alone influences disease progression or phenotypic classification over time. The presence of mucosal erythema or granularity is not sufficient to be considered as macroscopic disease. The Paris group subdivided the L4 Montreal category for upper GI tract disease into L4a (denoting disease proximal to the ligament of Treitz) and L4b (denoting disease distal to the ligament of Treitz).
3. *Disease behavior*: Disease behavior is inflammatory (B1) at diagnosis for the majority of patients but may evolve into a more complicated phenotype, stricturing (B2), or penetrating (B3) over time. The Paris classification allows capture of patients with both concomitant stricturing and penetrating behavior (B2B3 category).
4. *Disease location*: Since most pediatric patients with UC have extensive disease at presentation [17] (especially in comparison to adult patients), the Paris classification includes an additional category for disease extension proximal to the hepatic flexure (E4).
5. *Disease severity*: The Pediatric Ulcerative Colitis Activity Index (PUCAI) is used to determine whether or not a patient has ever had severe disease (PUCAI $\geq$ 65) [22]. The Paris classification incorporates disease severity, as studies have found that colectomy rates are higher in this patient group [23].
6. *Growth impairment*: Pertinent only to pediatric patients is the ability to capture growth impairment as part of the classification of disease [24, 25]. A growth category was introduced, which identifies normal growth at diagnosis and over the course of follow-up (G0), or impaired linear growth (using height velocity *Z*-scores) at any time point (G1). *Z*-scores should be adjusted for age (or bone age when delayed) and sex.

The Paris group also described a list of features that should direct the physician to consider a diagnosis of CD:

1. Perianal disease
2. Microscopic skip lesions
3. Stenosis, cobblestoned mucosa, and linear ileal ulcers (even in the setting of pancolitis)
4. Macroscopic inflammation of the ileum in the absence of cecal inflammation
5. The presence of a well-formed granuloma at a site that is not adjacent to a ruptured crypt
6. Absolute rectal sparing (no macroscopic or histologic features of inflammation)

The group advised that the finding of a few small ulcers in the small intestine during capsule endoscopy should not preclude the diagnosis of UC (if other features point to this diagnosis) since these may be nonspecific and are sometimes seen in healthy people.

A summary of the Paris classification of pediatric IBD is represented in Table 15.1

Table 15.1 Paris classification of inflammatory bowel disease (Adapted from Levine at al. [10])

Crohn disease	
Age at diagnosis	Location
A1a <10 years A1b 10–≤17 years A2 17–40 years A3 >40 years	L1 Distal 1/3 ileum ±limited cecal disease L2 Colonic L3 Ileocolonic L4a[a] Upper GI disease proximal to Ligament of Treitz L4b[a] Upper GI disease distal to Ligament of Treitz but proximal to distal 1/3 ileum
Behavior	Growth
B1 Non-stricturing, non-penetrating B2 Stricturing B3 Penetrating B2B3 Stricturing **and** penetrating P Perianal disease modifier[b,c]	G0: No evidence of growth delay at diagnosis and subsequently G1: Growth delay at any time (at diagnosis or over the course of follow-up)
Ulcerative colitis	
Disease extent	Definition
E1 Ulcerative proctitis E2 Left-sided disease E3 Extensive disease E4 Pancolitis	Disease limited to the rectum Disease distal to the splenic flexure Disease proximal to the splenic flexure but not extending proximal to the hepatic flexure Disease extends proximal to the hepatic flexure
Severity	Definition
S0 S1	Never severe (PUCAI score never ≥65) Ever severe (PUCAI score ≥ 65 at least once during course of follow-up)

[a]L4a and L4b can coexist with L1, L2, or L3 or can occur in isolation
[b] Perianal disease can coexist with any behavior B1, B2, B3, and B2B3
[c] Perianal disease is present if there are fistulae, abscesses, or anal canal ulcers. Skin tags do not form part of the definition of perianal disease

The Porto Criteria and the Revised Porto Criteria

In 2005, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) working group, consisting of 23 pediatric gastroenterologists from 12 European countries, published the Porto criteria which outlined criteria for diagnosing IBD and made recommendations for diagnostic workup [26]. The group recommended that symptoms should be present for a minimum of 4 weeks or that episodes have occurred at least twice within a 6-month period. Typical presenting symptoms of IBD, which are discussed in greater detail in another chapter of this book, include abdominal pain, diarrhea, weight loss, extraintestinal manifestations, and growth failure, the latter being more prominent in Crohn disease [27]. Other symptoms such as malaise, unexplained anemia (in the absence of gastrointestinal symptoms), and delayed puberty may also be manifestations of IBD, and physicians should maintain an index of suspicion when investigating patients with these symptoms.

The Porto criteria were revised in 2014, using an extensive evidence-based and iterative approach to develop recommendations and an algorithm for the evaluation of a pediatric patient with suspected IBD [11]. The new criteria consist of 12 recommendations, incorporating the Paris modification of the Montreal classification, the original Porto criteria, and consideration of fecal and serum biomarkers. The revised document also provided several practice points when suspecting the diagnosis of IBD:

(a) Enteric infections should be excluded before endoscopy; however, identifying a pathogen does not exclude the possibility of IBD, as the first episode or flare of disease can be triggered by an enteric infection (tests should include stool culture and C. difficile, as well as parasites such as Giardia lamblia, if in a high risk or endemic area)
(b) Fecal calprotectin is superior to blood markers for detection of gastrointestinal inflammation; however, it is not specific for IBD and does not differentiate UC from CD. Further, normal blood tests do not exclude the diagnosis of IBD (54% of mild UC and 21% of mild CD patients presented with normal labs in a study by Mack et al. [28].
(c) Low serum albumin can identify protein losing enteropathy, but also reflect disease activity and severity, as well as nutritional status.

The revised Porto criteria [11] introduced the idea of typical versus atypical UC as a new category for "type of IBD." The group felt that the previous definition of superficial disease, starting in the rectum and extending proximally, was too simplistic. Figure 15.1, from the Porto Group, provides an algorithm for assigning type of IBD, which considers atypical variants of UC. This creates four subtypes of IBD: UC, atypical UC, CD, and IBD-U.

Five different "atypical UC" variants are presented:

1. Macroscopic rectal sparing—the Paris classification [10] specifies that there must be at least microscopic inflammation in order to still consider a diagnosis of UC. However, macroscopically, there may be partial or complete rectal sparing. This was based on studies that found 5–30% of children with UC had macroscopic rectal sparing [11].
2. Histologically patchy disease—disease may be patchy (histologically), early in the disease course when the duration of symptoms is short. In addition, in children less than 10 years old or early in diagnosis, features of chronicity, such as architectural distortion may be absent.
3. Cecal patch—this can occur in children with left-sided UC and isolated inflammation in the cecum, usually periappendiceal in location, with normal intervening mucosa [29–31].

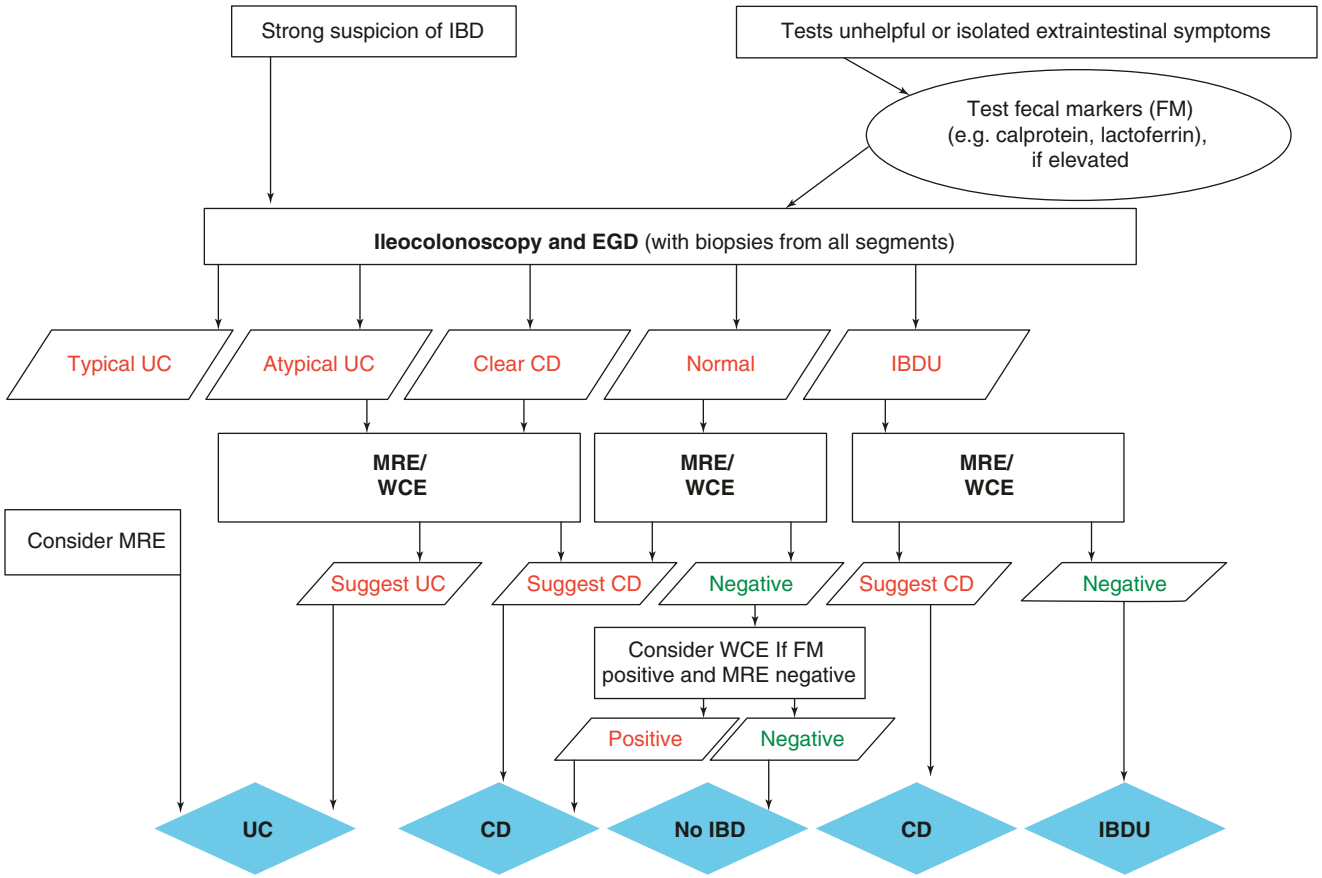

Fig. 15.1 Evaluation of child/adolescent with intestinal or extraintestinal symptoms suggestive of IBD. Atypical UC is a new IBD category consisting of five phenotypes defined in Table 15.1, and reflects a phenotype that should be treated as UC. IBD-U may be entertained as a tentative diagnosis after endoscopy, and can be used as a final diagnosis after imaging and a full endoscopic workup. UC is divided into typical and atypical UC. *CD* Crohn disease, *EGD* esophagogastroduodenoscopy, *FM* fecal marker, *IBD* infammatory bowel disease, *MRE* magnetic resonance enterography, *UC* ulcerative colitis, WCE wireless capsule endoscopy. Reprinted from Levine et al. [11], Fig. 1, page 797, with permission

4. Upper GI tract involvement—gastric erosions and mild ulcerations of the stomach (as well as microscopic involvement) can occur in UC. The presence of focal active gastritis or chronic gastritis can be present in both UC and CD [32]. The EUROKIDS registry described gastric erosions or small ulcers in 4.2% of pediatric UC patients [33].
5. Transmural inflammation with or without deep ulcers—this may be present in acute severe UC, as a marker of disease severity. In UC, the ulcers may be fissuring or V-shaped and lymphoid aggregates may be absent. However, most of these patients would likely be given the diagnostic label "IBD-U," but the disease may declare itself as UC over time.

The features of classic CD are described elsewhere in this book. However, even with isolated colonic disease, there would be no dispute on the diagnosis of CD for patients with cobblestoning of the mucosa, skip lesions (with microscopically normal mucosa in between), or well-formed non-caseating granulomas (remote from ruptured crypts). Other resolute features of CD include linear ulcers in the ileum, ileal inflammation with normal cecum, perianal disease (fistulae, abscesses, or large inflamed skin tags), and the presence of complicated disease behaviors such as stricturing or penetrating disease. Involvement of the small intestine with reliable interpretation of imaging would also point to a diagnosis of CD.

The Porto Group defined IBD-U as inflammation limited to the colon, but with features that make it difficult to differentiate between UC and CD. IBD-U is the phenotype chosen in children in 4–29% of cases (versus <10% in adults). Particularly in young children, colonic involvement in CD may be continuous, making it difficult to distinguish from UC (hence, the consideration for IBD-U classification). The group developed a general scheme of features of UC (or atypical UC) and classic CD. The latter was termed "class 1." As well, they identified and listed features that are "rare with UC" (<5%), termed "class 2" or "uncommon with UC" (5–10%), termed "class 3." If one "rare" (class 2) or two

"uncommon" (class 3) features are present, the group proposed that the IBD subtype should be labeled as IBD-U.

IBD-unclassified (IBD-U) and PIBD Classes

Using the previously defined IBD-U criteria,, the Porto Group validated the PIBD classes to provide a more comprehensive algorithm for labeling a patient as UC, CD, or IBD-U. This was done through a multicenter retrospective longitudinal study from 23 centers and involving 749 children with colonic IBD. A hypothesis-driven judgemental algorithm was chosen, with 80% sensitivity/84% specificity to differentiate UC from CD and IBD-U and 78% sensitivity/94% specificity to differentiate CD from IBD-U and UC [34].

The PIBD classes were further appraised and validated in a cohort of 184 children with all IBD subtypes (rather than just colonic). The group compared the PIBD classes classification to physician-assigned diagnosis. The criteria were also assessed for redundant and unnecessary items, and simplified to 19 items (from 23). In the proposed simplified PIBD classes, item 4 and 14 were removed. Further, items 12–13 were combined into one item, as were 17–18 [35].

Thus, the PIBD classes algorithm (Table 15.2 and Fig. 15.2) proposes to give a more consistent definition of IBD-U. This allows for a more standardized approach to IBD subtypes for both clinical and research purposes. While this tool is very helpful, it is important to remember that it is also relatively new. In a study that compared the PIBD classes to colectomy specimens of children, there was only fair agreement between PIBD class diagnosis and pathology diagnosis

Table 15.2 Original PIBD classes. Adapted from Birimberg-Schwartz et al. [34]

Class	Features
1 (not compatible with UC)	1. 1+ well-formed granuloma remote from a ruptured crypt (anywhere in the GI tract) 2. 1+ deep ulcers, cobblestoning, stenosis in small bowel, or esophagus 3. Fistulizing disease (internal or perianal) 4. Large inflamed perianal skin tags 5. Thickened jejunal or ileal walls or significant small bowel inflammation (on imaging) 6. Any ileal inflammation with normal cecum
2 (rare with UC)	7. Macroscopic and microscopic skip lesions (excluding rectal sparing and cecal patch) 8. Complete (macroscopic and microscopic) rectal sparing 9. Relative patchiness—macroscopically normal colon between areas of inflamed colon, but with microscopic inflammation 10. Significant growth delay with no alternative cause[a] (height velocity <-2SD) 11. Transmural inflammation of the colon without severe colitis 12. Small and not deep ulcers (includes aphthous ulcers) in the small bowel, duodenum, or esophagus, not explained by other causes 13. ≥5 small and not deep ulcers in the stomach or colon on the background of normal mucosa (and not explained by other causes[b]) 14. Backwash ileitis but with only mild inflammation in the cecum (therefore, not true backwash ileitis) 15. Positive ASCA and negative pANCA 16. Reverse gradient of mucosal inflammation in the colon (more severe proximally and milder distally) 17. Severe scalloping of the stomach or duodenum (without other cause[b]) 18. 1+ deep ulcer or severe cobblestoning in stomach (without other cause[b])
3 (uncommon with UC)	19. Focal chronic duodenitis on histology 20. 2+ biopsies with focal active colitis 21. <5 aphthous ulcers in the colon or stomach 22. Non-bloody diarrhea 23. Focal-enhanced gastritis on histology

[a]Other causes: celiac disease, prolonged steroid use, growth hormone deficiency
[b]Other causes: *H. pylori*, celiac disease, NSAIDs

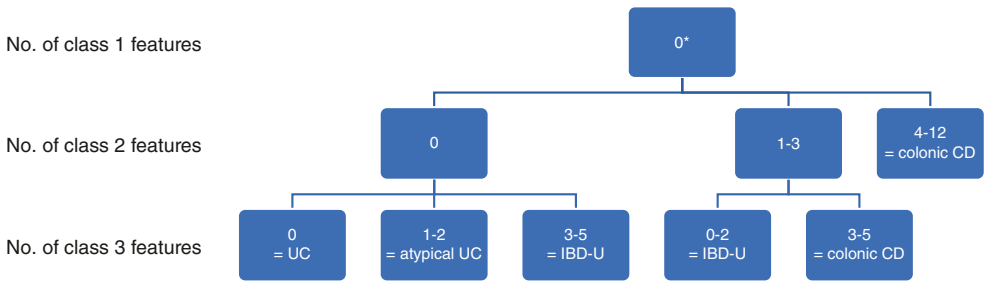

Fig. 15.2 Proposed algorithm for assigning "IBD subtype" using the PIBD Classes system. *If one or more class 1 features are present, this would be indicative of CD (and not compatible with UC). Adapted from Birimberg-Schwartz et al. [34].

[36]. Of note, three children were incorrectly given a diagnosis of CD based on a single class 1 feature. Further, two of the class 3 features were found to have a prevalence higher than the expected 10%—focally enhanced gastritis and focally enhanced duodenitis [36].

Special Considerations

Table 15.3 provides additional details around specific features that can help when assigning a diagnostic phenotype.

Evolution of Disease Phenotype

Disease phenotype in both adult and pediatric patents is not static [16, 53–55]. This represents a challenge when phenotyping both groups of patients. When the Montreal classification was proposed, the authors recommended waiting for 5 years, or until the time of surgery (whichever was sooner), before assigning a disease behavior. However, in reality, patients are being entered into prospective clinical and research registries requiring a phenotypic classification to be assigned at diagnosis.

Table 15.3 Special considerations when determining the IBD subtypes of CD versus UC

Cecal patch	
Described with variable frequency. The prevalence of a cecal patch in pediatric patients with UC is much lower than rates reported for adult patients. The EUROKIDS Registry assessed 643 pediatric patients with UC and found that only 2% met criteria for a cecal patch [33]. This likely reflects the fact that most pediatric patients with UC have pancolitis at presentation	
Macroscopic features Diffuse hyperemia (non-circumscribed margins) with discrete white punctate patches, erosions, or microulcers + friability Can be isolated to the cecum or include the ascending colon (but normal transverse colon)	**Histologic features** Crypt architectural changes of chronicity + findings of acute inflammation
Sources: Levine et al. (EUROKIDS registry) [33], de Roche et al. [37], Ekanayaka et al. [38]	
Backwash ileitis	
This is a nonspecific ileitis which can be seen only in the setting of pancolitis. There are no deep ulcerations, cobblestones, or strictures, which would be in keeping with Crohn ileitis and inflammation is typically limited to the distal 10 cm of terminal ileum. [2] In the absence of cecal inflammation, a diagnosis of backwash ileitis should not be made. Backwash ileitis has been described in close to 20% of adult patients with pancolonic UC [39, 40]. In the EUROKIDS registry, endoscopic evaluation of the terminal ileum was available in 296 of 397 (75%) patients with UC, with 10% having macroscopic terminal ileum abnormalities [33]. Sahn et al. have proposed a model that may be helpful to distinguish backwash ileitis from CD, using histologic and clinical variables [41]	
Macroscopic features Erythema, granularity; allowed to have aphthous ulcers but not deep or linear ulcers Only short segment of terminal ileum involved	**Histologic features** Neutrophilic cryptitis without surface ulceration Can have superficial small ulcers, mild villous atrophy and lymphocytic infiltration Generally, no erosions or ulcers Crypt abscesses uncommon No pyloric gland metaplasia No crypt distortion or features of chronicity No lamina propria (LP) expansion or acute LP inflammation May have mild degree of villous atrophy
Sources: Bousvaros et al. [2], Levine et al. (Porto Group) [11], Levine et al. (EUROKIDS registry) [33], Haskell et al. [39], Heuschen et al. [40], Sahn et al. [41], Fausel et al. [42], Putra et al. [43]	
Rectal sparing	
Absolute rectal sparing refers to normal macroscopic and microscopic findings in the rectum, while *relative rectal sparing* is said to be present when inflammation in the rectum is less severe than the remainder of the colon [2]. In the majority of patients, the presence of absolute rectal sparing will point a physician toward a diagnosis of CD or at least IBD-U. However, there are a minority of UC patients who have relative rectal sparing. Glickman compared mucosal biopsies from 73 pediatric and 38 adult patients newly diagnosed with UC. Among the pediatric group, relative rectal sparing was present in 23% of patients and absolute rectal sparing in 3% of patients, features which were not seen in the adult group [44]. Washington et al. [45] also examined rectal biopsy specimens from adult and pediatric patients with UC and found that children more frequently lacked classic histologic features and felt this may have been the result of shorter duration of inflammation in the pediatric group prior to diagnosis. In a small series of 30 pediatric patients with newly diagnosed UC, Rajwal et al. [46] found that 7% had macroscopic rectal sparing. The EUROKIDS registry described macroscopic rectal sparing in 28 of 553 (5%) UC patients. Rectal sparing was more common in younger patients (mean age of 9.9 years versus 11.8 years at diagnosis). The finding was also more prevalent in those with extensive (E3) or pancolitis (E4) than those with left-sided disease (6% vs. 1%, $P = 0.04$). Rectal sparing was also more likely to be present in patients diagnosed earlier in their disease course [33]	
Sources: Glickman et al. [44], Washington et al. [45], Rajwal et al. [46], Levine et al. (EUROKIDS registry) [33]	

(continued)

Table 15.3 (continued)

Cecal patch	
Upper gi tract (UGIT) inflammation	
The reported prevalence of upper GI tract disease in pediatric IBD patients is variable and may be related to the definitions used, with some centers reporting upper GI tract disease only when macroscopic disease is present, whereas other investigators consider upper GI tract disease to be present even when findings are only histologic. While deep ulceration and granulomas in the esophagus, stomach, or duodenum are suggestive of CD, the presence of nonspecific or microscopic inflammation in the upper GI tract should not preclude a diagnosis of UC if other features best fit this diagnosis. Isolated upper GI tract inflammation was described in 4% of children with Crohn disease in the EUROKIDS registry	
Macroscopic features May see erosions or small gastric ulcers, but not linear or serpiginous ulcers in UC [11] Ulcers, erosions, aphthous lesions, and cobblestone mucosa described in approx. 18% of CD patients in the EUROKIDS registry. Nonspecific macroscopic upper GI tract inflammation is present in up to 30–64% of CD patients [27, 47] and up to 50% of patients with UC [48, 49]	**Histologic features** [50] Duodenitis (0–29% UC, 33–38% with CD)—cryptitis (chronic active duodenitis), villous blunting, IELs, eosinophils Lymphocytic esophagitis (7% UC, 12–28% with CD) Gastritis: Focal-enhanced gastritis + superficial plasmacytosis Granulomas, not associated with crypt rupture: CD, not a feature of UC
Sources: Levine et al. [11], Sawczenko et al. [27], Lenaerts et al. [47], Tobin et al. [48], Ruuska et al. [49], de Bie et al. (EUROKIDS registry) [51], Abuqteish et al. 2019 [50], Levine et al. (EUROKIDS registry) [33]	
Acute severe colitis (fulminant colitis)	
Fulminant ulcerative colitis may have features that appear similar to Crohn disease	
Macroscopic features [37, 52] Can have rectal sparing and linear deep ulcers Can have "well like" ulcers (aphthous ulcers that have penetrated through muscularis mucosa)	**Histologic features** Focal transmural inflammation near deeply ulcerated areas can be seen No transmural lymphoid aggregates (away from ulcerations)
Sources: DeRoche [37], Magro et al. [52]	

It is important to remember the potential for evolution of the IBD phenotype, both in terms of IBD subtype, as well as disease behavior and location in CD and disease extent in UC. Adult CD studies, particularly in the pre-biologic era, have described relatively high rates of progression to penetrating and stricturing disease [53]. In a pediatric CD cohort of over 700 patients, progression of disease location was seen in 20%, change in disease behavior to stricturing or penetrating disease in 38% and new perianal involvement was found in 20% of patients [56]. A large prospective study of new-onset pediatric Crohn disease, involving 28 sites in North America and Canada (the RISK study), found that early use of biologic therapy was associated with a decrease in the development of penetrating disease behavior, but did not influence the occurrence of stricturing disease [57]. Burisch et al. found that approximately a third of patients (predominantly adults) with limited UC progressed, in terms of disease extent, over a 7-year follow-up period [58]. In a pediatric UC study, disease extension has been reported in 30% of patients who initially had limited disease, although half of the children studied had extensive disease at the time of presentation [59].

For some patients, the type of IBD (CD, UC or IBD-U) will change over time. Everhov et al. studied over 44,000 (approx. 4600 were children) patients using health administrative data. For the pediatric patients, over time, the diagnosis of pediatric CD increased from 43% to 44%, while UC decreased from 45% to 38% and IBD-U increased from 12% to 18% [60].

It is important that patient registries continue to have the ability to capture change in disease phenotype and assessments at multiple time points should be recorded. This will allow assessment of natural history as well as the impact of therapies on disease evolution.

Future Directions

Classification of IBD has progressed well beyond the classic categories of CD, UC, or indeterminate colitis. The advent of the Montreal classification and the subsequent Paris modification for pediatric IBD have allowed for granularity in the description of IBD phenotype for both clinical and research purposes. While these classification systems have been extremely valuable, disease location, and severity do not tell the full story of IBD. Some have suggested adding histology to the macroscopic description of the Paris modification to improve descriptive capability [61]. Further modifications for age and inclusion of very early onset IBD (VEO-IBD) should also be considered, as this group of patients have different disease prognosis and response to therapy [8, 9]. In addition, with advances in characterization of the role of gene, environment, and microbiome interactions and their effect on disease phenotype, we anticipate that future classification systems will incorporate new disease location categories, histology findings, protein expression characteristics, microbiome and metabolomic patterns, and other factors. In

the era of personalized medicine, treatment choice will depend on many more factors than those described in current classification systems. We anticipate that definition of the inflammatory bowel diseases will consist of a continuum of categories resulting in even more power to describe the disease characteristics of a child with IBD.

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Part III

Diagnosis

The History and Physical Exam

16

Steven Fusillo and Arthur J. Kastl Jr

Introduction

A thorough history and physical exam are essential elements in caring for all patients. A thoughtful interview with the patient and family will uncover clues which help focus not only the physical exam, but subsequent diagnostic evaluation. The history and physical exam also form the basis of indices like the Pediatric Crohn Disease Activity Index (PCDAI) (Table 16.1) and Pediatric Ulcerative Colitis Activity Index (PUCAI) (Table 16.2), among others, which are used in research and certain clinical settings [1, 2].

Table 16.1 Pediatric Ulcerative Colitis Activity Index (PUCAI) [1]

Item	Points
1. Abdominal pain:	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in less than 50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 h	
0–2	0
3–5	5
6–8	10
>8	15
5. Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of PUCAI (0–85)	

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Table 16.2 Abbreviated Pediatric Crohn Disease Activity Index (PCDAI) [2]

History (Recall, 1 week)	
Abdominal pain	
None	0
Mild: Brief, does not interfere with activities	5
Moderate/severe: Daily, longer lasting, affects activities, nocturnal	10
Patient functioning, general Well-being	
No limitation of activities, well	0
Occasional difficult in maintaining age appropriate activities, below par	5
Frequent limitation of activity, very poor	10
Stools (per day)	
0–1 liquid stools no blood	0
Up to 2 semiformed with small blood, or 2–5 liquid	5
Gross bleeding, >6 liquid, or nocturnal diarrhea	10
Examination	
Abdomen	
No tenderness, no mass	0
Tenderness, or mass without tenderness	5
Tenderness, involuntary guarding, definite mass	10
Perirectal disease	
None, asymptomatic tags	0
1–2 indolent fistula, scant drainage, no tenderness	5
Active fistula, drainage, tenderness or abscess	10
Weight	
Weight gain or voluntary weight stable/loss	0
Involuntary weight stable, weight loss 1–9%	5
Weight loss >10%	10
Extraintestinal manifestations	
Fever >38.5 °C for 3 days over the past week, definite arthritis, uveitis, EN, PG	
None	0
1	5
2+	10
Total score:	

History

A comprehensive patient history is the crucial first step in establishing clinical suspicion for IBD. Pediatric patients with IBD can present with an array of symptoms, including but not limited to abdominal pain, diarrhea, rectal bleeding, weight loss or growth failure, fever, fatigue, pallor, or extraintestinal manifestations. Presenting symptoms often differ based on the location and extent of disease involvement. Ulcerative colitis most commonly presents with bloody diarrhea, abdominal pain around bowel movements, and tenesmus, while Crohn disease involving the small bowel may have a more insidious course with progressive abdominal pain and weight loss. The frequency of presenting symptoms for ulcerative colitis (UC) and Crohn disease (CD) are summarized in Table 16.3 [3, 4].

Careful attention to pain patterns can reveal important clinical insights. Patients with esophageal ulcerations may complain of odynophagia or dysphagia while eating, or heartburn after meals. Gastritis or duodenitis may result in epigastric pain, early satiety, or vomiting. Small bowel inflammation is frequently associated with bloating and generalized malaise, while intestinal strictures may lead to abdominal distention, nausea, and vomiting developing an hour or so after meals. Crampy lower abdominal pain, often accompanied by defecation urgency, tenesmus, and hematochezia, typically reflects colonic and rectal inflammation. Nocturnal awakening due to abdominal pain is unlikely to be functional in nature and should raise suspicion for underlying pathology. It is important to note that children often underreport pain, and young patients may have difficulty characterizing or localizing their pain.

Table 16.3 Frequency of presenting symptoms in inflammatory bowel disease [3, 4]

Symptom	UC (%)	CD (%)
Abdominal pain	33–76	62–95
Diarrhea	67–93	52–78
Rectal bleeding	52–97	14–60
Weight loss	22–55	43–92
Fever	4–34	11–48
Delayed growth	6	30–33
Perianal disease	0	25
Extraintestinal manifestations	2–16	15–25

Information regarding patient bowel patterns can be difficult to ascertain but crucial to the clinical picture. Parents generally do not witness their child's stool beyond the toilet-training period. Many adolescents never look in the toilet or are apprehensive to discuss bowel habits. Parents may be able to provide useful clues such as observing their child making frequent trips to the bathroom or constantly cleaning residual loose stool or blood from the toilet bowl. Individuals may have different definitions of diarrhea, and thus, it is important to ask the patient or caregiver to describe the bowel movement in some detail. Directed questions such as whether stools are entirely watery, are partially formed but disintegrate when hitting the water may be helpful. The frequency of bowel movements as well as the presence of urgency, tenesmus, or blood can help assess the severity of colitis. When rectal bleeding is present, the frequency, quantity, and color (e.g., bright red versus maroon) should also be disclosed. As with awakening for pain, nocturnal bowel movements should never be considered normal and are a "red flag" for intestinal inflammation.

Patients with IBD often present with weight loss and, unique to the pediatric population, growth failure and pubertal delay. Growth failure is more common in Crohn disease, present in 10–40% of pediatric patients at the time of diagnosis, and less common in ulcerative colitis [5]. Growth curves from the primary care provider should be reviewed in detail, as decelerations in height or weight velocity may occur long

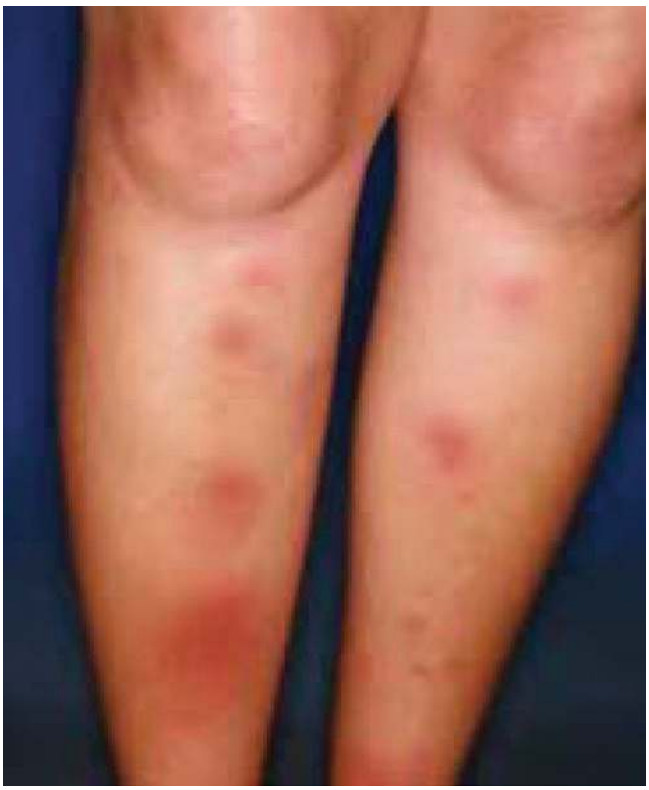

Fig. 16.1 Erythema nodosum

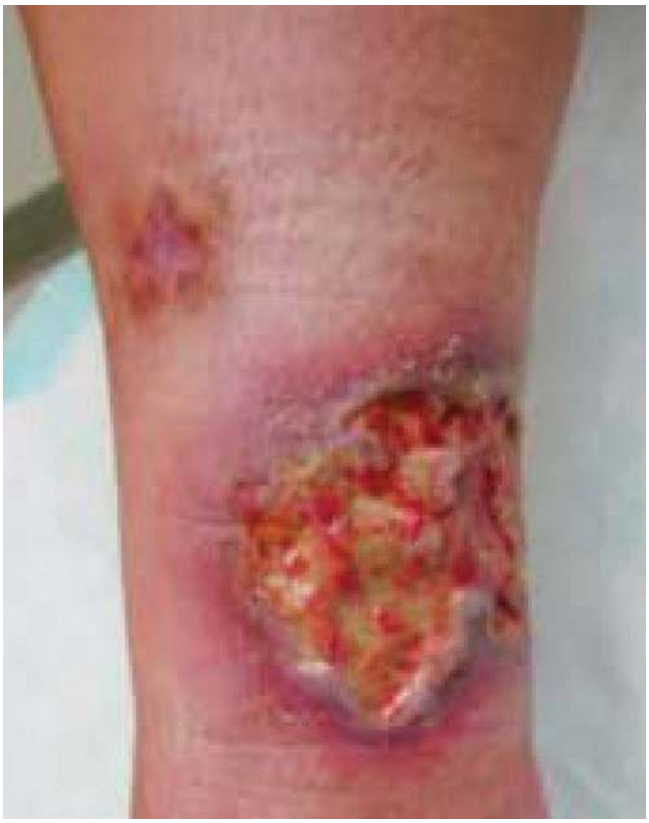

Fig. 16.2 Pyoderma gangrenosum

before the onset of clinical symptoms. Conversely, the presence of overweight or obesity should not preclude the diagnosis of IBD [6].

Extraintestinal symptoms are common in children with IBD and may involve dermatologic, ophthalmologic, musculoskeletal, hepatic, pancreatic, renal, or hematologic systems. These manifestations may predate gastrointestinal symptoms by several years, and as such, may be the sole presenting symptoms in some children [7]. Arthritis is most common, and approximately 4% of patients with IBD will present with arthritis as the predominant symptom. The arthritis associated with IBD is typically pauciarticular and involves large joints, and pain tends to be worse in the mornings. Some patients may first present to the pediatrician or dermatologist with painful, non-specific rashes, commonly involving the lower extremities. A large fraction of children presenting with erythema nodosum (Fig. 16.1) or pyoderma gangrenosum (Fig. 16.2) will be found to have IBD. Patient may also first come to medical attention with recurrent oral ulcers or other mucocutaneous lesions [8].

Patients with Crohn disease may present first to the surgeon with recurrent perianal abscess, small bowel obstruction, or an appendicitis-like picture. Free perforations are occasionally seen. Patients with Crohn disease may develop fistulae, or communications between bowel and bowel, bowel and skin, or bowel and genitourinary tract. Unless specifically asked, patients may not mention the presence of fecal material in the urine or vagina.

It is important to obtain detailed past medical and family histories, with a focus on gastrointestinal and autoimmune conditions. IBD is more likely in patients with a personal or family history of other autoimmune diseases, such as celiac disease, type 1 diabetes mellitus, autoimmune thyroid disease, primary sclerosing cholangitis, autoimmune hepatitis, lupus, or rheumatoid arthritis. Patients with first-degree relatives with IBD are 3–20 times more likely to develop IBD than the general population [9, 10]. A detailed history of infection and antibiotic use, as well as a thorough social history including any recent travel or potential exposures, should be routinely obtained.

Physical Exam

After taking a thorough history, the physical exam will often confirm or revise your impression. There are several key elements of an exam to focus on as you are evaluating a patient with IBD, including general appearance, vital signs, growth parameters, and several body systems. The first and most easily apparent part of the physical exam is the patient's general appearance, and having an accurate impression of this is

important in triaging the need for urgent care. Does the patient seem alert and energetic, or fatigued and withdrawn? Are they in distress? It may be helpful to ask for the parents' viewpoint on this matter, as they are likely the closest observers of the patient. It is also imperative to review vital signs, as active disease can contribute to fevers, tachycardia, and dehydration. The basis of these vital sign changes may be broad, including secondary to pain, anemia, and disease complications, among others. A patient with a toxic appearance and vital signs warrants urgent evaluation.

Careful review of growth metrics is important for characterizing a patient's global nutritional status, which often is closely linked to disease activity and subsequent symptoms. As a patient becomes malnourished, there will be a decrease, or "drifting" first of weight velocity, and if long standing, then followed by stunting of height velocity. While malnutrition is more common for patients with Crohn disease, particularly with small bowel involvement, patients with UC can lose significant weight through stool losses and poor appetite [11]. As mentioned in the History section above, for children affected during the peri-pubertal years, poor disease control can contribute to delayed sexual maturity. Thus, performing a genital exam for Tanner staging is an important part of growth and nutrition assessment.

The examination of the digestive system is central to diagnosis and monitoring of patients with IBD. Visceral pain is poorly localized, whereas parietal pain is more focal at the point of pathology. In patients with IBD, localized pain could arise due to inflammatory masses, abscesses, enterocutaneous fistulas, or mimickers like appendicitis, hernias, or ovarian pathology. Large inflammatory masses, which are often in the ileocecal region, may be palpated on exam. Abdominal distension with borborygmi, especially with the history of poor appetite, nausea, and vomiting, is a worrisome finding and should raise suspicion for bowel obstruction. Complete absence of bowel sounds in an ill-appearing child should increase suspicion for toxic enterocolitis, and trigger urgent evaluation.

The oral examination is also important in identifying ulcerations and/or orofacial granulomatosis [12]. Abnormal tongue appearance, poor gingival health, and tooth decay can be a sign of micronutrient deficiencies and can guide subsequent evaluation. For example, an enlarged and smooth-appearing tongue is characteristic of glossitis. Glossitis could result from B12 deficiency, which can occur in patients with distal ileal Crohn disease and/or in those with prior ileocecectomy [13]. Angular cheilitis may signify B vitamin and iron deficiency, which could suggest active disease and/or malabsorption. The perianal and rectal examinations may be overlooked but are of central importance in evaluating patients with IBD. Skin tags, particularly large ones and those not at the 12 o'clock position, may be present in a subset of patients with Crohn disease. The same is true for perianal abscesses and fistulae, which are often marked by erythema, induration, tenderness, and fluctuance [14]. Rectal examination may reveal stricturing disease which would also be characteristic of Crohn disease and less commonly UC. For patients with significant perianal and anorectal disease, it may be necessary to do an examination under sedation in order to have a thorough assessment.

Extraintestinal manifestations of IBD are present in roughly 15–20% of cases at presentation. They may develop later in the disease course, or particularly for erythema nodosum and arthritis, may be the only physical exam finding at presentation [12]. Extraintestinal conditions may involve the eye, skin, joints, other abdominal viscera, and other body systems. They are often associated with colonic disease but do not necessarily correlate with disease activity [7]. In some patients, they may be entirely idiosyncratic. In terms of ocular findings, episcleritis and/or scleritis may occur in <5% of patients with IBD, which on exam appears as redness of the ciliary vessels and injection of the episcleral tissue [15]. Uveitis is less common than episcleritis, but its consequences are potentially more severe [16]. Uveitis is often bilateral, posterior to the lens, and more common in females [17]. It is also important to be observant for cataracts, which may develop in patients who have been chronically treated with glucocorticoids and stress the importance of regular eye examinations. Several skin findings may be seen in patients with IBD, including not only most classically erythema nodosum and pyoderma gangrenosum, but also psoriasis and hidradenitis suppurativa. Erythema nodosum will appear as painful and raised lesions, about 1–3 cm in diameter, and most commonly occurring on the shins. It is more commonly seen in patients with Crohn disease compared to ulcerative colitis and usually resolves when therapy is started [12]. Pyoderma gangrenosum is a dramatic rash involving frank ulceration and is more often seen in patients with ulcerative colitis [12]. This rash similarly responds to immunosuppression. Psoriasis is also associated with IBD and may occur concurrently, or secondary to therapy, most notably the anti-tumor necrosis factor-alpha class [18]. Psoriatic lesions may occur anywhere on the skin. The painful axillary and inguinal nodules of hidradenitis suppurativa are reported most in adult literature but have been described in adolescents [19]. Lastly, the practitioner should consider a full dermatologic examination, at least yearly, paying close attention to any skin lesions concerning for malignancy. If present, additional evaluation by a Dermatologist should be considered.

Up to 20% of patients with IBD have arthralgia within the first few years or after diagnosis, and about 5% have arthritis [20]. Arthritis is more common in children with Crohn disease compared to ulcerative colitis, and particularly so with Crohn colitis. The arthritis usually affects the larger joints, is non-erosive, and mirrors the status of the intestinal disease [15]. By contrast, axial skeletal involvement including sac-

roiliitis or ankylosing spondylitis, is less common and may have its own trajectory independent of the gastrointestinal disease [15].

Jaundice and pruritis in a patient with IBD, particularly ulcerative colitis, may reflect primary sclerosing cholangitis (PSC) [21]. The severity of PSC is not correlated with the colitis disease activity. Other rarer conditions that are associated with IBD include thromboembolism, nephrolithiasis, cholelithiasis, osteopenia, pancreatitis, and granulomatous inflammation of other body sites.

Summary

A careful history and physical exam may reveal important information regarding the diagnosis of IBD, deciphering disease location, and activity level, and identifying complications of the disease.

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Differential Diagnosis of Inflammatory Bowel Disease

17

Raphael Enaud and Thierry Lamireau

A diagnosis of inflammatory bowel disease (IBD) is usually suspected in patients with chronic digestive symptoms, especially diarrhea (with or without blood in the stools), abdominal pain, and poor weight gain. Numerous other diseases can have similar symptoms. For some of them, laboratory investigations, endoscopic and even histological features may be difficult to distinguish from those of ulcerative colitis (UC) or Crohn disease (CD).

In the short term, the most important challenge is to rule out an infectious disease. In the long term, the differential diagnosis with other chronic diseases, such as eosinophilic gastroenteropathy, vasculitis, lymphoma, or immunodeficiency syndromes, may cause some diagnostic difficulties.

In some cases, the possibility of IBD, mostly CD, is considered in a child presenting with abdominal mass, isolated esophagogastroduodenal, or perineal involvement.

Acute Onset Diarrhea

In 10 to 20% of adults with IBD, patients present with apparently transient diarrhea, abdominal cramps, and low-grade fever [1]. In this acute onset disease, the diagnoses to be considered are mostly intestinal infection, food allergy, and acute appendicitis.

Intestinal Infection

In the case of acute diarrhea, patients are thought to have *viral gastroenteritis* particularly if they appear to recover promptly. However, prolonged diarrhea, right lower quadrant tenderness, or a slow recovery should alert the physician to the possibility of early IBD. A *bacterial or parasitic infection* of the intestine can also be responsible for prolonged symptoms. Stool sample should, therefore, be collected for culture and toxin assays that can identify one of the numerous pathogens responsible for intestinal infection (Table 17.1). In the last years, development of multiplex gastrointestinal pathogen panel tests allows to simultaneously

Table 17.1 Laboratory tests used to detect enteropathogens

Laboratory test	Organism suggested or identified
Microscopic stool examination	
• Fecal leukocytes	Invasive or cytotoxin-producing bacteria
• Trophozoites, cysts, oocysts, or spores	*Giardia lamblia*, *Entameoba histolytica*, *Schistosoma mansoni*
• Spiral or S-shaped gram-negative bacilli	*Campylobacter*
Stool culture	
• Standard	*Escherichia coli*, *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*
• Specific selective medium	*Clostridium difficile*, *E coli O157:H7*
(to be specified to the laboratory)	*Aeromonas*, *Plesiomonas shigelloïdes*, *Klebsiella oxytoca*, *Vibrio parahemolyticus*
Stool cytotoxicity assay	*Clostridium difficile* (A or B toxin)
Stool Multiplex gastrointestinal pathogen panel tests (PCR)	*Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, *E coli*, *Klebsiella oxytoca*, *Clostridium difficile*
	Adenovirus, *Astrovirus*, *Norovirus*, *Rotavirus*, *Sapovirus*
	Cryptosporidium, *Cyclospora*, *Entameoba histolytica*, *Giardia lamblia*
Culture of colonic biopsy sample	*Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, *Klebsiella oxytoca*, *E coli O157:H7*
PCR on colonic biopsy sample	*Mycobacterium tuberculosis*, *Yersinia Adenovirus*, *Cytomegalovirus*
Circulating antibodies	*Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, *Entameoba histolytica*

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identify common bacterial, viral and parasitic pathogens using molecular testing, with 100% sensitivity and 100% negative predictive value [2]. However, these tests also generate considerable additional positive results of uncertain clinical importance [3]. According to the age of the patient, the severity of symptoms and the type of bacteria, an appropriate antibiotic treatment may then be initiated. When no pathogen is present in the stools, imaging such as an abdominal ultrasound is usually performed. It can show enlarged mesenteric lymph nodes and thickening of the colonic and/or ileal wall, but these findings can be seen in infectious diseases as well as in IBD. In this setting, colonoscopy is useful, enabling the visualization of colonic lesions and collection of biopsy samples for histology and culture. The endoscopist should describe the lesions precisely without directly stating a final diagnosis of IBD. Besides *Clostridium difficile,* which is responsible for the typical pseudomembranous colitis, infection with numerous bacteria or parasites may lead to colonic lesions that can be very similar to those of UC or CD [4] (Table 17.2). Moreover, bacterial overgrowth or intestinal infection is part of initial manifestations in 10–20% cases of IBD. When symptoms are severe, it may be justified to propose a short-course empiric treatment with broad-spectrum antibiotics active against enteric pathogens (e.g., ceftriaxone or ciprofloxacin—usually after 15 years of age, and metronidazole).

If laboratory tests and evolution of symptoms do not confirm the hypothesis of infection, the diagnosis can be changed to IBD based on histological findings. Acute inflammatory changes of cryptitis, and crypt abscesses with neutrophilic infiltration, are not specific and are seen in both entities. The more discriminatory findings in favor of a first manifestation of IBD are the presence of glandular bifurcations and distortions, an infiltration of the mucosa with plasmocytes, and the presence of granulomata [5, 6]. However, these findings are rarely seen when endoscopy is performed at an early stage, and acute episodes of colitis may remain initially unclassified. Half of these patients will relapse in the following 3 years, leading to a diagnosis of IBD, usually UC [7]. When the diagnosis is uncertain, one should avoid starting long-lasting anti-inflammatory/immunosuppressive treatment and be cautious when giving information to the family.

Table 17.2 Main infectious agents responsible for IBD-like lesions during endoscopy

Microorganism	Possible Ileal involvement	Crohn-like aspect	UC-like aspect
Aeromonas	N	+	++
Campylobacter	Y	++	+
Clostridium difficile	N	+	+
Eschericchia coli	N	+	+
Klebsiella oxytoca	N	+	+
Mycobacterium tuberculosis	Y	+++	+
Plesiomonas shigelloides	N	+	+++
Salmonella enteritidis	Y	+	++
Shigella dysenteriae	Y	+	+++
Vibrio parahemolyticus	N	+	+
Yersinia enterocolitica	Y	+++	+
Entamoeba histolytica	N	+	+++
Cytomegalovirus	Y	+	+++

N = no; Y = yes

Food Allergy

Food proteins, usually milk or soy, may produce an allergic colitis which is typically encountered in infants under the age of 2 with a family history of atopy [8–10]. Rectosigmoidoscopy usually shows mucosal erythema and nodularity [11], but lesions may include aphthous ulcerations that mimic CD. The diagnosis of allergy is suspected if an eosinophilic infiltration of the mucosa is present on histology [12]. Allergy skin tests using a panel of the main allergens responsible for food allergy in children can be used to direct the exclusion of the offending protein. A rapid disappearance of symptoms will then confirm the diagnosis [12].

Acute Appendicitis

Acute appendicitis may cause some diarrhea, associated with the classic right lower quadrant pain and tenderness. If clinically warranted, then this diagnosis may be confirmed by ultrasound examination and/or computed tomography of the abdomen. In some rare cases, CD is discovered because of ileal involvement during operation [13, 14] or at the histological examination of the appendix [15, 16]. One should be aware of the possibility of CD in cases of ileitis associated to appendicitis because appendicectomy may lead to complications such as fistula, abscess, and peritonitis.

Chronic or Recurrent Intestinal Symptoms

Chronic or recurrent intestinal symptoms represent the most frequent presentation of IBD in the pediatric population and include symptoms such as abdominal pain and diarrhea lasting up to several months or years, especially in CD. This long delay until the diagnosis may be explained by the frequency in the general population of these non-specific symptoms, as up to 10% of children between 7 and 11 years old seek medical attention for recurrent abdominal pain [17]. A

periumbilical location of pain is typical in functional abdominal pain, but it is also present in most children with IBD. In patients with uncomplicated abdominal pain, constipation, lactose intolerance, peptic disease, food allergy, pathology of the urinary tract, or psychosocial causes should be considered and eliminated. The presence of fever, anorexia, weight loss or growth disturbance, perineal involvement, or blood in the stools suggests the possibility of IBD. This suspicion should be strengthened by laboratory investigations showing anemia and increased inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), ultrasound examination of the abdomen showing a thickening of the intestinal wall, and/or elevated fecal calprotectin [18]. However, these features are not specific to IBD and further investigations are useful to eliminate other diseases (Table 17.3).

Intestinal Infection

Even in case of chronic digestive manifestations, an infectious etiology remains the most frequent differential diagnosis to be considered [4, 19]. It is, therefore, important to collect stools for bacterial and parasitic pathogens at the initial evaluation of a patient with suspected IBD. Contrary to acute presentation, an anti-microbial treatment is generally not considered until laboratory tests have confirmed a specific infectious disease. Depending on the pathogen, the part of the gut involved and the symptoms may vary, leading to consideration of either CD or UC (Table 17.2).

Table 17.3 Useful investigations for differential diagnosis of IBD in children with chronic diarrhea

Blood	Polynuclear count and morphologic features
	Lymphocyte count
	FACS enumeration of T and B lymphocytes
	Serum electrophoresis
	IgG, A, M
	Total haemolytic complement
	C_3, C_4 concentrations
	Anti-Neutrophil Cytoplasm antibody
	Anti-Saccharomyces Cervisea antibody
	Anti-Transglutaminase antibody
	Specific IgE against food allergens
	Anti-bacteria antibody (*Shigella*, *Salmonella*, *Campylobacter, Yersinia, Entameoba histolytica)*
Stools	Fecal leukocytes
	Microscopic examination
	Standard and specific medium culture
	Clostridium difficile cytotoxin assay
Skin tests for	Tuberculosis
	Food allergens
Imaging of the abdomen	US examination
	CT-scan or MRI
Endoscopy	Oesogastroduodenoscopy
	Biopsy for histology
	Ileo-colonoscopy
	Biopsy for histology, bacterial culture, PCR

Infection with *Yersinia enterocolitica* is usually associated with a mild illness in children [20] but subacute and chronic ileitis or ileocolitis has been reported [20, 21] and may resemble CD [22]. This can also be associated with erythema nodosum and polyarthritis. Endoscopic features include aphthoid lesions of the cecum and ileum with round or oval elevations with ulcerations. Ulcers are mostly uniform in size and shape, in contrast to CD [23]. Histological findings of Yersinia infection are not pathognomonic and usually are only indicative of acute and/or chronic inflammation. US examination or MRI show mucosal thickening and nodular pattern of the terminal ileum and colon that can mimic CD, but also enlarged mesenteric lymph nodes [24]. In contrast to CD, fistula formation and fibrotic stenosis are not observed. Stool or biopsy sample cultures may require a specific enrichment medium, are time consuming and not always positive. Identification and characterization of pathogenic Yersinia enterocolitica isolates by PCR in stools or in paraffin-embedded tissue block [25]. The diagnosis can also be made with the identification of serum antibodies (Western blot) against Yersinia outer protein antigens (YOP antigens), the concurrent presence of both IgG and IgA antibodies indicating an ongoing infection [26]. Infection with enteropathogenic and enteroaggregative *Escherichia coli* (EPEC, EAEC) may be responsible for chronic diarrhea in children, especially when they live or travel in developing countries [27, 28].

Infection with *Clostridum difficile* leads to digestive disease ranging from self-limited diarrheal syndrome, to severe pseudomembranous colitis [29]. Sometimes, sustained symptoms lead to consideration of the possibility of IBD. *Clostridum difficile* infection must be sought in children receiving antibiotics, especially beta-lactams, although it may occur without prior antibiotic therapy. Rectosigmoidoscopy, performed with care and minimal insufflation, reveals the presence of typical yellow-white pseudomembranes in approximately one third of patients [29] and infection is confirmed by the presence of the toxin A or B in stool or by polymerase chain reaction. Nevertheless, *Clostridium difficile* infection can occasionally occur in patients with UC or CD, even without the use of antibiotics, and stool toxin positivity has been reported in 5 to 25% of IBD patients with relapse, mostly after antibiotic exposure [30, 31]. Reductions in gut microbial diversity as well as an increase in pro-inflammatory species have been identified in IBD patients, a dysbiosis that may play a role in increasing *Clostridum difficile* infection risk in IBD patients. Due to an overlap in symptomatology, diagnosis and treatment of *Clostridum difficile* infection are also challenging in the IBD population, and it is recommended that stool assay for

Clostridium difficile is obtained in children with IBD during acute relapses [32, 33].

Giardia intestinalis infection can be associated with chronic diarrhea, abdominal pain, and weight loss [34] which may occasionally lead one to consider the possibility of IBD. Giardia is found in most countries in the world, the prevalence being highest in developing countries. Trophozoites or cysts of *Giardia intestinalis* can be found in fresh stool specimens, or rectal biopsies. In some cases, it may be necessary to examine duodenal aspirations or biopsies. Jejunal morphology may be normal, although partial or even total villous atrophy has been reported [35, 36]. Failure to eradicate giardiasis can be due to hypogammaglobinemia or deficit in secretory IgA.

Entamoeba histolytica infection occurs mostly in developing countries. Infection may be asymptomatic or lead to a dysenteric syndrome. Demonstration of *Entamoeba histolytica* trophozoites and cysts in stools remains the mainstay of diagnosis. Chronic amoebic colitis could lead to clinical, radiologic, and endoscopic findings that can be indistinguishable from those of IBD [37, 38]. However, this differentiation is important because amoebiasis can become fulminant if the patient is treated with immunosuppressive agents for a presumed IBD [39]. In these chronic manifestations, the parasite can be difficult to find in stools samples or in rectal biopsies, even using a concentration technique. The presence of high titers of antibodies in the serum may then be helpful in the diagnosis of chronic amoebiasis.

Intestinal tuberculosis accounts for 2% of tuberculosis worldwide and remains a challenging diagnosis in developing countries, because treatments used for CD may adversely affect tuberculosis [40]. Intestinal tuberculosis can affect any part of the intestine but more frequently involves the ileocecal region, isolated colonic location being present in only 10–25% of cases. Symptoms can be very similar to those of CD; these include diarrhea, abdominal pain, fever, weight loss, abdominal mass of the right iliac fossa, and even suppurative perineal lesions. The presence of intramural swelling, mesenteric thickness, stricture or fistula on US examination, or MRI can be encountered in both diseases [41], although the absence or minimal asymmetric thickening of colonic wall and the presence of enlarged necrotic lymph nodes favor the diagnosis of tuberculosis [41–44]. Nodules, ulcers, and strictures can be seen at ileocolonoscopy, or possibly at enteroscopy in the case of isolated jejunal lesions [45–47], but these lesions can be indistinguishable from those of CD. Usually, intestinal tuberculosis has less than four segments involved, a patulous ileocecal valve, transverse ulcers (longitudinal in CD) and more scars [48]. The characteristics of histologic lesions may also be helpful, needing to perform multiple biopsies [49]: in tuberculosis, granulomata are typically bigger, often confluent, located beneath the ulcerations, and absent in non-inflamed mucosa, and half of them contain caseum. Tuberculin skin test is positive in only 70–80% of patients with intestinal tuberculosis. The diagnosis may be facilitated by the presence of active pulmonary tuberculosis (but this is present in only 20% of cases), ascites, or large lymphadenopathy on imaging [40, 42]. Unfortunately, acido-alcoolo-resistant bacilli are very rarely present on direct examination of intestinal biopsies, and culture requires at least 4 weeks and is positive in only 40% of cases. Tissue PCR assays for *Mycobacterium tuberculosis* on intestinal biopsies are faster and show an accuracy of more than 80% for the diagnosis of intestinal tuberculosis [50]. Amplification of insertion element IS6110 that is specific for *M. tuberculosis,* in the fecal samples [51] and the Quantiferon-TB gold, a blood test using an interferon-γ-release assay, look to be promising tools [52] but their diagnostic value for the diagnosis of intestinal tuberculosis remains to be evaluated. Combination of Interferon-gamma releasing assay and anti-Saccharomyces cerevisiae antibody has a high specificity for the diagnosis of ITB [53]. New prediction models using of a CD prediction score combining colonoscopy, laboratory, and radiologic factors, can also be useful for calculating the probability of either CD or ITB at initial evaluation [54]. In cases of persistent doubt, empiric treatment with antituberculosis drugs has been proposed in countries where the prevalence of tuberculosis is high, reconsidering diagnosis of CD if the patient's condition does not improve [55]. Nevertheless, this approach is not recommended by others who advise to make every effort to reach an accurate diagnosis before starting specific therapy [42].

Primary intestinal infection with *cytomegalovirus* (CMV) can occur in immunocompromised children but is exceptional in immunocompetent children [56]. Endoscopy reveals ulcerative and hemorrhagic colitis, and histological examination of the biopsy will confirm the infection with CMV by finding typical intra-nuclear inclusions in the colonic mucosa, associated with immunostaining with a specific antibody. PCR of colonic tissue can also be used to detect viral DNA in the colon, although the significance of a positive result remains unclear in the absence of histological features of CMV disease. CMV colitis is rare in CD or mild-moderate UC [57, 58]. In patients with severe and/or refractory UC, local reactivation of CMV can be detected in inflamed colonic tissue in about 30% of cases but does not influence the outcome in most studies [58]. Nevertheless, treatment with ganciclovir has allowed some patients with severe colitis to avoid colectomy despite poor response to conventional IBD therapies [59]. It is recommended to test for CMV reactivation via PCR and/or immunochemistry on colonic biopsies in patients with severe colitis refractory to immunosuppressive therapy and treat with ganciclovir when CMV is detected [33, 60, 61].

Celiac Disease

Celiac disease is easily recognized in the classic mode of presentation of children who present with chronic diarrhea, anorexia, failure to thrive, and abdominal distension. Presentation is often less typical in older children who complain of abdominal pain, chronic diarrhea, anorexia, short stature, or iron-resistant anemia—symptoms that may also suggest IBD. In this situation, laboratory investigations should include specific antibodies against tissue transglutaminase, endomysium, or deamidated gliadin peptides. If these antibodies are positive, the diagnosis of celiac disease will be further confirmed by duodenal biopsy showing villous atrophy with increased number of intra-epithelial lymphocytes [62].

Eosinophilic Gastroenteropathy

Eosinophilic gastroenteropathy is a rare condition characterized by infiltration of the gastrointestinal tract with eosinophils [63]. Most common symptoms are vomiting, abdominal pain, and growth failure. Diarrhea associated with rectal bleeding is present in 23% of cases, especially in infants**,** and symptoms of protein-losing enteropathy are present in 33–100% of cases [64, 65]. Endoscopic examination may show nodularity, erythema, friability, erosions, and ulcerations in the upper digestive tract and/or in the colon [11, 66]. The diagnosis is strongly suggested by a context of food allergy or the association with hypereosinophilia in the blood, which is present in 70–100% of cases [65]. The presence of excessive eosinophils in the digestive mucosa will confirm the diagnosis although it may also be encountered in CD. Gastric biopsies may demonstrate eosinophilic gastroenteropathy more consistently, most patients having more than 10 eosinophils per high power field in the antral or duodenal mucosa [67]. Allergic skin tests or serum-specific IgE against main food allergens are useful to guide dietary recommendations [64].

Primary or Acquired Immunodeficiency Diseases

The importance of the intestine as an immune barrier is highlighted by the proximity of gut-associated lymphoid tissue to the luminal surface of the gastrointestinal tract, an external environment which is rich in microbial pathogens and dietary antigens. Significant gastrointestinal disorders, leading to chronic diarrhea, malabsorption, and failure to thrive, are frequently present in primary [68] or acquired immunodeficiency diseases [69]. In the recent years, advances in technology, such as whole-exome sequencing and targeted sequencing panels, allowed exploring young patients with IBD-like manifestations [70], and led to identify a significant number of monogenic diseases [71–73], affecting the epithelial barrier, the inflammatory response, or the immune response (Table 17.4). These diseases should be sought after, especially in cases of very early (<6 years) or infantile (<2 years) onset symptoms, and often present with a distinct phenotype, i.e., indeterminate pancolitis or severe ulcerative or fistulizing perineal disease [70]. Although the frontier between these monogenic diseases (still currently being discovered) and classic IBD is vague, the precise characterization of the genetic defect is of importance because therapeutic options may be different in some cases, like bone marrow transplantation, for example. This emphasizes the importance of a close collaboration between pediatric gastroenterologists, immunologists, and specialists in immunodeficiency syndromes for early efficient medical care and for active research to discover involved genes.

The most frequent manifestations of immunodeficiency syndromes are recurrent, persistent, and severe or unusual infections [74]. Disturbance of the immune system in the gut may also lead to auto-immune diseases, excessive production of IgE, or malignancies [75, 76].

Immunodeficient patients may present with chronic non-specific enterocolitis, characterized at small bowel biopsy by subtotal villous atrophy with acute and chronic inflammatory cell infiltration of the lamina propria [77–79]. This chronic non-specific enteropathy is not responsive to a gluten-free diet and occurs in several immunodeficiency disorders, affecting humoral response (X-linked agammaglobulinemia, IgA deficiency, common variable immunodeficiency), T-cell function (Wiskott-Aldrich syndrome, Acquired Immuno Deficiency Syndrome), or both (combined immunodeficiency). In some cases, strictures of the intestine may develop [77–79]. In these patients, it is important to rule out infection with opportunistic bacteria or parasites, and also with more common pathogens, such as rotavirus, adenovirus, and picornavirus [74]. In rare patients, the cause of the chronic enterocolitis is a disease affecting the epithelial barrier (Table 17.4).

Enterocolitis that resembles CD is mostly associated with neutropenia or defects of phagocytic function. Patients with chronic granulomatous disease may present with chronic colitis, perirectal abscesses and fistulae, and antral narrowing [80, 81]. The similarity with CD also includes endoscopic appearance, radiographic abnormalities, and even histologic features showing granulomata and giant cells in the digestive mucosa. Nevertheless, a paucity of neutrophils, an increased number of eosinophils, eosinophilic crypt abscesses, pigmented macrophages, and nuclear debris suggest chronic granulomatous disease [82]. Patients with Leukocyte Adhesion Molecule Deficiency, a rare disorder of phagocytic function, also present with oral and perineal involvement that may be mistaken for CD. These manifestations include stomatitis with pharyngitis, gingivitis with peridontis, ischiorectal abcesses, and distal ileocolitis [83]. Other disorders of neutrophils, such as congenital neutropenia, glycogen stor-

Table 17.4 Gastrointestinal manifestations in genetic defects associated with immunodeficiency syndromes

Disease	Gastrointestinal manifestations	Gene
Epithelial barrier function defects		
Dystrophic epidermolysis bullosa	Moderate to severe colitis	*COL7A1*
Kindler syndrome	Haemorrhagic UC-like colitis	*FERMT1*
X linked ectodermal dysplasia	Atypical CD-like enterocolitis, villous atrophy and epithelial cell shedding	*IKBKG*
ADAM-17 deficiency	First week of life non-bloody later bloody diarrhoea	*ADAM17*
Familial diarrhea	Partially neonatal onset of familial watery diarrhea. CD developed in adult age	*GUCY2C*
Neonatal inflammatory skin and bowel disease TTC7A deficiency Kindler syndrome Epithelial NADPH oxidases defect	IBD-like enterocolitis Colitis Colitis Colitis	*EGFR* *TTC7A* *FERMT1* *NOX1, DUOX2*
Phagocyte defects bacterial killing		
Chronic granulomatous disease	Stomatitis, perineal absesses, IBD like enterocolitis	*CYBB, CYBA, NCF1, NCF2, NCF4, LACC1*
Glycogen storage disease type 1b	Perioral and perianal lesions, CD-like ileocolitis	*SLC37A4*
Congenital neutropenia	Stomatitis, CD-like colitis	*G6PC3*
Leucocyte adhesion deficiency 1	Stomatitis, ileocolitis, perianal abscess, fistulas, CD-like colitis	*ITGB2*
Hyper- and autoinflammatory disorders		
Mevalonate kinase deficiency	IBD-like enterocolitis	*MVK*
Phospholipase Cγ2 defects	UC-like colitis	*PLCG2*
Familial Mediterranean fever	UC-like colitis	*MEFV*
Familial haemophagocytic lymphohistiocytosis	IBD-like enterocolitis	*STXBP2*
X linked lymphoproliferative syndrome 2	CD-like enterocolitis, fistulising perianal disease	*XIAP*
X linked lymphoproliferative syndrome 1	IBD-like enterocolitis, gastritis	*SH2D1A*
Hermansky–Pudlak syndrome Multisystem autoimmune disease	CD-like enterocolitis, perineal lesions	*HPS1, HPS4, HPS6* *STAT3*
B cell and antibody defects		
Common variable immunodeficiency	Persistent intestinal infections, food allergies, autoimmune diseases, malignancies (gastric cancer, lymphoma), CD-like colitis	*ICOS, LRBA*
Agammaglobulinaemia	Persistent intestinal infections, gastritis, malignancies (gastric cancer, lymphoma), CD-like colitis	*BTK, PIK3R1*
Severe combined immunodeficiency	Severe persistent opportunistic infections, IBD-like enterocolitis	*ZAP70, RAG2, IL2RG, LIG4, ADA, CD3γ*
IL-21 deficiency Hyper-IgM syndrome	Severe early onset colitis Oral ulcers, IBD-like	*IL21* *CD40LG, AICDA*
Wiskott–Aldrich syndrome	UC-like colitis	*WAS, WIPF1*
Omenn syndrome	Stomatitis, IBD-like enterocolitis	*DCLRE1C, DCLRE1X*
Hyper IgE syndrome	buccal granulomatous disease, UC-like colitis.	*DOCK8*
Trichohepatoenteric syndrome	Intractable diarrhoea, colitis	*SKIV2L, TTC37*
Regulatory T cells defects		
IPEX, IPEX-like Autoimmune lymphoproliferative syndrome type 5	Autoimmune enteropathy, colitis Enteropathy	*FOXP3, IL2RA, STAT1* *CTLA4*
CD122 deficiency DEF6 deficiency RIPK1 IL-10 signalling defects	Enteropathy Enteropathy IBD-like Stomatits, perianal abscesses and fistula, CD-like ulcerative colitis.	*IL2RB* *DEF6* *RIPK1* *IL10RA, IL10RB, IL10*
NOD2 signaling defects Anhidrotic ectodermodysplasia	IBD Colitis	*NOD2, TRIM22* *IKBKG*

Gene names were used according to HUGO gene nomenclature
CD Crohn disease, *IBD* Inflammatory bowel disease, *IPEX* X linked immune dysregulation, polyendocrinopathy, enteropathy, *UC* Ulcerative colitis

age disease type 1b, and the Hermansky–Pudlack syndrome [84], are responsible for CD-like enterocolitis. The same presentation may be caused by T- or B-cell defects, IgA deficiency, and acquired immunodeficiency syndrome [68, 85].

Severe ulcerative or fistulizing perineal disease occurring in a very young child is suggestive of IL-10-signaling pathway defect [86–88] or X-linked lymphoproliferative syndrome 2 [89, 90] and may also be encountered in phagocytic defects or Hermansky–Pudlack syndrome.

Auto-immune enteropathy is characterized by severe persistent diarrhea associated with circulating auto-antibody against gut epithelial cell and/or another auto-immune disorder [91, 92]. An additional consideration is X-linked familial disease which includes polyendocrinopathy (IPEX syndrome) [93–95]. Although the colon is frequently involved [93, 96, 97], the lesions are predominant in the small intestine, with inflammatory cell infiltration of the mucosa, and subtotal or total villous atrophy [93, 94, 97], leading to secretory, and protracted diarrhea in the first months of life [98, 99]. Nevertheless, antibodies to colonic epithelial cells have been also found in patients with UC [100], and 10% of IBD patients suffer from one or more auto-immune diseases [101], leading to some diagnostic difficulties in the older child.

Intestinal Neoplasm

Patients with *intestinal lymphoma* often present with chronic digestive symptoms, such as abdominal pain, distension, and/or diarrhea. Lesions are usually located in the small bowel although some cases may involve the colon [102, 103]. Ultrasound examination shows a thickening of the intestinal wall, and/or narrowing of the lumen of the gut which can be very similar to CD [104]. Extent of the lesions is more precisely seen with a MRI of the abdomen, and upper digestive endoscopy and/or ileocolonoscopy are mandatory to provide histologic confirmation. Nevertheless, if the lesions are limited to part of the small intestine, the biopsy may require an enteroscopy or even a surgical procedure, by laparoscopy or laparotomy. Predisposing conditions for intestinal lymphoma in children include inherited or acquired immunodeficiency syndromes, immunosuppressive therapy, and Epstein-Barr Virus infection [105]. In developing countries, Mediterranean lymphoma is characterized by the proliferation of IgA-secreting B lymphocytes. The diagnosis is usually suspected because of the presence of alpha heavy chain in the serum [106].

Vasculitis Disorders

Henoch–Schoenlein purpura is a frequent vasculitis, involving the gut, skin, joints, and kidney. Diagnosis is easily made in a child presenting with typical skin purpura, but gastrointestinal symptoms, i.e., colicky abdominal pain and bleeding, may precede the skin rash by a number of days. In some cases, isolated duodenojejunitis without purpura may occur [107], and terminal ileitis mimicking Crohn disease has been described [108, 109].

In other less frequent systemic vasculitides, such as polyarteritis nodosa [110, 111], Wegener granulomatosis [112], Behçet's disease [113, 114], and lupus arteriosus [115], intestinal involvement can lead to chronic abdominal pain associated with bleeding. Endoscopic and histological findings may be very similar to CD, even with the presence of granuloma. Extra-digestive manifestations, especially neurological, respiratory, renal, and cutaneous lesions suggest systemic vasculitis [116] (Table 17.5). On the other hand, extra-intestinal vasculitis can complicate IBD, involving the retina, brain, skin, muscle, joints, and lung [117–122]. The

Table 17.5 Extra-digestive manifestations and useful investigations for the diagnosis of systemic vasculitis in children with digestive symptoms resembling Crohn disease

Vasculitis	Extra-digestive manifestations	Investigations
Periarteritis nodosa	Multiple neuritis	Skin, muscle biopsy
	Myositis	Angiography
	Arterial hypertension	
	Skin ulcerations and gangrene	
Wegener granulomatosis	Epistaxis, sinusitis, otitis, hearing loss	Thoracic CT-scan
	Stridor, hoarseness	c-ANCA
	Cough, wheezing, dyspnea, hemoptysis	Nasal mucosa biopsy
	Necrotizing glomerulonephritis	
	Skin ulcerations and gangrene	
	Conjunctivitis, uveitis, optic neuritis	
	Pseudotumor cerebri	
Behcet's disease	Serious buccal aphtous	HLA-B5
	Genital ulcers	
	Uveitis	
	Thrombophlebitis	
	Menigoencephalitis	
Lupus arteriosus	Typical facial erythema	Antinuclear antibody
	Myocarditis, pericarditis, endocarditis	Anti-DNA antibody
	Pleuropneumonitis	
	Glomerulonephritis	
	Thrombophlebitis	
	Hemolytic anemia and thrombopenia	
	Keratoconjunctivitis, retinitis	

differentiation between primary systemic vasculitis and IBD can be clinically challenging but is important because their treatment and outcome are different [123]. The confirmation of the vasculitic process is more often evident on extra-intestinal biopsies (skin, muscle, kidney) than on intestinal biopsies and on angiography showing aneurysms and caliber variation of visceral arteries [110].

Abdominal Mass

The discovery of an abdominal mass has been found to reveal ileocolic CD in some adults and children [124–126]. Ultrasound examination and MRI of the abdomen are first-line investigations which will exclude extra-digestive malignant tumors, such as lymphoma, sarcoma, nephroblastoma, or neuroblastoma. When the mass is developed from the digestive tract, glandular lymphoma or adenocarcinoma of the colon, although rare in children, can be suspected [127–129]. Radiologic findings may be very similar in some benign lesions, like leiomyoma, pseudoinflammatory tumor, or tuberculosis [130, 131]. Nevertheless, surgical exploration is generally required, leading to correct diagnosis after histologic examination of the excised tumor. Intestinal tuberculosis may be a challenging diagnosis because histologic findings may be very similar to those of CD, although granulomata are typically larger and contain caseum in the case of tuberculosis [49]. Polymerase chain reaction for *Mycobacterium tuberculosis* should be systematically performed [50, 51].

Isolated Esophagogastroduodenal Involvement

Esophagogastroduodenal involvement is present in 25–40% of children with CD, usually discovered during upper digestive endoscopy with systematic biopsies, performed at initial work-up [132–136]. More rarely, patients may present with symptoms suggestive of peptic disease, including epigastric burning pain and early satiety, these often being relieved by antacids or antisecretory treatment [137, 138]. Endoscopy can show heterogeneous lesions, but a bamboo-joint like appearance is suggestive of CD [133, 137, 139–141]. Uncommonly, CD patients present with an isolated gastric or duodenal ulcer [134]. In the case of long-lasting symptoms or altered growth rate, the possibility of CD should be kept in mind and a biopsy of the edge of the ulcer looking for the presence of granulomata should be performed [133, 137]. The differential diagnosis for upper gastrointestinal CD includes *Helicobacter pylori* infection, peptic ulcer disease, viral gastritis, eosinophilic GI disease, Wegener's granulomatosis, sarcoidosis, carcinoma, gastric lymphoma, and tuberculosis [142].

Isolated Perineal Disease

Skin tags, anal fissures, and perianal fistulae or abcesses are frequent in infants who are in diapers and/or have a history of constipation with hard stools.

Such perianal lesions also occur in half of patients with CD, mostly in the context of colonic inflammation [143]. These lesions may precede other manifestations of intestinal disease in about one third of these patients [144]. In adolescents, perianal lesions can be severe [145, 146], hidden, and unrecognized for several months. The diagnosis of CD should then be considered in the case of extensive or refractory perianal lesions occurring in children. Confirmation of diagnosis will be obtained by MRI showing abscesses and fistulae and their relationship to the elevators [147], the presence of granuloma on biopsies of perianal lesions that required surgery, and/or colonoscopy that will show colitis [144, 146]. Severe ulcerative or fistulizing perineal disease occurring in a very young child is suggestive of monogenic diseases such as IL-10-signaling pathway defect [86–88], X-linked lymphoproliferative syndrome 2 [89, 90], phagocytic defects [80], or Hermansky–Pudlack syndrome [84]. More rarely, perineal lesions can occur after trauma or sexual abuse [148, 149].

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Laboratory Evaluation of Inflammatory Bowel Disease

18

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Introduction

Although clinical history and physical exam may raise suspicion of Crohn disease (CD) or ulcerative colitis (UC), a focused laboratory evaluation can facilitate further differentiation between inflammatory bowel disease (IBD) and non-inflammatory bowel disease—in particular, distinguishing between IBD, infectious processes, and functional bowel disorders (Table 18.1). These blood and stool studies, in combination with clinical presentation (thorough history, including family history of IBD or other autoimmune conditions, and physical examination), can help determine which child may require more extensive or invasive testing, such as radiological and endoscopic evaluation to definitively diagnose IBD and provide information to facilitate IBD phenotype. Moreover, the blood and stool evaluations may also provide insight into the severity of disease, if indeed IBD (i.e., prognostication). The first part of this review will focus on the evaluation of blood tests in the work-up of a child with suspected IBD. Initially, the nonspecific markers of disease (e.g., anemia) and inflammation (e.g., C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) will be discussed. Subsequently, the more "specific" serological markers of IBD will be reviewed, and then, stool tests, which can be used to potentially delineate between IBD and non-IBD, will be discussed.

Table 18.1 Laboratory tests for suspected inflammatory bowel disease

Test	Findings	Significance
Complete blood count and differential	Anemia (microcytic, macrocytic, normocytic), thrombocytosis, leukocytosis	*Anemia:* Assess severity of blood loss, evaluate for iron and other macronutrient deficiencies. Reported prevalence 16–77% in Crohn disease and 9–67% in ulcerative colitis *Thrombocytosis:* Acute phase reactant, nonspecific measure of inflammation. Reported prevalence variable, occurring in up to 85% of patients with Crohn disease and 70% patients with ulcerative colitis.
ESR and CRP	Elevation	Nonspecific markers of inflammation, potential role in assessing disease activity, predicting disease relapse, and monitoring therapeutic response.
Liver function tests	Hypoalbuminemia Elevated transaminases Elevated alkaline phosphatase/GGT	*Hypoalbuminemia:* Surrogate marker of nutrition, possibly indicative of decreased liver production (negative acute phase reactant) or intestinal protein losses due to inflammation. *AST/ALT/Alkaline phosphatase/GGT:* Role in evaluating for extra-intestinal complications of inflammatory bowel disease.

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Table 18.1 (continued)

Test	Findings	Significance
Stool Cultures—*E. Coli*, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia* species	Infection	Evaluate for primary infectious colitis, which may mimic inflammatory bowel disease and exclude co-infection, which may complicate disease.
Clostridium difficile PCR	Infection	Evaluate for primary infection and co-infection. In patients with inflammatory bowel disease, *C. difficile* is the most common infectious agent identified
Stool calprotectin	Elevation	Alternative inflammatory marker, which appears to be a direct measure of intestinal inflammation. Role in assessing disease activity and predicting relapse in patients with inflammatory bowel disease
IBD serologies	Positive ASCA (IgA or IgG), pANCA, anti-OmpC, anti-CBir	May aid in classifying disease subtype and play a role in therapeutic decisions (prognostic factor). Inadequate screening tool due to low sensitivity compared to clinical history and routine laboratory tests

ESR Erythrocyte sedimentation rate, *CRP* C-reactive protein, *IBD* Inflammatory bowel disease, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *GGT* Gamma glutamyl transpeptidase, *ASCA* Anti-Saccharomyces cerevisiae (ASCA), *pANCA* Perinuclear antinuclear cytoplasmic antibody, *OmpC* Outer membrane protein

Blood Tests

Most clinicians, adult and pediatric, will agree that blood tests should be part of the initial screening process in children with symptoms compatible with UC or CD [1–6]. The specific blood evaluations performed should, at minimum, consist of a complete blood count, including white blood cell number with a differential, hemoglobin and hematocrit, iron/red blood cell characteristics or indices such as mean corpuscular volume, as well as studies to further characterize iron deficiency including ferritin, total iron-binding content (TIBC), and iron. In addition, liver biochemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), albumin, and total protein, and systemic inflammatory markers, such as ESR and CRP, should be included in the initial laboratory evaluation of a child with suspected IBD [6, 7]. Although normal tests do not rule out the possibility of intestinal inflammation, if abnormalities are present, further diagnostic studies are generally warranted. In addition, serum biomarkers such as CRP and ESR can distinguish between quiescent and active disease, and in some studies, elevations in these biomarkers have correlated with endoscopic evidence of mucosal disease [7]. As several of these parameters are included in the Pediatric Crohn Disease Activity Index (CDAI) (e.g., albumin, ESR), these blood tests may offer additional insight into disease activity, and potentially, disease severity [6, 8, 9].

Anemia

Anemia is a well-known complication of inflammatory bowel disease occurring in both UC and CD [10–15]. Anemia is generally defined as a hemoglobin value <120 g/L. With respect to IBD, severe anemia is defined as a hemoglobin level <100 g/L. For reasons that are not well characterized, many patients with IBD are intolerant of oral iron replacement therapy or their anemia is refractory to such supplementation, with inflammation likely playing a role [15, 16]. Several studies in both adult and pediatric populations have shown that parenteral iron therapy is safe and more efficient than oral iron therapy, especially when active inflammation in present [17–20]. Further, there are some reports that suggest that oral iron therapy affects the gut microflora in a manner counter-productive to successful treatment compared to those receiving parenteral therapy [21].

The reported prevalence of anemia is variable in IBD, but anemia appears to be more prevalent in CD compared to UC [22, 23]. In one population-based adult Scandinavian study from Denmark, Norway, and Sweden, the overall prevalence of anemia in IBD was 19% with iron deficiency and anemia of chronic disease being the primary etiologies [22]. A retrospective review of pediatric patients diagnosed with IBD from 2005 to 2012 found that 67% were anemic at diagnosis, with 28% having either iron deficiency or a combination of iron deficiency and anemia of chronic disease, and 38% with isolated anemia of chronic disease [23]. At one-year follow-up, the prevalence of anemia decreased, but 20% of patients remained anemic despite treatment [23]. A larger retrospective review of a cohort of 2446 pediatric patients with IBD showed a similar high prevalence of anemia; of the patient that were screened for anemia, 51% with CD and 43% of patients with UC had anemia [24]. However, only a fraction of these patients (20–24%) were evaluated for iron deficiency as the etiology of their anemia.

Anemia may be more common in younger children compared to adolescents and adults [25]. Using the WHO age-adjusted definitions of anemia, Goodhand et al. [25] assessed the prevalence, severity, type, and response to treatment of anemia in patients attending pediatric, adolescent, and adult IBD clinics at a single center. These authors observed the prevalence of anemia to be 70% (41/59) in children, 42% (24/54) in adolescents, and 40% (49/124) in adults ($p < 0.01$). Overall, children (88% [36/41]) and adolescents (83% [20/24]) were more often iron deficient than adults (55% [27/49]) ($p < 0.01$). In other studies, anemia has been described occurring in 16–77% of patients with CD (16%, 58%, 70%, and 77% reported in pediatric cohorts) [13–15, 25–29] and 9–67% of patients with ulcerative colitis (30% reported in one pediatric cohort) [15, 26, 29].

The cause of anemia with or without iron deficiency is likely multifactorial in both CD and UC [30]. In CD, anemia may result from iron, folate, vitamin B12, and other micronutrient deficiencies from malnutrition secondary to small-bowel disease, particularly if the ileum is involved [30]. In addition, anemia may result from gross or occult gastrointestinal blood loss due to underlying intestinal inflammation. Finally, iron deficiency and/or anemia may be due to decreased overall iron stores from chronic disease and lack of appropriate dietary intake to replace iron stores [30]. The anemia observed in ulcerative colitis is generally the result of iron losses from chronic intestinal bleeding, but as with CD, anemia can be due to chronic disease.

The assessment of iron status in IBD in many cases is rather difficult due to coexistent inflammation of chronic disease [31]. For this assessment, several indices and markers have been suggested. Ferritin seems to play a central role in the definition and diagnosis of anemia in IBD and transferrin, transferrin saturation (Tsat), and soluble transferrin receptors have also been found to be useful markers in clinical practice. All these biochemical markers have limitations because they may be influenced by factors other than changes in iron balance. In addition, the iron metabolism regulators, hepcidin and prohepcidin, are still under investigation in IBD. Synthesis of hepcidin, which regulates iron metabolism, increases during systemic inflammation, and binds and inactivates ferroportin, inhibiting iron absorption from the bowel. While hepcidin synthesis is decreased in iron deficiency anemia, hepcidin overall appears to be increased in patients with inflammatory bowel disease [16, 32]. In a retrospective study of 50 children with IBD compared with an equivalent number of celiac disease and healthy controls, serum hepcidin was higher in patients with active IBD compared to celiac patients and healthy controls, with disease activity independently associated with elevated hepcidin levels [16]. A recent cross-sectional comparative study of newly diagnosis pediatric patients with CD or UC between 2012 and 2016 determined that patients with CD ($n = 53$) had significantly higher serum hepcidin levels (22.6 ng/mL, range 8.5–65.0) compared to patients with UC ($n = 23$) (6.5 ng/mL, range 2.4–25.8) ($p < 0.05$) [33]. In another cross-sectional study of 75 patients with IBD (46 UC, 29 CD) and 21 children with functional gastrointestinal disorders, hepcidin levels did not differ significantly among different subtypes of IBD, but mean serum hepcidin concentration was significantly decreased in IBD patients (5.98 ng/mL) compared with controls (10 ng/mL) ($p = 0.03$), likely related to iron deficiency in the IBD cohort [34]. In both the latter studies, hepcidin was correlated solely with ferritin in patients with IBD [33, 34].In addition to hepcidin, erythrocyte parameters like the red cell distribution width (RDW) and the percentage of hypochromic red cells as well as reticulocyte parameters such as hemoglobin concentration of reticulocytes, red blood cell size factor, and reticulocyte distribution width could be useful markers for the evaluation of anemia.

Anemia of chronic disease in IBD is also believed to be multifactorial in its etiopathogenesis. Three potential mechanisms leading to the anemia associated with chronic disease have been recently postulated, namely, (1) anemia results as a consequence of cytokine activation and subsequent alteration of iron homeostasis, (2) anemia occurs due to the inhibition of erythropoiesis, and (3) a shortened red blood cell half-life is associated with chronic disease and thereby results in the anemia [14, 35]. Additionally, the anemia of chronic disease such as that found in IBD involves erythropoiesis disturbance due to circulating inflammation mediators. In one study by Tsitsika et al. [36], erythropoietin (Epo) levels in children and adolescents with IBD were investigated and correlated to disease activity. Thirty-three patients with IBD were evaluated (18 boys, 15 girls) ages 4–15 years (median 11 years) [36]. Patients were separated into two study groups related to their disease activity: those with active disease ($n = 21$) and those in remission ($n = 12$). Chronic disease-associated anemia was present only in patients with active disease, and those patients also had a significantly higher possibility of low, altered Epo levels than expected compared with patients with inactive disease. Thus, it appears that impaired Epo production is another mechanism of anemia of chronic disease development.

Once the diagnosis of anemia is established, the etiology should be further investigated so treatment can be initiated. For macrocytic anemias, folate, vitamin B12, and methylmalonic acid levels should be obtained. Iron studies including ferritin, total iron-binding content (TIBC), and iron levels should be evaluated in cases of microcytic anemia. However, the results of these studies may be difficult to interpret, as ferritin, a measure of iron stores, is also an acute phase reactant and may be elevated in inflammatory conditions [16]. Thus, in patients with a microcytic anemia, obtaining a soluble transferrin receptor in addition to standard iron studies may be helpful in differentiating iron deficiency anemia and

anemia of chronic disease [37–39]. Soluble transferrin receptor (sTfR) concentration, which is not affected by inflammation, is elevated in iron deficiency anemia but remains normal in anemia of chronic disease [37–39]. Utilizing other indices along with sTfR may have better diagnostic utility than sTfR alone in detecting iron deficiency anemia in pediatric IBD. Krawiec et al. [40] assessed a small group of patients with iron deficiency anemia, anemia of chronic disease with iron deficiency, and anemia of chronic disease. STfR/log ferritin index was significantly higher in patients with iron deficiency anemia (median: 1.76) than in patients with anemia of chronic disease (median: 0.55), anemia of chronic disease with iron deficiency (median: 0.68), or patients without anemia (median: 0.72) [40].

In a recent analysis of 75 children with IBD, erythrocyte indices including MCV, MCH, MCHC, and RDW, and biochemical markers including iron, transferrin, sTfR, and sTfR/log ferritin, were evaluated for their sensitivity, specificity, accuracy, and positive and negative predictive values in identifying iron deficiency [41]. Utilizing receiver operating characteristic (ROC) analysis to compare the ability to predict iron deficiency, the best predictors for iron deficiency among these indices were STfR/log ferritin, followed by sTfR [41]. In addition to soluble transferrin receptor, intestinal ferroportin expression may be considered as a marker of anemia in relationship to inflammatory bowel disease and particularly Crohn disease in children. In a small study performed by Burpee et al. [42], intestinal iron exporter ferroportin expression was studied in subjects with and without CD. In this investigation, the authors evaluated duodenal mucosal biopsies from 29 pediatric subjects, 19 of whom had CD and 10 were without CD. The authors observed that intestinal ferroportin protein was higher in anemic CD subjects than in nonanemic CD subjects, whereas ferroportin mRNA levels were not significantly different. Thus, intestinal ferroportin protein appears to be upregulated in anemic CD subjects, suggesting yet another pathway for the iron deficiency and the anemia observed in children with CD [42].

Acute Phase Reactants: Platelets

In inflammatory conditions such as CD and UC, there is a rise in acute phase reactant proteins as a result of chemokine stimulation. The assessment of acute phase reactants has been employed as laboratory tests in the standard work-up of the child with suspected IBD, as well as other inflammatory conditions in pediatric patients (e.g., juvenile rheumatoid arthritis) [43, 44]. Reactive thrombocytosis, a nonspecific marker of inflammation, is a result of this acute phase response. Since the first published paper describing the association of thrombocytosis with chronic IBD by Morowitz et al. [45], the characterization of platelet elevation in the peripheral blood has been a "standard" part of the work-up of patients for suspected IBD, and in the monitoring of their disease activity. Some studies of the pathogenesis of IBD have implicated platelets in the propagation of intestinal inflammation. In a murine model of intestinal inflammation, CD40–CD40L appears to be involved in the pathogenesis of intestinal inflammation and suggests that modulation of leukocyte and platelet recruitment by activated, CD40-positive endothelial cells in colonic venules may represent a major action of this signaling pathway. In addition, Kayo et al. [46] evaluated the role of platelets in inflammation in peripheral blood and in the mucosa of a cohort of patients with active UC. These investigators compared the group of patients with active UC to patients with inactive UC and a small cohort of healthy controls. The authors observed a close association between activated platelets and neutrophils in both the affected colonic mucosa and peripheral blood of patients with active-phase UC compared to the normal volunteers (i.e., healthy controls) and those with inactive UC. The investigators inferred from their study results that a platelet–neutrophil association may play a role in the progression of inflammatory processes in UC [46].

There is also evidence that coagulation activation may mediate and amplify inflammatory cascades in IBD, especially via activating proteinase-activated receptor related pathways [47]. Patients with CD and UC are at increased risk of developing thromboembolic (TE) complications, especially during periods of active inflammation [47–50]. Although the etiology is multifactorial, thromboembolic phenomena in IBD is largely attributable to coagulation activation and platelet aggregation during systemic inflammation [47]. Thus, platelets may play more of a role in the propagation of intestinal inflammation and potentially some of the severe sequelae (e.g., thromboembolic processes) of the system inflammation of IBD, rather than being a simple "biomarker" of IBD [43, 47].

In children referred for endoscopy for evaluation of abdominal pain, diarrhea, rectal bleeding, weight loss, or mouth ulcerations, 85% of patients with CD and 70% of patients with UC had elevated platelet counts compared to 6% of children with normal endoscopic assessment [26]. The presence of thrombocytosis may be overestimated in this study, or a unique response in the child with IBD as a lower prevalence of increased platelets in IBD is reported in adults [51–53]. However, an elevated platelet count in a child with chronic intestinal symptoms should raise clinical suspicion of underlying intestinal inflammation. In one study evaluating pediatric patients with chronic abdominal complaints, the presence of an abnormal hemoglobin and/or elevated platelet count on a routine CBC was able to differentiate between IBD and healthy controls, with 90.8% sensitivity and 80.0% specificity [54]. Furthermore, the platelet count

may help differentiate between IBD and infectious processes, as thrombocytosis is a relatively uncommon finding in diarrhea associated with enteric pathogens [51]. In patients with a diagnosis of Crohn disease, platelet count may reflect the severity of disease independent of other disease markers (e.g., anemia). A recent study of 137 patients with CD, 69 with UC, and 412 healthy controls assessed differences in platelet counts; the effect of anemia, CRP, Crohn disease activity index (CDAI), and Mayo score were also analyzed [55]. CD and UC patients had higher platelet counts than healthy controls. Multivariate analysis revealed that platelet count and severity of CD were positively correlated ($p < 0.001$) after eliminating the interference of hemoglobin, with a cutoff value of 298 × 109/L. The authors found no such relationship in UC.

Mean platelet volume (MPV) is influenced by the degree and type of mucosal and system inflammation. One study analyzed overall accuracy of MPV in disease activity and compared MPV with other inflammatory markers in 61 UC patients and 27 healthy subjects [56]. MPV was compared to ESR, CRP, and white blood cell count. The authors found that MPV accuracy was roughly equivalent to standard acute phase reactants and was significantly lower in UC patients and particularly active UC patients than controls [56]. Thus, MPV may be another indicator of intestinal inflammation and a useful marker in patients with symptoms concerning for IBD.

There may be utility in tracking platelet count as a noninvasive marker of mucosal healing. A recent study by Furukawa et al. [57] assessed 345 Japanese patients with UC. Platelet counts were assessed for all study subjects and divided into quartiles (low, moderate, high, and very high). Mucosal healing (MH) and partial MH were evaluated by endoscopic specialists and defined as a Mayo endoscopic subscore of 0 and 0–1, respectively. The percentage of patients achieving partial MH was 63.2% and MH was 26.1%. After adjusting for age, sex, CRP, steroid use, an anti-tumor necrosis factor alpha (TNF-alpha) use, moderate and very high platelet counts were independently inversely associated with partial MH and MH.

Acute Phase Reactants: Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) and Other Markers

ESR and CRP are two other nonspecific measures of inflammation which should be included in the evaluation of patients with suspected IBD [58]. Both ESR and CRP have been investigated in IBD for a number of reasons, namely, (1) diagnostic and differential diagnostic purposes, (2) assessment of disease activity (i.e., PCDAI) and risk of complications, (3) prediction of CD or UC relapse, and (4) for monitoring the effect of therapy. Under normal circumstances, CRP is produced by hepatocytes in low quantities but following an inflammatory stimulus, hepatocytes rapidly increase production of CRP under the influence of interleukin (IL)-6, tumor necrosis factor α, and IL-1β—all proinflammatory chemokines which are present in active IBD in both children and adults. CRP has a relatively short half-life (19 h) compared with other acute phase proteins and will, therefore, rise early after the onset of inflammation and rapidly decrease after the stimulus is resolved. Overall, CRP may be a better measure for assessing disease activity and predicting relapse. In CD in particular, CRP appears to correlate well with disease activity and, thus, is one objective marker that may be helpful in distinguishing IBD from noninflammatory conditions [59]. Additionally, in clinical trials with biological therapies, elevated CRP levels prior to initiation of therapy are associated with higher response rate, whereas normal CRP levels are predictive of higher placebo response rates [59]. However, despite the advantages of CRP over other markers, it is still far from ideal. Not all IBD patients, CD or UC, mount a CRP response, and this must be kept in mind when measuring inflammatory markers in individual patients. It is unclear if this is due to differences in cytokine levels such as IL-6 or due to mucosal as compared to transmural disease differences among UC and CD, or whether this acute inflammatory marker elevation is genetically driven.

Both ESR and CRP can be elevated to varying degrees in IBD and, therefore, are helpful in distinguishing inflammatory from functional disorders. In a study of 91 children referred for chronic gastrointestinal symptoms, the CRP was elevated in 100% of patients with CD and 60% UC, and ESR was elevated in 85% of patients with CD and 23% of patients with UC [26]. None of the patients with polyps or normal investigations had elevation of either marker. In adults with chronic abdominal symptoms, all patients with CD and 50% of patients with UC had elevated ESR and CRP, whereas none of the patients with functional disorders had elevation of both markers [60]. Therefore, using these markers in combination may increase the diagnostic yield [61].

Overall, the response of ESR and, in particular, CRP in UC appear to be less robust, with elevated values found in more extensive colitis compared to limited disease [62–65]. However, the development of highly sensitive CRP assays may improve the sensitivity of this test, even in patients with limited disease [66]. In a study by Poullis et al. [66], the authors evaluated 224 adult patients and determined the accuracy of the CRP in distinguishing IBD from functional GI disease. Using an enzyme-linked immunoassay approach to CRP measurement, the authors determined that a CRP cutoff value of 2.3 mg/L had a sensitivity of 100% and a specificity of 67% in differentiating functional bowel disease from new cases of IBD [66]. Compared to ESR, CRP has a

shorter half-life and, thus, returns to baseline values more rapidly once the inflammatory stimulus has resolved. Because of this rapid decline, CRP may be a better measure of remission and response to therapy than other inflammatory markers in patients with IBD [59].

Other laboratory markers, including leukocyte and platelet count, and albumin have been studied either less extensively in IBD, particularly in pediatric populations, or, have proven to be less useful than more traditional biomarkers such as CRP [59]. Conversely, more common laboratory markers are being used in novel ways to predict mucosal healing in patients with inflammatory bowel disease. Bertani et al. [67] evaluated 88 patients with ulcerative colitis who started anti-TNF monotherapy. Platelet-to-lymphocyte (PLR) and neutrophil-to-lymphocyte ratios (NLR) were calculated, and fecal calprotectin was collected both before treatment and after induction. The PLR and NLR values were correlated with clinical remission and mucosal healing at 54 weeks [67]. The authors determined that patients who reached mucosal healing after 54 weeks of therapy had lower baseline levels of both PLR and NLR ($p = 0.04$ and $p = 0.0001$, respectively). Patients who had active ulcers at baseline endoscopy displayed higher baseline levels of PLR and NLR compared to those who had no ulcers at initial endoscopy ($p = 0.0007$ and $p = 0.002$, respectively) [67]. Clearly as we continue to understand more about the pathogenesis of IBD, CD, and UC, these types of biomarkers and others to be developed can serve as noninvasive, objective biomarkers for the diagnosis, and monitoring of IBD.

Other Laboratory Evaluations

Liver function tests and electrolyte panels may add additional information to aid the clinician in differentiating IBD from non-IBD, in the determination of the IBD phenotype and, in particular, the presence or absence of extra-intestinal manifestations such as liver disease [68, 69]. Although severe liver disease can be the first presentation of IBD in pediatric patients, hypoalbuminemia is a more frequent finding at diagnosis [69]. Hypoalbuminemia is observed in both CD and UC; however, overall decreased serum albumin appears to be present at a much higher frequency in CD. In pediatric cohorts, hypoalbuminemia has been reported in 35–64% of patients with CD and 15% of patients with UC [26, 27, 70–74]. In a relatively small-sized ($N = 57$) pediatric study of children with UC from Saudi Arabia, hypoalbuminemia was observed in over half (54%) of the cohort evaluated, with disease severity correlating with the degree of hypoalbuminemia [75]. In addition to being useful in the diagnosis of IBD compared to non-IBD, as well as a factor in the assessment of the child's overall nutritional status, hypoalbuminemia when present, may have value as a prognostic factor for surgical risk [70]. Albumin can also be used as a marker for response to therapy. In an adult multicenter clinical trial evaluating one of the biologics for therapy of CD, the authors investigated the effect of adalimumab on changes in laboratory values using data from CHARM trial[76]. In a total of 778 adult patients, adalimumab every other week ($N = 260$), adalimumab weekly ($N = 257$), or placebo ($N = 261$), the authors observed significant improvements in nutritional, hematologic, and inflammatory markers, including and specifically albumin, in moderately to severely active CD [76].

Similar to the pathobiology of anemia associated with IBD, the etiology of hypoalbuminemia in the child or adolescent with IBD is multifactorial, with protein loss from intestinal inflammation, decreased albumin production (negative acute phase response), and long-term poor nutrition all contributing to the overall low circulating levels of this important protein [63, 71, 73].

Elevation of AST and ALT may also be present on initial screen in the evaluation of a patient with suspected IBD. In one study by Mendes et al. [77], the prevalence of abnormal hepatic biochemistries and chronic liver disease in a cohort of IBD patients was described in a retrospective case–control fashion. Patients with normal and abnormal liver biochemistries were compared, and in the cohort of 544 patients, abnormal hepatic biochemistries were present in nearly one third of these adult patients. Contrary to what the investigators hypothesized, abnormal liver biochemistries in this single center cohort were not associated with IBD activity. These authors recommended that persistently abnormal hepatic biochemistries should be evaluated, but to use caution and not immediately attribute these abnormal liver biochemistries to IBD activity [77]. Abnormal liver biochemistries may also be primarily related to poor nutrition as a result of active disease, and thus, spontaneous resolution of these transient elevations can occur [78].

When AST/ALT is persistently elevated or seen in association with an elevated alkaline phosphatase, elevated direct bilirubin, and/or γ-glutamyl transpeptidase, the extra-intestinal complication of primary sclerosing cholangitis (PSC) or autoimmune hepatitis/overlap syndrome should be considered. PSC is reported complication in 3–15% of children with IBD and can precede or occur coincident with diagnosis of IBD [79–82]. In a U.S. population-based health maintenance organization study, the prevalence of PSC in conjunction with IBD was characterized in addition to the demographic differences between racial/ethnic groups in patients with PSC compared to non-IBD and non-liver disease controls. Using the Northern California Kaiser Permanente (KP) database, the authors identified 169 (101 males) cases fulfilling PSC diagnostic criteria with a mean age at diagnosis of 44 years (range 11–81); age-adjusted point prevalence was 4.15 per 100,000 [83]. IBD was present in 64.5% (109/169) cases and was significantly more fre-

quent in men than women with PSC (73.3% and 51.5%, respectively, $p = 0.005$) [83]. In another small-sized single center study ($N = 29$), the incidence of IBD in PSC patients was 68.9% (20/29) [84]. The investigators showed two peaks in the age distribution of PSC with male PSC patients demonstrated a first peak and female patients a second peak. Male PSC-IBD patients were in their teens at diagnosis and 20s, and female PSC-IBD patients were in their 50s and 60s. Of note, the study demonstrated that PSC-IBD patents were significantly younger than the patients without IBD (33.6 vs. 58.9 years, $p < 0.001$) [84]. With regard to pediatric patients, Wilschanski et al. [81] demonstrated of 32 children with PSC, the majority were diagnosed in their second decade (median age: 13 years), and four children presented before the age of 2 years. Seventeen of the 32 patients had inflammatory bowel disease (IBD), all with colitis: 14 UC, and 3 CD [81]. Eight patients presented with chronic liver disease before clinical onset of IBD. Thus, of the hepatic pathologies reported associated with IBD in children and adults, PSC remains the more common presentation.

Other pediatric studies have demonstrated that even a mild elevation of GGT at diagnosis may raise suspicion of future risk of developing PSC. In a longitudinal, population-based study, Chandrakumar et al. [85] evaluated 95 children with UC/IBD-unclassified in Manitoba, Canada between 2011 and 2018 (median age at diagnosis, 14 years [IQR: 10.4–15.9 years]) . There were 9 total children in this cohort that developed PSC-UC; the authors noted that 8 of 11 children (72.7%) with high GGT levels at baseline developed PSC-UC compared to only 1 (1.2%) of 84 children with normal baseline GGT levels ($p < 0.001$) [85]. Further, all children with high baseline GGT had pancolitis, compared to 63.9% of children with normal GGT ($p = 0.01$). In another longitudinal, cohort study by Feldstein et al. [79], 52 children with cholangiography-proven PSC were followed to determine the long-term outcome (mean follow-up was 16.7 years) of children with PSC diagnosed over a 20-year period (34 boys and 18 girls; mean age 13.8 ± 4.2 years; range, 1.5–19.6 years). Two thirds presented with symptoms and/or signs of PSC and 81% had concomitant IBD [79]. During follow-up, 11 children underwent liver transplantation for end-stage PSC and 1 child died with the median (50%) survival free of liver transplantation being 12.7 years. Compared with an age- and gender-matched U.S. population, survival was significantly shorter in children with PSC ($p < 0.001$). Using a statistical regression model for analysis, the authors determined that lower platelet count, splenomegaly, and older age were associated with shorter survival. The presence of autoimmune hepatitis overlapping with PSC ($p = 0.2$) or medical therapy ($p = 0.2$) did not affect survival. Thus, the authors concluded that PSC, whether associated with IBD or not, significantly decreases survival in this child population [79].

The presence of PSC may also raise the risk of other morbidities. Ricciuto et al. [86] performed a retrospective study of 74 children diagnosed with PSC-IBD between 2000 and 2018; these children were age and sex matched to children with both UC and IBD-unclassified as a control group. Clinical parameters including evidence of clinical and endoscopic remission and patient growth were compared between groups. Patients with PSC-IBD more often had pancolitis, rectal sparing, and more severe right-sided disease compared to patients without PSC ($p < 0.05$) [86]. Patients with PSC were more often in clinical remission (OR, 2.94; 95% CI, 1.78–4.87), and risk of colectomy or biologic use was lower (HR, 0.24; 95% CI, 0.12–0.52). However, among all patients in remission, those with PSC-IBD were less likely to achieve endoscopic remission (OR, 0.44; 95% CI, 0.20–0.96) and were shorter with lower weights than their non-PSC controls [86].

Renal as well as pancreatic disease may also be important extra-intestinal manifestations of IBD or can be adverse events associated with IBD pharmacotherapy [87–92]. In a multicenter study from Israel, both adults and children presenting with acute pancreatitis as the first symptom of IBD were retrospectively identified (10 years, 7 university hospitals) [92]. These authors demonstrated that 10 of 460 pediatric patients with IBD (2.17%), compared with only 2 in 3500 adults (0.06%) presented with pancreatitis. Eight children had colonic disease (four CD, disease, four UC [three pancolitis]) with the mean amylase level being 1419 (range 100–1370) [92]. The median time between onset of the first episode of acute pancreatitis in relation to onset of IBD was 24 weeks (range 1–156), and the most common presentation in this cohort was abdominal pain. Amylase and lipase may, therefore, be considered at some point in the initial evaluation when clinical signs and symptoms raise suspicion of pancreatic disease, and prior to or after initiation of therapy particularly those medications with a predilection (e.g., thiopurines, 5-aminosalicylates) for pancreatitis as a side effect.

Similarly, renal disease may precede diagnosis of IBD, and this risk may change over the course of a person's lifetime. Despite small in sample size, Izzedine et al. [93] described that four patients with severe interstitial nephritis demonstrated on histopathological examination of kidney biopsy specimens. Renal failure was discovered before or simultaneously with the diagnosis of CD, and patients were not treated with mesalamine. More importantly, impairment of renal function progressed to end-stage renal failure in three of the four patients [93]. A similar small case series of two pediatric patients with renal disease occurring concurrently with diagnosis of IBD has been reported [94]. Recent studies with larger sample sizes provide more insight into potential relationships between renal disease and IBD. A recent retrospective review of 456 children with IBD (346 with CD and 110 with UC) found that the incidence of

kidney-related symptoms was 14.7%, which the authors noted were higher than in healthy children [95]. Renal biopsies performed in 7 children revealed immunoglobulin A nephropathy in 5/7 (71.4%) [95]. Vajravelu et al. [96] performed a retrospective cohort study in which 17,807 patients with IBD were matched for age, sex, and practice to 63,466 patients without IBD. After controlling for risk factors associated with chronic kidney disease (CKD), the authors found IBD to be associated with development of CKD in adolescent and adult patients' ages 16–77 years [96]. The adjusted hazard ratio for CKD decreased with increasing age (from 7.88 [95% CI 2.56–24.19] at age 16–1.13 [95% CI 1.01–1.25] at age 77). Thus, with respect to appropriate adjunct or complementary lab tests to obtain in the work-up of a child with suspected IBD, given the reports of kidney disease in patients with Crohn disease in the absence of 5-aminosalicylate exposure and risk of CKD in patients with IBD, a baseline comprehensive chemistry panel should be considered during the initial evaluation.

The above paragraphs highlight the standard evaluation that is recommended for all children with history and physical exam findings suspicious for IBD. These diagnostic tests may aid the clinician in the differentiation of UC and CD from functional bowel disorders and infectious etiologies. However, because the clinical presentation of IBD is so diverse and symptoms can be nonspecific, at times, it may be difficult to distinguish between inflammatory and functional disorders. In fact, since May 13, 1932, when Dr. Crohn and his colleagues, Oppenheimer and Ginzburg, presented a paper on terminal ileitis describing the features of Crohn disease to the American Medical Association, the average time from onset of symptoms to definitive diagnosis continues to be prolonged, ranging from 6 to 18 months [97, 98].

Several other noninvasive studies have been proposed to aid in the diagnosis of inflammatory bowel disease including IBD serologies and fecal calprotectin. The following section reviews these tests including a brief overview of the use of IBD serology and the evidence to support or disprove their use in the preliminary evaluation of the child with suspected IBD. In addition, this section will describe the stool tests which are an essential part of the initial work-up of the child with suspected IBD, and includes a discussion of fecal calprotectin, a marker of intestinal inflammation.

Specific Blood Tests: Inflammatory Bowel Disease Serologies

Anti-*Saccharomyces cerevisiae* (ASCA), an antibody response against *Saccharomyces cerevisiae* and perinuclear antinuclear cytoplasmic antibody (pANCA), an antibody response toward nuclear antigens with a perinuclear pattern, are two immunologic markers detected in IBD. There continues to be debate in both the pediatric and adult clinical settings regarding the proper use of these serologies in the evaluation of IBD, and there have been several studies assessing the accuracy and clinical utility of ASCA and pANCA in children with IBD [1, 5, 99–108]. Although these investigations differ in their study design and, in some cases, the type of serological profile obtained, overall, these markers appear to be reasonably specific for both CD and UC. In the reported studies, ASCA (IgG or IgA) specificity ranged from 88% to 97% for CD [101, 103–106] and pANCA specificity ranged from 65–95% for UC [100, 101, 103–106]. In children, the specificity of the combined serologies in differentiating IBD from non-IBD has been reported to range from 84% to 95% [1, 5, 101, 103, 107]. Unfortunately, the sensitivity of these serologies has been shown to be poor with overall sensitivity ranges reported between 55% and 78% [1, 5, 99, 101, 103, 107]. A meta-analysis of 60 adult and pediatric studies yielded similar findings and reported the sensitivity and specificity of ASCA IgG or IgA positive and pANCA negative for the detection of Crohn disease as 55% and 93%, respectively [109]. The sensitivity and specificity of positive pANCA for detection of UC were lower at 55.3% and 92.8%, respectively [109]. Therefore, a negative test result does not exclude the diagnosis of IBD, particularly in those patients with nonspecific symptoms such as abdominal pain and intermittent diarrhea. The addition of anti-OmpC, an antibody to the outer membrane porin of *Escherichia coli*, appears to add little to the diagnostic accuracy of this serologic panel in children [105, 106]. In two pediatric studies, the overall sensitivity of anti-OmpC for both CD and UC was very low [105, 106]. However, the use of the additional IBD serologies may help identify a small number of IBD patients who had negative ASCA and pANCA [105, 106, 110]. Younger children appear to have the greatest proportion of seronegativity to ASCA and ANCA, and therefore, these additional markers, particularly anti-cBir, may be most helpful in this population [110]. Moreover, with an increasing number of candidate genes identified in patients with IBD, particularly CD, other serological markers have been identified that may increase the overall sensitivity of the assays [111]. For example, patients carrying the NOD2 mutations have an increased adaptive immune response to commensal organisms as measured by higher titers of antimicrobial antibodies, such as anti-CBir and ASCA [111]. Thus, use of a combination of serologic, genetic, and inflammatory markers may further improve the diagnostic accuracy and utility of these tests for discriminating IBD from noninflammatory conditions [112].

Although their specificity is reasonable, overall ASCA and pANCA appear to be less sensitive than clinical history and routine laboratory tests (hemoglobin and ESR) in the

evaluation of pediatric IBD. In a retrospective study, Khan et al. [107] evaluated 177 pediatric subjects who had pANCA and ASCA, hemoglobin, ESR, and colonoscopy as part of their initial evaluation. In this study, 90 patients were diagnosed with IBD, and of those, 52 had UC and 39 had CD. Combining abnormal hemoglobin and/or ESR with rectal bleeding, the most distinguishing symptom for IBD in this study cohort, was more sensitive than positive ASCA and/or pANCA (86% versus 68%) and identified 86% of patients with IBD prior to endoscopy. A study by Sabery et al. [1] yielded similar findings. In this retrospective study which included 210 pediatric subjects, 40 with IBD, the sensitivity of ASCA and pANCA was again compared to hemoglobin and ESR [1]. The presence of an abnormal hemoglobin or ESR was the more sensitive screen, with a sensitivity of 83%, compared to 73% for the First Step® modified assay (Prometheus laboratories, San Diego, CA), and 60% for the confirmatory panel, which included anti-OmpC. In the subset of patients without rectal bleeding, a group whose symptoms may be more difficult to differentiate from functional disorders, the sensitivity of ASCA and pANCA decreased to 55% whereas the sensitivity of an abnormal hemoglobin or ESR remained high at 91%. In pediatric patients, the addition of antibodies to cBir flagellin to the serological panel does not appear to improve the diagnostic yield of this panel. A retrospective study of 304 pediatric patients with suspected IBD reported a sensitivity of 67% and specificity of 76% of the combined serological panel, and for anti-cBir specifically, the sensitivity and specificity were 50% and 53%, respectively [108]. As mentioned, combination of standard laboratory tests (hemoglobin, platelet count, and ESR) had higher predictive value, with sensitivity of 72%, specificity of 94%, and positive predictive value of 85% [108]. Additionally, as hemoglobin and ESR are both components of the PCDAI, they have added value as markers of disease severity and clinical response.

Given the cost of these tests and overall poor sensitivities documented in several pediatric studies, particularly compared to other clinical and laboratory parameters, currently, serology testing does not appear to have additive value as a screening test in the initial diagnostic work-up for patients with suspected IBD. However, these serologies may have a role in predicting disease course and identifying patients at risk for complicated disease. In a study by Targan et al. [113], 484 sera previously employed for a study evaluating other serological markers of IBD (namely, ASCA, pANCA, OmpC) were tested for anti-CBir1 by enzyme-linked immunosorbent assay. Interestingly, the authors observed that the presence and level of immunoglobulin G anti-CBir1 were associated with CD independently and were associated with a unique phenotype of CD, namely, small-bowel, internal-penetrating, and fibrostenosing disease. Papadakis et al. [114], also demonstrated that anti-CBir1 serum reactivity in CD patients is independently associated with fibrostenosing disease and complicated small-bowel CD. In a large prospective inception cohort of pediatric patients with newly diagnosed Crohn disease (n-913), CBir1 seropositivity was significantly associated with structuring disease behavior, whereas both CBir1 and ASCA IgA positivity were associated with penetrating complications [115]. As a single marker, ASCA may be most predictive of aggressive disease and several studies have demonstrated that ASCA positivity (IgG or IgA) alone was associated with complicated disease behavior, perianal disease, and risk for surgery in both pediatric and adult cohorts [105, 116–120]. In children with CD, the presence of multiple serologic markers and degree of antibody elevation has been associated with more severe disease phenotypes, with frequency of internal-penetrating and fibrostenosing disease increasing with the number of antibodies present [121, 122]. Similar to adult data, anti-Omp C and anti-IL2 were independently associated with these complications [122]. A cross-sectional study of adults with CD suggests that in addition to quantitative serologic markers, the presence of NOD2 genetic variants is associated with complicated disease [123]. Overall, the data for pANCA and disease stratification/course are less robust. While one study demonstrated no correlation between disease severity and pANCA titers [124], another recent multicenter study found that while pANCA did not correspond to a specific phenotype, a level ≥100 was significantly associated with pancolitis ($p = 0.003$) [125]. Additionally, pANCA reactivity may be associated with primary nonresponse to anti-TNF therapy in pediatric patients, and the absence of this marker may help predict long-term response to this medication [126, 127].

Approximately 10% of patients with IBD are diagnosed with IBD-unclassified (IBD-U), and this diagnosis may be higher in younger children as isolated colonic CD is more common [110]. There is interest in using these serologies to classify disease subtype in children with IBD-U and to assist in therapeutic decisions such as colectomy. In one longitudinal study of 406 children with Crohn colitis, UC, and IBD-U, ASCA positivity differentiated well between Crohn colitis, IBD-U, and UC (specificity 83%, PPV 96%); pANCA positivity had similar positive predictive value, but much lower sensitivity and specificity (65% and 66%, respectively) [128]. However, as the most common serologic profile in IBD-U is ASCA−/pANCA−, serology overall has lower utility in predicting subsequent disease type [128, 129]. Therefore, based on the above data the use of these serologies, particularly cBir and ASCA IgA, should be reserved as a potential prognosticator of a severe disease course and assessment for risk for stricturing and/or penetrating disease.

Stool Evaluation

The presentation of pediatric inflammatory bowel disease can be markedly variable. However, those children who present with "classic" gastrointestinal complaints such as diarrhea and abdominal pain should have a thorough stool evaluation for potential bacterial and parasitic etiologies of these symptoms. Standard stool cultures to look for enterohemorrhagic *Escherichia. coli*, *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter* species, *Clostridium difficile* assay, preferably by PCR, and ova and parasite studies to look for *Entamoeba histolytica* and other parasites are a necessary part of the work-up to differentiate infectious versus inflammatory enterocolitis and should be obtained prior to invasive procedures. In particular, *Yersinia enterocolitica* infections may mimic CD, and thus, specific emphasis should be placed on looking for this organism as isolation can be increased by using selective media [130, 131]. Also, defects in mucosal barrier function can predispose patients with IBD to infectious colitis, and *Clostridium difficile (C. difficile)* is the most common infectious agent identified [132, 133]. Overall *C. difficile* infection has been a growing problem and the rates of *C. difficile* infection have been increasing as have pediatric hospitalization due to this infection [134]. *C difficile* infections are important to identify in children with IBD as the presence of *C. difficile* infection (CDI) may have prognostic utility. A recent study of 261 children with IBD found that those with CDI were at increased risk of future escalation of IBD therapy compared with children who did not develop CDI [135]. Further, CDI has been associated with a more severe disease course subsequent to CDI diagnosis [136]. Clinical symptoms of *C. difficile* and IBD are similar and the prevalence of *C. difficile* is significantly greater in pediatric patients with IBD compared to children without this diagnosis [137, 138]. A positive stool test, therefore, does not rule out the possibility of IBD, and thus, patients with a suspicious clinical history who do not improve with appropriate treatment of stool pathogens should have further diagnostic evaluations.

Fecal Calprotectin

Calprotectin, a calcium-binding protein in the S100 family, is an abundant protein in neutrophils, and to a lesser extent, macrophages and monocytes, accounting for approximately 60% of the cytosolic protein in neutrophils [139–141]. Calprotectin has bacteriostatic and antifungal properties, and thus, likely contributes to neutrophilic defenses [142]. In healthy individuals, concentrations of calprotectin are approximately six times higher in stool than plasma [141]. In IBD, a spot fecal calprotectin level correlates well with fecal excretion of [111] indium white cells, and therefore, this protein can be an alternative marker of intestinal inflammation [143, 144]. Fecal calprotectin is easy to measure, resistant to proteolysis and stable in stool for 7 days, and thus, is a simple noninvasive investigative tool, which may help distinguish inflammatory from functional disorders [58, 141, 145–149].

Several studies have shown elevated fecal calprotectin levels in adult and pediatric patients with both UC and CD compared to healthy controls and patients with irritable bowel syndrome (IBS) [58, 145–149]. In one large study of 602 new patient referrals who had symptoms compatible with either irritable bowel syndrome or organic disease, including 189 patients later diagnosed with IBD, fecal calprotectin levels of >10 mg/L had a sensitivity of 89% and specificity of 79% for organic diseases [150]. This test was more sensitive than either ESR or CRP and an abnormal fecal calprotectin had an odds ratio for disease of 27.8 [150]. A subsequent meta-analysis of six prospective adult studies that assessed the diagnostic accuracy of fecal calprotectin in patients with suspected IBD revealed a pooled sensitivity and specificity of 93% and 96%, respectively [151]. A more recent meta-analysis of 19 studies with combined 5032 patients calculated a lower pooled sensitivity of 88.2% and specificity of 79.9% [152]. However, there was significant heterogeneity of the studies and 4 of the studies had a cutoff calprotectin level of >50 μg/g, which may have contributed to the lower pooled sensitivity and specificity in this analysis. Other studies have demonstrated that fecal calprotectin may be superior to CRP in discriminating between IBD and irritable bowel syndrome with a diagnostic accuracy of 80–89% compared to 64–73% for CRP [153, 154].

There have also been several studies evaluating fecal calprotectin in the pediatric population. Carroccio et al. [155] study cohort included 50 children with chronic diarrhea, and the assay had a higher sensitivity (70%) and specificity (93%) in pediatric patients than in adults. Some pediatric studies have reported even higher sensitivity of the fecal calprotectin assay. Fagerberg et al. [145] obtained fecal calprotectin levels in 36 pediatric patients with gastrointestinal symptoms who underwent colonoscopy for suspected inflammation. Using the standard upper reference limit of <50 μg/g for the modified assay, the test has a sensitivity and specificity for inflammation of 95% and 93%, respectively. Using an older assay, Bunn et al. [156] reported a sensitivity of 90% and specificity of 100% for identifying intestinal inflammation in 36 pediatric patients who underwent either colonoscopy or [99]Tc-labeled white blood scans for suspected inflammatory bowel disease. As there was a strong suspicion of IBD in these studies, there may be some selection bias, which resulted in these higher sensitivities and specificities. However, when used in the primary care set-

tings, sensitivity and specificity appear similar. Walker et al. studied 195 children ages 4–18 years in the primary care setting in the UK and found that fecal calprotectin had a 91% diagnostic accuracy with a sensitivity of distinguishing IBD from non-IBD of 100%, a specificity of 91%, utilizing a cut-off value of <100 μg/g. While the positive predictive value was low (43%), the negative predictive value was high (100%).

Other pediatric studies have reported similar sensitivities but lower specificities of the fecal calprotectin assay in differentiating IBD from other conditions [157, 158]. Two meta-analyses of prospective pediatric studies revealed a pooled sensitivity and pooled specificity of 92–97% and 70–76%, respectively [151, 159], whereas meta-analyses that also included respective pediatric case–control studies, which may introduce more bias, reported slightly lower pooled specificities (65–68%), with similar high pooled sensitivities [61, 160]. With relation to CD, disease location (small bowel versus colonic involvement) does not appear to limit the utility of this test [161–164]. Based on these collective results, it appears fecal calprotectin that correlates well with the presence of histologic inflammation in pediatric patients. In patients where symptoms overlap with both IBD and IBS, obtaining fecal calprotectin testing prior to endoscopy may be a cost-effective screening strategy, particularly when the suspicion of IBD is low [165].

Fecal calprotectin may offer some insight into the severity of inflammation in children with IBD, with levels correlating with severity of mucosal disease, with a correlation superior to clinical activity indexes and CRP [161, 162, 166, 167]. As it correlates with mucosal disease, fecal calprotectin may be surrogate for mucosal healing. In one small prospective study of 24 newly diagnosed children with CD, a drop in fecal calprotectin of >50% after therapy had a specificity of 82% for predicting inactive endoscopic disease [168]. In multicenter study of 151 pediatric patients with CD, calprotectin of 100 μg/g identified children with deep healing with 71% sensitivity and 92% specificity [169]. In this cohort, calprotectin of 300 μg/g identified children with mucosal healing with 80% sensitivity and 81% specificity. In adults, low FC also correlates well with histologic remission and mucosal healing [170–172]. In one study of 126 adult patients with IBD, a level ≤250 μg/g predicted endoscopic remission in CD with 94.1% sensitivity and 62.2% specificity, whereas, in UC, a level >250 predicted active mucosal disease with a sensitivity of 71% and specificity of 100% [170]. Additionally, there have been several studies evaluating fecal calprotectin's role in predicting disease relapse. One prospective study of 32 children with IBD found that 90% of patients with fecal calprotectin >400 μg/g experienced clinical relapse whereas 89% with fecal calprotectin below this threshold remained in clinical remission [173]. A larger prospective multicenter adult study also demonstrated that calprotectin concentrations in patients who relapsed were higher than those who did not, with a fecal calprotectin level of >150 μg/g having a sensitivity of 69% and specificity of 69% to predict relapse [174]. A recent systematic review of 6 studies showed similar findings with asymptomatic patients who had repeated elevated calprotectin (upper limit of normal 55–300 μg/g) having a 53–83% probability of disease relapse within thin next 2–3 months, whereas patients with a repeat normal calprotectin had a 67–94% probably to remain in remission during the same time period [175]. Therefore, the assay offers an advantage over other nonspecific inflammatory markers as appears to be a direct measure of intestinal inflammation and consequently may be followed prospectively in patients as a marker of disease activity and relapse. Although additional large prospective pediatric clinical studies are still needed, fecal calprotectin is valuable in the evaluation of patients with suspected IBD and for monitoring disease activity prospectively.

Summary

In the preceding paragraphs, we attempted to provide an overview of the laboratory tests, both blood and stool studies, available that can be used in the initial work-up of the child with suspected inflammatory bowel disease. Although a thorough clinical history and physical exam can raise suspicion of CD or UC, it is important to include a focused laboratory evaluation. A combination of blood and stool tests may further differentiate between IBD and non-IBD in particular, inflammatory disease, compared to infectious processes and functional bowel disorders. Not only can a carefully chosen combination of blood and stool studies help determine which child may require more invasive testing, but they can also be used in the initial phenotyping of the disease, i.e., CD versus UC. Moreover, there are laboratory tests available, specifically IBD serologic markers such as ASCA and anti-CBir1, which can be employed to subtype CD and potentially provide the clinician with the ability to prognosticate disease severity. The definitive diagnosis of IBD is made by combining historical features, physical examination, radiological findings, and endoscopy and biopsy. However, laboratory investigations provide important information about inflammation and function of other organ systems in the child with IBD, which ultimately helps guide the clinician toward more invasive testing, making a definitive diagnosis and even phenotyping the IBD that facilitates the ability for the clinician to employ more precise targeted optimal therapies.

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Fecal Markers in Inflammatory Bowel Disease

19

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Introduction

Inflammatory bowel diseases (IBD) include ulcerative colitis (UC) and Crohn disease (CD). These diseases are defined by mucosal inflammation. Endoscopy and histology are necessary for diagnosis and are often used as monitoring tools. For many years, symptoms and laboratory studies (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and albumin) have been used to monitor disease activity, despite with relatively low specificity for mucosal inflammation or disease severity. Fecal calprotectin can detect mucosal inflammation, and an extensive body of literature has developed confirming its utility in detecting new inflammatory bowel disease and monitoring disease activity once diagnosed. While there are other stool markers such as lactoferrin, this chapter will focus on fecal calprotectin as it is the most well-studied stool marker including recent meta-analyses and systematic reviews, as well as current guideline suggestions for the use of fecal calprotectin testing. Table 19.1 includes selected recent meta-analyses, Table 19.2 includes selected systematic reviews, and Table 19.3 includes guideline recommendations for use of fecal calprotectin.

Table 19.1 Fecal calprotectin meta-analysis

Reference	Number of Studies	Number of Patients	Type of Patients	Goal Of Study	Results
PMID: 31464777	19	5032 IBD Patients	Pediatric and Adult	Screening/ Diagnostic Marker for IBD	Sensitivity 0.882 (95% CI 0.827–0.921)
Petryszyn P, Staniak A, Wolosianska A, et al. Faecal calprotectin as a diagnostic marker of inflammatory bowel disease in patients with gastrointestinal symptoms: meta-analysis. Eur J Gastroenterol Hepatol 2019;31:1306-1312.					Specificity 0.7999 (95% CI, 0.693-0.875)
PMID: 23670113	8	394 IBD	Pediatric	Screening/ Diagnostic Marker for IBD	Sensitivity 0.978 (95% CI, 0.947–0.996)
Henderson P, Anderson NH, Wilson DC. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol 2014;109:637-45.					Specificity 0.682 (95% CI, 0.502-0.863)
					Postive Likelihood Ratio 3.07 (95% CI,
					Negative r3 (95% CI,
PMID: 25373864	9	742	Pediatric	Screening/ Diagnostic Marker for IBD	Sensitivity 0.97 (95% CI 0.92–0.99)

(continued)

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Table 19.1 (continued)

Reference	Number of Studies	Number of Patients	Type of Patients	Goal Of Study	Results
Degraeuwe PL, Beld MP, Ashorn M, et al. Faecal calprotectin in suspected paediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2015;60:339-46.					Specificity 0.70 (95% CI, 0.59–0.79)
					Positive Likelihood Ratio 3.2 (95% CI 2.3–4.5)
					Negtiave Likelihood Ratio 0.04 (95% CI 0.01–0.12)
					Pooled Optimal Cutoff was 212 ug/g (Sensitivity 0.90, Specificity 0.85)
PMID: 26681783	10	867	Pediatrics	Screening/ Diagnostic Marker for IBD	Sensitivity 0.99 (95% CI, 0.92-1.0)
Holtman GA, Lisman-van Leeuwen Y, Reitsma JB, et al. Noninvasive Tests for Inflammatory Bowel Disease: A Meta-analysis. Pediatrics 2016;137.					Specificity 0.65 (95% CI, 0.54–0.74)
					Positive Likelihood Ratio 2.8 (95% CI, 2.1–3.7)
					Negative Likelihood Ratio 0.01 (95% CI 0.00–0.13)
PMID: 30240474	25	2822 IBD Patients	Adults	Assessing Endoscopic Activity	Sensitivity 0.85 (95% CI, 0.82–0.87)
		298 Controls			Specifiticy 0.75 (95% CI, 0.71–0.79)
Rokkas T, Portincasa P, Koutroubakis IE. Fecal calprotectin in assessing inflammatory bowel disease endoscopic activity: a diagnostic accuracy meta-analysis. J Gastrointestin Liver Dis 2018;27:299-306.					
PMID: 34069684	16	622 Crohns	Adult	Mucosal Healing	Crohns—Diagnsotic Odds Ratio 13.8 (95% CI, 9.1–20.9)
		1794 UC			UC—Diagnostic Odds Ratio 16.0 (95% CI, 12.2–21.1)
Bromke MA, Neubauer K, Kempinski R, et al. Faecal Calprotectin in Assessment of Mucosal Healing in Adults with Inflammatory Bowel Disease: A Meta-Analysis. J Clin Med 2021;10.					
PMID: 31275056	14	1110 UC Patients	Adults	Predicting relapse in UC	Sensitivity 0.75 (95% CI 0.0.70–0.79)
Li J, Zhao X, Li X, et al. Systematic Review with Meta-Analysis: Fecal Calprotectin as a Surrogate Marker for Predicting Relapse in Adults with Ulcerative Colitis. Mediators Inflamm 2019;2019:2136501.					Specificity 0.77 (95% CI, 0.74–0.80)
					Positive Likelihood Ratio 3.45 (95% CI, 6.16–18.02)
					Negative Likelihood Ratio 0.37 (95% CI, 0.28–0.49)
					Diagnostic Odds Ratio 10.54 (95% CI, 6.16–18.02)
PMID: 33361549	12	961 Patients	Adults	Detection of Small Bowel Crohn Disease	Sensitivity 0.725 (95% CI 0.657–0.784)
Jung ES, Lee SP, Kae SH, et al. Diagnostic Accuracy of Fecal Calprotectin for the Detection of Small Bowel Crohn's Disease through Capsule Endoscopy: An Updated Meta-analysis and Systematic Review. Gut Liver 2020.					Specificity 0.728 (95% CI 0.622–0.814)
					Diagnostic Odds Ratio 7.894 (95% CI 4.315–14.440)
PMID: 25569739	10	613	Adult	Post-operative Recurrence in Crohns	Sensitivity 0.82 (95% CI, 0.73–0.89)
Qiu Y, Mao R, Chen BL, et al. Fecal calprotectin for evaluating postoperative recurrence of Crohn's disease: a meta-analysis of prospective studies. Inflamm Bowel Dis 2015;21:315-22.					Specificity 0.61 (95% CI, 0.51–0.71)
					Positive Likelihood Ratio 2.11 (95% CI, 1.68–2.66)
					Negative ikelihood Ratio 0.29 (95% CI, 0.197–0.44)

Table 19.2 Fecal Calprotectin Systematic Reviews

Reference	Number of Studies	Number of Patients	Type of Patients	Goal Of Study	Results
PMID: 33967560	12 Studiies	842 patients	Adult	UC and CD	FC demonstrated excellent sensitivity and specificity for mucosal healing
State M, et al. Surrogate markers of mucosal healing in inflammatory bowel disease: A systematic review. World J Gastroenterol 2021;27:1828-1840.					FC use in CD (Sensitivity 50%-95.9% and Specificity 52.3%-100%)
					FC use in UC (Sensitifity 89.7%-100% and Specificity 62%-93.3%)
PMID: 32048751	12 Studies	1168 patients	Adult	UC	Fecal Calprotectin can be used to predict HISTOLOGIC Remission in patiens with UC
D'Amico F, Bonovas S, Danese S, et al. Review article: faecal calprotectin and histologic remission in ulcerative colitis. Aliment Pharmacol Ther 2020;51:689-698.					
PMID: 31795013	65 Studies	Varies for outcome	Adult	Endoscopic Findings	FC correlation with SES-CD/ CDEIS
				14 Studies	Sensitivity 69%–96%
Vernia F, et al. Is fecal calprotectin an accurate marker in the management of Crohn's disease? J Gastroenterol Hepatol 2020;35:390-400.					Specificity 44%–95.5%
					Cutoff Level 50–252.9 μg/g
				Capsule Endoscopy	FC correlation with CE Score (Lewis Score, CESI)
				13 Studies	Sensitivity 46.7%–96%
					Specificity 23%–91%
					Cutoff Level 50–275 μg/g
				Response to Therapy	FC correlation with clinical or Endosocpic score
				9 Studies	Sensitivity 80%–99%
					Specificity 83%–100%
					Cutoff Level 70–250 μg/g
				Prediction of Relapse	FC correlation to Clinical/ Endoscopic Relapse
				11 Studies	Sensitivity 37%–100%
					Specificity 48%–95.2%
					Cutoff Level 82–340 μg/g
				Postoperative Recurrence	FC correlation to Rutgeerts Score
				16 Studies	Sensitivity 47%–98%
					Specificity 25%–93%
					Cutoff level 50–283 μg/g
PMID: 30704158	10 Studies	179 Small Bowel Crohn's	Adult (16 and over)	Small Bowel vs Large Bowel Fecal Calprotectin	No difference between small bowel and coloic location in 6 studies
		238 Large Bowel Crohn's			Higher fecal calprotectin in large bowel disease in 4 studies
Simon EG, et al. Does fecal calprotectin equally and accurately measure disease activity in small bowel and large bowel Crohn's disease?: a systematic review. Intest Res 2019;17:160-170.					
					Small Bowel Sensitivity 42.9%–100%
					Small Bowel Specificity 50%–100%
					Large Bowel Sensitivity 66.7%–100%
					Large Bowel Specificity 28.6%–100%
PMID: 28511198	6 Studies	470 UC	Adult	Predict Relapse	Normal FC—relapse 6%–33% in 3–4 months

(continued)

Table 19.2 (continued)

Reference	Number of Studies	Number of Patients	Type of Patients	Goal Of Study	Results
		77 CD		Repeated FC measurements in Asymptomatic IBD	Elevated FC—Relapse 53%–83% in 3-4 months
					Repeated FC Measurements can predict relapse
Heida A, et al. Clinical Utility of Fecal Calprotectin Monitoring in Asymptomatic Patients with Inflammatory Bowel Disease: A Systematic Review and Practical Guide. Inflamm Bowel Dis 2017;23:894-902.					

Table 19.3 Fecal calprotectin recommendations in guidelines

Reference/Organization	Guildeline	Recommendations
American College of Gastroenterology (ACG)	ACG Clinical Guideline: Management of Crohn Disease in Adults	Fecal Calprotectin is a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (Strong recommendation, moderate level of evidence)
PMID: 29610508		Fecal calprotectin and fecal lactoferrin measurements may have an adjuntive role in montoring disease activity
Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol 2018;113:481-517.		As there is often a disconnect between clinical symptoms and underlying inflammation, it is of crucial importance to monitor disease and therapy at regular intervals based on objective and measurable markers [endoscopy, C-reactive protein [CRP], calprotectin, imaging].
European Crohn's and Colitis Organisation (ECCO)	Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications	
PMID: 30137275		Response to treatment in active UC should be determined by a combination of clinical parameters, endoscopy and laborator markers such as CRP and fecal calprotectin
Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis 2019;13:144-164.		In patient siwth UC who clinically respond to medical therapy, mucosal healing should be determined endoscopically or by fecal calprotectin approximately 3 to 6 months after treatment initiation
Brtitish Societ of Gastroenterology	British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults	We recommend that, for patients aged 16–40 presenting in primary care with chronic diarrhoea and symptoms that may be consistent with either IBD or IBS, faecal calprotectin is a useful screening tool with a high negative predictive value. If significantly elevated, patients should have an infective cause excluded and be referred for further investigation (GRADE: strong recommendation, moderate-quality evidence. Agreement: 97.9%).
PMID: 31562236		
		We suggest that, in IBD patients where it is unclear if symptoms are due to ongoing inflammation or other non-inflammatory causes (such as bile acid malabsorption, functional bowel disorder or short bowel), faecal calprotectin measurement may be used to provide evidence of mucosal inflammation (GRADE: weak recommendation, low-quality evidence. Agreement: 97.8%).
Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:s1–s106.		We suggest that faecal calprotectin is a validated biomarker for endoscopic and histological disease activity. It may therefore be a useful non-invasive parameter to inform decisions on treatment escalation or de-escalation (GRADE: weak recommendation, moderate-quality evidence. Agreement: 100%).

Table 19.3 (continued)

Reference/Organization	Guildeline	Recommendations
European Socitety for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)	The Medical Management of Paediatric Crohn Disease: an ECCO-ESPGHAN Guideline Update	
PMID: 33026087		In patients with luminal CD following induction therapy, a decrease of faecal calprotectin in the context of clinical improvement can be used as a marker of treatment response. LoE: 3 | Agreement: 100%.
van Rheenen PF, Aloi M, Assa A, et al. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update. J Crohns Colitis 2020.		In patients with luminal CD in clinical remission, a significant rise of faecal calprotectin should trigger further investigations and consideration of treatment escalation. LoE: 3 | Agreement: 92%.
European Socitety for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)	Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care-An Evidence-based Guideline From European Crohn and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition	If available, fecal calprotectin should be obtained while in sustained clinical remission and endoscopic evaluation should be considered when calprotectin is high, as defined below [EL2, adults EL2]. (88% agreement)
PMID: 30044357		
		Fecal calprotectin may be used to assess pouch inflammation to minimize repeated pouchoscopies in recurrent pouchitis and to monitor response to treatment. Calprotectin >300 mg/g is suggestive of pouchitis while lower levels do not preclude pou- chitis (57% sensitivity, 92% specificity). (95% agreement)
Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care-An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2018;67:257-291.		There is no ideal cutoff value of fecalcal protectin to reflect mucosal inflammation and predict disease outcome (Tables 19.2 and 19.3). Values differ substantially in the different studies using different reference standards. Cutoff value <100 mg/g usually reflects remission while >250 mg/g more accurately predicts mucosal inflammation. The value that should trigger an endoscopic evaluation or a change in treatment should be, thus, individualized based on these values, especially when values increase over time. (98% agreement)

Overview of Stool Tests

Stool studies often help clinicians when non-specific symptoms such as diarrhea, bloating, weight loss, nausea, vomiting, and abdominal pain affect the patient. These symptoms can be found in many diseases and distinguishing between infectious, functional disorders such as irritable bowel syndrome, and inflammatory conditions such as inflammatory bowel disease, specifically Crohn disease and ulcerative colitis can be challenging. There is a need for sensitive, accurate, and non-invasive markers to help differentiate between functional and organic disorders.

Fecal biomarkers to detect gastrointestinal inflammation have been used for years, however, with decreased costs, increased insurance coverage, and an ever growing body of research that the use of fecal biomarkers has grown exponentially.

Fecal biomarkers include calprotectin (S100A8/S100A9), fecal leukocyte degranulation markers (lactoferrin, polymorphonuclear elastase, and myeloperoxidase), and calgranulin (S100A12). Fecal calprotectin and lacroferrin are the most commonly used and studies markers. These commercially available enzyme-linked immunosorbent assays (ELISAs) have become reliable non-invasive markers to aid with diagnosis and therapy trends in IBD.

Introduction to Calprotectin

Calprotectin is a 36-kDa protein, specifically a calcium- and zinc-binding heterodimer, belonging to the S100 family which was first described in 1980. Calprotectin is a major protein in n0eutrophilic granulocytes, specifically neutrophils, and macrophages, accounting for as much as 60% of the total protein in the cytosol fraction of these cells [1]. With its direct antimicrobial effect, it can facilitate the recruitment of monocytes and macrophages to sites of inflammation, specifically to the gastrointestinal tract [1]. Calprotectin is released into the gastrointestinal tract when inflammatory epithelial cells die. Calprotectin is resistant to bacterial degradation, remains stable in stool for up to 1 week, and is reliably measured by enzyme-linked immunosorbent assay (ELISA) [1]. A strong correlation of FC with active inflammation in the gut has been shown by many studies [2].

Fecal Calprotectin Collection

Fecal calprotectin measurement is influenced by both stool consistency and time between collection and measurement. Recent data suggest some instability of fecal calprotectin with a decrease in fecal calprotectin when stored at room temperature, and thus, there is a suggestion to freeze samples prior to submission when collected at home [3]. Meanwhile, stool consistency and specifically diarrhea are likely to falsely decrease the fecal calprotectin concentration. This is best demonstrated by low calprotectin when collected during bowel cleanout [4]. Infants have been described to have high fecal calprotectin in the first year of life; however, most are collected in diapers, and thus, there is the possibility that absorption of water in the diaper may falsely elevate the fecal calprotectin. A recent study demonstrated a high fecal calprotectin in healthy infants, but all samples were collected in diapers [5]. These findings are consistent with what one would suspect since, unlike blood volume, stool volume is highly variable with the amount of water present in stool which can affect the measurement of concentration in a sample.

Cuffoff Levels

Normal cutoff varies from 50 to 200 μg/g depending on laboratory and clinical practices. Many studies have shown FC to be helpful in distinguishing organic intestinal disease from functional disorders. Von Roon et al. assessed the diagnostic precision of FC for IBD in both adults and children [6]. They found that the diagnostic precision of FC was higher in children and adults with better accuracy at a cutoff level of 100 μg/g vs. 50 μg/g. In a recent meta-analysis, examining the optimum FC cutoff levels, the best sensitivity (90.6%) was achieved at 50 μg/g, whereas the best specificity (78.2%) was found at levels >100 μg/g [7].

Clinical prediction of IBD relapse can also be assessed using non-invasive biomarkers such as FC. This has been shown in patients with both CD and UC. Tibble et al. showed that a single FC level >50 mg/L that the sensitivity and specificity of calprotectin for predicting relapse in all patients with IBD were 90% and 83%, respectively [8].

Finally, another meta-analysis by van Rheenen et al. investigated whether FC use could reduce the number of unnecessary endoscopic procedure in both children and adults [9]. Their pooled sensitivity and specificity were 0.93 and 0.96, respectively, for adults, and 0.92 and 0.76, respectively, in children. Screening with FC resulted in a 67% reduction in the number of adults requiring endoscopy; however, this delayed diagnosis in 6% of adults because of a false-negative test result. They found that in children and teenagers, 65 instead of 100 would undergo endoscopy, and 9 of these 65 will not have IBD. Diagnosis was delayed in 8% of the affected children.

We suggest that FC cutoff level should be tailored to the specific patient and reason for use. For instance, when screening children for IBD, a low threshold such as 50 μg/g would limit those with IBD that are undiagnosed, although it would increase the number of unnecessary endoscopies. Likewise, with data on small bowel Crohn disease suggesting lower FC levels, a low threshold such as 50 μg/g to monitor disease may be ideal. Meanwhile, for colonic disease, one could consider a higher FC cutoff up to 250 μg/g to monitor disease.

Reliability, Sensitivity, and Specificity

FC has been compared to symptom-based clinical scoring systems as well as laboratory markers to study its sensitivity in evaluating disease activity. FC has higher sensitivity and specificity rates than CRP and stool lactoferrin [10]. A recent systemic review and meta-analysis aimed to determine the usefulness of FC in children with suspected IBD. The authors found a pooled sensitivity and specificity for the diagnostic utility of FC in suspected pediatric IBD of 0.978 and 0.682, respectively [11]. After induction therapy, FC was found to normalize in patients with clinical remission. Molander et al. aimed to evaluate whether a normal FC after induction therapy with TNF-alpha antagonist could predict the outcome of IBD patients during maintenance therapy [12]. With a cutoff concentration of 139 μg/g, they found FC had a sensitivity of 72% and a specificity of 80% to predict a risk of clinically active disease after 1 year.

Another more recent meta-analysis aimed to determine the diagnostic performance of FC in assessing IBD endoscopic activity in adults [7]. Rokkas et al. included 49 sets of data from 25 eligible studies, with 298 controls and 2822 patients with IBD. They found that FC in IBD showed a pooled sensitivity of 85%, specificity of 75%, and AUC of 0.88 in diagnosing active disease. FC performed better in UC than in CD (pooled sensitivity 87.3% vs 82.4%, specificity 77.1% vs. 72.1%, and AUC 0.91 vs. 0.84).

Fecal Calprotectin as a Screening Tool

The use of fecal calprotectin to differenctiate functional gastrointestinal disorders from inflammatory bowel disease has been well documented. There have been multiple meta-analyses in both adults and children that demonstrate excellent sensitivity and specificity for the use of fecal calprotectin in screening for IBD and, thus, differentiating between IBD and functional gastroeinterstinal disorders. In one of the largest adult meta-analysis including over 5000 patients, the

pooled sensitivity for use of FC to screen for IBD was 0.882 (95% CI 0.827–0.921), and the pooled specificity for use in screening was 0.7999 (95% CI, 0.693–0.876). Similarly, multiple pediatric meta-analysis demonstrated excellent sensitivity and specificity in the use for screening for possible IBD (sensitivity 0.97, specificity 0.70).

Fecal Calprotectin Comparison to Endoscopy

There is a large body of evidence comparing fecal calprotectin to endoscopy and endoscopic disease measures such as the CDEIS (Crohn Disease Endoscopic Index of Severity) and the SES-CD (Simple Endoscopic Score for Crohn Disease). In a large meta-analysis of over 3000 total patients, the sensitivity and specificity for assessing endoscopic activity were 0.85 and 0.75 respectively. Fecal calprotectin sensitivity and specificity vary in a systematic review with a sensitivity from 69% to 96% depending on the study; however, most studies demonstrate a sensitivity near 90%. Specificity also demonstrated a large range from 44% to 95% with most studies demonstrating a specificity near 80%. These data suggest excellent agreement between calprotectin and endoscopy.

Fecal Calprotectin and Comparison to MRI

MRI enterography (MRE) has become a common tool in the assessment of small bowel CD. Somwaru et al. investigated the correlation between all three biometric tests including FC, MRE, and colonoscopy, and found significant positive correlation between FC and MaRIA (Magnetic Resonance Index of Activity) as well as FC and CDEIS [13]. Another study found FC correlating with the degree of MRE inflammatory activity as well as surgical pathology damage in ileal CD for 120 patients [14]. The MaRIA score was significantly associated with FC levels, and FC reflected MRE inflammatory activity with an area under the receiver operating characteristic curve of 0.914 [14]. FC correlated well with MRE assessment of ileal CD in 104 patients with ileal CD [15]. An AUC is of 0.77 for FC and MRE score >1, with an optimal cutoff of 145 μg/g for severe inflammation on MRE with 69.3% sensitivity and 71.4% specificity [15]. This outperformed other serum markers such as CRP and helped predict biologic-free survival to 3 years but did not predict the risk of intestinal resection.

Fecal Calprotectin and Disease Location

Fecal calprotectin has somewhat decreased sensitivity and specificity when detecting small bowel disease as demonstrated by correlation with capsule endoscopy indices. However, most studies still demonstrated excellent sensitivity and specificity when using a lower cutoff value of 50 μg/g. A recent systematic review suggested that most studies demonstrated higher fecal calproetecin in colonic disease in 4 studies while 7 studies demonstrated no difference between small bowel and colonic disease [16]. While diagnostic accuracy of small bowel versus colonic disease varied and was lower in small bowel disease, the study that used a low 50 μg/g cutoff level demonstrated excellent sensitivity and specificity for both small bowel and colonic disease.

Fecal Calprotectin Use to Monitor Pediatric Inflammatory Bowel Disease

The prediction of relapse of inflammation in both CD and UC is important in clinical practice. Twenty five patients with CD and 19 patients with UC that relapsed over 12 months had increased concentrations of FC which can help predict clinical relapse of disease activity [8]. Six studies were found in a systematic analysis of repeated FC measurements in asymptomatic patients to predict IBD relapse, and found that two consecutive elevated FC values (within 2-3 months) are highly associated with disease relapse, urging to consider proactively optimizing IBD therapy plans [17]. ESPGHAN clinical guidelines for CD suggest a decrease in FC can be used as a marker of treatment response with 100% agreement. Similarly, ESPGHAN guidelines for UC suggest the use of fecal calprotectin to assess for remission and detect pouchitis if applicable (Table 19.3) [18, 19].

Fecal Calprotectin to Evaluate Post-Operative Recurrence

In adults, a meta-analysis of more than 600 patients demonstrated sensitivitiy of 0.82 and specificity of 0.61 in detecting post-operative recurrence after surgical resection [20]. Similarly, fecal calprotectin in children demonstrated excellent ability to detect post-operative recurrence [21].

Fecal Calprotectin to Evaluate for Pouchitis

Total colectomy with ileal pouch anal anastomosis (IPAA) is necessary in some children with severe refractory ulcerative colitis. Pouchitis can occur at any time following colectomy. A recent systematic clinical review in adults demonstrated excellent sensitivity for detection of pouchitis suggesting that fecal calprotectin can be used as a screening tool for pouchitis [22].

A small study in pediatic ulcerative colitis after colectomy demonstrated that calprotectin correlated positively

with the frequency of pouchitis. Mean fecal calprotectin was 71 ± 50 μg/g among patients with no history of pouchitis (n = 10), 290 ± 131 μg/g among patients with a single episode of pouchitis (n = 15), and 832 ± 422 μg/g among those with recurrent pouchitis (p = 0.019 between recurrent pouchitis and no pouchitis). [23]

Fecal Calprotectin to Predict Mucosal Healing

Given the high correlation of FC to endoscopy, it is not a surprise that FC predicts mucosal healing. A recent meta-analysis in adults demonstrated a diagnostic odds ratio of 16.0 in UC and 13.8 in CD for the use of FC to predict mucosal healing [24]. Similarly, a systematic review demonstrated similar findings with excellent sensitivity and specificity for mucosal healing in both ulcerative colitis and CD [25].

Fecal Calprotectin to Predict Histologic Remission

A recent systematic review described 12 studies and over 1000 patients and concluded that fecal calprotectin correlates with histologic remission in patients with ulcerative colitis. (PMID 32048751).

Fecal Calprotectin to Predict Relapse

A meta-analysis demonstrated a pooled sensitivity of 75% and specificity of 71% in use of FC to predict relapse within 12 months. Studies used a variety of cutoff values; however, they demonstrated reasonable ability to predict relapse using clinical and/or endoscopic measures if FC was elevated. The most recent study demonstrated excellent sensitivity (92.3%) and specificity (82.4%) for relapse in the following year when using a FC cutoff value of 327 μg/g [26].

Fecal Calprotectin as a Marker of Tight Control—CALM Study

The recent CALM study, a multicenter randomized control study performed in 22 countries compared endoscopic and clinical outcomes in adult patients with active Crohn disease, specifically moderate to severe disease based on clinical symptoms and biomarkers versus clinical management alone [27]. This study found that a significantly higher proportion of patients in the tight control group (followed via clinical symptoms and biomarkers, specifically FC and CRP) achieved the primary endpoint of mucosal healing versus the clinical management group (without biomarkers). In the tight control group, 50 patients met treatment failure criteria at 11 weeks, 39 at 32 weeks, and 20 at 35 weeks. An increased FC concentration escalated therapy for 31 of the 50 patients (at 11 weeks), and 22 of the 39 patients (at 23 weeks). A treatment algorithm in which FC was used to monitor inflammatory activity in the tight control group leads to superior outcomes. A higher proportion of patients achieved mucosal healing, no deep ulcers on endoscopy, deep remission, biological remission (FC <250 μg/g, CRP <5 mg/L, and CDEIS <4), and steroid-free remission. This study suggests that tight control of symptoms and fecal calprotectin results in improved outcome.

Fecal Calprotectin Recommendations in Clinical Guidelines (Table 19.3)

Given the extensive data on fecal calprotectin, multiple clinical guidelines now recommend use of fecal calprotectin for screening for IBD and monitoring of known IBD. Both the American College of Gastroenterology (ACG) and the British Society of Gastroenterology (BSG) recommend use of fecal calprotectin for screening patients with possible IBD. Additionally, the ACG guidelines, European Crohn's and Colitis Organisation (ECCO) guidelines, and European Society for Pediatric Gastroenterology, and Hepatology and Nutrition (ESPGHAN) guidelines recommend use of fecal calprotectin in monitoring pardigms for both UC and CD.

Summary

In summary, fecal calprotectin has been demonstrated to be an excellent marker for screening patients for inflammatory bowel disease and differentiating between IBD and functional gastrointestinal disorders. In addition, it has demonstrated excellent correlation with endoscopic (SES-CD, CDEIS) and MRE findings, and good correlation with capsule endoscopy (Lewis score). Furthermore, its utility has been demonstrated clinically with predicting clinical relapse, histologic remission in UC, post-operative recurrence in CD, pouchitis in UC, and response to therapy. Perhaps most importantly, tight control with the use of fecal calprotectin results in improved outcome and suggests the pro-active use to monitor mucosal disease.

Continued questions regarding cutoff values are becoming more clear, suggesting that cutoff values depending on purpose may be most appropriate. Similarly, data demonstrating good correlation with capsule endoscopy and small bowel disease suggest a use for small bowel CD, albeit with perhaps a lower cutoff value. While some may point to these two areas for uncertainty for the use of FC, the data are clear

that FC can screen potential patients, measure disease activity, and be used to improve outcome.

Fecal calprotectin as a non-invasive measure of disease activity should be used in the diagnosis and management of IBD. We suggest the use in screening patients for potential IBD, as well as the widespread use in monitoring IBD in both symptomatic and asymptomatic patients.

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Radiologic Evaluation of Pediatric Inflammatory Bowel Disease

20

Michael R. Acord, Rebecca A. Dennis, Abhay S. Srinivasan, and Sudha A. Anupindi

Introduction to Imaging

Imaging is a standard component of disease evaluation in the child with inflammatory bowel disease (IBD). For these patients, imaging plays a vital role in diagnosis and in disease monitoring. At initial presentation, imaging aides in the diagnosis of IBD by assessing the location, extent, degree of inflammatory activity, and overall severity of disease. During disease monitoring, both throughout and after treatment, imaging provides insight into selecting the appropriate treatment options, planning surgical strategies, and evaluating complications that may prompt additional therapeutic interventions.

Given the current advances in imaging technology, plain radiographs and the small bowel follow-through exam are utilized with less frequency. At present, computed tomography enterography (CTE) and magnetic resonance enterography (MRE) are the dominant modalities used. In recent years, advanced expertise in ultrasound (US) and contrast-enhanced ultrasound (CEUS) has provided an alternative means of disease assessment, which may help decrease the over-utilization of CTE and MRE in the future.

This chapter will discuss the current role of these various modalities in the clinical management of pediatric patients with Crohn disease (CD) and ulcerative colitis (UC) with a focus on the techniques, benefits, and findings of each modality along with a brief discussion on the findings of extraintestinal manifestations of IBD. Finally, interventional radiology techniques in this setting will also be discussed, as minimally invasive options are becoming more available at pediatric hospitals.

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Crohn Disease

The hallmark of CD is segmental, transmural bowel involvement with a chronic relapsing course, and the propensity to affect any portion of the gastrointestinal tract. The disease may be limited to a single segment of bowel, commonly the terminal ileum. However, multiple segments may be affected, with intervening normal bowel, known as "skip lesions." CD may also be complicated by perianal disease, strictures, fistulas, and abscesses. With several imaging modalities available, the age and clinical condition of the patient, availability of expertise for an imaging examination, and the clinical question to be answered will determine which techniques are utilized.

Ulcerative Colitis

Ulcerative colitis is a chronic, idiopathic, and inflammatory disease of the rectal and colonic mucosa that is characterized by mucosal inflammation, edema, and ulceration. Several distinguishing features permit clinical and radiological distinction from CD. As a rule, UC nearly always affects the rectum and extends proximally to involve a variable length of colon in a contiguous fashion. Other than the occasional "backwash ileitis" of the terminal ileum, the small bowel is not affected. On rare occasions, variants with transmural involvement or without rectal inflammation also occur. In the majority of cases, diagnosis is dependent on clinical presentation, laboratory tests, and findings on colonoscopy and biopsy. Imaging is usually utilized to confirm diagnosis and evaluate complications associated with UC.

Radiographs

Abnormalities in plain abdominal radiographs consistent with IBD are present in two thirds of pediatric patients, but these are non-specific findings such as mural thickening,

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dilatation, and abnormal pattern of gas and feces [1]. As such the plain film has little role in the initial evaluation of the patient with IBD, rather, plain films remain the first-line investigation in the patient with an acute abdomen. Findings such as dilated bowel loops and air-fluid levels indicate acute intestinal obstruction and pneumoperitoneum signifies intestinal perforation.

In UC, the non-specific finding of submucosal edema, noted on plain films as thumb printing along the colonic wall, is occasionally supportive of the diagnosis. However, in the patient presenting acutely with symptoms of toxic megacolon serial abdominal radiographs may show marked colonic dilatation and may be considered for monitoring the response to treatment and for potential bowel perforation [1].

Fluoroscopic Examinations

The small bowel follow-through (SBFT) involves ingestion of contrast by mouth (or through a tube) to assess the bowel mucosa from the level of the esophagus through the colon. Particular attention is paid to the right lower quadrant and terminal ileum, where fluoroscopic compression images are obtained, and bowel pliability is assessed (Fig. 20.1). Bowel wall thickening and enteric fistulas can be identified during a SBFT; however, this technique is limited by its two-dimensional nature, and extraluminal extension of disease or extraintestinal manifestations may be missed. Further, due to the poor capability of detecting transmural inflammation, SBFT is poor at identifying terminal ileal disease when compared to MRE, CTE, or ileoscopy [2, 3]. For these reasons, the American College of Radiology (ACR) does not recommend SBFT as a primary imaging modality, but rather states it "may be appropriate" imaging at diagnosis, during suspected acute exacerbation, and for disease surveillance as utilization of this technique will likely depend on institution and surgeon preferences [4]. The trend in pediatric imaging has been to reduce the radiation burden; therefore, fluoroscopic examinations have an even more limited role to date and have largely been replaced by cross-sectional imaging. The reported sensitivity and specificity for the detection of terminal ileitis on barium studies are 76% and 67%, respectively, whereas MRE showed a sensitivity and specificity of 83% and 95% in the same cohort using histology as the gold standard [5].

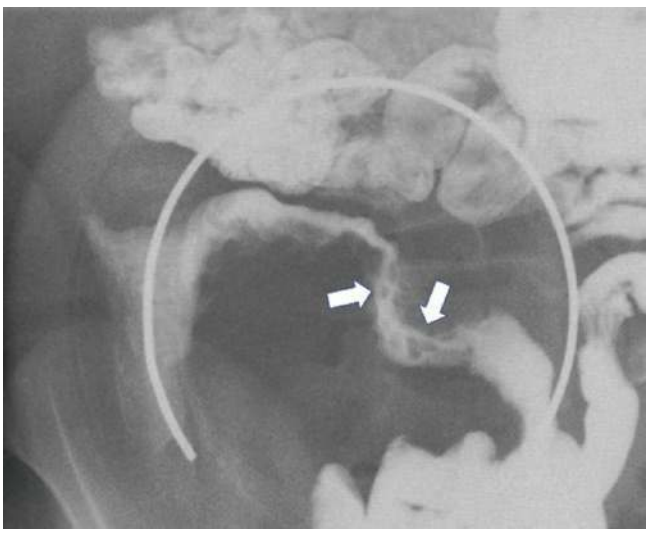

Fig. 20.1 Compression view of the terminal ileum from a small bowel follow-through in a 13-year-old male with Crohn disease presenting with IBD flare. The entire terminal ileum is involved (arrows) with luminal narrowing and irregularity, ulcerations, and nodularity representing the classic "cobblestone" appearance. Separation of the bowel loops is attributed to mesenteric inflammation and fatty proliferation

A historic imaging exam, small bowel enteroclysis, involved direct injection of contrast and air via a nasojejunal catheter placed under fluoroscopic guidance with a child under sedation. A double-contrast view of the small intestine was obtained to provide bowel distension and superior mucosal detail. This procedure, however, has several disadvantages that include a long exam time, the need for sedation/general anesthesia, a greater radiation dose, and the need for an experienced radiologist to perform and interpret the study. For these reasons, small bowel enteroclysis is avoided and has been replaced by CTE and MRE. Similarly contrast enema (CE), no longer called barium enema as barium, has been replaced with water-soluble contrast and may be used to evaluate the colon. This is a single-contrast examination performed on an unprepped colon. If reflux across the ileocecal valve is obtained, it also may provide a double-contrast view of the terminal ileum. Given the availability of endoscopic assessment, patient discomfort with an enema, radiation burden, and the risk for complicating toxic megacolon, CE has been largely replaced by colonoscopy. Additionally, although MRE is targeted to assess the small bowel, the colon can be adequately evaluated by this modality as well.

On fluoroscopic small bowel barium studies, early changes of CD include aphthous lesions, a coarse granular pattern, nodularity, and fold thickening that may progress to deeper ulceration, cobblestoning, and fissuring (Fig. 20.1). In practice, some of these findings can be challenging to identify without a double-contrast technique, not commonly employed in children. In the colon, ulceration occurs within a background of normal-appearing mucosa. Inflammatory edema produces mucosal elevations seen more commonly in the colon than the small bowel. In the patient with more severe CD, mucosal distortions and pseudopolyps may occur due to the elevation of submucosa at the margins of healing ulcers. As inflammation spreads in transmural and circumferential dimensions, the radiologic findings progress to strictures and shortening, with the most severe cases producing the characteristic "string sign." In addition, bowel may

appear adhered to adjacent loops or to other viscera and deep ulcers may extend to create fistulae. Mesenteric inflammation, thickening, and fibrosis may cause separation and shortening of bowel loops (Fig. 20.1).

A contrast enema should not be used to diagnose UC in a child due to its low-yield and high radiation burden; rather, the diagnosis is made with colonoscopy and biopsy. The contrast enema, performed with water-soluble contrast by standard in children, is useful when a child with the known diagnosis of UC may have a stricture. With long-standing disease, the colonic wall becomes rigid, shortened, and narrow due to fibrosis of the submucosa, giving the appearance of the "lead pipe" colon. A contrast enema should also not be performed in a child with an acute abdomen or toxic megacolon as the bowel is friable and such a procedure could lead to a perforation. Finally, unlike cross-sectional CT or MR exams, contrast studies are limited in their ability to image extraluminal extension of disease or extraintestinal manifestations [6]. Only indirect assessment of bowel wall thickening or mesenteric involvement can be made.

Ultrasound and Contrast-Enhanced Ultrasound of the Bowel

There are no set guidelines by the ACR for the use of US in the evaluation of IBD for children. The non-invasive nature, the lack of ionizing radiation, the lower cost compared to CTE and MRE, and the lack of patient preparation make ultrasound an ideal imaging modality in children. Ultrasound can be performed without sedation and results are more immediate and real time for the families to reduce anxiety. Despite these advantages, there are also several important disadvantages to the use of US including that it may not be widely available for this indication, requires experienced technologists and radiologists, and is limited in large body habitus patients, those with significant surgical history and excessive bowel gas. With US, the assessment of terminal ileal disease is excellent, and it is a helpful tool when evaluating fluid collections to distinguish abscess from an inflammatory mass. US, however, is poor at imaging the distal portions of the colon and superficial lesions seen in early disease can be missed in both adults and children [7–9]. In centers with experienced staff, US can be used as a first-line imaging modality especially in the very early onset IBD patients [10]. Patient preparation for bowel US is minimal with a four-hour fasting guideline for solids only, but patients are encouraged to drink clear non-carbonated liquids to help reduce bowel gas and fill the bladder, which helps displace small bowel loops out of the pelvis. Scanning begins in the right lower quadrant at the terminal ileum/ileocecal valve and then continues in a clockwise fashion around the whole colon to the left lower quadrant small bowel loops. Subsequently, the jejunum in the left upper quadrant is evaluated as well. For each segment of bowel, gray-scale and color Doppler images are acquired, and peristalsis of diseased segments can be assessed in real time. Elastography and intravenous contrast-enhanced US images can be performed and provide additional information.

The intramural and extramural features of IBD seen on US are similar to those seen on CTE and MRE. In general, normal bowel wall on US is less than 3 mm with very little vascularity of the bowel wall and surrounding mesentery. When a bowel segment is diseased, there is increased thickening, hyperemia, loss of stratification, and abnormal perienteric mesentery (Fig. 20.2a, b). Loss of bowel wall stratification and degree of hyperemia correlate well with active disease and the sonographic value of bowel wall thickening as an index of increased disease activity has been demonstrated in children [7, 11]. Assessment of disease severity can also be enhanced by measuring the vessel density in the affected bowel segment using color Doppler US [12]. In expert hands, US has been used to assess fistulae and strictures, and also monitor postoperative disease recurrence [8, 13, 14].

Differentiating active from fibrotic disease is a diagnostic challenge despite advances in technology as active inflammation and fibrosis co-exist in the same segments of bowel [14]. US elastography which assesses the stiffness of the bowel wall is still in its incipient stages, but a recent case report by Thimm MA et al. showed that US elastography was valuable in identifying bowel wall fibrosis with high stiffness values in specific diseased segments of bowel in pediatric patients with CD when correlating with surgery and histology [15]. Further validation of this technique is needed for it to be adopted widely.

Contrast-enhanced US (CEUS) is gaining traction recently and is another tool that can be combined with conventional gray-scale and color Doppler US [16]. The main disadvantages of CEUS in children are that it requires placement of a peripheral intravenous line, and it is not yet widely available and requires experience to perform and interpret. Using the main FDA-approved ultrasound contrast agent, Lumason® (Bracco Diagnostics, Monroe Township, NJ), is also considered an off-label use for evaluation of bowel. This agent, composed of non-nephrotoxic microbubbles, has a very high safety profile. Imaging of the bowel is performed after administering the microbubbles intravenously, and diseased loops are assessed for rapid and persistent hyperenhancement (Fig. 20.2c). Time–intensity curves can be generated using the available vendor software found on all US machines, thereby enabling one to analyze the magnitude of perfusion of the bowel wall and generate a more quantitative assessment of disease compared to gray-scale ultrasound alone. CEUS for bowel may be helpful in a variety of situations, including when evaluating severity of disease, deter-

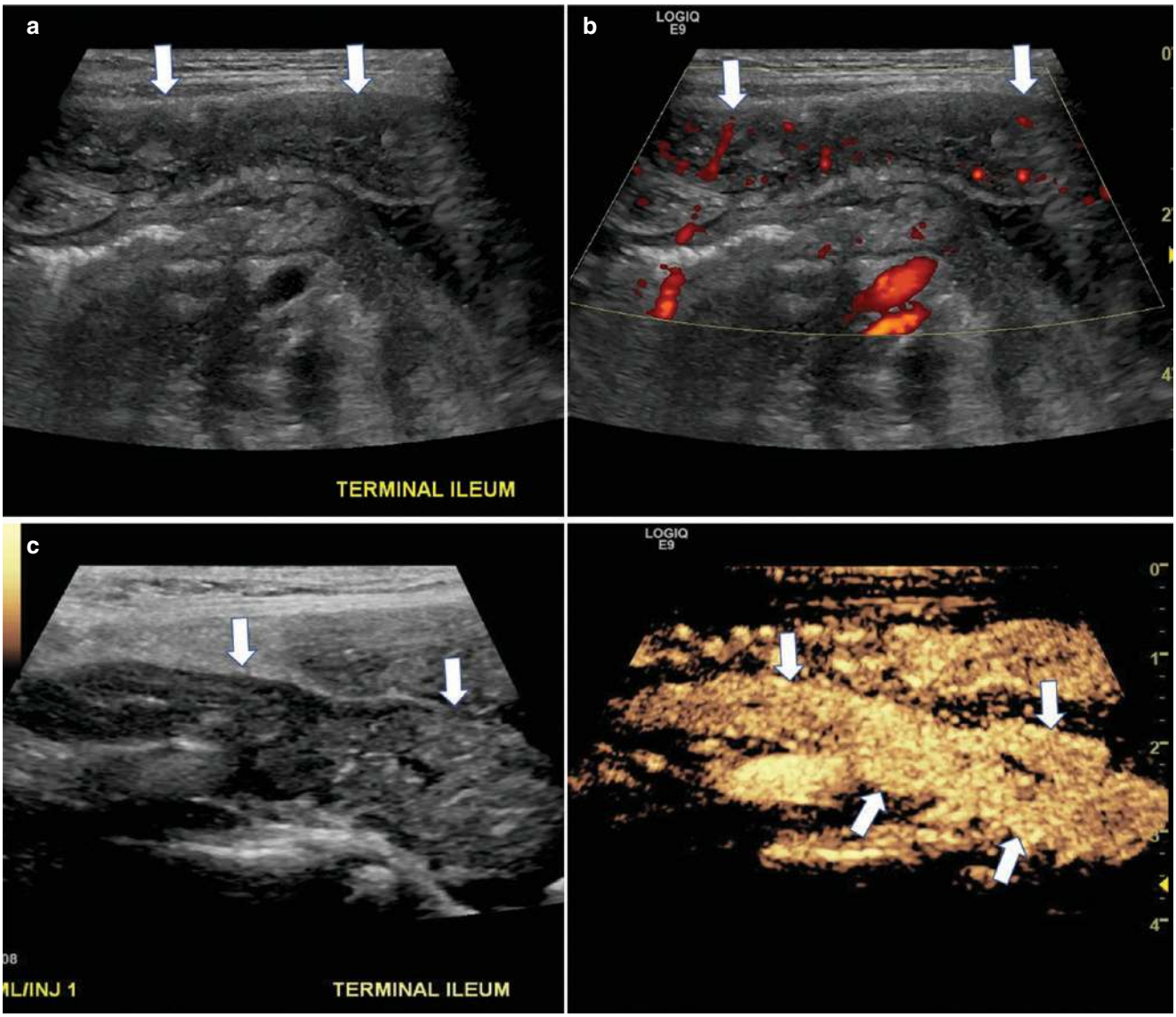

Fig. 20.2 6-year-old female with VEO-IBD confirmed by colonoscopy status post-infusion therapy and here for baseline bowel ultrasound with contrast. (**a**) Sagittal gray scale and (**b**) color Doppler ultrasound images of the terminal ileum (TI) show marked bowel wall thickening and hyperemia (arrows) indicative of active inflammation. The bowel wall thickness measures 6.5 mm, normal is less than 3 mm. (**c**) Dual gray-scale (left) and contrast screen (right) from a CEUS examination of the same loop of TI in the sagittal plane show rapid enhancement of the entire bowel wall (arrows). The inflamed bowel persistently enhanced with a slow wash-out over a period of 2 min

mining a treatment response, assessing for complications, and differentiating between an inflammatory mass and abscess more definitively [16]. Although CEUS is being used by many pediatric centers, the use of CEUS for pediatric IBD to date has been limited. Currently, most of the publications are in adults and experiences in children with IBD continue to be explored.

Computed Tomography Enterography (CTE)

For pediatric patients, the ACR considers CTE as "usually appropriate" imaging at diagnosis, during suspected acute exacerbation, and for disease surveillance due to the wide availability of CT among institutions [4]. Other major advantages over MRI include better spatial resolution, fewer imaging artifacts, and lower cost. While a major limitation of CTE in children is the use of ionizing radiation, modern techniques and reconstruction algorithms have led to a marked reduction in dose compared to historic levels. Therefore, CTE should not be avoided purely on the basis of radiation exposure as it is possible to obtain diagnostic quality images with doses less than background radiation [17]. Compared to the variable dose of small bowel fluoroscopic imaging, for example, CTE has been shown to have an overall lower gonadal dose [18, 19].

Indeed, if the dose of CTE can be lowered enough, one model determined that in the future, CTE may be the preferred, cost-effective modality, even for patients under the age of 30 years [20].

The ease and availability of CTE makes it useful in the acute setting, such as when evaluating for a bowel obstruction or free air. Additionally, the speed at which the exam can be performed often obviates the need for sedation, which is especially useful when imaging younger children who cannot tolerate an MRI awake. For example, patients with very early onset IBD are usually of an age that they are unable to hold still throughout an entire MRI exam (Fig. 20.3). Although CT has not been validated in this population and interpretation is limited by the paucity of intraabdominal fat, it might be considered after an inconclusive or abnormal small bowel ultrasound when MRE cannot be performed [10]. CTE, however, should not be used to routinely evaluate for small bowel disease involvement in these very young patients. In some institutions, a CTE may be performed at baseline with follow-up by MRE, especially if bowel US is not available.

The technique of pediatric CTE involves administration of a low-density oral contrast agent to distend the bowel lumen while simultaneously allowing evaluation of the mucosa. Contrast agents, such low-density barium sulfate, VoLumen, (Bracco, Princeton, NJ) or a flavored sorbitol and mannitol beverage, Breeza, (Beekley Medical, Bristol, Connecticut) are administered orally using a weight-based volume. The flavored nature of the latter agent has shown improved rates of complete ingestion in children without a decrease in diagnostic confidence compared to barium [21, 22]. CT enteroclysis, a technique that introduces oral contrast via a nasojejunal (NJ) tube, is usually not appropriate or tolerated by children and usually requires the use of sedation [4]. The sensitivity of CTE to depict small bowel findings is equal or better than SBFT and similar to that of capsule endoscopy but has the additional benefit of being able to depict extraintestinal findings [23, 24]. Due to the amount of barium ingested, children also tend to prefer CTE over SBFT [23]. In addition to oral contrast, intravenous contrast is always administered unless there is a contraindication, in which case consideration of an alternative modality is necessary.

CTE Features of CD

Changes readily detected by CT include bowel wall thickening, luminal narrowing, and mesenteric involvement. Small bowel changes and skip lesions are often present, and mesenteric findings include thickening due to fibrofatty infiltration, lymphadenopathy, and fatty encroachment of the affected loop of bowel (Fig. 20.3).

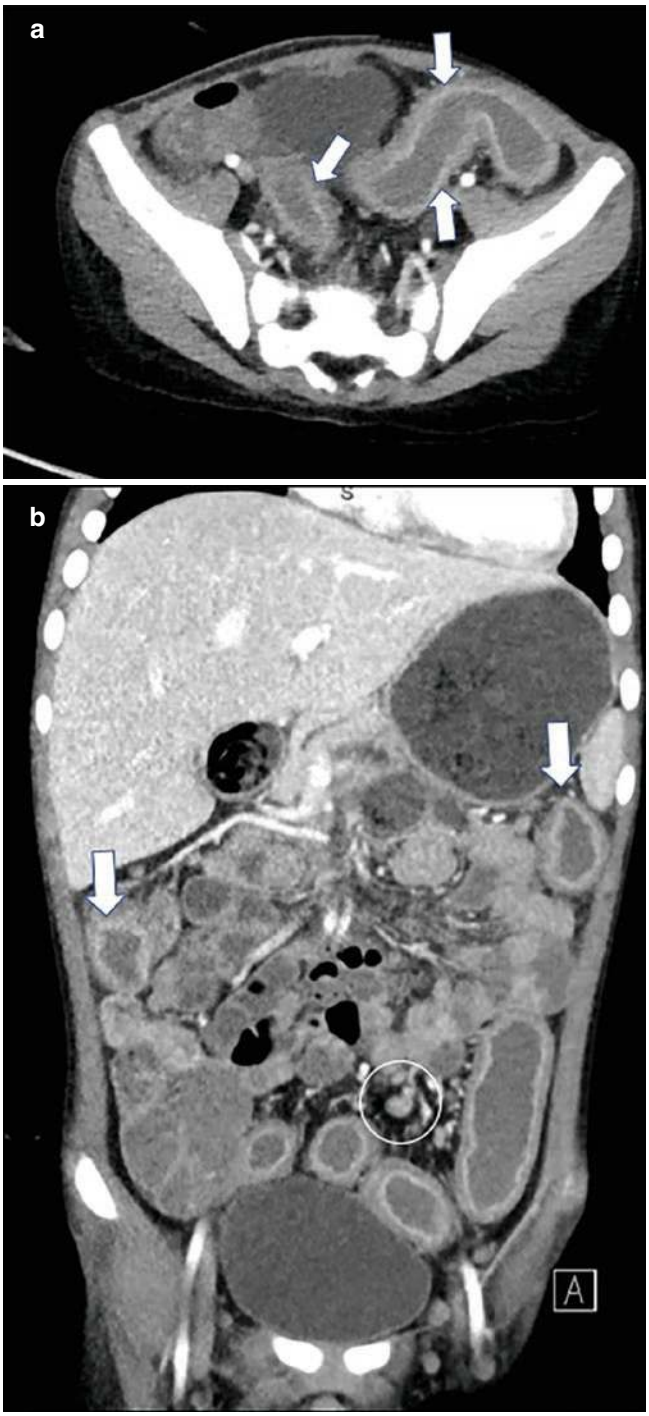

Fig. 20.3 5-year-old male with severe VEO-IBD with fever and extremely elevated inflammatory markers underwent a CTE without sedation but with the support of child life. (**a**) axial CT enterography image shows marked mural thickening of the distal sigmoid colon and rectum with mural stratification and hyperenhancement (arrows) and fatty proliferation of the mesentery (**b**) coronal CTE image shows that there is extensive involvement of the other areas of colon the hepatic and splenic flexure (arrows), mesenteric enhancing nodes (circle). No inflammatory mass or perforation was present to further explain the acute presentation

CTE Features of UC

Early mucosal changes of UC are difficult to detect on CT, but in chronic disease, bowel wall thickening and luminal narrowing are readily seen [25]. These, however, are rather non-specific and findings overlap with those of other colitides including Crohn colitis [18]. Characteristic CT features in UC include a symmetric, contiguous wall thickening involving the rectum and extending proximally in a contiguous manner. Small bowel changes and skip lesions are absent. Thickening of the mesentery or mesenteric lymphadenopathy are rare, but proliferation of perirectal fat can occur. In the diagnostic work-up of UC in a child, CTE is rarely used.

Extraintestinal manifestations of CD and UC in children are better depicted on MRE compared to CTE, especially those involving the liver, biliary system, pancreas, urinary tract, and musculoskeletal systems. In emergent cases where a child presents after hours with an acute abdomen with concerns for potential abscess or obstruction, a CT is most beneficial to quickly provide diagnostic information. However, given IBD patients who will likely need multiple studies throughout their lifetime to monitor disease, MR enterography should be considered for follow-up to keep overall radiation burden to a minimal.

Magnetic Resonance Enterography (MRE)

Similar to CTE, for pediatric patients, the ACR considers MRE as "usually appropriate" imaging at diagnosis, during suspected acute exacerbation, and for disease surveillance [4]. In addition to the absence of ionizing radiation, MRE has superior soft tissue contrast resolution, which is ideal for imaging bowel and perianal disease. These qualities have made MRE the dominant modality to image children today. Gee MS et al. in a prospective study concluded that MRE can be substituted for CTE as the first-line imaging modality in pediatric patients with CD [26]. This viewpoint is based on the ability of MRE to detect intestinal pathologic abnormalities in both small and large bowel as well as extraintestinal disease manifestations. A retrospective study, comparing the two modalities, showed that wall thickening and mural enhancement had a 91% and 96% specificity on MRI and 91% and 91% specificity on CT, respectively, without a statistically significant difference [27]. CTE, however, better depicted perienteric findings, such as fibrofatty proliferation and vasa recta engorgement, due to the ease at which the mesentery is visualized and the greater spatial resolution of this modality.

Optimal image quality with MRE depends on adequate luminal distention and limitation of motion artifacts. Bowel distension is achieved similar to CTE, with ingestion of oral contrast agents such as VoLumen and Breeza. Oral contrast is administered in large volumes ranging from 15 to 20 mL/kg, which the patient is instructed to begin drinking 60 min prior to the scan. If the patient is unable or unwilling to drink the contrast, a nasogastric (NG) tube can be placed to facilitate administration. MR enteroclysis, which requires placement of an NJ tube, has not been widely adopted in children due to the need for sedation. Similar to CTE, intravenous contrast is always given unless there is a contraindication.

Bowel motion artifacts may be overcome by a variety of techniques. Imaging may be performed in the prone position to limit bowel peristalsis and separate bowel loops. Prone positioning, however, is used with caution in children with (CD), such as those with ostomies, nausea, or those who are being imaged under anesthesia. Although not utilized at all institutions, an anti-peristaltic agent, such as glucagon, can be administered intravenously to further limit bowel motion artifact [28]. This is typically given in split doses of 0.25 mg at the start of the exam and 0.25 mg just prior to the administration of IV contrast. Allergies to glucagon, beef or pork products, lactose, diabetes mellitus, and adrenal insufficiency are contraindications to administration, and the most common side effects include nausea and vomiting, particularly in children less than 8 years old.

Most adolescent and teenage patients tolerate MRE well, without the need for sedation or anesthesia. Younger patients, however, may require sedation to limit patient motion and allow for diagnostic images. As oral contrast is necessary for bowel distention, this can lead to logistical challenges with anesthesia. Every effort should be made to avoid the use of anesthesia for these studies, which includes use of in-scanner video googles, utilizing child life staff, or choosing an alternative modality such as ultrasound or CTE. Abbreviated MRE protocols are also emerging, whereby avoiding the use of glucagon and IV contrast, the study can be completed in under 30 min and may be suitable for children as young as 4 years of age [6]. If the consensus between the radiologist and gastroenterologist is to proceed with an MRE under anesthesia, the patient should be intubated for airway protection and oral contrast administered via NG tube. At our institution, after confirming NG tube position by abdominal radiograph, 15 mL/kg of oral contrast is administered over 40 min. To decrease the risk of emesis and aspiration, glucagon is not administered, and the patient is imaged supine.

The field of view includes the entire abdomen and pelvis. The perineum may be included separately if needed, as high-resolution imaging can be performed to further characterize a perianal fistula. Prior to the administration of contrast, T2-weighted sequences to assess bowel wall thickening and edema and diffusion-weighted images are performed. After contrast, multiplanar images are obtained to evaluate enhancement pattern along with delayed images to highlight mural fibrosis. Most institutions will also perform dynamic

steady-state imaging to subjectively assess bowel peristalsis; however, in the future quantitative assessment of motility using emerging software technologies may also be possible, which will enable the radiologist to provide even further objective data.

MRE Features of CD

Findings of active inflammation of CD at MRE like that on CTE include asymmetric wall thickening, segmental mural enhancement and edema, restricted diffusion, engorgement of the vasa recta, and reactive prominent enhancing mesenteric nodes [29, 30]. (Figs. 20.4 and 20.5). These changes of CD may progress to deeper ulceration, fissuring, and transmural disease penetrating outside of the bowel wall. Discontinuous and asymmetric colonic mucosal changes are a hallmark of CD. Fibrotic lesions may show homogenous T2 hyperintensity although less than in active inflammation, variable contrast enhancement, and minimal adjacent inflammatory changes [31]. Delayed contrast-enhanced sequence has been utilized with some success to evaluate for late enhancement seen in mural fibrosis; however, this is not standard practice in pediatric imaging given that active inflammation is present in fibrosed segments.

MRE Features of UC

Characteristic findings of MRE in the active stage of UC include loss of haustral markings, thickening, and contrast enhancement of the colonic wall [32]. As with CTE, these findings overlap those of CD. The absence of small bowel disease, perianal disease, or fibrofatty proliferation can support the diagnosis of UC; however, mild terminal ileitis (backwash ileitis) is not uncommon and the ability of MRE to categorize disease into either CD or UC with high specificity remains a challenge.

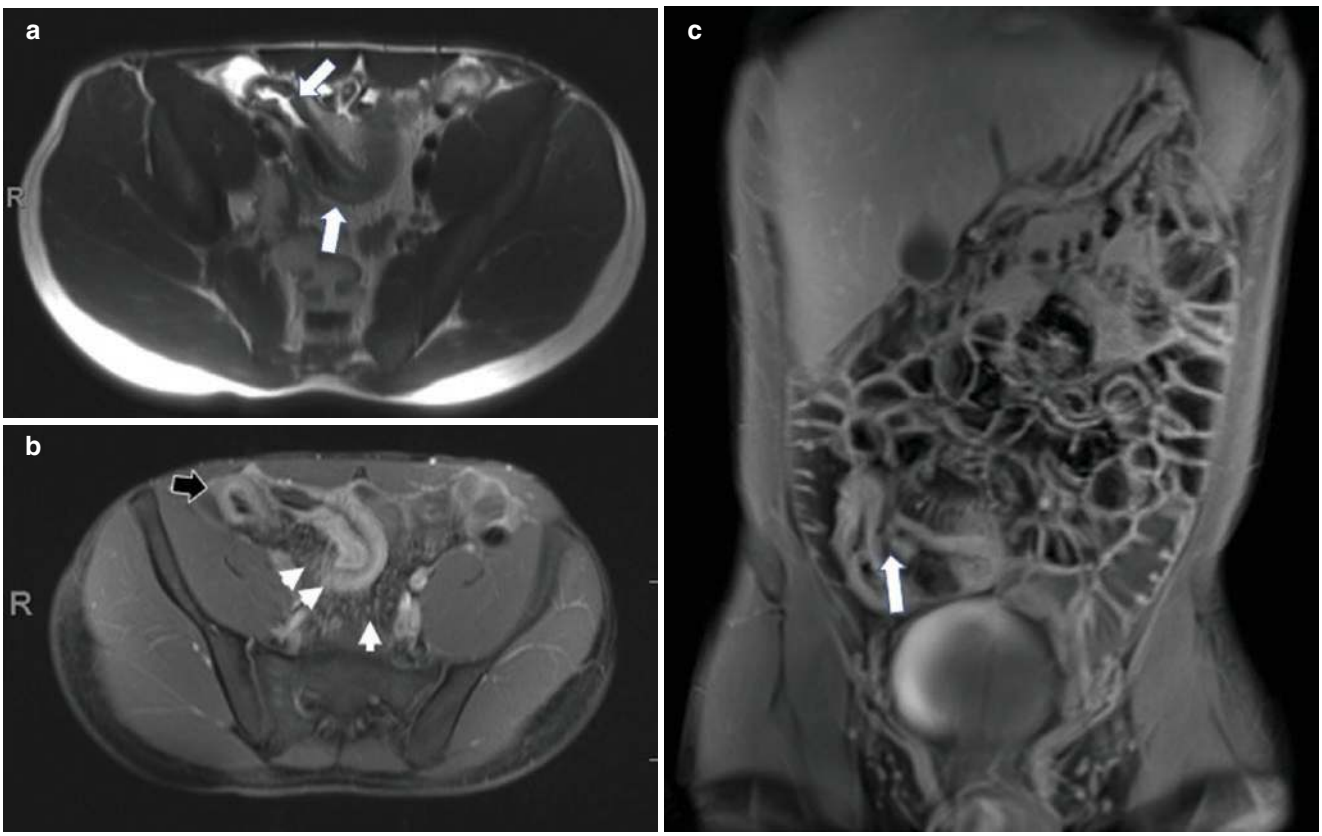

Fig. 20.4 19-year-old male with history of CD and worsening abdominal pain. (**a**) Axial T2 HASTE MRE image shows a thickened loop of distal ileum with mural edema (bright signal in the bowel wall) and surrounding fibrofatty proliferation (arrows), (**b**) axial post-contrast T1-weighted fat suppressed image slightly more cephalad shows marked enhancement of the terminal ileum (TI) (black arrow) and that same loop of distal ileum with engorgement of the vasa recta appearing as small vessels in the mesentery (arrowheads), (**c**) coronal post-contrast T1-weighted fat-suppressed image shows an entero-enteric fistula as a linear-enhancing tract between the inflamed TI and distal ileum (arrow)

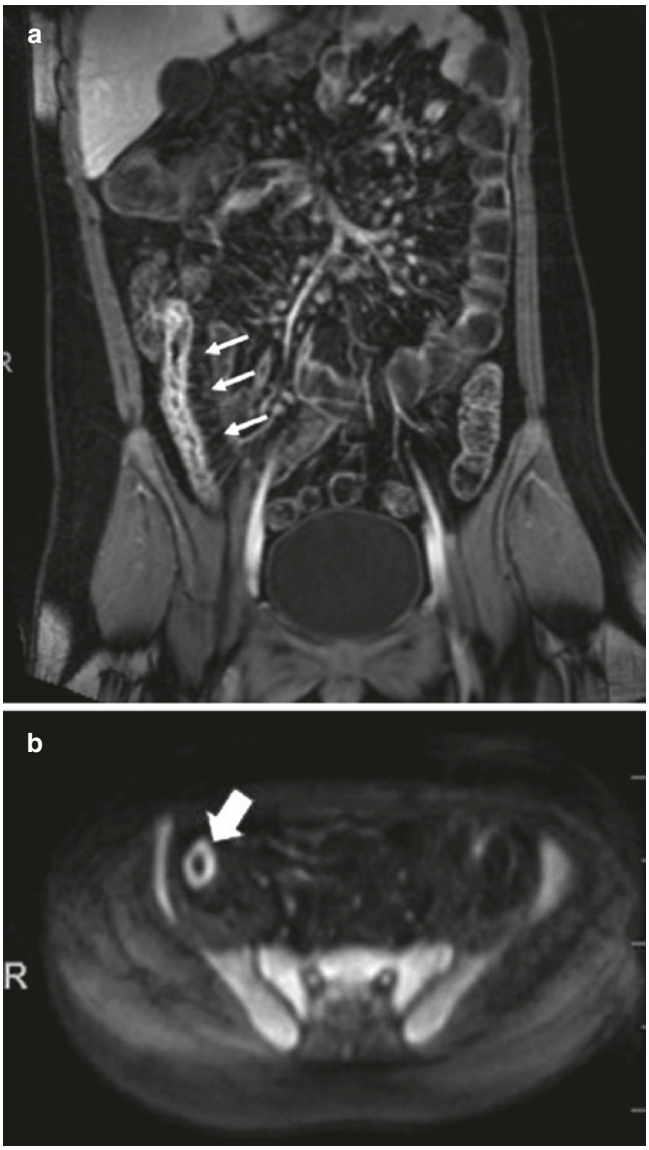

Fig. 20.5 14-year-old male with CD. (**a**) Coronal MRE post-contrast T1-weighted fat-suppressed image shows increased enhancement of the entire terminal ileum (TI) with engorged vasa recta depicted by prominent perienteric vessels, the classic "comb sign" (arrows) indicative of active inflammation, (**b**) axial diffusion-weighted image shows restricted diffusion of the TI (arrow) consistent with edema and active inflammation

Nuclear Medicine Imaging Studies

White Blood Cell Scans

Radionuclide-labeled autologous WBC scans are not used conventionally in the diagnostic work-up for a child with IBD or used in monitoring disease burden. The WBC scan is a helpful diagnostic tool for the detection of inflammation and abscesses; however, these studies are not used in our institution for assessment of IBD and will not be discussed further in this chapter.

PET and PET-MR Examinations

Positron emission tomography (PET) is a functional imaging technique that has been applied to the detection of inflamed areas of bowel. The high metabolic activity of inflamed tissue results in the uptake of the glucose analog, fluoro-2-deoxy-D-glucose (FDG), which has been radiolabeled with a positron-emitting isotope such as fluorine-18 (F-18). It is transported into cells at a rate proportional to the metabolic activity of the cell. Within an hour of the intravenous injection of F-18-labeled FDG, the scan is performed, with a total image acquisition time of less than a half hour. PET scans are functional studies and performed alone do not provide anatomical information. However, a novel noteworthy technique, PET-MR enterography, combines the functional with the anatomical data into one study (MRE with oral and IV contrast and a PET) and has been reported to be successful in the assessment of patients with CD with a high accuracy in detecting inflamed segments of bowel [33]. Catalano et al. reported that PET-MR enterography technique can help distinguish fibrotic from mixed fibrotic/inflamed strictures [34]. The current publications are few and in adult populations and, to date, the lack of availability of PET-MR, the added radiation dose and the greater overall cost, make this examination impractical in the assessment of children with IBD.

Imaging of Complications

Perianal Disease

At some point in their disease course, approximately 62% of children with CD will experience manifestations of perianal disease [35]. External manifestations are usually diagnosed by physical inspection and include skin tags, fissures, simple abscesses, and ulcerations. More complex abscesses and fistulas may need further evaluation under anesthesia or with imaging studies. Transperineal ultrasound with color Doppler may be used as the initial modality at diagnosis and can be useful in determining the degree of active inflammation present [36]. Transperineal ultrasound, however, only has fair agreement with MRI, which is the imaging modality of choice when evaluating perianal disease [37]. The poor soft tissue resolution of CT limits its reliability in assessment of perianal fistula and should not be used in this setting. MRI can provide exquisite soft tissue detail and anatomic relationships that yield high concordance with surgical findings to guide management [38]. Identifying the presence or absence of an abscess, describing the location using the Parks Classification, and assessing the length of the fistula, are all important characteristics that MRI is capable of discerning.

Stricture

A stricture is defined as focal luminal narrowing of bowel with upstream dilation of ≥3 cm [29]. These are best demonstrated on cross-sectional imaging and, however, can also be demonstrated on ultrasound. If severe, a stricture can result in an acute bowel obstruction, which on imaging is seen as unequivocal dilation of proximal bowel with a paucity of gas distally. In the acute setting, CTE is the preferred modality to assess bowel obstruction, as these patients may not be able to tolerate an MRE exam and CTE can be obtained quickly.

Penetrating Disease—Intraabdominal Abscesses and Enteric Fistulas

Manifestations of penetrating disease include intraabdominal abscesses and enteric fistulas and occur in approximately 27% of children within 5 years of diagnosis, usually in the setting of active inflammation and luminal narrowing [39, 40]. Although no comparative studies have been performed in children, CTE and MRE have comparable and moderately high accuracy for depiction of these findings in adults [30].

An inflammatory mass, formerly termed phlegmon, occurs adjacent to an inflamed bowel wall segment and appears as a poorly defined region of inflammation within the mesentery. An abscess, on the other hand, appears as a well-defined, walled-off fluid collection that can develop in the abdominal wall, peritoneal cavity, retroperitoneum or iliopsoas, and subphrenic region [29]. US may be the initial modality utilized when an abscess is expected; however, CTE, MRE, or CEUS are also appropriate for imaging in this setting.

Fistulas can be simple, a single sinus tract arising from the bowel and connecting to another epithelialized surface, or complex where multiple tracts arise from a single bowel loop appearing as an asterisk configuration on CTE or MRE. Demonstration of enteric fistula by imaging can be challenging, particularly with US and when the tracts are not filled with fluid.

Toxic Megacolon

Toxic megacolon is a complication more frequently seen with UC but may also occur in patients with severe CD. The clinical scenario is a patient with IBD presenting with an acute abdomen and signs of sepsis. Occasionally, toxic megacolon is the initial presentation of the patient with UC. The diagnosis can be made on a plain radiograph that shows marked colonic dilatation with absent haustral pattern is seen. The threshold for colonic dilation is age dependent and in adolescents, a colonic diameter >5 cm is considered abnormal. Following initial medical treatment, serial films are obtained to monitor for progression, evidence of perforation, or improvement. Contrast enema studies are contraindicated as they increase the risk of perforation.

Bowel Obstruction/Perforation

The radiologic hallmark of bowel obstruction is dilatation of proximal bowel with paucity of gas distally. Air-fluid levels may also be noted in proximal bowel. It is important to distinguish between partial obstruction where initial nonoperative treatment may be appropriate and complete obstruction, where surgical intervention is often required. The diagnosis of intestinal perforation is made when free extraluminal gas is detected by either plain film or CT.

Imaging of Extraintestinal Manifestations

As IBD is mediated by the immune system, there are numerous extraintestinal manifestations that may occur. In order of prevalence, the musculoskeletal (osteoporosis, arthritis), skin (erythema nodosum, psoriasis, pyoderma gangrenosum), ophthalmic (uveitis iritis), hepatobiliary (sclerosing cholangitis, gallstones, autoimmune hepatitis), and renal (urolithiasis) systems can be involved. Multiple extraintestinal manifestations may occur concomitantly, and the presence of one confers a higher likelihood in developing others [41]. The radiologic assessment of some of these manifestations is important in the comprehensive assessment of the patient with IBD. A discussion of other disorders will be found in the appropriate chapters in this book.

Musculoskeletal System

Osteopenia and osteoporosis are known complications of IBD with potential mechanisms including inhibition of remodeling and growth, malnutrition, and treatment with corticosteroids [42, 43]. The most common method for assessment of bone mineral density and bone mass (reported as bone mineral content) is dual-energy X-ray absorptiometry (DXA). The densities measured by DXA of the lumbar spine, femoral neck, and radius are expressed as Z-scores, the number of standard deviations of the measured density with respect to normal values for age and sex. Bone mineral content or density that falls >2 standard deviations below expected is labeled "low for age." Osteoporosis requires the presence of a non-traumatic and non-pathologic vertebral fracture, or low bone density with a history of multiple (2–3)

fractures. Pediatric reference data are now available for children and teenagers, but it is essential to select norms specific to equipment used, as there are manufacturer-specific differences [44].

IBD-related arthropathy may be axial or peripheral. Peripheral arthropathy presents as a seronegative arthritis and affects 10–20% of patients UC and 5–10% of patients with CD. It may be pauci-articular (mainly large joints such as the knee ankle) or poly-articular (propensity for smaller joints such as metacarpophalangeal joints). Peripheral arthropathy is generally a clinical diagnosis, as imaging is often normal and shows little or no joint destruction. Axial arthropathy is less common and can be categorized as ankylosing spondylitis or sacroiliitis [45]. Radiographs and T2-weighted MRI with fat suppression techniques are useful for assessing axial arthropathy, with MRI having greater sensitivity.

Hepatobiliary Disease

Primary sclerosing cholangitis (PSC) is the most frequent hepatobiliary manifestation of IBD, with a reported incidence of about 6% in children, and approximately 80% of patients with PSC will have IBD [41]. PSC is more strongly associated with UC than CD and presents clinically with cholestasis. It is characterized by inflammatory fibrosis of the intra- and extra-hepatic bile ducts, with progression to stricture, cholestasis, and cirrhosis, which then confers a risk of hepatocellular carcinoma and cholangiocarcinoma. While direct cholangiography via ERCP has high sensitivity for detecting early ductal changes, MRCP is favored as the means of assessment. Common findings of PSC include multifocal bile duct strictures, segmental or general duct dilatation, or beading. Advanced disease can show mural thickening, nodularity, and enhancement [46]. ERCP should be considered when MRCP is negative, but a strong clinical suspicion persists.

There is an increased incidence (about 2%) of gallstones in patients with IBD, but the association is stronger with CD than UC [41]. Ultrasound is the favored modality for assessing gallstones; if obstructive cholangiopathy or pancreatitis is suspected, MRCP or contrast-enhanced abdominopelvic CT is recommended.

Urolithiasis

The prevalence of symptomatic nephrolithiasis is higher in IBD patients compared to the general population, typically in patients who underwent extensive small bowel resection or in those with persistent severe small bowel inflammation. Patients present with signs and symptoms of urinary obstruction, and stones are typically of calcium oxalate [47]. Initial imaging assessment is often with renal ultrasound and further assessment with a non-contrast renal stone protocol CT scan should be considered.

Interventional Radiology in IBD

Percutaneous Abscess Drainage

Percutaneous drainage has been described as effective in children for the management of abscesses [48]. Although the reported average duration of drainage in IBD (about 20 days) is longer than for other etiologies, effective drainage may allow earlier resumption of immunomodulating medicine, obviate surgery, or render subsequent surgery easier and less invasive [48, 49]. Percutaneous drainage has also shown effectiveness in the drainage of post-surgical anastomotic leak in IBD patients [50].

Abdominopelvic CT or MRI is often required for pre-procedure assessment, to characterize the extent and number of collections. In general, abscesses greater than 3 cm are considered appropriate for drainage. Smaller collections may be aspirated, without the placement of a drain if specimens are needed for antibiotic tailoring. Multiple drains may be necessary when non-communicating collections are seen, but if there are more than 3–5 large collections, surgical exploration, and wash-out may be more effective. Abdominal abscesses are often drained with an anterior approach using US and fluoroscopic guidance. Deep pelvic abscesses may require a trans-gluteal or trans-iliopsoas approach, as trans-rectal drainage is not commonly performed in patients with IBD. It should be noted that abdominal wall abscesses may have a higher rate of failure of percutaneous drainage, and this is thought to be due to the presence of fistulous tracts [51].

The presence of a fistulous tract from bowel can complicate drainage. Principles of nonoperative fistula management include control of bowel efflux (e.g., bowel rest or diversion) and evacuation of abscess. Closure rates of fistulae (encompassing multiple etiologies) by percutaneous drainage alone are reported to be 50–60%, but this may be aided by immunomodulating medicine [52, 53].

Additional Applications of Interventional Radiology

Interventional radiology techniques, such as vascular and enteral access, may be applied for therapeutic and supportive care for IBD. For IBD-related arthropathy, steroid injections can be performed with greater confidence using image guidance. For example, image guidance is necessary for successful access of the sacroiliac joints for treatment of symptomatic

sacroiliitis [54]. Percutaneous biliary drainage and cholangioplasty may be required for treatment of dominant strictures that are not accessible by endoscopy, or in cases wherein endoscopic management was not successful [55]. Mesenteric vein thrombosis is a rare, but serious complication of IBD and can produce adverse sequelae such as venous bowel ischemia and pre-hepatic portal hypertension [56]. Fulminant mesenteric thrombosis may require catheter-directed thrombolysis and thrombectomy, which can be performed through trans-hepatic or trans-jugular intra-hepatic access.

Conclusion

The imaging arsenal for the evaluation of pediatric IBD is composed of many examinations from radiographs to sophisticated MR and PET imaging. Each imaging study has advantages and disadvantages with some modalities having very practical roles. MRE has become the first line of imaging over CTE and conventional fluoroscopic small bowel studies. In the future, we hope that bowel ultrasound and contrast-enhanced ultrasound will be embraced in many more pediatric centers. The development of faster and shorter MRE protocols will emerge to make these exams more comfortable and facile for the youngest of patients, perhaps avoiding sedation and contrast altogether.

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Endoscopy and Inflammatory Bowel Disease

21

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Introduction

Safe, informative, and effective endoscopy performed in a child-friendly situation with the minimum of distress to child and parent alike is a sine qua non of a unit adhering to the best practice in the care of children and adolescents with pediatric inflammatory bowel disease (PIBD). The care of children and adolescents differs in important ways from that of adults. This is reflected in the emphasis placed on various aspects of endoscopy especially ileocolonoscopy (IC), such as the frequent use of general anesthesia, the number and location of mucosal biopsies, and the routine inclusion of ileal intubation during a complete examination. The question of who should conduct the procedure continues to receive attention among pediatric gastroenterologists. The current evidence and consensus recommend that endoscopy should be performed by a pediatric gastroenterologist or a gastroenterologist who has pediatric experience, under general anesthesia or deep sedation [1]. There can be few more satisfying experiences in medicine than making a clinical judgment and diagnosis in a child, confirming the nature and extent of the disease oneself by endoscopy, treating appropriately, and then visually demonstrating the success of such endeavors to child and parent by a follow-up procedure.

Endoscopy plays an important role in the initial diagnosis of inflammatory bowel disease (IBD), differentiation of IBD into Crohn disease (CD) and ulcerative colitis (UC), assessment of disease extent, monitoring of response to therapy, surveillance of cancer, and to perform endo-therapeutic procedures such as stricture dilatation [2].

Endoscopy: Background History

The evolution of endoscopy in the diagnostic armamentarium was initially a slow process. Rigid esophagoscopes and sigmoidoscopes were introduced in the late nineteenth century and semiflexible endoscopes in the 1930s. They remained the only endoscopes in use until the 1960s. This was partly because of the lack of understanding about inflammatory bowel disease, which was for a long time thought to be a disease mainly confined to the rectosigmoid region. However, the invention of fiber optics in the 1950s heralded a new era leading to the development of the first flexible sigmoidoscope in 1963 and colonoscope in 1966. This made it possible to visualize, take biopsies, and perform endo-therapeutic procedures and reach the duodenum and the ileo-colon. The next major breakthrough was the arrival of video-chip technology in the 1980s. This allowed digital images to be displayed on a monitor and further to be stored, analyzed, and transmitted as necessary. Further advances have seen the development of Sonde enteroscopy [3], which was limited by lack of therapeutic potential, and then push enteroscopy, allowing the therapeutic endoscopist an access of up to 70–100 cm small bowel beyond the pylorus. Intraoperative endoscopy (IOE) appeared to be the only means available to access the whole of the small bowel at the turn of the century until the development of wireless capsule endoscopy (WCE). This technological breakthrough allowed the direct visualization of the entire small bowel without the need of external wires, fiber-optic bundles, or cables but as yet is limited to diagnostic input alone. Double-balloon enteroscopy (DBE) is a more recent modality, which enables high-resolution endoscopic imaging of the entire small bowel, with the advantage over WCE of potential for mucosal biopsies and interventional endo-therapy.

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Patient Preparation

Ideally, both the child and the parents should be offered a preparatory visit to the endoscopy unit to answer questions and defuse any potential concerns and anxieties regarding the procedure and admission. Children with greater knowledge of the procedure exhibit less distress and report less anxiety toward the procedure [4]. Younger children undoubtedly benefit from preadmission visits and the involvement of a play therapist to enable some understanding of what is to take place and why [5–7]. Diagrams may help in explanations to older children. Preparatory videotapes are also useful for informing the patient and parent regarding what to expect. Units can benefit from devising a sample videotape specific to their own facility. A reduction in anticipatory anxiety may even reduce the amount of intravenous sedation required [8].

A child-friendly decorated endoscopy room with age-appropriate videotapes and familiar faces is important at this time of high stress. Parents may stay to watch the procedure in some units when intravenous sedation is provided. Most anesthesiologists would object to having parents present during administration of a general anesthetic, beyond the initial induction. Improved medical compliance and belief in the treatment are potential advantageous consequences of allowing parents to directly view the initial disease and its remission at follow-up ileocolonoscopy [9]. Young children often request photographs or a videotape of the ileocolonoscopy, and older adolescents may view the procedure themselves.

A full screening is important to identify potential sedation or anesthetic risks. Although there is little correlation of mildly deranged peripheral coagulation indices with hemorrhage after mucosal biopsies, more pronounced bleeding diatheses may require forethought and appropriate blood product backup [10]. Properly informed consent should be obtained with an information sheet detailing potential complications and their incidence, and a separate consent should be signed in the event of research biopsies being requested.

Antibiotic Prophylaxis

Guidelines concerning antibiotic prophylaxis in children with lesions susceptible to endocarditis or in the immunocompromised child are available in the historical literature [11] but are now superseded by the American Society for Gastrointestinal endoscopy (ASGE) guidelines for antibiotic prophylaxis for gastrointestinal endoscopic procedure [12]. American Heart Association has also published new recommendations of antibiotic prophylaxis for infective endocarditis (IE) and does not advise antibiotics for routine diagnostic or therapeutic gastrointestinal endoscopic procedure, solely for prevention of IE [13]. AHA recommends antibiotic prophylaxis for patients undergoing gastrointestinal procedure with established gastrointestinal infections where Enterococcus is the suspected causative organism and with the following cardiac condition: (1) a prosthetic cardiac valve, (2) previous IE, (3) cardiac transplant recipients with valvulopathy, (4) unrepaired cyanotic CHD (including palliative shunts and conduits), (5) repaired CHD having residual defects at the site or adjacent to the site of a prosthetic device, and (6) completely repaired CHD with prosthetic device placed within the last 6 months of the gastrointestinal procedure. The recommended antibiotic regimen in the above situations should include ampicillin (50 mg/kg every 4–6 h, maximum 2 g every 4 h) or amoxicillin (50 mg/kg every 4–6 h, maximum 2 g every 4 h) in combination with gentamicin. Vancomycin or teicoplanin can be used in patients who are allergic to ampicillin/amoxicillin. The British Society of Gastroenterology recommends the above antibiotic prophylaxis in combination with metronidazole for patients with severe neutropenia (<0.5 × 109/L) and/or who are profoundly immunocompromised (e.g., advanced hematological malignancy) and are undergoing procedures that are known to be associated with a high risk of bacteremia (Table 21.1) [14]. The preferred choice of antibiotics for biliary procedures is either ciprofloxacin or gentamicin or ceph-

Table 21.1 Infection risk associated with various gastrointestinal procedures

High risk of bacteremia	High risk of infection unrelated to bacteremia	Low risk of infection
Dilatation of esophageal stricture	Endoscopic ultrasound with fine-needle aspiration (EUS-FNA)	Routine EGD, IC, or sigmoidoscopy
Sclerotherapy of esophageal varices	Percutaneous endoscopic gastrostomy (PEG) or jejunostomy (PEJ)	Polypectomy
ERCP in patients with: (i) Biliary disorders, e.g., cholangitis, primary sclerosing cholangitis (ii) Conditions where complete biliary drainage is difficult to achieve, e.g., cholangiocarcinoma (iii) Liver transplantation (iv) Pancreatic pseudocyst		

ERCP Endoscopic retrograde cholangiopancreatography, *EGD* Esophagogastroduodenoscopy, *IC* Ileocolonoscopy

alosporins given intravenously just before the procedure. In our unit, prophylactic intravenous cefuroxime or co-amoxiclav is given for 24 h for percutaneous endoscopic gastrostomy (PEG) or jejunostomy (PEJ). The other condition where routine use of antibiotic prophylaxis is recommended is cirrhosis with acute GI bleed. The above recommendations are primarily based on evidence from adult studies but are also used for pediatric population.

Bowel Preparation

Poor bowel preparation is a major factor that may prevent or impede successful ileocolonoscopy. Although administration of regimens is not always easy, modern protocols can be remarkably effective in clearing the colon and ileum. Until 5 or 6 years ago, large volumes of oral electrolyte lavage solutions were used with variable success, coupled with the significant disadvantages of nasogastric administration and potential for fluid-electrolyte shifts in smaller children and infants. In one study, 40 mL/kg/hr. resulted in clear fecal effluent after a mean of 2.6 h [15]. Subsequently, more favorable results and compliance were reported with low-volume oral agents and enemas, along with decreased oral intake [16–19]. Use of sodium phosphate preparations was associated with a transient rise in mean serum sodium and phosphate but with no change in serum calcium [17, 18]. Refinements were made to these oral and enema regimens as newer preparations, which were more acceptable to children, became available; low-volume nonabsorbable polyethylene glycol preparations are becoming increasingly popular in pediatric units and are well tolerated, with no observable electrolytic disturbance [20, 21]. Table 21.2 outlines several low-volume regimens that have been used successfully in children. The regimen employed in our unit, shown in Table 21.3, combines the beneficial effects of oral low-volume administration of Senna and combination of sodium picosulfate with magnesium citrate, with the backup of an enema 1–2 h beforehand if no clear fecal effluent is observed [22]. No clinically significant fluid shifts or electrolyte imbalances have been observed in over 2000 colonoscopies over a 5-year period in our unit.

The above medications are repeated 10 h apart with a backup of enema 1 h before procedure (1/2 h for infants). One Picolax sachet contains sodium picosulfate 10 mg with magnesium citrate (K^+ 5 mmol, Mg^{2+} 87 mmol).

The benefit of an antispasmodic agent administered directly before the ileocolonoscopy has recently been demonstrated in an adult study where hyoscyamine 0.5 mg was given intravenously [23]. An effective alternative could be hyoscine butylbromide 20 mg administered intravenously during the procedure. The use of such an agent given just prior to IC is determined by personal preference. The antispasmodic agents are certainly of benefit in spastic colonic situations as their use may facilitate ease of luminal visualization. On the other hand, these can turn out to be counterproductive, as they may also increase the compliance of the colon, theoretically allowing a greater chance of loop formation.

However, it should be remembered that the antispasmodic agents work only for a short period of time, perhaps as short as 5 min, and these may be readministered in certain situations, e.g., when one needs to relax a haustral fold to visualize a polyp which is just beyond and obscured by it or occasionally when one needs to relax a spastic ileocecal valve. Glucagon at a dose of 0.5 mg intravenously is also used as an alternative to Buscopan, especially while performing DBE.

Table 21.2 Successful low-volume regimens for the preparation of the bowel for colonoscopy

Study	Regimen	Diet	Success rate
Gremse et al. (1996) [17]	Oral sodium phosphate (45 mL/1.7 m^2) 6 pm and 6 am for am procedure	Clear liquid 24 h	18/19
Da Silva et al. (1997) [18]	Oral sodium phosphate (22.5 mL if <30 kg, 45 mL if >30 kg) pm and 5 am for am procedure	Clear liquid after first dose	10/14
Pinfield et al. (1999) [20]	Sodium picosulfate with magnesium citrate (2.5 g <2 years., 5 g 2–5 years., 10 g >5 years per dose) 24 and 18 h pre procedure	Clear liquid for 24 h	32/32 (3 vomited)
Dahshan et al. 1999 [21]	Magnesium citrate and X-prep	Clear liquid for 48 h	

Table 21.3 Bowel preparation for children undergoing colonoscopy

Medicine	<1 years	1–4 years	>4 years
Sodium picosulfate + Magnesium citrate (Picolax)	¼ sachet	½ sachet	1 sachet
Senna	1–2 mg/kg (maximum 30 mg)		

*M*onitoring and *S*edation

"Sedation and analgesia" comprise a continuum of states ranging from minimal sedation (anxiolysis) through general anesthesia. Moderate sedation is a medically controlled state of depressed consciousness that allows protective reflexes to be maintained and retains the patient's ability to maintain the airway independently and continuously. Deep sedation is a medically controlled state of depressed consciousness or unconsciousness from which the patient is not easily aroused and accompanied by a partial or complete loss of protective reflexes with inability to maintain a patent airway. General anesthesia is a controlled state of unconsciousness accompanied by a loss of protective reflexes [24, 25].

The aims of adequate sedation include patient safety, anxiolysis, analgesia, amnesia, as well as adequate endoscopic examination, time, and cost efficiency [26]. Debate has surrounded the relative merits and safety of sedation and general anesthesia for esophagogastroduodenoscopy (EGD) and IC in children for several years [27–29].

The risks of general anesthesia include those associated with intubation and administration of an anesthetizing agent, which can be minimized by proper preparation and good intubation technique. However, the benefits include complete amnesia and total avoidance of pain to the patient as well as freeing the endoscopist from managing airway, monitoring vital signs, and recovering the patient [27].

Intravenous sedation (IV-S) usually consists of a narcotic (meperidine or fentanyl) and a benzodiazepine (diazepam or midazolam), the former for analgesia and the latter for anxiolysis and amnesia. Ketamine and midazolam have also been used with reportedly lesser side effects [30]. Propofol is now being used increasingly as the preferred choice for controlled sedation. Table 21.4 lists some of the commonly used sedation regimens with the reversal agents. IV-S has been argued to be safe, effective, and less costly in comparison to general anesthesia with successful sedation achieved in more than 95% of elective procedures [32, 33]. However, careful monitoring of IV-S throughout the procedure is important [33–35]. In spite of the advantages of IV-S, pediatric gastrointestinal endoscopy has moved toward general anesthesia since it is now acknowledged that, to get the requisite cooperation, and therefore, a properly conducted procedure with minimum distress to the child, deep sedation is usually necessary. It is further recognized that there are attendant safety issues of airway maintenance in this situation, and at the very least, a specific individual with appropriate advanced pediatric life support skills should be responsible for the child's cardiorespiratory welfare during such a procedure. The vast majority of pediatric gastrointestinal endoscopy in the United Kingdom, for instance, now occurs under general anesthesia.

When a child is sedated, resuscitation equipment should be easily accessible, and one or more people trained in pediatric advanced life support should be responsible for maintaining the airway and monitoring respiration, heart rate, blood pressure, and oxygen saturation [24, 36]. Sedation of younger children can be aided by environmental comforts such as a soothing voice or dimmed lights [37]. In all age groups, it is often necessary to use deep sedation because of the pain that can be associated with this procedure [38]. With deep sedation, it is clear that the risks are significant, including hypotension, respiratory compromise, and even respiratory arrest.

Recent studies examining the safety of general anesthesia for day-case IC in children refute the claims that there may be more risk of perforation because the operator cannot judge the degree of discomfort as a marker of impending traction injury [39, 40]. There is indeed a lack of evidence to support the contention that there is a higher complication rate with a general anesthetic than with sedation [41]. In fact, the airway is protected in a more effective and safer manner than with sedation, especially in upper endoscopy, with an improved operator satisfaction [42].

Pre-procedural medication with a benzodiazepine has been found to be useful in reducing patient anxiety and improves patient and parent acceptance of the procedure without any significant adverse effects [31].

Table 21.4 Sedation and reversal medications commonly employed in pediatric endoscopy

Ketamine: IV 1–2 mg/kg as a single dose [30]
Propofol: IV 1–2 mg/kg for induction and then 1.5–9 mg/kg/h using 1% injection for maintenance
Midazolam: IV initial dose 25–50 microgram/kg, if necessary titrate to maximum 6 mg (1 month to 6 years), 10 mg (6–12 years), or 7.5 mg (12–18 years) [30, 31]
Fentanyl: IV initial dose 0.5–1.0 μg/kg and then titrate to max 5 μg/kg
Meperidine/pethidine: IV initial dose 0.5 mg/kg and then titrate to max 2 mg/kg or 75 mg whichever lower
Flumazenil: IV 0.02 mg/kg (max 0.2 mg) and repeat every minute to max of 0.05 mg/kg or max 1 mg
Naloxone: IV 0.1 mg/kg (max 2 mg) and repeat every 2–3 min to max 10 mg

Endoscopic Techniques in Inflammatory Bowel Disease

Upper Gastrointestinal Endoscopy

While it is generally accepted that ileocolonoscopy(IC) and biopsy have a central role in the initial diagnosis and differentiation of pediatric inflammatory bowel disease (PIBD) [43], it is now recommended that in nonemergency situations, the diagnostic workup for pediatric patients should start with a combined EGD and ileocolonoscopy [43–46] except in situations such as acute severe colitis, where a lim-

ited sigmoidoscopy is preferred over complete IC as the latter may increase the risk of perforation. However, a follow-up IC should be performed after the resolution of the acute attack.

The presence of upper gastrointestinal symptoms has been commonly considered as an indication to perform EGD [47]. Typically described upper gastrointestinal symptoms include dysphagia, nausea and/or vomiting, and aphthous lesions of the mouth. Diagnosis was often based on radiological changes [48], and EGD was reserved for those patients who had upper GI symptoms and/or uncertain diagnosis. However, several studies have shown a higher incidence of microscopic mucosal disease in the upper GI tract [47, 49–53] than previously thought even in the absence of any upper GI symptoms [44, 54]. Cameron et al. [49] in a prospective study described histological abnormalities on gastroduodenal biopsies in 71% of patients with CD. Histological abnormalities including granulomas are seen even when the gross appearance of the tissue is normal [43, 47, 53–55]. Therefore, it is important to take multiple biopsies (2 or more per section) from all sections of the visualized gastrointestinal tract, even in the absence of macroscopic lesions.

In a prospective 3-year study involving 420 patients with IBD from 27 centers, EGD was performed in 237 patients. Eighty percent of patients with CD had macroscopic and/or histologic changes in the upper GI tract, while in 9% of the patients, EGD was helpful in making a definitive diagnosis [56]. In another prospective single-center study, 24/45 patients with CD had an upper GI involvement and presented at an younger age, had more severe disease, and were more likely to have extraintestinal manifestations [57].

Esophageal disease in CD (Fig. 21.1) can vary from small erosions to transmural involvement resulting in perforation and fistulization into adjacent organs [58]. Granulomas are reported in 20–39% of esophageal biopsies in patients with CD [59, 60]. Other findings include erythema, ulceration, polypoid lesions, pseudomembranous formations, strictures, and mucosal bridges [59, 61–64]. Endoscopic findings in the stomach and duodenum include linear and serpiginous ulcers, diffuse superficial ulcers, aphthous lesions, nodularity, cobblestone appearance, rigidity of the GI wall, and narrowing of the lumen [65].

Focal-enhanced gastritis as an important feature of CD was first described by Schmitz-Moorman et al. [66] (Fig. 21.2). Further, several studies confirmed this finding with a positive predictive value of 71–94% [50, 52, 67, 68]. Parente et al. [68] found focal antral gastritis more frequently in *Helicobacter pylori*-negative adults with CD and then in those with UC or noninflammatory bowel conditions. Also, they reported focal antral gastritis to be specific in 84% of patients with CD. While the presence of focal antral gastritis is suggestive of Crohn disease, it is not pathognomonic of the condition.

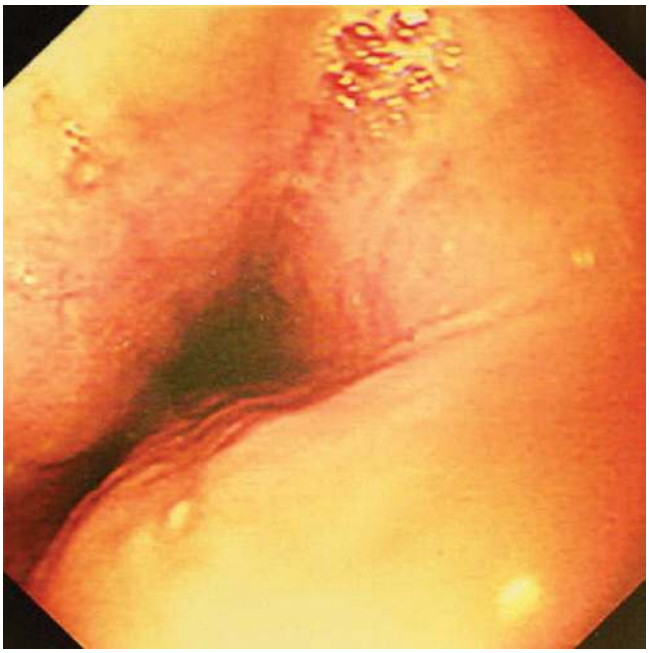

Fig. 21.1 Crohn disease of the esophagus showing discrete ulcers

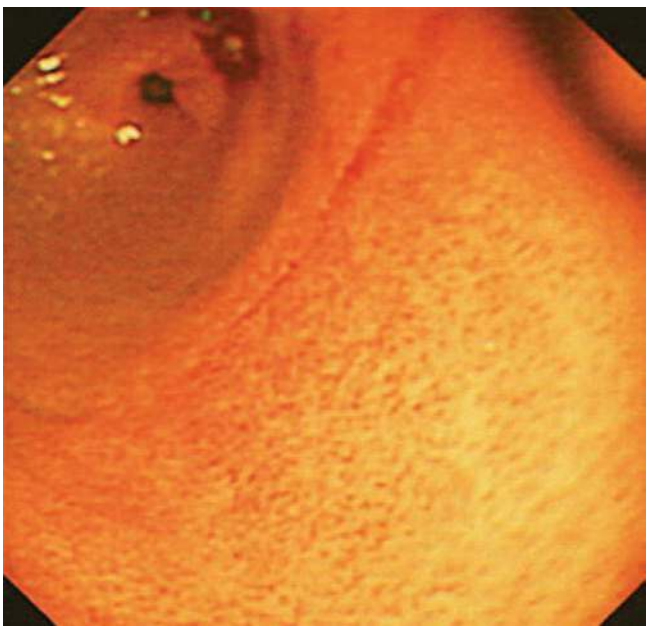

Fig. 21.2 Focal enhanced gastritis in Crohn disease

The presence of noncaseating granuloma is characteristic of CD. Granulomas are found in 7–68% of patients with CD in the upper GI tract [43, 47, 59, 65, 66] and often help in making a definitive diagnosis when none are found at other sites. Noncaseating granuloma in the upper gastrointestinal tract in the CD tends to occur in the superficial mucosa as

compared to ileal CD where the muscularis or the serosal layers are primarily involved.

Ulcerative colitis conventionally was thought to involve only the colon and possibly ileum (backwash ileitis). However, it is increasingly recognized that features of inflammation in the upper GI tract [44, 52, 53, 69, 70] are seen in UC. Ruuska et al. [53] in a prospective study reported either macroscopic or histological upper gastrointestinal lesions in 75% of patients with UC. Abdullah et al. [43] also reported an incidence of 70% of histological abnormalities in the upper GI tract in patients with UC. Tobin et al. [52] in a controlled blinded study described esophagitis in 72% and 50% of patients with CD and UC, respectively. Gastritis was, however, more common and seen in 92% of CD and 69% of UC.

Ileocolonoscopy

Equipment

Most modern units employ adult and pediatric videocolonoscopes, and the general technical specifications for the pediatric instruments differ little between manufacturers (Table 21.5). When and in whom to use a pediatric colonoscope is mainly a matter of personal preference. We use personal judgment based on age and/or body weight. In general terms, the lower limit for the adult colonoscope is 3–4 years of age and/or 12–15 kg. The extra stiffness of the adult versions diminishes the likelihood of forming sigmoid loops, but extra care must then be taken, especially in younger children and with general anesthesia, not to advance against undue resistance, to avoid the unlikely complication of colonic perforation. The larger diameter of the adult colonoscopes can also lead to problems of maneuverability within the smaller colonic lumen of a young child. The variable-stiffness colonoscope (Table 21.5) may negotiate some of these problems. A control dial on the upper shaft of this small-diameter colonoscope (Olympus XCF-240AL/I, Olympus Inc., Tokyo, Japan) allows an increase in the stiffness of the insertion tube when passing through the sigmoid and transverse colon to avoid looping [71].

Table 21.5 Technical specifications of various pediatric colonoscopes

Parameter	Fujinon (EC-410 MP15)	Olympus (PCF 240 L/I)	Olympus variable stiffness (CF 240AL/I)	Pentax (EC-3440PK)
Angle of vision	140°	140°	140°	140°
Depth of field	6–100 mm	4–100 mm	3–100 mm	6–100 mm
Distal end	11 mm	11.3 mm	12.2 mm	11.5 mm
Insertion tube	11.1 mm	11.3 mm	12.0 mm	11.4 mm
Channel	2.8 mm	3.2 mm	3.2 mm	3.8 mm
Angle up/down	180°/180°	180°/180°	180°/180°	180°/180°
Angle right/left	160°/160°	160°/160°	160°/160°	160°/160°
Working length	1520 mm	1330 mm (I) 1680 mm (L)	1330 mm (I) 1680 mm (L)	1500 mm

More recently, magnifying colonoscopes have been developed, and their value in combination with dye spray or chromoscopy in various gastrointestinal diseases has been described [72]. For instance, the decrease in the number of cryptal openings in ulcerative colitis can be observed and correlated to disease activity [73], but this does not substitute for histologic assessment.

For insufflation, there may be some advantage awarded by the use of carbon dioxide in place of air because it is more rapidly absorbed, leading to less patient discomfort and, theoretically, less risk of perforation [74, 75].

Ileocolonoscopy Basic Technique

Getting Started and Patient Positioning

The patient is usually positioned in the left lateral knee to chest position, although some operators prefer the right lateral position, citing easier sigmoid negotiation. Certainly, if the procedure is not subsequently allowing easy access to the splenic flexure, then patient repositioning from one side to the supine and then to the other side may be advantageous. In general, frequent turning of the patient is conducive to easier ileocolonoscopy as a whole and is to be advocated. An assistant stands on the operator's left to administer any abdominal pressure that may subsequently be deemed necessary to control, or try to prevent, loop formation in the sigmoid or transverse colon.

Practical Tips in Ileocolonoscopy

One important "trick" in learning ileocolonoscopy is to grasp the concept of the lumen and the positions of a clock face. For instance, if the lumen is at 9 o'clock, then to enter this requires anticlockwise rotation combined with upward deflection of the scope tip from the "neutral" position of 12 o'clock. Similarly, a combination of upward deflection of the tip with clockwise rotation of the colonoscope will allow

entry of the lumen, suggested by a dark crescent, if seen at anywhere clockwise from 12 o'clock to 6 o'clock. Obviously, one may equally use downward tip deflection combined with the opposite rotatory control to that with upward tip deflection, and the execution and teaching of this concept are at personal discretion. With either approach, this is the most important maneuver that can be learned to assist in three-dimensional spatial orientation in the colon.

Prolonged "side viewing" of the bowel wall as it slides by should be avoided. Generally, the only place where, very temporarily, the lumen should be out of view is the occasional difficult negotiation of the splenic flexure. The patient's position may be changed throughout the procedure to facilitate removal of loops and to allow a better view of the lumen because the gravity-dependent material in the colonic lumen changes position. Relatively minimal insufflation of air is desirable in the sigmoid colon because excess air may increase the chance of sigmoid loop formation (carbon dioxide, provided by a specific commercially available delivery system attached to the colonoscope, as the insufflating gas of choice may be preferable because it is absorbed much more quickly, decreasing the pain sensation and the very unlikely chance of perforation; see "Complications."

In handling the colonoscope, it is good practice to have a flat unimpeded surface on which to place the remainder of the colonoscope that is not yet inserted; this is particularly important since any resistance encountered by the operator to forward advancement of the colonoscope can be attributed to colonic obstruction or loop formation within the child's colon. Hence, relatively quickly, the trainee can acquire a realization of the normal expected resistance to scope advancement. This, in turn, allows understanding of the likelihood of loop formation, without any external resistance to scope advancement, causing confusion with regard to the behavior of the colonoscope within the patient.

Generally, in ileocolonoscopy, gentle scope advancement with clear lumen visualization is desirable, and, usually, only the forefinger and thumb will be required to advance the colonoscope. If greater pressure is required, then the operator is not performing an optimum procedure, and loop formation is likely to have occurred.

Rectal Intubation

Prior to any colonoscopy, it is considered good practice to perform an anal and then a rectal digital examination, the latter to avoid missing, by colonoscopy, very low-lying rectal polyps (although, where possible, retroflexion of the colonoscope in the rectum should occur prior to removal of the instrument to avoid missing lesions close to the anal margin). Adequate water-soluble lubrication, avoiding the tip of the instrument, allows easy passage into the rectum, which can occur with or without digital guidance from the operator's index finger. The tip of the scope aimed posteriorly toward the spine combined with air insufflation allows visualization of the rectal mucosa and the three semilunar folds, or valves of Houston, occurring on alternating sides of the lumen. Subsequently, direct visualization of the bowel lumen is mandatory, except in some circumstances at the splenic flexure. If, at any point, a maneuver results in loss of visualization of the lumen, then reversal of what the operator has just done will often return the lumen to view; if not, the gentle scope retraction combined with minor tip deflections using the wheels and minor rotation of the scope in both directions will usually result in reorientation in the lumen. Obviously, if luminal contents are blocking the view, then lens cleaning will help.

Sigmoid and Descending Colon

Gentle torquing of the shaft clockwise and anticlockwise combined with upward or downward tip deflection and scope advancement is ideal for negotiating the sigmoid colon, the so-called "torque-steering" technique. The initial sigmoid fold or valve can usually be passed by 90–120 of anticlockwise torsion. The different loops encountered in the sigmoid are demonstrated in Fig. 21.3. A so-called N loop may be overcome by transabdominal pressure by an assistant on the apex of the loop pushing toward the feet (see Fig. 21.3a). This often allows a so-called α loop to form, which can usually be tolerated as the instrument advances toward the splenic flexure (see Fig. 21.3b). Reducing an α loop is accomplished by initial clockwise rotation and then slow removal of the colonoscope, keeping the lumen in the center of the field of vision. This may not be possible until the transverse (or even ascending) colon has been entered, in which case, hooking the tip of the scope over the splenic flexure may assist it. Paradoxical movement of the tip forward may be observed as the instrument is withdrawn and the bowel "concertinas" over the colonoscope. Abdominal pressure in the left iliac fossa may be helpful. The sigmoid and descending colons are relatively featureless, with less haustral folds than more proximally in the colon.

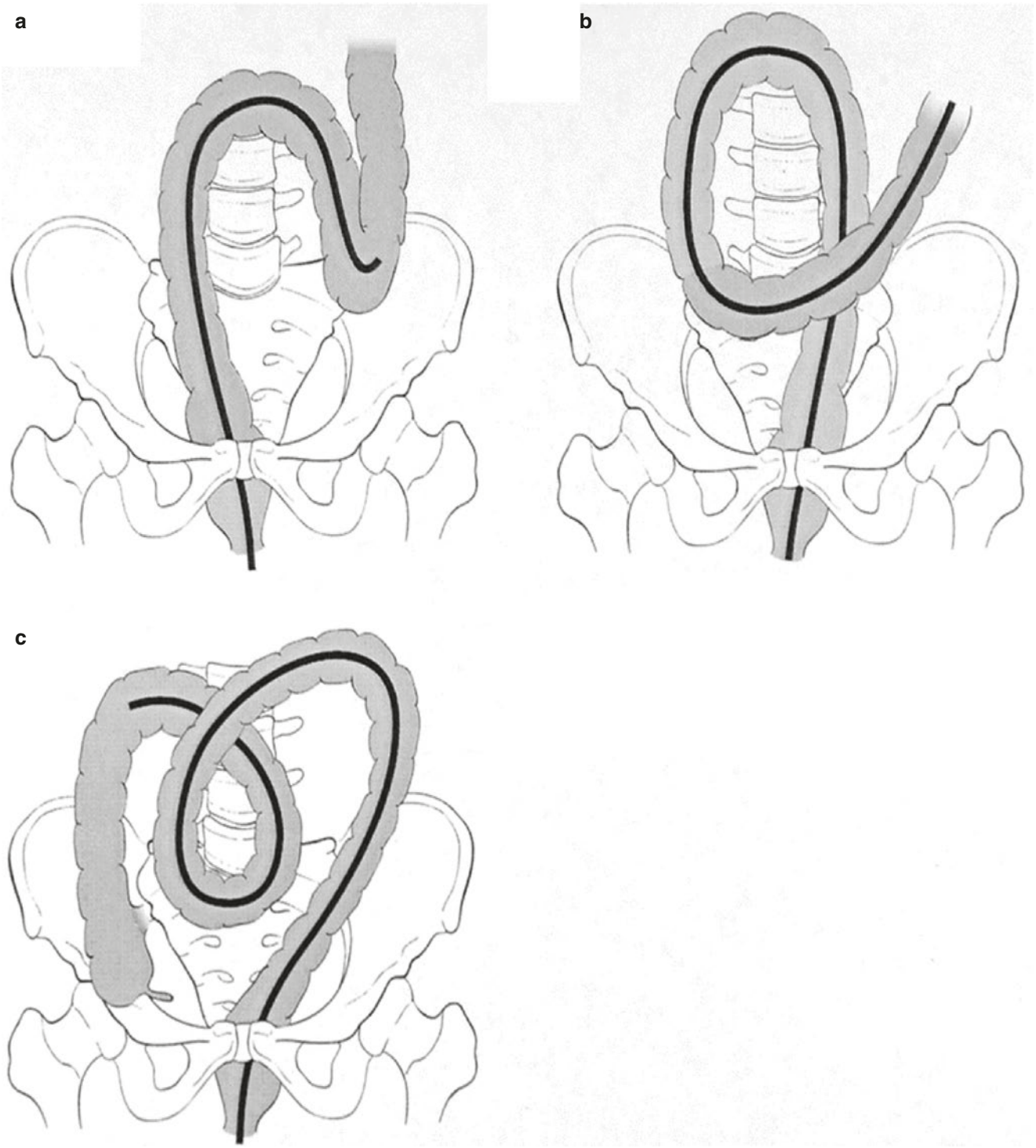

Fig. 21.3 Diagram of colonoscope sigmoid loops that may form (**a**) an N loop in the sigmoid colon, (**b**) an α loop in the sigmoid colon, and (**c**) a γ loop in a redundant transverse colon

Splenic Flexure and Transverse Colon

Non-looped colonoscope length used at this point might be 40 cm in older children and even 20–25 cm in those under the age of 3–4 years. This is valuable in determining whether a loop is present. At the splenic flexure, the spleen may then be seen as a dark blue transmural discoloration. When negotiating the splenic flexure, the most successful combination of tip maneuvers is that of clockwise, right, and up followed by anticlockwise after passing the flexure. Occasionally,

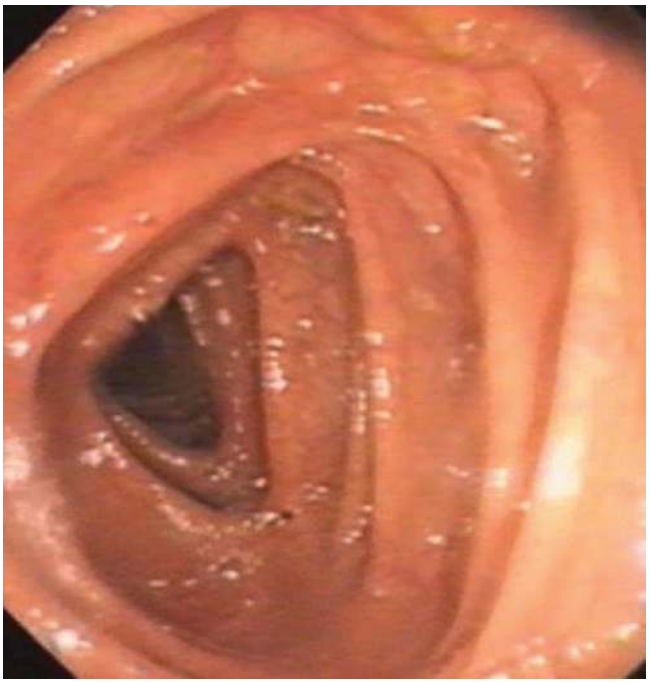

Fig. 21.4 Normal triangular appearance of transverse colon

placing the patient in the right decubitus position may assist. The transverse colon is recognized by the triangular haustral folds and is usually easily passed (Fig. 21.4). Supine or right decubitus positioning may ease this. A loop in the shape of a "U" may occur in a dependent transverse colon, which is supported by abdominal pressure. The more difficult γ loop may occur in a redundant transverse colon (Fig. 21.3c). In addition, a good bit of advice is to apply gentle suction as the tip is advanced in an attempt to concertina a potentially long-dependent transverse colon over the colonoscope, thus, maintaining a relatively short colonoscope and, hence, good control and maneuverability.

Hepatic Flexure and Ascending Colon

Non-looped colonoscope length used at this point might be 60 cm in older children and even 40 cm in those under the age of 3–4 years. This is valuable in determining whether a loop is present. The hepatic flexure is also recognized by the dark, usually blue, discoloration seen through the bowel wall, and positional change to the supine or right decubitus may again facilitate identification of the lumen. The combination of right, up, and clockwise followed by anticlockwise rotation and suction down into the ascending colon once around the sharply angled hepatic flexure is usually the most effective maneuver, but various combinations, including position change and scope withdrawal, may be required. Another tip is to remember that it is easy to be too far advanced into the vault of the hepatic flexure, leading to advance into a blind end, and often slight withdrawal of the instrument may reveal the fact that one is trying to negotiate this blind-ended area. The two or three sharp folds then observed may then be most successfully negotiated by tip deflection using both up/down and left/right wheels with minimal advancement of the scope. This is most easily performed in the supine patient position, however.

Once the hepatic flexure is negotiated, the transverse colonic γ loop may be reduced with anticlockwise or clockwise rotation followed by withdrawal of the colonoscope and suction. Loop withdrawal is essentially informed guesswork initially. Studies with the colon map guider (ScopeGuide®, Olympus, Inc. Tokyo, Japan), based on using a colonoscope with an inbuilt electromagnetic loop that allows accurate real-time colonoscope three-dimensional positioning by detection using an external positioning device and displayed on a screen next to the patient, have shown that even expert colonoscopists get the type of loop present wrong in half of the cases [76–78]. Once one starts to remove the loop, using rotation only initially, a tip is to gently start to remove the colonoscope and try to determine whether within-patient resistance is increasing or whether the colonoscope is trying to push your hand away from the patient as the loop unfolds. Usually, trying clockwise or anticlockwise combined with instrument withdrawal will, with experience, allow early determination of which rotation direction is likely to be successful in "de-looping" the colonoscope. It is best to try for maintaining good luminal vision during this procedure, but, not infrequently, the lumen is lost; however, if this loop removal technique is effective, it is then not unusual to find oneself then looking at the appendiceal orifice, and hence, the cecum because the scope will have naturally traveled down the ascending colon. It is important to remember that the ascending colon, which in children is of variable length, may be as short as 5 cm in some younger patients.

Cecum

Three useful ways to ensure that one has reached the cecum are as follows:

1. Observing the colonoscopic illumination in the right iliac fossa (using the specific high-intensity light transillumination application available with some colonoscopes is not usually necessary in children, except with some obese adolescents, for whom it can be helpful when applied in a dark environment).
2. Digitally indenting the abdominal wall over the right iliac fossa and observing the corresponding effect on the colonic wall with the colonoscope.

3. Identifying the triradiate fold, appendiceal orifice, and (especially if gas bubbles and ileal effluent are being excreted from it) the typical two lips-like appearance of the ileocecal valve or Bauhin's valve.

A good maxim is that if there is any doubt in the operator's mind about having reached the cecum, then one is usually at the hepatic or even splenic flexure. Only about 80 cm of scope from the anus is needed when all loops are removed in an adult, and in smaller children, only 40–60 cm may be needed. This assumes normal anatomy of the ascending colon and cecum. Obviously, cecal strictures can confuse the picture.

Ileal Intubation and Its Importance

The Bauhin's valve is present approximately 1–4 cm distal to the appendiceal orifice opening into a smooth asymmetric fold and opens perpendicular to the axis of the colon. Figure 21.5 shows the steps of the easiest technique for ileal intubation. Removal of any colonic loops is important to allow for a responsive scope with no paradoxical movement. Figures 21.5b and 21.6 show the valve maneuvered to the 6 o'clock position, usually after clockwise rotation of the scope and wheel–tip deflection to maintain a centered cecal view. Anticlockwise rotation can also be used but is less efficient. If too much gas is present, then the cecum may be

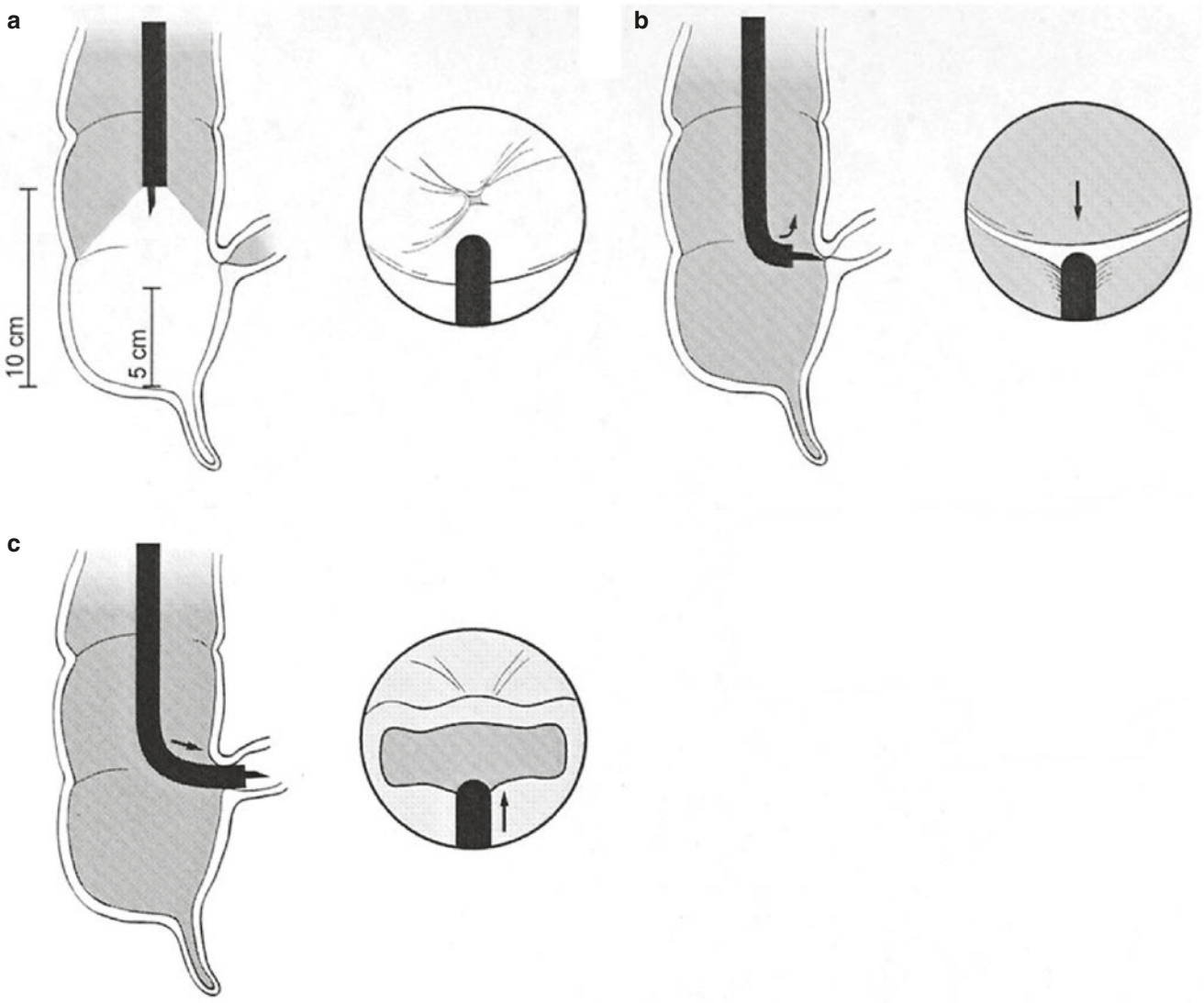

Fig. 21.5 (**a**) Identification of cecum with triradiate fold, appendiceal orifice, and ileocecal valve; (**b**) ileocecal valve at 6 o'clock position; (**c**) forceps opening up ileocecal valve with downward defection of colonoscope tip

"tented," and this should be suctioned prior to an ileal intubation attempt. Figures 21.5c and 21.7 show the insertion of the biopsy forceps such that just the tip or the first few millimeters are visibly exposed beyond the end of the scope. The scope is then inserted just beyond the fold (using the downward deflecting wheel with the scope as above already in the 6 o'clock position), and the tip is inclined downward so that the forceps gently press into the wall. Slight left inclination may be required at this point to open the valve like a pair of lips on slight withdrawal of the scope (Fig. 21.5c). Once the valve is opened, the scope may be passed into the ileum with further downward deflection. Often this is facilitated by small right and left deflections with an assistant pressing on the abdomen over the transverse colon to support a dependent transverse and also prevent loop formation. In the absence of ileocecal valve strictures, and with practice, this technique will allow an ileal intubation rate of up to 100%. Perforation of the cecum or ileum with this technique is a theoretical concern raised by some observers unfamiliar with this technique, but this has not occurred in our experience of over 5000 ileocolonoscopies and is extremely unlikely.

An alternative technique is "blind" intubation of the ileocecal valve. This involves the same positioning of the valve at 6 or 9 o'clock and then slowly withdrawing the scope back from just beyond the valve's fold while insufflating with air and deflecting the scope tip downward. The disadvantage of this technique is that it is not under direct vision.

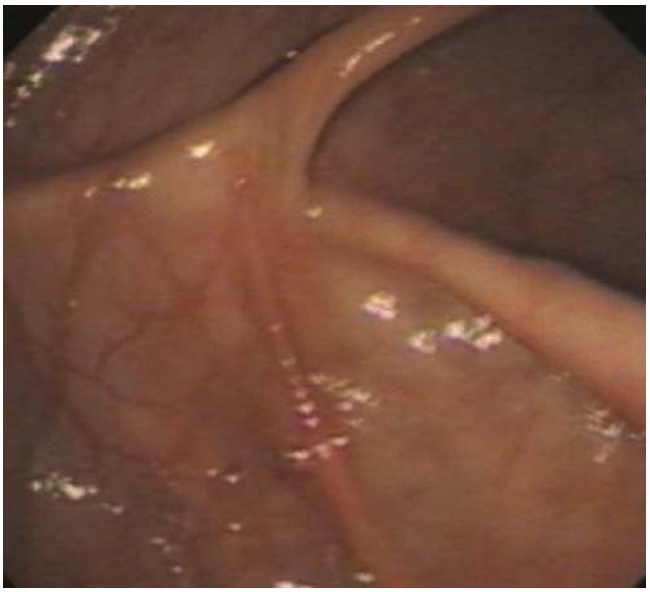

Fig. 21.6 Ileocecal valve at 6 o'clock

Ileum

The ileal mucosa will have the typical velvetlike appearance of small bowel (Fig. 21.8), with the presence of smoother raised areas, which are Peyer patches, and, occasionally, lymphonodular hyperplasia of varying degrees (Fig. 21.9). Villi are more easily seen if the lumen is flooded with water. The ileal surface is shown in greater relief with a spray of standard blue or black ink (methylene blue in a 1:20 dilution may also be used); this is also useful in showing the detail of

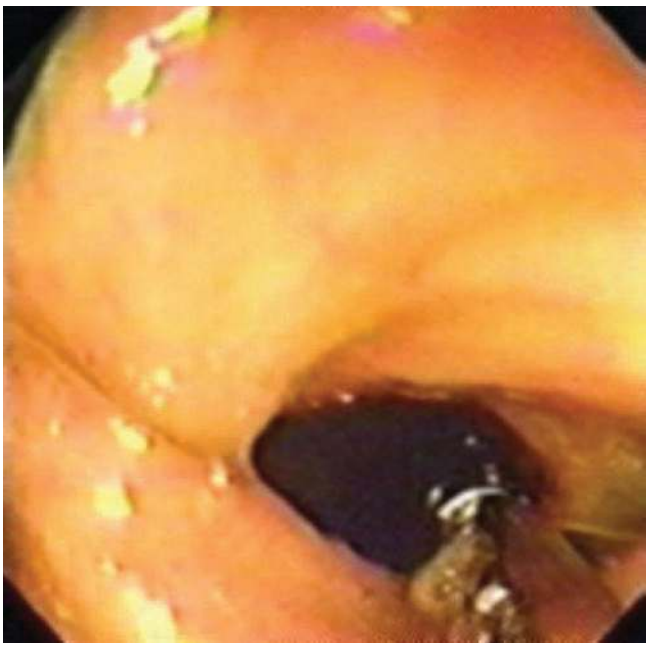

Fig. 21.7 Ileocecal entry using forceps

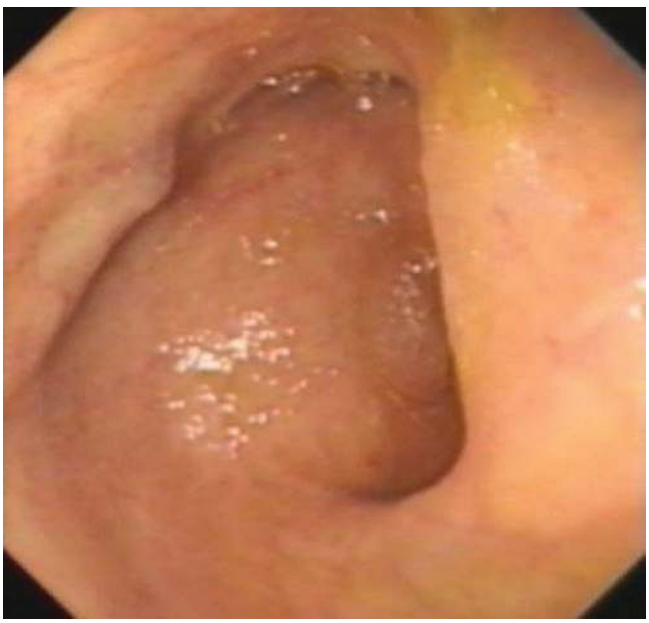

Fig. 21.8 Normal appearance of terminal ileum

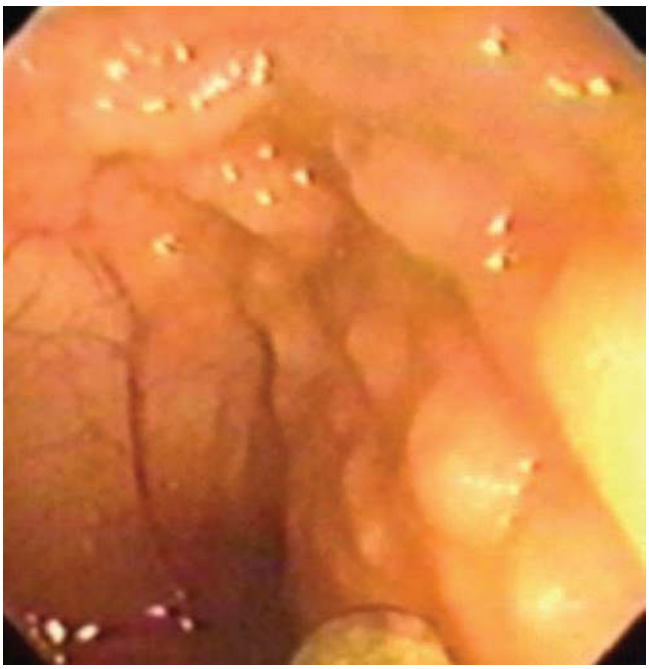

Fig. 21.9 Lymphonodular hyperplasia of the terminal ileum

sessile polyps in the colon. Deeper intubation of the ileum by either technique is similar to duodenal negotiation during upper gastrointestinal endoscopy, and up to 40 cm of ileum can be observed.

It is pertinent here to discuss the diagnostic need for entering the ileum in children suspected of inflammatory bowel disease. Williams and colleagues, in 1982 [77], reported their experience of total ileocolonoscopy in children in which the terminal ileum was examined in 63 patients. In six children, ileitis detected by ileocolonoscopy was the sole finding of Crohn disease, which was previously unrecognized by radiologic contrast studies. Lipson and colleagues compared ileoscopy and barium studies, with an endoscopy specificity of 0.96 for diagnosis of Crohn disease in the terminal ileum [78]. In 14 of 46 children, ileoscopy revealed diagnosis, which would otherwise have been missed. This study also made clear that the endoscopic appearances could be completely normal, yet the diagnosis of Crohn disease could be made histologically by the presence of granulomata. Also, a pronounced lymphoid hyperplasia pattern was present radiologically in 24% of children and would have been a source of error in two cases that had contrast radiographs been relied on to make the diagnosis without ileoscopy. More recently, Deere and colleagues showed that sigmoid, colonic, and rectal biopsies confirm the diagnosis of inflammatory bowel disease in only 60% of cases, and diagnosis based on morphologic criteria was possible in only 85% of cases when the cecum was reached without ileal intubation [79]. Geboes and colleagues assessed 300 patients, including adolescents and children, and found endoscopic and histologic ileal lesions in 123 and 125, respectively, of whom no colonic disease was present in 44 [80]. Ileal biopsies were essential for the diagnosis in 15 patients and contributory in 53. The Porto criteria now mandate terminal ileal intubation for diagnosis of IBD [1].

The Eurokids registry reports terminal ileal intubation (TII) rate of up to 79%. In individual center studies, TII rate has been reported up to 89%. In our center, the TII rate is 98%, which is probably because of an active training environment and the use of ScopeGuide®.

There are, of course, other indications apart from the principal one, that is, diagnosis of chronic inflammatory bowel disease, for entering the ileum in children. For instance, ileoscopy will facilitate diagnoses of other causes of ileitis such as infection with tuberculosis or Yersinia [81–83]. In addition, therapeutic dilatation of short terminal ileal strictures by per endoscopic balloon catheter may be attempted.

Endoscope Withdrawal

A more careful inspection of the colon is necessary on withdrawal of the scope, especially for the presence of polyps, which may have remained hidden behind a haustral fold during the initial insertion of the scope. Biopsies should be taken from all areas, including normal-looking mucosa to allow for accurate histological diagnosis. Biopsy technique is similar to EGD, with the exception that many colonoscopic biopsy forceps have a central barb, allowing more than one biopsy to be taken each time the biopsy forceps are passed.

Lastly, before removing the scope from the anus, a retroflexion maneuver obtained by maximum upward and right- or left-tip deflection and slight advancement of the scope into the rectal vault, followed by rotation clockwise and anticlockwise through 180°, completes the examination. This is necessary to observe the anorectal junction and distal rectum. Distal ulcers, inflammation, or even polyps can be missed if this is not done.

Dilatation of Strictures

Trans-endoscopic balloon dilators are appropriate for ileocolonic dilatation, employing the same concept and method as for upper gastrointestinal strictures, employing radiologic screening control. Long-term symptomatic relief can be afforded in some carefully selected patients, including adolescents in reported studies [84, 85]. Pressures of 35–50 psi in balloons of 12–18 mm are available. Theoretically, as for neoplastic or diverticulitis-associated strictures in adults, stent placement could be used as a last resort in inflammatory bowel disease-type strictures, but there are no reported cases of this occurring in childhood as yet.

Complications of Ileocolonoscopy

Complications, excluding those due to sedation, are summarized in Table 21.6. Complications are more common following therapeutic procedures. The literature to date reveals over 3000 colonoscopies under 20 years of age reported, with five perforations—four post-polypectomy and one in a patient with severe ulcerative colitis. Ten procedure-related minor complications are noted, including four small post-polypectomy hemorrhages, three cases of post-procedure abdominal pain with spontaneous resolution, one common peroneal nerve palsy secondary to peri-procedure positioning, and two with a post-procedure fever for more than 24 h [39, 40, 86–91]. This equates to a complication rate owing to the procedure itself of approximately 0.3% and, without polypectomy, of about 0.05%. This is in keeping with the British definition of "minimal" risk and the American definition of "minor risk over minimal" [92].

A single case of a child with serosal surface tears owing to a rigid colonoscope and a large sigmoid loop was reported in 1974 [93]. Flexible pediatric colonoscopes or the new variable-stiffness colonoscopes may prevent this nowadays. The merits of conservative therapy for selected cases of colonic perforation have been discussed [94], and it would seem reasonable to adopt conservative management, for instance, in the case of silent asymptomatic perforations and those with localized peritonitis without signs of sepsis who continue to improve clinically without intervention [95]. In one study in adults, only 3 of 21 patients were managed non-surgically, and there was no difference in the morbidity or mortality between primary repair and resection and anastomosis [96]. In another, conservative management was successful in 13 of 48 patients, and 12 of the 13 were post-polypectomy perforations [97].

In contradistinction to adults, bacteremia is not often detected in children, and only a low rate of bacteremia owing to bacterial translocation across the bowel wall has been demonstrated following pediatric ileocolonoscopy [98]. In addition, modern cleaning machines seem to largely prevent the glutaraldehyde-associated colitis reported in the past [99].

Splenic rupture is rarely seen and will present with hypovolemia and shoulder tip or abdominal pain within 24 h of the ileocolonoscopy [100]. Similarly, direct trauma to the tail of the pancreas is the proposed mechanism of injury in the rare case of pancreatitis reported [101].

Because of the rarity of complications in pediatrics, most pediatric endoscopists, when presented with such a clinical situation, will be unfamiliar with the etiology of the symptoms, and colleagues' opinions should often be sought [102].

Table 21.6 Procedure-related and post-procedure complications in pediatric colonoscopy

Diagnostic procedure related
Vasovagal reactions
Hemorrhage
Perforation—traction serosal; direct transmural
Pancreatitis
Splenic trauma
Therapeutic procedure related
Perforation
Hemorrhage
Thermal injury—transmural
Post-procedure
Distension and discomfort (less if CO_2 insufflation used)
Delayed evidence of perforation or hemorrhage

Small Bowel Assessment

Wireless Capsule Endoscopy

The revised Porto criteria recommend small bowel imaging for completion of PIBD assessment and are essential in cases of CD, atypical UC, and IBD-U. Magnetic resonance enterography/enteroclysis (MRE) is a good tool to assess intestinal inflammation and damage, but there is no validated scoring tool for its use in PIBD [103]. Here, we would like to discuss the role of wireless capsule endoscopy (WCE) as an effective and feasible tool for small bowel assessment.

In patients where endoscopy and MRE have failed to reach a conclusive diagnosis, WCE has been proven to be beneficial in reaching or refuting a diagnosis and describing disease distribution. WCE findings have been shown to be contributory toward change in the management of IBD, especially CD in about 75–92% of the cases [104, 105].

WCE is approved for use in children above 2 years of age, though there are case reports of this to be used in children as young as 8 months. It is usually delivered in the duodenum with the help of an age-appropriate upper GI endoscope. However, in children aged 6 years or more, this can be easily swallowed under direct supervision. Some centers use the same bowel preparation as for ileocolonoscopy. Simethicone (20 mL) before capsule deployment has been shown to improve luminal visualization [106].

We do not routinely use patency capsule before deploying the WCE. The patency capsule has dissolvable open ends and is easily expelled, if its passage through the bowel is delayed.

In our center, the child is allowed only clear fluids for at least 2 h post-deployment of the capsule.

The capsule is usually expelled within next 24–48 h but can stay inside the bowel for up to 2 weeks. Capsule retention has been reported in the pediatric population but is more common in children with known small bowel pathology, malnutrition, or PIBD. In such situations, high-dose laxatives can be tried as a first resort to remove the capsule, and

in PIBD, steroids and other anti-inflammatory agents are often successful as they reduce the inflammatory component of the stricture—double-balloon enteroscopy (DBE) can be used to retrieve a capsule, but if no symptoms are occurring, the capsule is usually left in situ—surgery is rarely if ever required and only with stricture symptoms when it would be required in any case.

Enteroscopy

Enteroscopy (ES) is now a standard and recently reviewed [107] endoscopic procedure in adult medicine. Although ES plays a role in examination of the small bowel and it has a place in PIBD that defies diagnosis by standard endoscopy and WCE, it is not routinely used. Indeed, ES may be preferable to WCE if there is a clinical suspicion of obstruction, need for biopsy, or for a therapeutic procedure. It becomes a necessity when small bowel biopsy is required for differential diagnostic purpose or when both MRE and WCE fail to prove a strongly suspected small bowel pathology.

Push Enteroscopy

Sonde-type, intraoperative-assisted push enteroscopy [108–110] and more recently nonsurgical push enteroscopy [111] have been described in children. Sonde enteroscopy has largely been abandoned in favor of push enteroscopy [112, 113] given the desire for therapeutic capability. Push ES (PES) is endoluminal examination of the proximal jejunum using a long, flexible endoscope with or without an overtube.

The techniques of per oral push enteroscopy and laparoscopy-assisted enteroscopy continue to evolve and have been superseded by device-assisted enteroscopy (DAE).

Device-assisted ES (DAE) is either balloon assisted or spiral. Single-balloon-assisted ES (SBE) uses an overtube equipped with balloon, and double-balloon-assisted ES (DBE) allows examination of the whole small bowel (via oral or anal route) due to assistance of balloons at the distal end of both endoscope and overtube. DBE usually requires two individuals (operator and assistant). Spiral ES uses assistance of single-use overtube, which has helical spirals at its distal end and rotates independently from the enteroscope.

The term intraoperative ES (IOE) is used when ES is performed during abdominal surgery (orally or via enterostomy). In such case, progression of the endoscope (gastroscope, colonoscope, pediatric colonoscope, or enteroscope) is manually assisted by the surgeon.

Instruments and Technique

Although a pediatric colonoscope can be used for enteroscopy, specifically designed enteroscopes up to 230 cm in length are now available. The Olympus SIF Q140 (Olympus, Center Valley, Pennsylvania, USA) has a diameter of 10.5 mm and is 250 cm long. A push enteroscope, like a colonoscope, allows four-way tip deflection to 160°–180°. An overtube, typically 60–100 cm in length with a soft Gore-Tex tapered tip, stiffens the enteroscope within the stomach and upper duodenum limiting looping, thereby allowing deeper advancement into the small bowel [112]. A push enteroscope can be introduced 120–180 cm beyond the ligament of Treitz, and with laparoscopic assistance, even the terminal ileum can be reached, allowing lesions such as a Meckel's diverticulum to be found [110].

Preparation for enteroscopy is the same as for EGD, although the procedure may be substantially longer and more uncomfortable. Therefore, it is the practice at our unit to use general anesthesia even in adolescents. Patients are positioned left lateral or semi-prone. After normal examination of the esophagus and stomach, air is removed, and minimal insufflation of the stomach allows deeper penetration into the small bowel when not using an overtube. At 60–80 cm in older children and adolescents, the ligament of Treitz is found, and extreme tip deflection is needed to find the lumen. The first jejunal loop is more readily identified because it is straighter and travels down to the pelvis. If using an overtube, which has been threaded over the enteroscope prior to oral insertion, this is deployed down the esophagus and into the second part of the duodenum; prepyloric deployment will not aid in deeper small bowel penetration. Some exponents use fluoroscopy to aid in overtube tip positioning [107]. When advancing the overtube, the enteroscope needs to be pulled back with clockwise rotation to straighten it, similar to the maneuver used to achieve the shortened scope position during endoscopic retrograde cholangiopancreatography.

A number of reports demonstrate the utility of push enteroscopy in adults. One of few studies in children, using push enteroscopy, investigated the possibility of Crohn disease in children with growth retardation [114].

Double-Balloon Enteroscopy

Double-balloon enteroscopy (DBE) enables high-resolution endoscopic imaging of the entire small bowel. While push enteroscopy can aid in visualization of the proximal jejunum, DBE goes a step further making it possible to examine, take biopsies, and perform therapeutic procedures such as hemostasis and balloon dilatation throughout the

entire small bowel. The potential for mucosal biopsies and interventional endo-therapy provides significant advantage over WCE [115–117].

Instruments and Technique

The DBE system (Fujinon; Fujinon Inc., Japan) consists of a high-resolution video enteroscope (EN-450P5/20) with a flexible overtube. The video enteroscope has a working length of 200 cm and an outer diameter of 8.5 mm, while the flexible overtube has a length of 140 cm and outer diameter of 12 mm. The enteroscope has a 2.2 mm forceps channel that enables routine biopsy as well as other common therapeutic interventions. The enteroscope as well as the overtube is fitted with a balloon each at the tip. The overtube and balloons are disposable. The balloons can be inflated and deflated with air from a pressure-controlled pump system with maximum inflatable pressure of 45 mm (Figs. 21.10 and 21.11).

Both balloons are deflated at the start of the procedure. On reaching the duodenum, the overtube balloon is inflated to fix and stabilize the overtube within the lumen. Subsequently the enteroscope is advanced as far as possible. Then the enteroscope tip balloon is inflated, and the overtube balloon is deflated. The overtube is now advanced to reach the enteroscope tip. The overtube is again inflated, and both enteroscope and overtube are gently withdrawn together in order to "concertina" the small bowel over both. The whole procedure is repeated, and each set of maneuvers can allow up to 40 cm of small bowel to be examined, until the terminal ileum (TI) is reached. If the TI is not reached, then the distal most region reached is "tattooed" in the submucosal plane with an endo-

Fig. 21.10 Double balloon with balloon inflated

Fig. 21.11 Double balloon with balloon deflated

needle. The DBE can then be repeated via the trans-anal route and retrograde movement from the TI proximally up the ileum allowing full examination of the whole small bowel. On withdrawal in either procedures, close examination of the mucosal surface occurs as with standard endoscopy, but lesions are dealt with as soon as found, whether this is on intubation or withdrawal. Bowel preparation is as for standard IC. The procedure is carried out under general anesthetic or deep sedation in the presence of an anesthetist.

DBE has been extensively evaluated in adults with obscure GI bleeding and to a lesser extent in CD. In a retrospective study involving 40 CD adult patients, active small bowel CD was found in 24 (60%) patients, leading to a change in therapy in 18 patients (75%). After a mean follow-up of 13 months, 83% of patients had persistent clinical improvement [118]. In another study of 37 patients with CD, the overall diagnostic yield of DBE was 59.4% [119]. In a pediatric study conducted by one of the authors, the diagnostic yield was 78.5%, and therapeutic success rate was 64.2%. None of the patient had any complication, suggesting that DBE is a safe and effective procedure in pediatric population [120].

Since CD can be confined to the small bowel alone, DBE has a definite role in the evaluation of patients with suspected CD with negative ileocolonoscopy and radiological investigations. In one study comparing DBE to small bowel follow-through (SBFT) [121], DBE was able to detect early or faint lesions like aphthoid lesions, erosions, and small ulcers which were not found by SBFT. Also DBE was better in differentiating open and healed ulcers, thus, helpful in evaluation of response to treatment in CD. However, small strictures were difficult to detect with DBE since they could be mistaken for an intestinal band. Complications reported in the

literature include perforation, pancreatitis, bleeding, and aspiration pneumonia [122, 123].

Endoscopic Findings in Inflammatory Bowel Disease

It is important to recognize the normal appearance of the bowel macroscopically and histologically. The colonic mucosa when seen through an endoscope appears glistening salmon pink in color with a visible network of branching vessels seen beneath the mucosa. The smoothness of the mucosal surface is the hallmark of a healthy colon, and there is a lack of contact bleeding, friability, or exudates [124]. Microscopically the mucosa appears flat with normal crypt density, undistorted crypt architecture, intact surface epithelium, normal mucin content, and without any neutrophil infiltration [125].

Ulcerative Colitis

The earliest changes seen in UC are the presence of diffuse erythema and dull appearance of the vascular architecture consequent to the vascular congestion and edema. The engorged mucosa leads to contact bleeding and friability when touched with an endoscope. Progressively minute ulcers appear which coalesce to form large ulcers within a background of diffuse colonic inflammation with loss of vascular pattern and granularity [124]. The colonic mucosa is involved in a continuous fashion from the rectum extending further up the colon. Long-standing UC leads to the development of pseudopolyps (Fig. 21.12). The microscopic findings typical of UC include diffuse mucosal involvement from rectum up to cecum without granulomas. The presence of architectural distortion, basal plasmacytosis, cryptitis, and crypt abscesses are suggestive of chronicity. The severity of inflammation is worse distally, and reversal of this gradient should prompt for reconsideration of the diagnosis. However, there is no single set of microscopic or macroscopic findings for diagnosis of UC. At least five atypical phenotypes of UC have been described in the recently revised ESPGHAN Porto Criteria [103] (Table 21.7). The classic notion of noninvolvement of the upper GI tract in UC no longer holds true, as gastric erosions, ulcers, and microscopic features can be seen in 4–8% of patients with UC [126]. Therefore, the presence of focal gastritis or chronic gastric inflammation should not be a sole criterion to refute the diagnosis of UC. Besides, the EUROKIDS registry data suggest that rectal sparing can be seen in around 5% cases of pediatric UC [1].

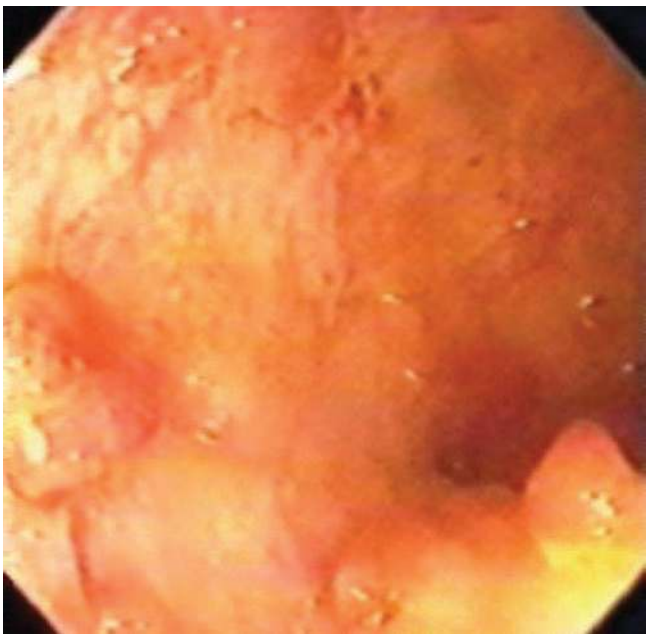

Fig. 21.12 Pseudopolyps in ulcerative colitis

Table 21.7 Phenotypes of pediatric UC at diagnosis

Presentation	Macroscopic	Microscopic
Typical	Contiguous disease from the rectum	Architectural distortion, basal lymphoplasmacytosis, disease most severe distally, no granulomas
Atypical		
1. Rectal sparing	No macroscopic disease in rectum or rectosigmoid	Same as typical, especially in the involved segment above sparing
2. Short duration	Contiguous disease from the rectum may also have rectal sparing	May have focal, plus signs of chronicity or architectural distortion may be absent; other features are identical. Usually occurs in young children with short duration of symptoms
3. Cecal patch	Left-sided disease from rectum with area of cecal inflammation and normal appearing segment between the two	Typical; biopsies from the patch may show nonspecific inflammation
4. UGI	Erosions or small ulcers in stomach, but are neither serpiginous nor linear	Diffuse or focal gastritis, no granuloma (except peri-cryptal)
5. Acute severe colitis	Contiguous disease from the rectum	May have transmural inflammation or deep ulcers, other features typical. Lymphoid aggregates are absent; ulcers are V-shaped fissuring ulcers

Crohn Disease

Typical macroscopic findings of CD commence as mucosal aphthous lesions, which enlarge to form linear or transverse serpentine ulceration (Fig. 21.13). Characteristically the ulcers are focal with normal intervening mucosa, the so-called skip lesions (Fig. 21.14). As the disease progresses, it leads to nodularity, giving a cobblestone appearance (Fig. 21.15) and stenosis/stricturing (Fig. 21.16) of bowel with pre-stenotic dilatation. Bowel wall thickening with luminal narrowing is typically seen on imaging, WCE, or during surgery. The other typical macroscopic findings are skip lesions and jejunal and ileal ulcers. The extraluminal findings include perianal fistulas, abscesses, anal stenosis, anal canal ulcers, and large and inflamed skin tags.

Nonspecific macroscopic findings of CD include edema, erythema, friability, and granularity. Terminal ileum is the most common site to be involved in CD (Fig. 21.17), hence,

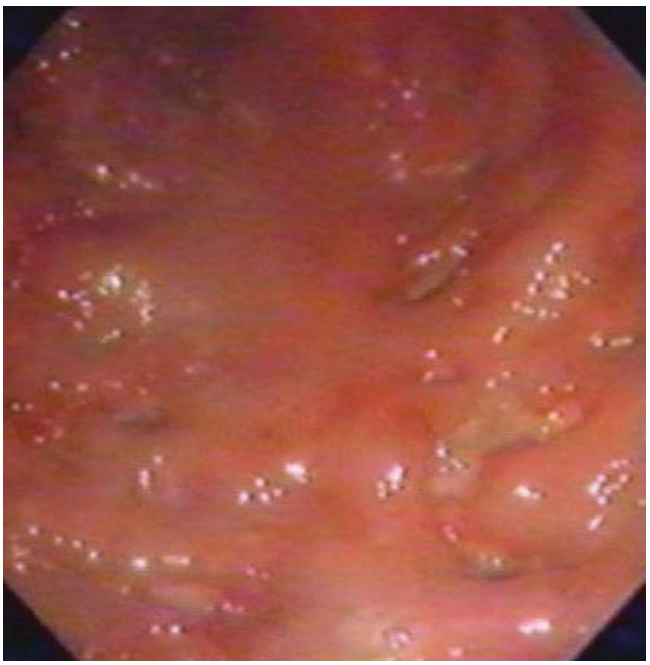

Fig. 21.13 Deep aphthous lesion in Crohn disease

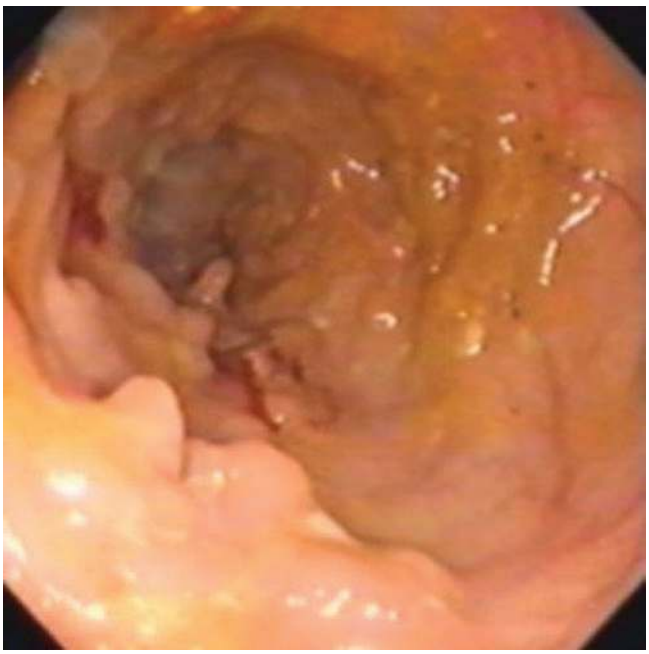

Fig. 21.15 Typical cobblestone appearance in Crohn disease

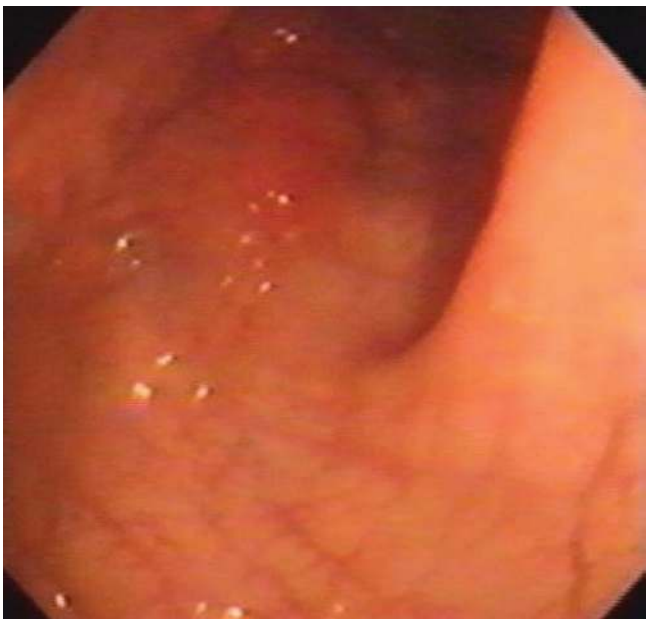

Fig. 21.14 Skip lesions in Crohn disease

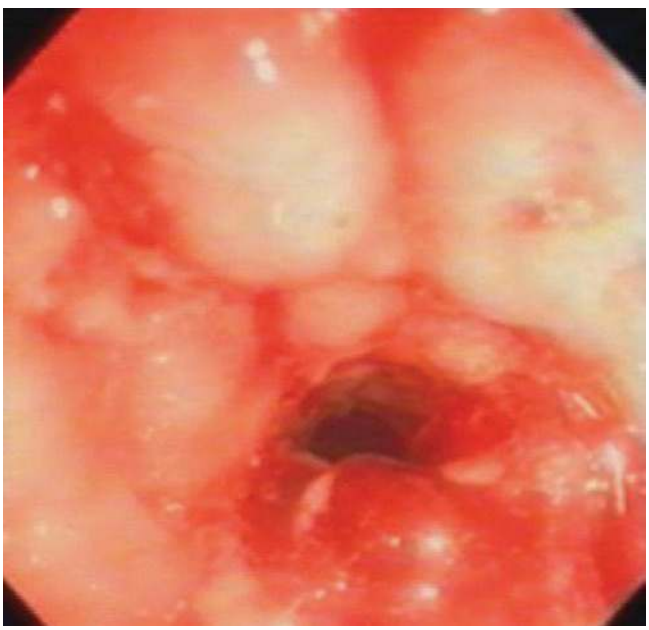

Fig. 21.16 Colonic stricture in Crohn disease

as has been stressed earlier; it is imperative that every attempt should be made to reach the terminal ileum at colonoscopy.

The presence of noncaseating granulomas on ileal biopsy is the classical histopathological finding in CD of the ileum.

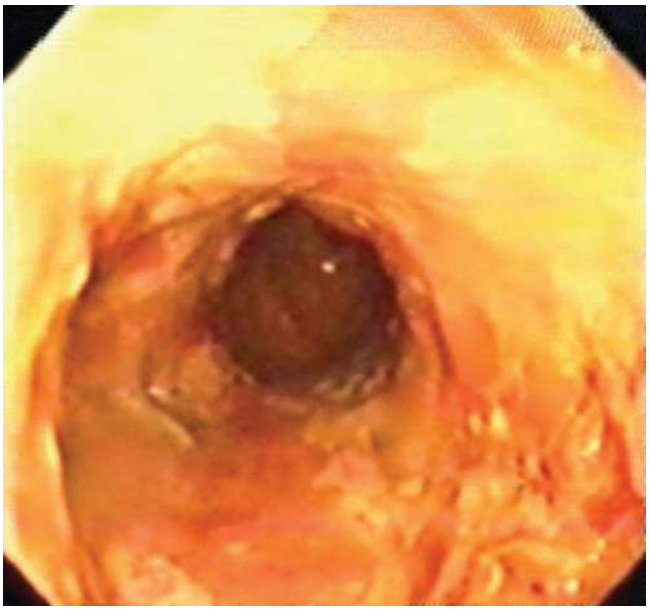

Fig. 21.17 Terminal ileal Crohn disease

The other typical microscopic findings of CD include focal chronic inflammation, transmural inflammatory infiltrate, and submucosal fibrosis.

Nonspecific microscopic findings of CD are granulomas adjacent to a ruptured crypt, mild nonspecific inflammatory infiltrate in the lamina propria, and mucosal ulceration/erosions. The signs suggestive of chronicity are crypt architectural changes, colonic Paneth cell metaplasia, and goblet cell depletion. The presence of epithelioid granulomas is sufficient to make a diagnosis of CD even without classical macroscopic findings.

Inflammatory Bowel Disease-Undefined (IBD-U)

In the recently revised ESPGHAN Porto Criteria for the diagnosis of inflammatory bowel disease in children and adolescents, it is suggested that the term IBD-U is used for patients with colitis and clearly defined findings that are atypical for either CD or UC. Colitis features in children with untreated colitis are categorized in three classes, and patients with at least one class II and two to three class III features are diagnosed as IBD-U (Table 21.8).

Table 21.8 UC v IBD-U v CD differentiation

Likelihood of UC	Features	Diagnostic approach
Class I: Nonexistent	Well-formed granulomas anywhere in the GI tract, remote from ruptured crypt	Diagnose as CD
	Deep serpentine ulcerations, cobblestoning, or stenosis anywhere in the small bowel or UGI tract	
	Fistulizing disease (internal or perianal)	
	Any ileal inflammation in the presence of normal cecum (i.e., incompatible with backwash ileitis)	
	Thickened jejunal or ileal bowel loops or other evidence of significant small bowel inflammation (more than a few scattered erosions) not compatible with backwash ileitis	
	Macroscopically and microscopically normal appearing skip lesions in untreated IBD (except with macroscopic rectal sparing and cecal patch)	
	Large inflamed perianal skin tags	
Class II: Rare with UC (<5%)	Combined (macroscopic and microscopic) rectal sparing, all other features are consistent with UC	IBD-U if at least 1 class II feature exists
	Significant growth delay (height velocity <2 standard deviation), not explained by other causes	
	Transmural inflammation in the absence of severe colitis, all other features are consistent with UC	
	Duodenal or esophageal ulcers, not explained by other causes (e.g., *Helicobacter pylori*, NSAIDs, and celiac disease)	
	Multiple aphthous lesions in the stomach, not explained by other causes (e.g., *H. pylori* and NSAIDs)	
	Positive anti-Saccharomyces cerevisiae antibody (ASCA) in the presence of negative pANCA	
	Reverse gradient of mucosal inflammation (proximal >distal) (except rectal sparing)	
Class III: Uncommon (5–10%)	Severe scalloping of the stomach or duodenum, not explained by other causes (e.g., celiac disease and *H. pylori*)	Diagnose as IBD-U if at least 2–3 features exists
	Focal chronic duodenitis on multiple biopsies or marked scalloping of the duodenum, not explained by other causes (e.g., celiac disease and *Helicobacter pylori*)	
	Focal active colitis on histology in more than one biopsy from macroscopically inflamed site	
	Non-bloody diarrhea	
	Aphthous lesion in the colon or UGI tract	

Follow-Up and Surveillance Ileocolonoscopy

Intraluminal disease should be reassessed electively as guided by biochemical markers including fecal calprotectin. However, patients who do not respond to therapy or who are treatment dependent or who have doubtful diagnosis should have an early reassessment. It is the practice in many units to perform a follow-up ileocolonoscopy 2–3 months after the start of treatment in a newly diagnosed case of inflammatory bowel disease since Modigliani and colleagues showed that only 29% of adults with Crohn disease in clinical and biochemical remission actually achieved endoscopic remission [127]. It allows the physician to observe the mucosal efficacy of the therapy, because, in many instances, such as steroid use in colitis, the clinical improvement of the patient may not be mirrored by the mucosal improvement, which is regarded by most as the most important meter of a successful treatment regimen [9]. Ileocecal transcutaneous Doppler ultrasonography may be of benefit as a noninvasive alternative to repeat ileocolonoscopy in this situation, as noted above. In addition, the activity of mucosal inflammation may determine the long-term risk for carcinogenesis in the bowel.

Treatment Targets

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) [128] program initiated by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) has recommended treatment targets for IBD to be used for a "treat-to-target" clinical management strategy based on clinical/patient reported outcome (PRO) and endoscopic remission.

The clinical/PRO remission for Crohn disease is defined as resolution of abdominal pain and diarrhea/altered bowel habit, which should be assessed at a minimum of 3 months during active disease, and endoscopic remission defined as resolution of ulceration at ileocolonoscopy (or resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy), which should be assessed at 6–9-month interval during the active phase.

Similarly for ulcerative colitis, the clinical/PRO remission is defined as resolution of rectal bleeding and diarrhea/altered bowel habit, which should be assessed at a minimum of 3 months during active disease, and endoscopic remission defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy, which should be assessed at 3-month interval during the active phase.

Although the CRP and fecal calprotectin are not the treatment targets, these can be used as adjunctive measures of inflammation for monitoring in CD. Failure of CRP or fecal calprotectin normalization should prompt further endoscopic evaluation, irrespective of symptoms.

Scoring Systems for Endoscopic *PIBD* Disease Activity

The focus is increasingly being shifted to mucosal healing as an important aspect of the treatment target of PIBD. This is further stressed upon by the STRIDE recommendations as above. There are various scoring systems currently in practice, namely, Mayo score, UCEIS, UCCIS, CDEIS, SES-CD, and Rutgeerts score. The standard scores used for Crohn disease are the Crohn Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn Disease (SES-CD). Of these two, SES-CD seems to be more simplistic and also correlates well with CDEIS. The interobserver variability for SES-CD is less as compared to CDEIS [129–131]. The Rutgeerts score is primarily used in postoperative patients. None of these scores are fully validated in the pediatric population.

For UC, the STRIDE Committee recommends the use of the Mayo score which, though not fully validated, has less inter- and intra-observer variation, is easy to use, and has well-established predictive values [132, 133]. The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) also has less interobserver variability but is not fully validated. The Ulcerative Colitis Colonoscopic Index of Severity (UCCIS) assesses four variables: vascular pattern, granularity, bleeding/friability, and ulceration. All are assessed in five segments throughout the colon. This index also needs further validation and cutoff values are not well defined.

Endosonography

Endoluminal ultrasonography of the rectum has been an established technique for years; however, more recently, an echocolonoscope has allowed combined examination of the mucosa and the bowel wall. This is a forward-viewing colonoscope with the transducer (7.5 MHz) situated in the rigid tip of the scope [134]. Alternatively, an ultrasound miniprobe can be introduced via the biopsy channel (7.5 or 12.5 MHz). A fluid interface is necessary for all endosonography, and this can be achieved either with a fluid-filled balloon or filling the relevant colonic segment with water. Because this may be time consuming, it is easier to concentrate on the region of interest rather than attempt to examine the entire colon. In adult practice, staging of cancers is the major indication for endosonography. In children and adolescents, indications for this technique might include suspicion of early invasive cancer arising from an adenoma, assessment of the extent and depth of sessile polyps to guide reception

technique, assessment of colonic strictures/fistulae/anastomoses, assessment of the extent and depth of inflammatory bowel disease, assessment of the extent and depth of vascular lesions, examination of rectal and colonic portal hypertension with varices, and suspicion of lymphoma.

Inflammatory bowel disease appears as wall thickening and subsequent loss of the normal layer structure of the colon with progressive inflammation. Although theoretical differentiation between ulcerative colitis and Crohn disease is possible owing to the transmural nature of Crohn disease, it has been shown recently that active ulcerative colitis can have echo-texture changes extending into the submucosa and that these changes correlate with disease activity [135]. Surgical decisions were made in one study of patients with Crohn disease in which endoscopic ultrasonography was used to differentiate between superficial and transmural involvement [136]. An ileo-anal pouch was undesirable when transmural disease was identified. Perirectal and peri-colonic fistulae and abscesses have been seen using the rigid rectal ultrasound probe, and this is a potential application for endoscopic ultrasonography [137]. Catheter probe-assisted endoscopic ultrasonography in inflammatory bowel disease has advantages over an echocolonoscope, which may be technically difficult to use. One study recently showed that wall thickness was twice as great in active inflammatory bowel disease, but ulcerative colitis could not be differentiated from Crohn disease [138]. Loss of wall structure correlated with disease activity score in the Crohn disease group, and wall thickness correlated with disease activity in the ulcerative colitis group. Other parameters, such as superior mesenteric artery maximum flow velocity and increased Doppler ultrasonography demonstrating mural blood flow, are being examined as viable noninvasive substitutes for the determination of posttreatment ileocecal Crohn disease activity, thus, potentially avoiding the need for follow-up ileocolonoscopy, as some units advocate.

New Endo-Diagnostic Methods

High-Magnification Chromoscopic Colonoscopy (HMCC)

Recent improvements in technology have led to the development of a generation of endoscopes with the ability to magnify endoscopic images. The high-magnification endoscope allows conventional video imaging with the facility to increase magnification instantaneously up to 100 times by a thumb-activated lever. By pushing the lever downward, the magnified picture is obtained immediately, and by reverting back to the normal position, the image is returned to normal [139]. A topical dye-like indigo carmine 0.2–2% is sprayed on the mucosa helping further to delineate the pathology. During magnification chromoscopic colonoscopy, pit patterns are observed. These pit patterns are classified according to the modified Kudos' criteria [140], and based on the pit patterns, it is possible to predict the histology as well as take targeted biopsies.

This technique has been extensively used in cancer surveillance in adults [141, 142]. Matsumato et al. [73] observed that the presence or absence of network pattern (NWP) and crypt opening (CO) highly correlated with the severity of disease in ulcerative colitis both clinically and histologically. Fujiya et al. [143] devised a classification system based on minute findings. In a prospective study, they compared HMCC with the established Matt's criteria [144] and histopathological findings and found that while colonoscopy correlated well with histopathology and correctly identified normal and clearly defined abnormal mucosa, it was insufficient for the assessment of minute mucosal changes that reflect smoldering histopathological changes. HMCC, on the other hand, not only helped to recognize distinctive features in such mucosa predicting the severity of the disease state, but it also helped in predicting relapses in those who were in a quiescent state. Further, in another prospective study, Sugano et al. [145] have found HMCC effective in the evaluation of minute mucosal changes in patients with UC in remission. HMCC has also been evaluated in cancer surveillance in UC [146] and has been shown to assist in taking targeted biopsies.

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) is an exciting new technology developed in the recent years. It is an adaptation of light microscopy, whereby a low-power laser illumination is focused to a single point in a microscopic field of view. Light emanating from that specific point is focused to a pinhole detector. Light emanating from outside the focally illuminated spot is not focused to the pinhole and, therefore, is geometrically rejected from detection. The beam path is scanned in a raster pattern, and measurements of light returning to the detector from successive points are digitized to produce two-dimensional images. Each such image, thus, is an optical section representing one focal plane within the specimen [147–149].

The components of the confocal laser endomicroscope are based on the integration of a confocal laser microscope mounted in the tip of a conventional colonoscope (EC3870K; Pentax, Tokyo, Japan), which enables confocal microscopy in addition to standard videoendoscopy. The diameter of the distal tip and insertion tube is 12.8 mm. The distal tip contains an air and water jet nozzle, two light guides, a 2.8 mm working channel, and an auxiliary water jet channel. The water jet channel is used for the topical application of the

contrast agent. During CLE, an argon ion laser delivers an excitation wavelength of 488 nm with a maximum laser output of <1 mw at the surface mucosa. Confocal images can then be collected at a scan rate of 0.8 frames/second (1024 × 1024 pixels) or 1.6 frames/second (1024 × 512 pixels). The optical slice thickness is 7 μm with a lateral resolution of 0.7 um and z-axis range of 0–250 um below the surface layer. Sodium fluorescein is given intravenously at the time of the procedure as a contrast agent. Thus, it is possible to get cellular and subcellular microscopic images at the time of endoscopic procedure. Features of IBD seen at CLE include bifid crypts, crypt distortion and destruction, crypt abscess/cryptitis, goblet cell depletion, inflammatory cell infiltration, and enlarged tortuous vessel architecture [150]. In a recent prospective study involving 21 patients with IBD, CLE was able to identify intramucosal bacteria with a sensitivity of 89% and specificity of 100% using fluorescence in situ hybridization (FISH) as gold standard. The authors further performed a retrospective study in 113 patients with CD and UC and found intramucosal bacteria significantly more often than in control patients (66% vs 60% vs 14%, $p < 0.001$) [151].

The advantages of using CLE are that as it is less invasive, there are potentially significant time, histopathology input, materials, manpower, and consequent financial savings to institutions conducting pediatric endoscopic services. There is no doubt that this new technique will be useful in taking targeted biopsies in patients with IBD and reduce the need to take biopsies.

Therapeutic Endoscopy in IBD

Besides being essential for the diagnosis and reassessment of IBD, endoscopic expertise is also required for therapeutic procedures in PIBD. It is estimated that about half of pediatric Crohn disease patients require some kind of surgical intervention within a decade of diagnosis [152, 153], the common indications being structuring or penetrating disease of the terminal ileum and colon or at an anastomotic site [154–156].

Traditionally, the strictureplasty and bowel resection have been the mainstay of treatment for stricturing disease, but recently, endoscopic balloon dilatation (EBD) is emerging as a safe and effective alternative to the above surgical procedures in patients with Crohn disease with ileocecal and anastomotic strictures [157–163]. The decision to perform EBD depends on patient choice, endoscopist expertise/experience, procedural feasibility, and the stricture characteristics, e.g., number, nature, and length.

The success rate of EBD in adults has been reported to vary from 83 to 87% at 1 year to 64–58% at 5 years [157–163]. There is a lack of evidence and controlled trials to compare the recurrence rate post-EBD and postsurgical procedure.

A surgery-free outcome is reported to be highest when stricture length is <4 cm and when EBD is performed for anastomotic strictures [157, 164, 165]. There is an increased need of post-procedural surgery with prolonged Crohn disease duration and high C-reactive protein [157]. The success rate is demonstrated to be poor if the stricture is present at the Bauhin's valve [160, 166].

Although there is no reported use of EBD for duodenal strictures in PIBD, the authors have recently performed trans-endoscopic balloon dilatation of a duodenal stricture in an 11-year-old boy with Crohn disease.

The possible complications associated with EBD are bleeding and perforation. The presence of fistulizing disease and abscesses at or adjacent to the site stricture increases the risk of perforation and is, thus, considered to be a contraindication [167].

Intraluminal stenting has also been reported as a possible alternative to surgery to treat strictures, but current date does not suggest its routine or safe use.

Colon Capsule Endoscopy

Colon capsule endoscopy (CCE) is still in a nascent stage and is considered to be useful in situations where full colonoscopy could not be achieved or where patient is not compliant for an endoscopic procedure. The colon capsule when deployed goes into a sleep mode as it traverses through small bowel and gets reactivated as it reaches colon. It has been reported to have high specificity and sensitivity as compared to routine colonoscopy [106], but further randomized clinical trials are required to recommend its routine use.

Conclusions

Pediatric endoscopy differs significantly from their adult parallels in nearly every aspect, including patient and parent management and preparation, selection criteria for sedation and general anesthesia, bowel preparation, expected diagnoses, instrument selection, imperative for terminal ileal intubation, and requirement for biopsies from macroscopically normal mucosa.

The chapter has highlighted the importance of endoscopy in general and ileocolonoscopy in particular in the diagnostic and therapeutic management of IBD. Also, the role of other advanced diagnostic techniques like DBE has been discussed, while wireless capsule endoscopy is discussed in a separate chapter.

Endoscopy is a necessary and important investigation in the various stages of management of inflammatory bowel disease from diagnosis to surveillance of cancer. There is no dispute in the use of ileocolonoscopy in the initial assessment

of patients with IBD. Recent data have shown that upper GI endoscopy also has an important role in the initial diagnosis and differentiation of IBD and, hence, is recommended as a part of initial investigation of all cases presenting with symptoms suggestive of IBD. Other endoscopic investigative modalities like WCE, DBE, HMCC, confocal endomicroscopy, and endosonography aid in further management of IBD. Apart from diagnosis, endoscopy also has an important role in the therapeutic management of IBD.

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The Pathology of Chronic Inflammatory Bowel Disease

22

Pierre Russo

Major Histologic Features Noted in Mucosal Specimens

Preparation and Procedure-Induced Artifacts

Nondisease-related alterations in the colonic mucosa may be induced by certain enemas used in bowel preparation or by the procedure itself. For example, soap suds enemas may result in hyperemia and edema of the bowel, especially noted on endoscopy [1]. Oral sodium phosphate solutions (oral FLEET™) may cause aphthoid-like erosions endoscopically similar to Crohn disease (CD) [2]. These correspond histologically to large lymphoid aggregates, although edema, hemorrhages, or mild acute inflammation have also been described [3] (Fig. 22.1). Mucin depletion and increased cell proliferation can be noted in the crypts [4, 5]. Hypertonic saline and biscodyl enemas can cause mucin depletion, focal disruption of surface epithelium, mild acute inflammation, and edema, which usually resolve within 1 week [6]. Minor trauma to the mucosa may allow penetration of gas insufflated into the bowel during endoscopy, resulting in "pseudolipomatosis," characterized by the formation of numerous clear spaces in the mucosa [7] (Fig. 22.2). Cleansing solutions used to disinfect endoscopes, such as hydrogen peroxide, may produce adherent mucosal plaques, mucosal vacuolar changes, congestion, hemorrhage, and even pseudolipomatosis [8, 9] (Table 22.1).

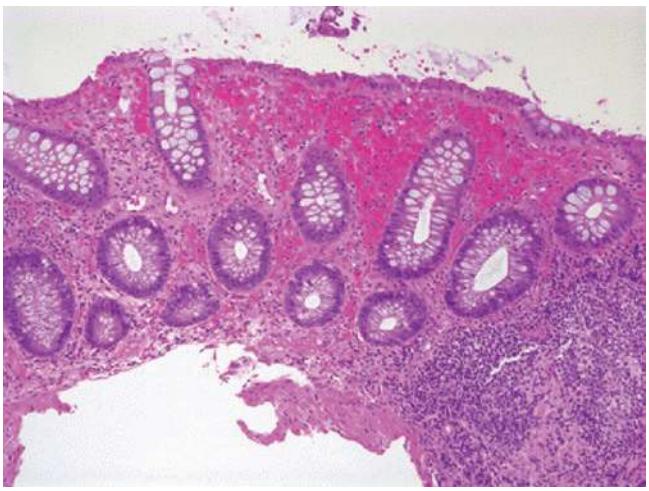

Fig. 22.1 Histologic features of phosphate enema effect. Superficial mucosal hemorrhage and focal mucin depletion of the colonic surface epithelium are noted. There is no inflammation of the crypts (hematoxylin-eosin (H + E), ×100)

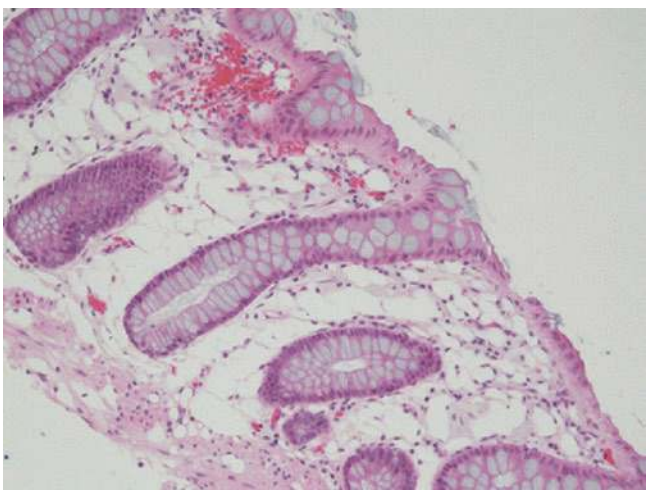

Fig. 22.2 Pseudolipomatosis. Numerous clear spaces in the lamina propria resulting from infiltration of the mucosa by insufflated gas during endoscopy suggests the presence of fat vacuoles (H + E, ×200)

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Table 22.1 Differential diagnosis of colitis in infancy and childhood

Allergic	Eosinophilic colitis
Vascular	Necrotizing enterocolitis Henoch–Schönlein purpura Hemolytic uremic syndrome
Neuromuscular	Hirschsprung disease Chronic pseudo-obstruction
Immunodeficiencies (congenital and acquired) Infectious	Bacterial, parasitic, viral
Chronic idiopathic	Ulcerative colitis Crohn disease Lymphocytic colitis Collagenous colitis Autoimmune enterocolitis
Treatment related	Antibiotic-associated colitis Changes induced by other drugs Diversion colitis Neutropenic colitis Pouchitis Graft versus host disease Fibrosing colonopathy

Histologic Patterns in Colitis

Active colitis refers to the presence of neutrophils either in the lamina propria, in crypt epithelium (cryptitis) or within the lumen, forming small abscesses (crypt abscesses). Neutrophils confined to the lumen of mucosal vessels are not considered part of the process of active colitis. A predominantly neutrophilic infiltrate without significant architectural changes is generally a feature of diseases with a self-limiting course, such as infections and drug reactions. Neutrophils in these cases are frequently confined to the superficial portion of the mucosa, and may be associated with small erosions or ulcers (Fig. 22.3).

Focal active colitis (FAC) is observed in acute self-limited colitis and can be an early manifestation of idiopathic inflammatory bowel disease. In a recent report of 29 pediatric patients with FAC, 8 developed Crohn disease, whereas the other patients had either infectious colitis or remained idiopathic [10].

Eosinophilic colitis refers to a patchy or diffuse infiltrate dominated by eosinophils, usually with infiltration of the crypt or surface epithelium. Wide variations in the number of eosinophils in the normal colonic mucosa are due to differences in specimen site (greater numbers of eosinophils in the cecum as opposed to the rectum), age, and geography [11, 12]. In infants, the main consideration is milk allergy; parasitic infection and chronic inflammatory bowel disease (very early-onset IBD) are also possibilities.

The features of ***chronic colitis*** are based on the recognition of architectural changes in the mucosa, such as a "villiform" aspect of the surface epithelium, crypt destruction, and atrophy, and shortening of the crypts with irregular branching and loss of their regular outline. Shortening of the crypts is most often due to the presence of a basally situated chronic inflammatory infiltrate (basal plasmacytosis), which separates the base of the crypts from the muscularis mucosae (Fig. 22.4). Paneth cell metaplasia and pyloric metaplasia are other useful findings (Fig. 22.5). In the normal colon, Paneth cells usually extend into the right colon, but their presence in the left colon is a feature of chronic damage, especially in the

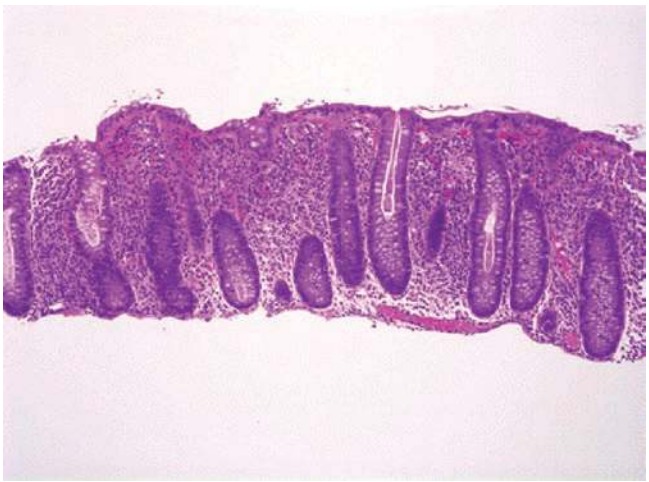

Fig. 22.3 Colitis in a 3 year old due to Salmonella. There is a superficial, mild inflammatory infiltrate with small crypt microabscesses without significant crypt architectural changes, associated with superficial hemorrhages. Hematoxylin-eosin (H + E), ×100

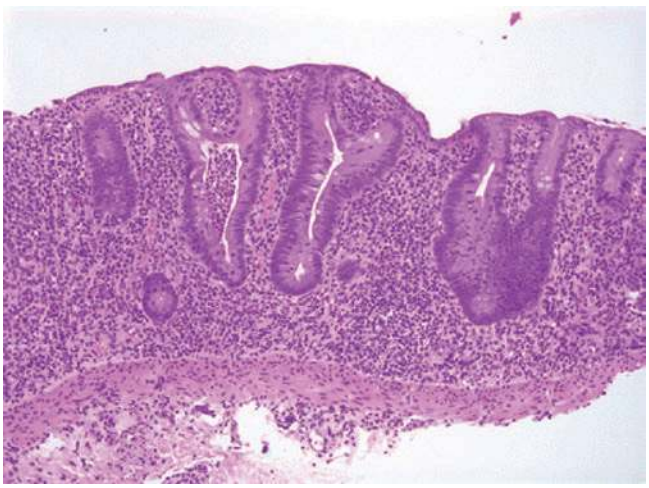

Fig. 22.4 Histologic features of IBD. Chronic mucosal damage is characterized by irregular branching of the crypts, increased intercryptal distance, and shortening of the crypts due to the presence of an inflammatory infiltrate in the deep mucosa separating the base of the crypts from the muscularis mucosa (basal plasmacytosis). In addition, there is goblet cell depletion and a microabscess. H + E, ×100

older child. Pyloric metaplasia is the presence of mucous glands normally present in the gastric antrum and pylorus. It is more frequently noted in Crohn disease than ulcerative colitis (UC) but is also a useful feature of chronic damage. The presence of an increased mononuclear inflammatory cell infiltrate, usually an integral part of the process, is the least useful histologic parameter given the wide range in numbers of lymphocytes and plasma cells in normal specimens. Although considered a hallmark of chronic idiopathic inflammatory bowel disease, histologic features of chronicity may also be seen in other settings in pediatrics, such as immunodeficiency disorders, metabolic diseases such as glycogen storage disease type Ib, or result from mucosal injury due to ischemia or Hirschsprung's disease. ***Chronic active colitis*** refers to the presence of a neutrophilic infiltrate superimposed on the above changes and is usually seen during exacerbations of IBD.

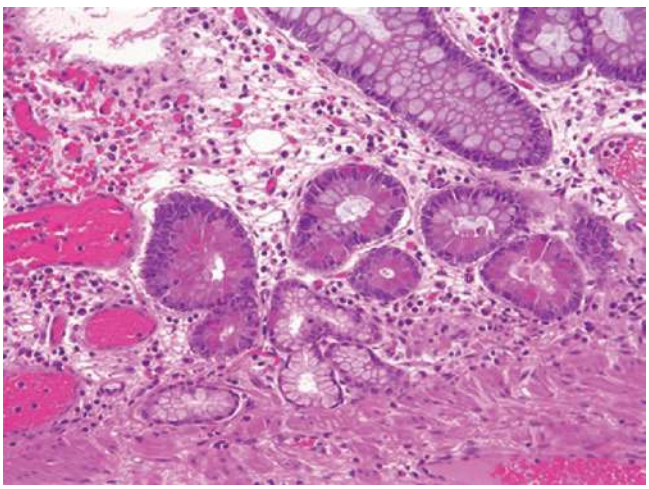

Fig. 22.5 Pyloric metaplasia and numerous crypts containing Paneth cells are noted in the deep mucosa of a patient with Crohn disease

Acute Self-Limited Colitis and its Distinction from IBD

Endoscopic features alone may not reliably distinguish acute self-limited colitis (ASLC) from IBD. Stool cultures and duration of diarrhea may help, as patients without an identifiable pathogen or in whom diarrhea lasts more than several weeks are more likely to have IBD. However, microbiologic investigations can reveal a colitis-causing pathogen such as *Salmonella*, *Campylobacter*, and *Yersinia* in up to 15% of patients with IBD [13]. ASLC is characterized by a predominantly neutrophilic infiltrate without significant crypt architectural changes. Neutrophils in these cases predominate in the superficial portion of the mucosa, and may be associated with small erosions or ulcers [14]. Neutrophils may also invade the crypt epithelium (cryptitis) or form small abscesses within the crypt lumen (crypt abscesses). Although numerous crypt abscesses suggest UC, they may be noted in CD as well as in infections and *Clostridium difficile*-related injury. The histologic diagnosis of IBD rests on the recognition of chronic mucosal damage, *chronic colitis*. Multiple biopsy studies of new-onset IBD in adults have shown that histologic features of chronic damage as noted above can reliably distinguish IBD from self-limited colitis [14–17].

Histologic Features of Early IBD

Despite the importance of recognizing chronic mucosal changes in the biopsies of patients with IBD, it has been well documented that initial colonic or rectal biopsies from 10% to 34% of pediatric patients ultimately shown to have UC lacked architectural distortion or other histologic features of chronic colitis [18–23]. This is seen particularly in younger patients (<10 years) and may be due to shorter duration of symptoms or longer progression to chronicity in children [24] (Fig. 22.6a, b). Focal active colitis may be a feature of

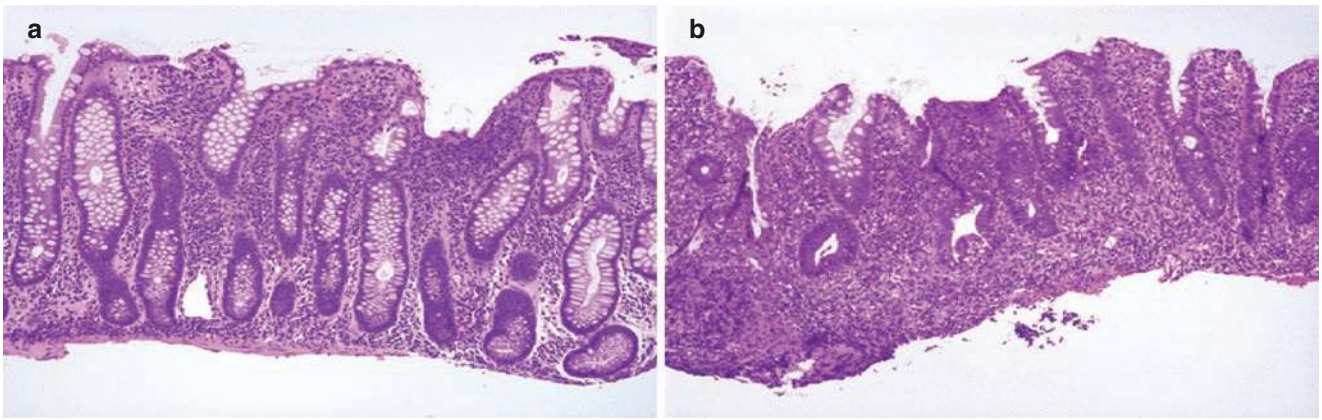

Fig. 22.6 (**a**) Colon biopsies of a 3-year-old girl with several months onset of diarrhea and abdominal pain. There is a lymphoplasmacytic inflammatory infiltrate with mild architectural distortion manifested by a slight irregularity in the outline of the crypts. (**b**) Follow-up biopsies several months later show more advanced disease with crypt atrophy and basal plasmacytosis (H + E, ×100)

self-limited colitis but may also be an early manifestation of IBD [10]. Close follow-up and repeat biopsies may be necessary in these cases. Increased mucosal eosinophils may be seen in the earliest biopsies of children eventually proven to have IBD, prompting a diagnosis of food allergy. In a case series of IBD diagnosed in 16 children less than 2 years of age, six children had an initial diagnosis of allergy [25]. On the other hand, histologic features similar to IBD may be seen in patients with primary immunodeficiencies and autoimmune enteropathy [26]. These conditions should always merit consideration when clinical manifestations of IBD occur in younger children. Histologic features that may point to a correct diagnosis in these patients include lack or paucity of plasma cells in the inflammatory infiltrate (as in Common Variable Immunodeficiency or Severe Combined Immunodeficiency), extensive crypt apoptotic activity, or absence of goblet and Paneth cells (as in autoimmune enteropathy). [27].

Very Early-Onset IBD

An increasing number of rare monogenic diseases have been observed in patients with very early-onset inflammatory bowel disease, which has been defined as onset of IBD before the age of 6 years, and which may account for 3%–15% of all pediatric IBD [28]. Many of these cases demonstrate histologic features not typically seen in older-onset IBD, such as increased apoptosis, unusually severe crypt architectural changes, conspicuously increased eosinophils in the lamina propria, crypt and surface epithelium, and small bowel villous atrophy [29] (Fig. 22.7).

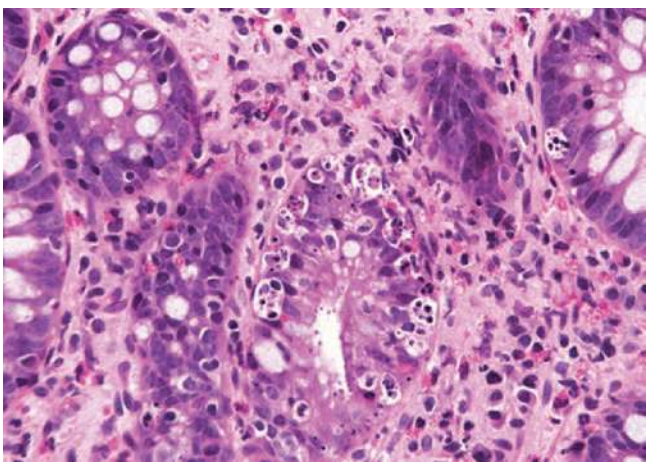

Fig. 22.7 Biopsy from a 3-year-old patient with a mutation in *DOCK8* and early-onset inflammatory bowel disease. Unusual features of this biopsy include extensive crypt apoptosis and numerous eosinophils. Cryptosporidia are noted in the crypt lumen

Characteristic Features of Ulcerative Colitis and Crohn Disease

The macroscopic and microscopic features which distinguish UC and Crohn disease are, in most respects, similar in children and adults, and are outlined in Table 22.2. Biopsy features helpful in differentiating these two entities in mucosal biopsies are outlined in Table 22.3. It should be noted, however that, especially in early stages of disease, biopsies, even in combination with clinical and radiologic features, may not allow distinction between these two entities. The absence of ileal involvement does not rule out CD and appears to be more frequent in younger patient with CD than older children or adults [30]. Similarly, diffuse colitis may be a manifestation of both CD and UC in children.

Table 22.2 Distinguishing features of ulcerative colitis and Crohn disease

	Ulcerative colitis	Crohn disease
Macroscopic		
Rectal involvement	Yes[a]	Variable
Distribution	Diffuse[a]	Segmental or diffuse
Terminal ileum	"Backwash" ileitis	Often thickened and stenosed
Serosa	Usually normal	"Creeping fat"
Bowel wall	Normal thickness	Frequently thickened
Mucosa	Hemorrhagic	Cobblestone and ulcers linear
Pseudopolyps	Frequent	Less common
Strictures	No	Common
Fistulas	No	Common
Involvement of gut proximal to colon	No[b]	Common
Microscopic		
Inflammation	Confined to mucosa and superficial submucosa	Transmural
Lymphoid hyperplasia	Infrequent	Common
Crypt abscesses	Extensive	Focal
Mucus depletion	Frequent	Infrequent
Deeply situated sarcoid-like granulomas	No	Yes
Fissures and sinuses	No	Yes
Villous surface transformation	Common	Infrequent
Submucosal fibrosis	Rare	Common
Neuromatous hyperplasia	Rare	Common

[a]Treatment may create the appearance of rectal sparing and discontinuous involvement
[b]See text

UC is classically defined as diffuse chronic mucosal inflammation limited to the colon, which invariably affects the rectum, and extends proximally in a symmetric uninterrupted pattern to involve part or all of the large intestine. The mucosa characteristically exhibits a diffuse hemorrhagic appearance (Fig. 22.8).

Microscopically, ulcerative colitis is characterized by inflammation limited to the mucosa and superficial submucosa (Fig. 22.9); deeper layers of the bowel are only exceptionally involved, as in toxic megacolon. Infiltration of the mucosa by neutrophils, with cryptitis, epithelial degeneration, goblet cell depletion, and crypt abscesses are characteristic though relatively nonspecific microscopic features of active UC. Chronicity, as previously defined, is characterized by crypt architectural changes such as irregular branching and atrophy, usually accompanied by a mononuclear inflammatory infiltrate. Increased crypt epithelial turnover in UC results in goblet cell depletion and Paneth cell metaplasia [31], less frequently observed in CD. The latter must be interpreted with caution in pediatric cases, as Paneth cells can be present in the distal colon in normal young children. Crypt abscesses are not specific, but when diffuse are suggestive of UC, whereas they tend to be more isolated in Crohn disease [32]. Rupture of crypt abscesses into the lamina propria or erosions may result in collections of histiocytes which may simulate but should be distinguished from true granulomas (Fig. 22.10).

Table 22.3 Distinguishing features of ulcerative colitis and Crohn disease in biopsies

	Ulcerative colitis	Crohn disease
Distribution of inflammation	Diffuse	Frequently focal
Rectal involvement	Yes[a]	Variable
Proximal > distal colonic involvement	No[a]	Frequent
Crypt abscesses	Diffuse	Variable, often focal
Villous surface appearance	Common	Occasional
Pyloric metaplasia	Infrequent	Typical
Mucin depletion	Frequent	Infrequent
Granulomas	Superficial; foreign body	Deep; sarcoid-like

[a]See text

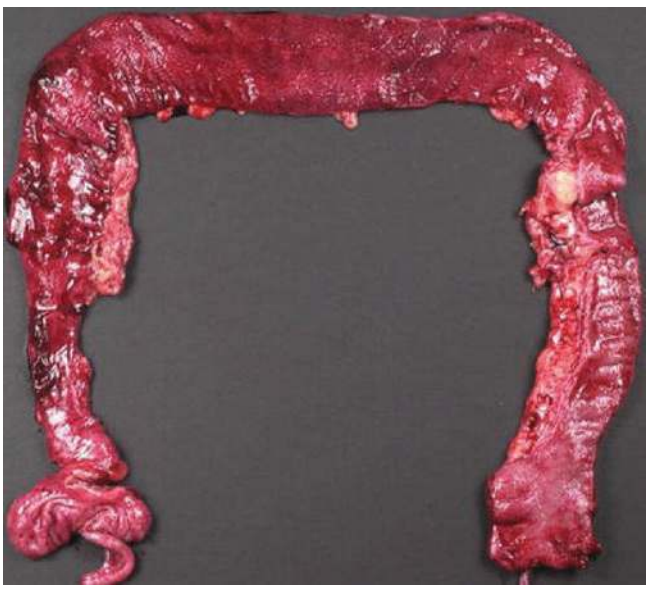

Fig. 22.8 Ulcerative colitis. Specimen from a total colectomy reveals a diffusely hemorrhagic granular mucosa from the rectum (*on the right*) to the ascending colon (*on the left*). The process is macroscopically continuous, without "skip" areas. Uninvolved appendix with a small amount of terminal ileum is also present

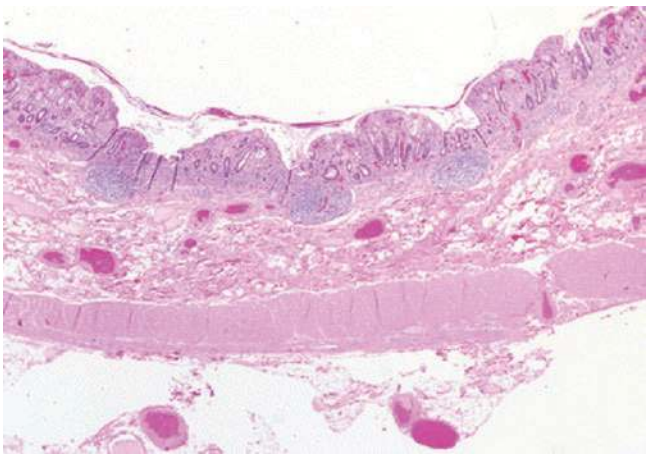

Fig. 22.9 Histologic section from the specimen in Fig. 22.6 is characterized by a diffuse inflammatory process limited to the mucosa and superficial portion of the submucosa. The colonic wall is of normal thickness

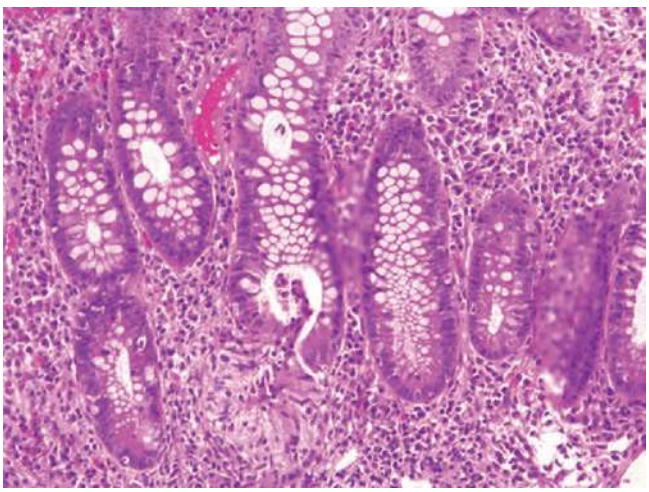

Fig. 22.10 Crypt microabscess with rupture resulting in a histiocytic reaction around the base of a crypt in a colonic biopsy from an 8-year-old girl with ulcerative colitis. H + E, ×200

Pseudopolyps, more commonly found in UC than CD, are discrete areas resulting from surviving islands of mucosa or heaped-up granulation tissue. The latter are more accurately referred to as "inflammatory polyps." Occasionally, regenerating mucosa within such an inflammatory polyp may form irregular, dilated glands, which bear a marked resemblance to retention or "juvenile" polyps [32]. In contrast to adenomas, pseudopolyps have a short stalk and are generally smooth surfaced (Fig. 22.11). Extensive arborization and fusion of the polyps may result in mucosal bridging.

In contrast to UC, *CD* features segmental intestinal involvement, with thickening of the bowel wall consequent to transmural inflammation and fibrosis, resulting in obstructive strictures, especially in the ileocecal area. The serosa is typically congested, with the presence of adhesions and fat wrapping, or "creeping fat." Mucosal involvement can be patchy and discontinuous. Aphthous ulcers overlying lymphoid tissue are among the earliest lesions observed endoscopically but are nonspecific and may be seen in other conditions. Uneven involvement of the mucosa results in a typical "cobblestone" appearance (Fig. 22.12). Transmural involvement in resected specimens and the presence of granulomas are the major histologic features which distinguish CD from UC and other colitides. Transmural disease in CD usually results from submucosal edema, fibrosis, and inflammation, typically in the form of lymphoid aggregates, also involving the muscle layers and the serosa (Fig. 22.13). Intramural abscesses are also noted, with fistulae, perforations, and adhesions, which can involve multiple loops of bowel and form a mass. The identification of pyloric metaplasia indicates chronic damage [33] and is seen more frequently with Crohn disease than with UC. Lymphangiectasia, neural hyperplasia, and vascular changes are frequently observed in CD and are almost never seen in UC.

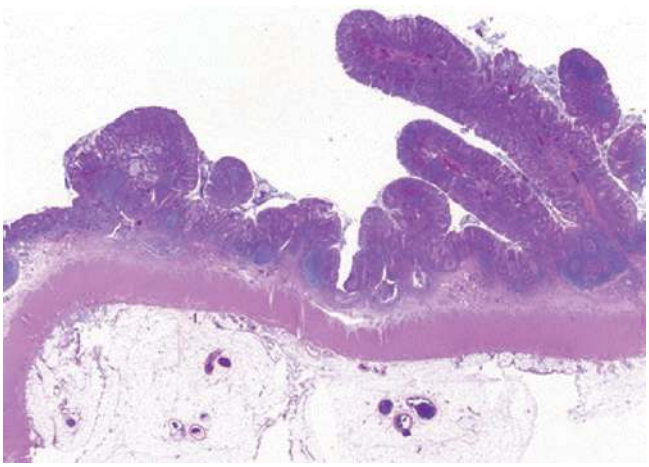

Fig. 22.11 Inflammatory "pseudopolyps" in a patient with ulcerative colitis. The base of the polyps are broad, and the polyps consist of heaped-up regenerating mucosa with an inflammatory infiltrate

Granulomas are virtually diagnostic of CD when they are well formed, nonnecrotic, basally situated, and remote from areas of active inflammation (Fig. 22.14). Their presence in biopsies may predate radiologic evidence of disease, and prolonged follow-up is necessary when they are observed in the absence of grossly evident disease [34]. The likelihood of finding granulomas is clearly a function of the diligence with which they are sought, increasing with the number of biopsies and sections examined [35]. Granulomas appear to be more frequently observed in the pediatric age group. One large study in Germany found them in 26% of biopsy specimens from 42% of patients, twice as commonly as in adults [36]. Comparison of initial biopsies of children with and without rectosigmoid granulomas showed similar age of onset of disease in the two groups, though those with granulomas tended to have more extensive disease and perianal complications [37]. Shepherd and colleagues observed granulomas more frequently in their younger patients and those with a shorter clinical course, with an increased prevalence in the more distal por-

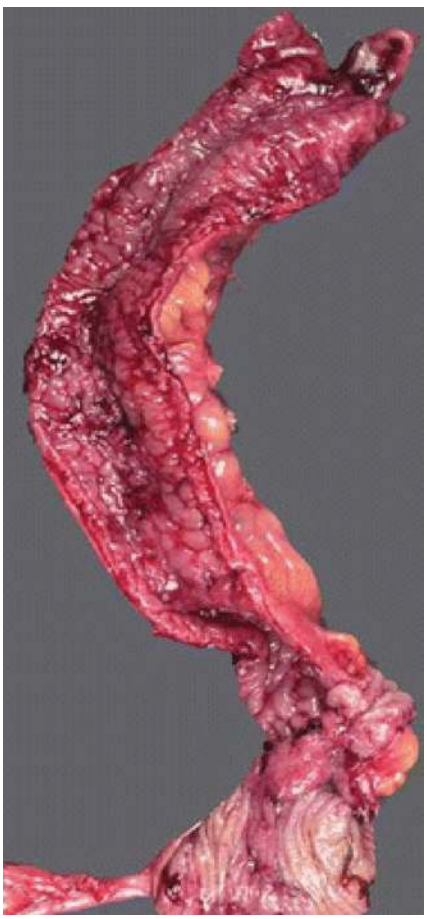

Fig. 22.12 Crohn disease. Ileocecectomy specimen is characterized by a stricture in the area of the ileocecal valve. The mucosa has a "cobblestone" appearance, and the wall appears thickened with prominent and extensively adherent serosal fat. Contrast with Fig. 22.6

tion of the gastrointestinal tract [38]. In a recent study at The Children's Hospital of Philadelphia, granulomas were identified in 61% of pediatric CD patients undergoing upper and lower endoscopy and were more frequent in untreated patients [39]. In nearly half of those patients, granulomas were present in the upper GI tract, in the terminal ileum, or both, but not in the colon.

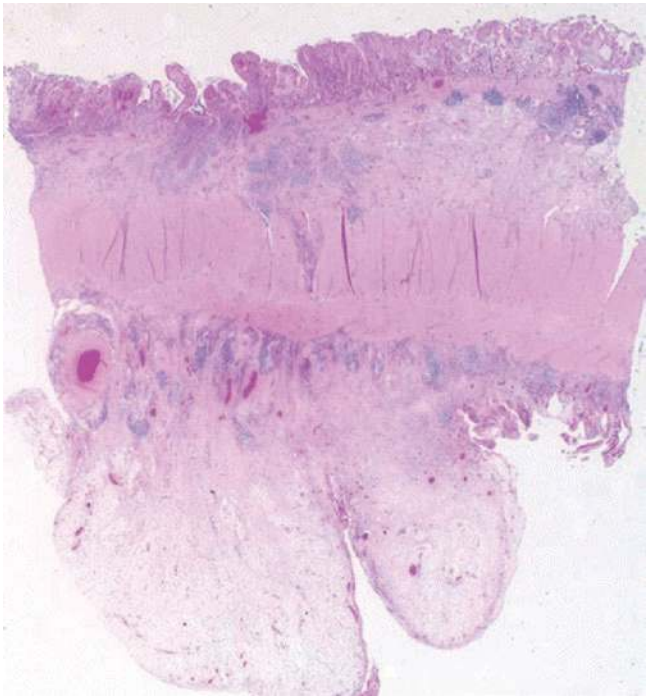

Fig. 22.13 Crohn disease. Low-power microscopic section demonstrates transmural involvement. Inflammation, in the form of lymphoid aggregates, extends through the muscularis propria into thickened serosal fat. Contrast with Fig. 22.9. H + E, ×10

Granulomas can also be seen, however, in a number of other conditions (Table 22.4). The granulomas seen in tuberculous infections of the gastrointestinal tract are typically multiple, large, and have caseous necrosis [40]. Those associated with yersiniosis are also necrotic and frequently present in mesenteric lymph nodes [41]. Chronic granulomatous disease (CGD) can present with a colitis similar to CD [42]. Numerous necrotizing granulomas may be observed; in non-inflamed or quiescent cases, collections of pigmented macrophages may be noted in the mucosa (Fig. 22.15).

Colonic malignancy is a well-recognized long-term complication of UC. Recent evidence suggests that patients with Crohn colitis incur a similar risk of colorectal cancer [43]. Duration of disease and pancolitis are well recognized as risk factors for the development of malignancy, with the risk of cancer increasing over that of the general population by 1% each year after 10 years of disease [44,

Table 22.4 Differential diagnosis of granulomas in colon specimens

Crohn disease
Infections
Salmonella (microgranulomas)
Campylobacter (microgranulomas)
Mycobacteria (tuberculosis and avium-intracellulare)
Yersinia
Brucellosa
Tularemia
Schistosomiasis
Fungal infections
Mucin and foreign body granulomas
Chronic granulomatous disease
Pneumatosis intestinalis
Malakoplakia
Sarcoidosis

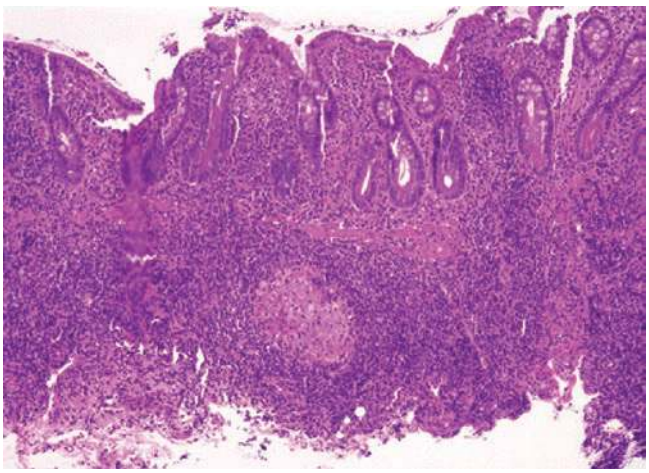

Fig. 22.14 Crohn disease, terminal ileum. A well-formed, nonnecrotic granuloma is present in the superficial submucosa, away from any ruptured crypt. Contrast with Fig. 22.10. H + E, ×100

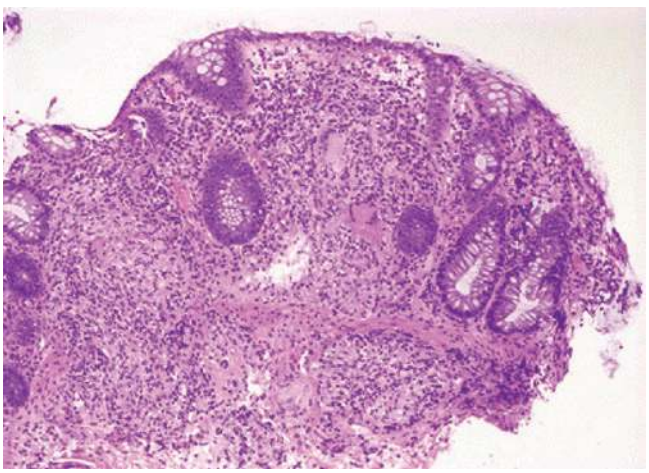

Fig. 22.15 Chronic granulomatous disease. Colon biopsy from a 5-year-old boy reveals numerous granulomas throughout the mucosa and submucosa. H + E ×100

45]. Unfortunately, there is a paucity of prospective data describing long-term inflammatory bowel disease with early-onset ulcerative colitis and ultimate cancer risk in pediatric patients. Other less well-characterized risk factors include concomitant sclerosing cholangitis, an excluded, defunctionalized or bypassed segment and depressed red blood cell folate levels [44]. Children who develop colitis before the age of 10 years should undergo colonoscopy screening during their adolescence, and dysplasia and adenocarcinoma have been documented in adolescents and young adults with long-standing colitis [46]. Dysplasia in colitics is generally plaque-like or nodular, frequently referred to as the DALM (dysplasia-associated lesion or mass) lesion [47] (Fig. 22.16a, b). Epithelial dysplasia generally precedes carcinoma; therefore, yearly surveillance colonoscopy is recommended. Since reliability and patient compliance of serial colonoscopy to detect dysplasia are not perfect, prophylactic colectomy should be considered in any individual who developed ulcerative colitis during childhood.

"Atypical" Features in the Diagnosis of Ulcerative Colitis

Rectal Sparing and Patchiness

Although ulcerative colitis is traditionally considered to be a diffuse process that begins in the rectum and extends proximally in a continuous fashion, a number of studies suggest that initial rectal biopsies in children with UC may not demonstrate mucosal architectural changes as consistently as in adults or may even be "normal" (rectal sparing) (Fig. 22.17). An unequivocal diagnosis of IBD may be more difficult in these cases, as may be distinction between UC and CD.

Five of twelve children with untreated UC in one study were found to have mild patchy inflammation or normal histology in the rectum [21], whereas relative rectal sparing compared to adults was found in one study of 53 children [23]. In one study, "absolute" rectal sparing, in which evidence of both inflammation and chronicity is absent, is infrequent in children with UC (4% of 73 pediatric cases), though

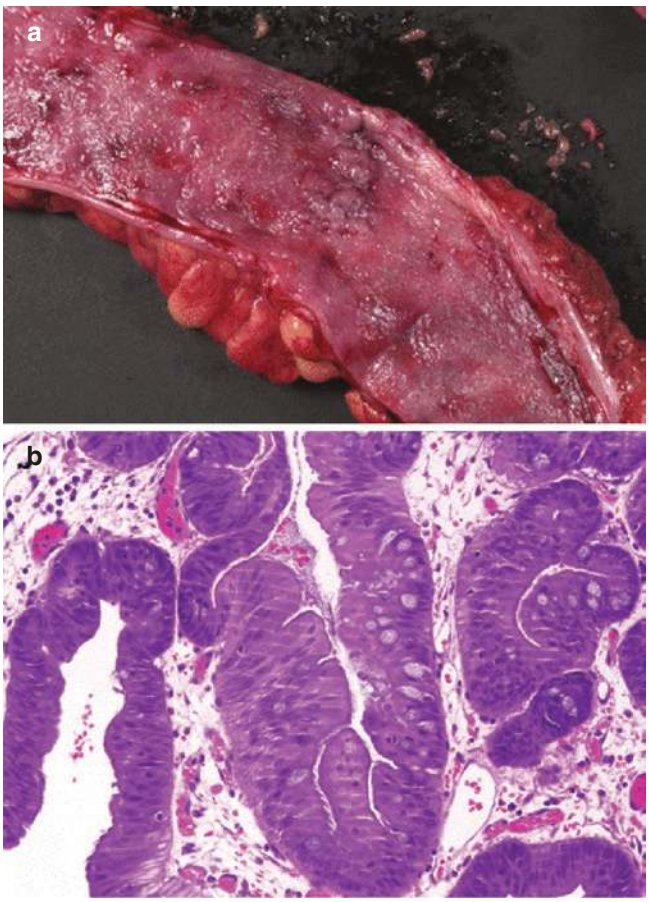

Fig. 22.16 Dysplasia in 16-year-old boy with 10 year history of ulcerative colitis. (**a**) plaque-like lesions present in the colon. (**b**) Histologic section through area of dysplasia in crypt and surface epithelium shows piled-up enterocytes with hyperchromatic nuclei and loss of polarity

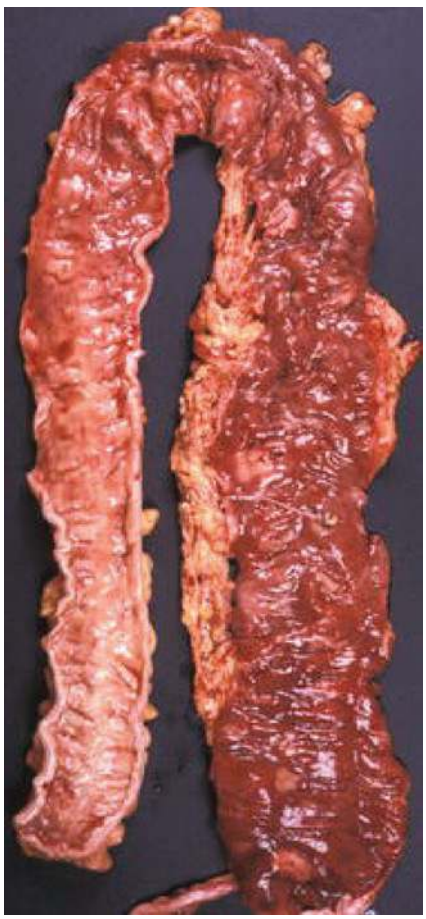

Fig. 22.17 Rectal sparing in ulcerative colitis. A 15-year-old female with several years history of ulcerative colitis which became refractory to medical therapy. The colectomy specimen reveals a diffuse colitis, much milder in the rectum than proximally

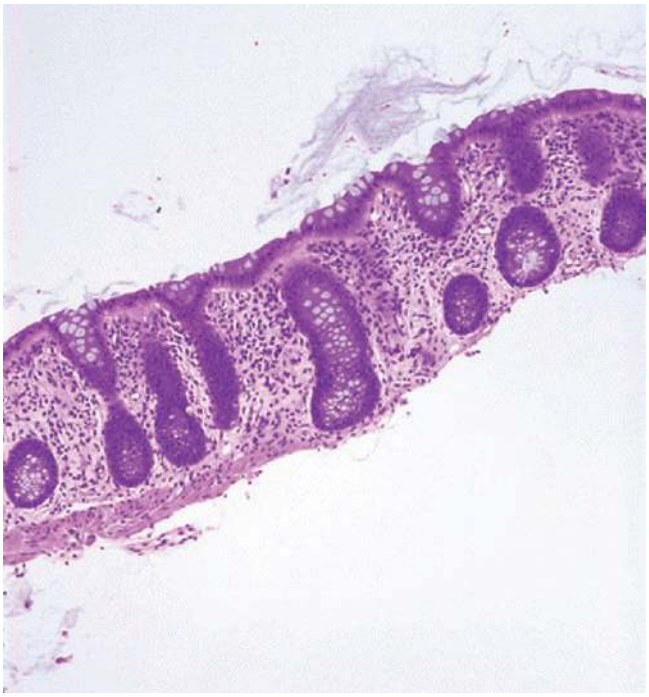

Fig. 22.18 "Quiescent" colitis. Rectal biopsy in an 11-year-old boy with history of ulcerative colitis while on therapy. Mild-crypt architectural changes are present without active inflammation. H + E, ×100

"relative" rectal sparing, defined as the presence of inflammation without changes of chronicity, is more frequent, noted in 26% of cases [19]. Faubion et al. identified a 27% prevalence of rectal sparing in children with IBD and sclerosing cholangitis, suggesting the possibility that rectal sparing may be more common in this subset of patients [48]. Moreover, discontinuous involvement and rectal healing have been reported during the course of long-standing disease in adults, which likely results from treatment effect or natural variation in the course of disease and also reflects the current clinical practice of sampling multiple mucosal biopsies over time [49, 50]. *Medical therapy* can have a profound but variable effect on mucosal histology, ranging from decreased intensity of the inflammatory infiltrate to complete normalization of the mucosa, including discontinuity of mucosal disease in UC [51]. Quiescent colitis is characterized by mucosal atrophy and crypt architectural changes in the absence of the acute inflammation, ulceration, and mucus depletion seen in the active phase (Fig. 22.18).

Backwash Ileitis

"Backwash ileitis" refers to an abnormal radiologic or endoscopic appearance of the terminal ileum, usually in patients with an ulcerative pancolitis, which is postulated, as the name implies, to result from reflux of inflamed colonic contents into the terminal ileum. Strict morphologic criteria for this diagnosis, though not defined, rest mainly on a combination of length of involvement of the ileum (usually <10 cm), a normal ileocecal valve without radiologic and/or endoscopic signs of transmural disease or stenosis, and mild mucosal inflammation without granulomas. In a study by Heuschen, 22% of patients with pancolitis had evidence of backwash at colectomy, whereas none of those with left sided colitis had evidence of backwash [52]. However, ileitis in UC may also represent primary ileal disease [53]. Recently, Haskell and colleagues found a 17% (34 of 200 patients) prevalence of inflammation in the terminal ileum of ileocolectomy specimens from patients with ulcerative colitis [54]. These changes were generally mild, consisting of villous atrophy, increased mononuclear cells in the lamina propria, and scattered crypt abscesses. Of these 34 patients, 32 had pancolitis, but in two patients colonic inflammation was subtotal or left sided. Furthermore, in the absence of granulomas, differentiating "backwash ileitis" from CD of the ileum can be problematic. Pyloric gland metaplasia has been suggested as a useful differentiating feature, if present [33]. "Backwash ileitis" is not believed to be a contraindication to the use of the ileum as a pouch nor to predispose to pouchitis after ileoanal anastomosis [55]. In one pediatric study, the presence of backwash ileitis, defined as a mild mixed inflammatory infiltrate of the lamina propria without crypt distortion, atrophy, or epithelial changes, and contiguous to active inflammation in the colon, did not increase the risk of pouch failure [53].

Upper GI Tract Involvement in UC

Disease of the upper intestinal tract in CD is well documented and present in 30% of patients, in whom it may cause functional abnormalities such as delayed gastric emptying [56–59]. Endoscopic biopsies of the upper GI tract in children with IBD have revealed esophagitis, duodenal ulcers, and villus atrophy, with a comparable prevalence in both CD and UC in some prospective studies [60, 61]. Upper GI tract disease with extensive duodenal involvement has been reported to occur concomitant with or many years after a well-established diagnosis of UC [62]. Whether upper GI tract disease reflects aberrant anatomic expression of UC, misdiagnosed CD or a coexisting illness is still debatable. In one study by Kundhal et al., granulomas were present on antral biopsy in 5 of 39 children with a diagnosis of ulcerative or intermediate colitis (14%), thus, changing the diagnosis to CD [63]. On the other hand, conditions such as reflux esophagitis and *Helicobacter pylori*–associated gastritis are common and may be coincidental in patients with UC [64], to which must be added the confounding effects of long-standing use of medications such as corticosteroids.

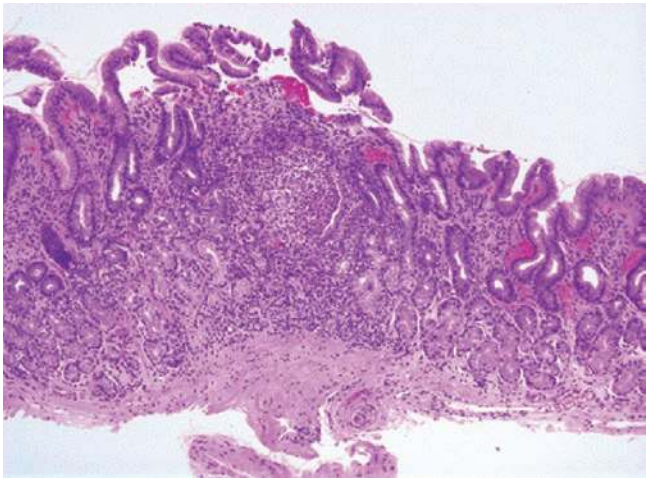

Fig. 22.19 Focal gastritis. Antral biopsy in a 14-year-old boy with IBD reveals a clustering of neutrophils and mononuclear inflammatory cells around several glands, in a background of diffuse mild chronic inflammation. H + E, ×200

Lymphocytic esophagitis, defined histologically as >20 lymphocytes per high power field without neutrophils, has been associated with IBD in pediatric patients, particularly Crohn disease, where it may be prevalent in up to 28% of patients [65]. Focally enhanced gastritis, defined as a perifoveolar or periglandular mononuclear or neutrophilic inifiltrate around gastric crypts, appears to be significantly more common in CD than in UC in patients without *H. pylori* [63, 64] (Fig. 22.19). In a retrospective study of 238 children with UGI biopsies, focal gastritis was present in 65% of patients with CD and in 20.8% of patients with UC, compared to 2.3% of controls without IBD and one of 39 with *H. pylori* [66]. Pascasio reviewed 438 consecutive biopsies in children with gastritis looking for histologic markers for CD such as granulomas, and focal glandulitis [67]. Of 58 patients diagnosed as having CD by colonic biopsy and other standard criteria, 34 (77%) were predicted to have CD by gastric biopsy alone. Eosinophils were a significant component in many of the inflammatory foci. In their experience, none of the focal glandulitis biopsies had a history of UC. Duodenal inflammation, with villous blunting, lamina propria eosinophils and increased intraepithelial lymphocytes may also be noted in a significant proportion of patients and need to be distinguished from other causes such as celiac disease [65].

Periappendiceal Inflammation in Ulcerative Colitis

Ulcerative colitis is classically regarded as a diffuse disease beginning in the rectum and extending proximally in a continuous fashion without skip areas. However, studies have documented *discontinuous mucosal disease*, or "skip" areas, in patients with ulcerative colitis: cecal involvement (cecal patch) separated by normal mucosa from distal colitis in 15–86% of patients undergoing surgery [68–72], and appendiceal involvement [73, 74]. D'Haens et al. found that 75% of patients had periappendiceal involvement at the time of diagnosis of distal UC, in whom inflammation was limited to the left side of the colon [69]. In a more recent study, 29 of 367 patients with UC who did not have a pancolitis and had no prior appendectomy were found to have periappendiceal inflammation, the severity of which paralleled that of the distal colon [75]. Yang et al. reported that involvement at the appendiceal orifice is not a consequence of therapy for extensive UC, but rather a distinctive "skip" lesion in patients with distal UC [76]. It has been suggested that the appendix may be a "priming" site for UC by acting as a reservoir for early-activating T-cells [77]. One pediatric study examined appendices from resected intestinal specimens of patients with IBD who failed medical therapy and found that all the patients in the study (17 UC, 24 CD) had appendiceal involvement [78]. Appendiceal inflammation in these cases of UC is usually described as superficial, whereas inflammation in typical acute appendicitis is transmural.

Fulminant and Indeterminate Colitis

Severe fulminant colitis, also referred to as toxic megacolon, is a medical and surgical emergency, which, although reported to occur in up to 5% of all ulcerative colitis patients, is relatively uncommon in pediatric patients. Toxic megacolon usually occurs in the presence of severe pancolitis and results in profound dilatation of the colon secondary to severe intestinal inflammation with consequent disturbed intestinal motility. Under these conditions, disrupted mucosal integrity may allow entry of bacteria to submucosal tissues which may lead to necrosis, perforation, and peritonitis. The use of antidiarrheal agents, a recent barium enema or colonoscopy, has been implicated [79]. Histopathologic examination of these cases at presentation may not always adequately distinguish between UC and CD. Deep linear ulcers and fissuring with a "cobblestone" mucosa are commonly observed in these cases (Fig. 22.20a, b). Identification of small bowel involvement (other than "backwash ileitis") and deep lymphoid aggregates away from areas of mucosal ulceration and epithelioid granulomas are useful indicators in making a diagnosis of CD [80].

The term "indeterminate colitis" (IC) has been used for years to identify patients with IBD limited to the colon, but with features that do not allow distinction between UC and Crohn disease. As originally used by Price, IC was applied to cases presenting as fulminant colitis with overlapping features of UC and CD [81]. An extended study by Wells et al.

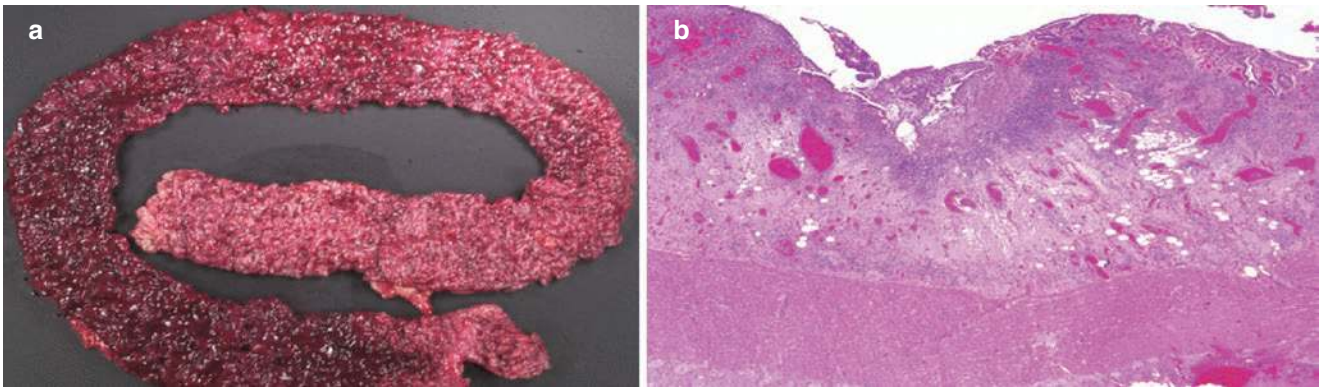

Fig. 22.20 Fulminant colitis. (**a**)Total colectomy specimen from a 17-year-old boy shows a granular diffusely hemorrhagic mucosa, predominantly towards the proximal portion of the colon (*left side* of the photograph). (**b**) Low-power histologic section

of the cohort of patients initially published by Price revealed that after histologic re-examination of 46 cases initially diagnosed as IC, 19 cases were considered to have CD, and 11 cases were classified as probable UC, leaving 16 cases of IC. Four patients were further classified as UC or CD after a follow-up period of 2.5 years [82]. Thus, long-term follow-up studies of mostly adult patients initially classified with IC suggest that an eventual diagnosis of either UC or CD can be obtained in most patients. Silverberg et al., in a report of the Working Party of the 2005 World Congress of Gastroenterology, have suggested that the diagnosis of "indeterminate colitis" is rendered only in patients with suspected IBD after colectomy, and "unclassified IBD" for patients diagnosed after a biopsy that did not suggest UC or CD [83]. Epidemiologic studies cite a prevalence rate of IC of 5–10% in adults [84]. The outcome of ileal pouch procedures in patients with a diagnosis of IC (mainly adults) is also controversial, some studies reporting a higher rate of complications [85–87], others suggesting no difference in outcome between patients with IC and UC [88, 89]. The prevalence rate of IC may be higher in children, though there is a paucity of reliable epidemiologic data regarding that issue. In a Swedish study, 27% of cases of pediatric IBD were initially diagnosed as IC. During a 12-year period, diagnoses were changed in 32 of these 171 cases, 23 to UC [90]. One fifth of cases of IBD in children less than 5 years of age were classified as IC in a study at the Children's Hospital of Philadelphia [91]. After a median follow-up of 7 years, 5 of 19 cases initially assigned to the IC group were reclassified as either CD or UC. Changes in diagnosis were made more frequently in those cases diagnosed before 1990, which could either be due to longer duration of follow-up, or to technical improvements in pediatric colonoscopy. A longitudinal study of 250 pediatric IBD patients reported that 74 (29%) were initially classified as IC, and only 29 were reclassified after a 7-year follow-up [92]. According to recent recommendations from a working group of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, and the Crohn and Colitis Foundation of America, a diagnosis of IC may be rendered in a pediatric patient with disease limited to the colon in cases where there is absolute rectal sparing, the presence of ileitis with disease limited to the left colon, severe focal gastritis or colitis with growth failure [93].

Pouchitis

In UC patients who undergo ileal pouch anal anastomosis (IPAA), the ileal mucosa commonly undergoes histologic modifications to a colon-like appearance resulting from changes in bacterial population, short-chain fatty acid, and bile salt concentrations [94, 95]. Morphological similarity to an inflamed colon is reinforced by the detection of a mucin histochemical profile similar to that of colonic epithelium and by an inflammatory immunoprofile like that seen in ulcerative colitis [95]. At endoscopic examination, pouchitis may be mild, with mucosal hyperemia and edema, to severe, with ulcers, hemorrhage, and pseudomembrane formation [96–98]. A minority of patients develop inflammation of the ileal limb proximal to the pouch, strictures (typically in the proximal pouch) and fistulas, and even extraintestinal disease which can mimic CD. Histologic examination of mucosal biopsy specimens obtained from these pouches typically demonstrate partial to complete villous blunting with crypt hyperplasia and increased mononuclear inflammatory cells and eosinophils in the lamina propria (Fig. 22.21). Areas of pyloric gland metaplasia may be present. Active inflammation, usually focal, is characterized by neutrophils in the lamina propria, cryptitis, crypt abscesses, and, in severe cases, erosions, or ulcers. Deep or transmural inflammation may be observed [95, 99–101]. Granulomas of the mucin or foreign body type may also be identified [95, 101]. Although these granulomas are not diagnostic of CD, as previously noted,

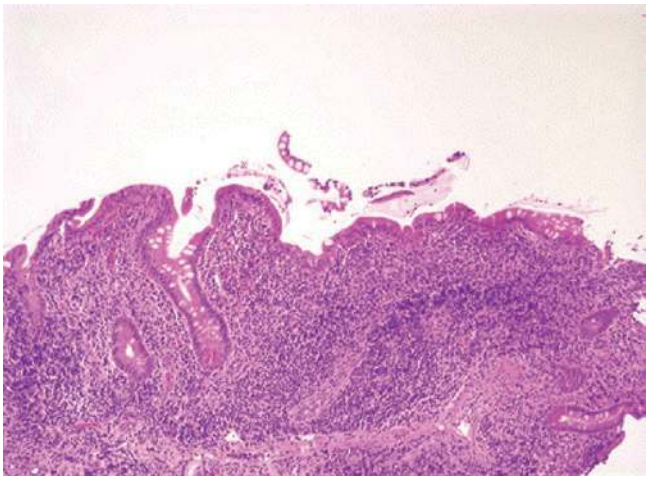

Fig. 22.21 Pouchitis. Biopsy from the neorectum in an 18-year-old female following an ileoanal pull-through reveals active chronic inflammation of the ileal mucosa with crypt loss and distortion

they nonetheless cause concern; however, if such granulomas are found only in the pouch and not upon review of the colectomy specimen, it suggests that these granulomas may have arisen as a result of the abnormal luminal environment of the pouch and not from unrecognized CD. In addition, ischemic changes secondary to vascular compromise and pouch mucosal prolapse may occur, such as crypt hyperplasia, extension of smooth-muscle fibers from the muscularis mucosae into the lamina propria and superficial erosions with a fibrino-inflammatory exudate.

In view of the previous discussion, a diagnosis of CD should be considered only when review of the prior colectomy specimen reveals unequivocal features of CD, such as nonmucin granulomas, or when unequivocal CD develops in parts of the gastrointestinal tract distant from the pouch [99]. No single histologic feature in the colectomy samples of patients with UC or IC seems to be associated with pouch-related complications [102].

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Capsule Endoscopy in Pediatric Inflammatory Bowel Disease

23

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Introduction

Since capsule endoscopy (CE) was introduced in 2001, this tool has been adopted widely for the evaluation of mucosal small bowel (SB) disease. Its use particularly increased after North American and European marketing clearance for patients 10 years of age and older was obtained in 2003 and expanded to 2 years of age and older in 2009, with patency capsule use approved the same year [1].

Advances in the video capsule's technical aspects (dual or rotational cameras, wider field of vision, longer battery life), the software (dynamic imaging speed, real-time viewing), and better bowel cleansing have all contributed to improved diagnostic accuracy. Currently, 5 CE systems are marketed and available internationally (PillCam, Medtronic, formerly Given, US; Endoscapsule, Olympus, Japan; MiroCam, Intromedic, Korea; CapsoCam, Capso Vision, US; and OMOM, Chongqing, China), though not all are available in every country.

The desire to expand CE beyond the small intestine has led to the development of a colon capsule (Medtronic) and a pan-enteric capsule (dubbed the Crohn's capsule, Medtronic) to evaluate the small and large intestine in the same procedure, both available in Europe.

Indications

The suspicion of small intestinal Crohn disease (CD) and evaluation of existing inflammatory bowel disease (IBD) are the most common pediatric indications for CE in pediatrics accounting for 63% of the total procedures according to a meta-analysis of 723 procedures, with subsequent articles bringing the total to 1013 analyzed procedures [2–23]. Together with the presentation of abdominal pain and diarrhea in another 10%, this accounts for 73% of pediatric evaluations with CE. Additionally, 16% of the total CE examinations are performed in order to monitor those with known CD, while evaluation of indeterminate colitis (IC) represents 2% of total, and ulcerative colitis (UC) 1% of the total procedures.

The clinical indications vary with age [20]. Among 83 children ages 1.5–7.9 years who underwent CE, the most common indication was occult gastrointestinal bleeding (OGIB) amounting to 36% (30/83) of patients in the cohort. Suspected CD indication after negative endoscopic evaluation accounted for 20 patients (24%) with 11 (55%) positive findings, while CD monitoring was performed in an additional 3 patients. Abdominal pain was the primary indication for another 12 patients (14%), while protein loss and malabsorption were the indications for 9 and 12 patients, respectively (11% and 14%). In contrast, OGIB in older children (10–18 years of age) accounts for only 13–24% overall, while CD accounts for 40–86% of the indications [2, 7, 9, 14, 16, 20].Of note, patients with protein losing enteropathy and malabsorption are younger than those with recurrent abdominal pain or suspected CD [20]. Of further interest, the indication for CE in both of these pediatric cohorts differs from the adult population where 66% of CE use has been for OGIB, including iron deficiency anemia (IDA); 10.6% for clinical symptoms, such as pain, diarrhea, and weight loss without OGIB; 10.4% for CD; and the balance (13.0%) for other indications [24].

Small Bowel Capsule Endoscopy in IBD

Pediatric European and North American GI societies' guidelines suggest full evaluation of the gastrointestinal tract at the approximate time of CD diagnosis in pediatric patients in

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order to assess the extent and severity of the disease since as many as 70% of patients will have SB involvement with 40% estimated to have active disease exclusively in the SB [25–27]. This cannot be accomplished by routine upper endoscopy or colonoscopy since neither traverses more than about 25 cm of the small intestine at either end. Since CE does not require ionizing radiation, sedation, or general anesthesia required by some other imaging methods, it has the potential to be particularly valuable in pediatric IBD assisting in the initial diagnosis and classification of the disease (Figs. 23.1 and 23.2) and providing a mechanism for the mucosal healing (MH) assessment.

Whether or not CE is utilized, another modality is often needed to assess the small intestine. The options include upper GI with SB follow-through (with or without enteroclysis), CT, MRI, push enteroscopy, or small intestine contrast-enhanced abdominal ultrasound (SICUS) as listed in Table 23.1.

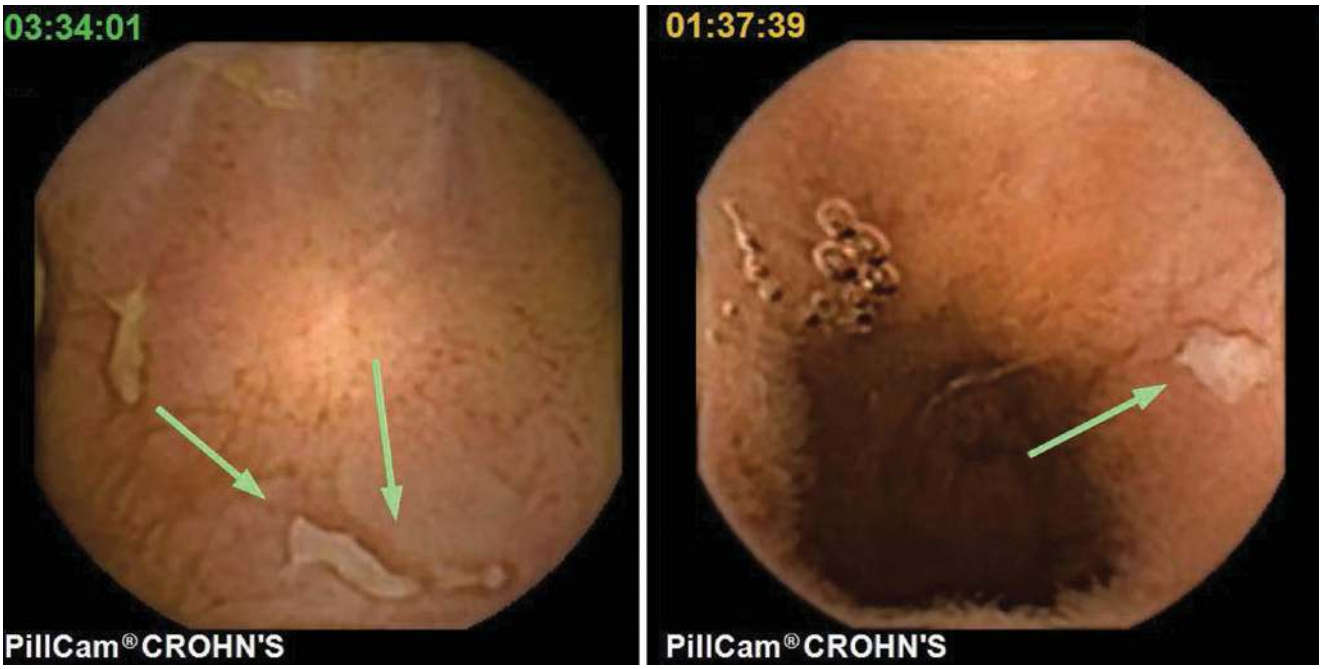

Fig. 23.1 Mild small intestinal Crohn disease, demonstrated by superficial ulcers with minimal surrounding erythema

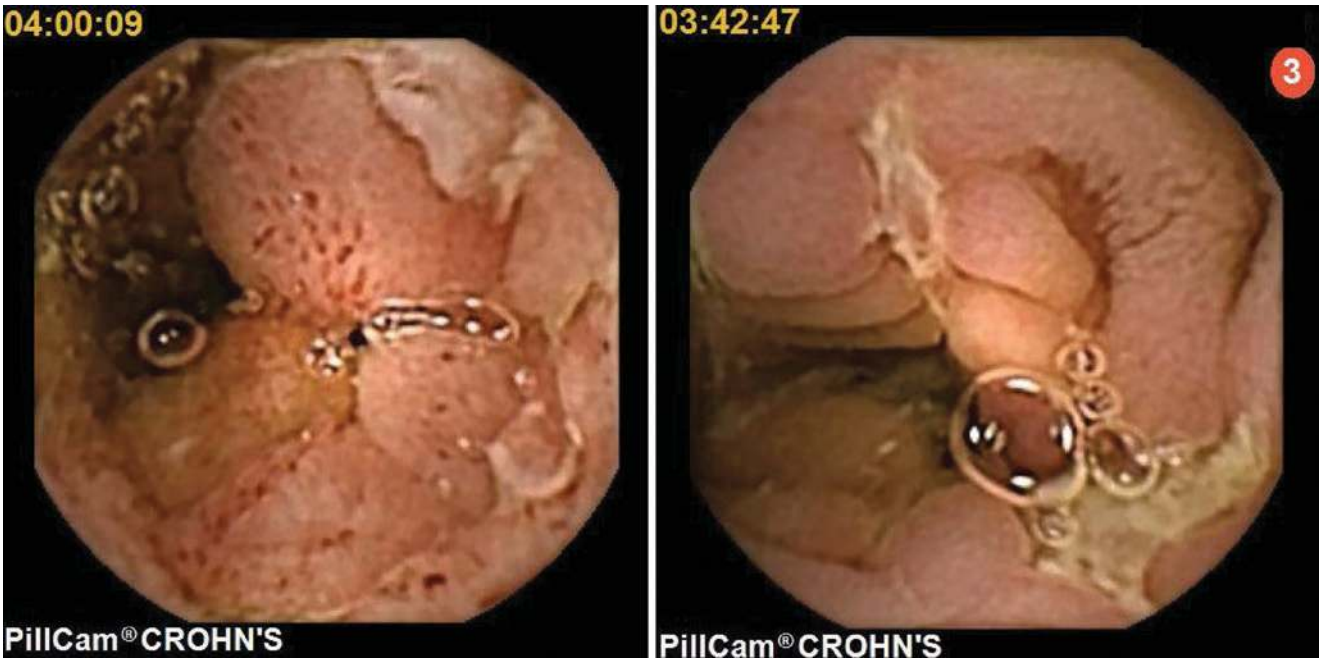

Fig. 23.2 Moderate–severe Crohn disease, with edema and narrowing (stenosis) ulcerations, and superficial hemorrhage

Table 23.1 Comparison of modalities to detect small bowel Crohn disease

Modality	Advantages	Disadvantages	Comparison to CE (Diagnostic yield)
UGI/SBFT/ enteroclysis	Easily obtained, least expensive	Radiation Misses early lesions	CE 63% / SBFT 23% [32]
SICUS	Focuses primarily on ileocecal	Primarily available in Europe, oral contrast	CE 85% / SICUS 81% [33]
CT enterography	Detects strictures and disease external to bowel	Radiation, oral contrast	CE 69% / CT 30% [29, 30]
MR enterography	Differentiates active disease and scarring, detects disease external to bowel	Long procedure, requires no movement	CE 93% / MRE 79% [31–33]
Enteroscopy	Can biopsy tissue	Anesthesia or sedation required, radiation. Long procedure with insertion above and below, can be technically difficult. Not widely available in pediatrics	Studies not reported for detection of IBD
Capsule endoscopy	No radiation or anesthesia, detects early disease, best at jejunal disease	Rare incomplete studies or capsule retention, can have false positives, should not be done if strictures	–
Ileoscopy	Obtain biopsies	Anesthesia or sedation required	CE 61%/Ileoscopy 46% [7]

The initial standard in SB imaging was an upper GI X-ray with fluoroscopic follow-through of barium through the entire small intestine (SBFT). This technique can be modified (enteroclysis) to include an enteric tube placement and double contrast (air or methylcellulose) in order to provide enhanced mucosal imaging. However, a meta-analysis reported that CE was able to detect SB abnormalities more often in those with suspected or known CD (OR 13.0 with a 95% confidence interval of 3.2–16.3) compared to routine SBFT and enteroclysis (OR 5.4 with a 95% CI 3.0–9.9) [28]. Computerized tomography (CT) with intestinal contrast (enterography) administered orally largely replaced fluoroscopy and has been better able to detect the degree or inflammation, the severity of strictures, and the presence of fistula. However, it also requires ionizing radiation and has a lower diagnostic yield than CE in adults and in children [29, 30]. Magnetic resonance imaging can be similarly employed with oral contrast and it is often referred to as magnetic resonance enterography (MRE). The advantages include greater clarity of the imaging findings, the ability to recognize extraintestinal disease manifestations (phlegmon/abscess), and differentiation of active inflammation from fibrosis. The disadvantage is the need for a patient to remain still for 30–45 min in order to allow the image capture, which may be difficult for some pediatric patients, especially at an early age. In large studies, the diagnostic yield is often comparable (CE 93% vs. 79% with MRE) with the sensitivity greater for CE and variable specificity [31, 32]. In a meta-analysis of 13 European studies, the diagnostic yield of CE for detection of active SB CD was similar to that of MRE (10 studies, 400 patients, OR 1.17; 95% CI 0.83–1.67) and SICUS (5 studies, 142 patients, OR 0.88; 95% CI 0.51–1.53). The outcomes were similar for the subgroups, including suspected versus established CD and adult versus pediatric patients. When looking at just the proximal SB, CE was superior to MRE (7 studies, 251 patients, OR 2.79; 95% CI 1.2–6.48), though the difference versus SICUS was not significant [33]. Another adult study demonstrated that CE often changes the disease classification. Using CE, SB lesions were found in 36 of 47 patients, while MRE showed SB involvement in 21 of 47 patients (76.6% vs. 44.7%, $p = 0.001$). Jejunal inflammation was detected by CE in 31.9% of patients and by MRE in 6.4% of patients (15/47 vs. 3/47; $p = 0.03$); lesions in the ileum were detected in 57.4% of patients by CE and in 21.3% of patients by MRE (27/47 vs. 10/47; $p = 0.04$). Finally, in the terminal ileum, CE showed lesions in 68.1% (32/47) of patients, whereas MRE detected lesions in 38.3% (18/47 patients; $p = 0.001$). The original Montreal classification was changed in 53.1% of patients (25/47) based on CE findings and in 12.7% of patients (6/47) based on MRE findings ($p < 0.05$) [34].

By comparison to these primarily adult studies, a group of pediatric investigators in Italy compared multiple modalities and surrogate markers using a consensus reference panel as a gold standard (Table 23.2). The study panel included an investigator representing each modality and the referral pediatric gastroenterologist; and an exam was considered positive only if the whole panel agreed with the evaluation. CE was found to be superior in evaluating proximal SB lesions compared to other imaging tools [30, 35].

An additional prospective pediatric study of 20 patients with CD and 7 with IC showed the sensitivity of MRE and CE of 100% and 83%, respectively, while the specificity of MRE and CE was 57.14% and 78.6%, respectively, using the Pediatric Crohn Disease Activity Index (PCDAI) as a reference. When histology in the ileum or/and duodenum was

Table 23.2 Pediatric studies CE vs. other modalities [35]

Segment	Test	SE, 0/o (95°/o Cl)	SP, 0/o (95°/o Cl)	NPV, 0/o (95°/o Cl)	PPV, 0/o (95°/o Cl)	ACC, 0/o
Jejunum[a]	SICUS	92 (61–100)	89 (65–99)	94 (71–99)	85 (54–98)	90
	CE	92 (61–100)	61 (36–83)	92 (61–100)	61 (36–83)	73
	MRE	75 (43–94)	94 (73–100)	85 (62–97)	90 (55–100)	87
Proximal and mid ileum[a]	SICUS	80 (43–99)	92 (73–99)	96 (79–100)	67 (42–96)	89
	CE	100 (48–100)	74 (49–90)	100 (77–100)	5o (29–81)	79
	MRE	100 (56–100)	92 (73–99)	100 (84–100)	67 (43–96)	93
Terminal ileum[b]	SICUS	94 (64–100)	79 (49–95)	91 (61–100)	85 (62–96)	87.5
	CE	81 (54–96)	90 (55–100)	75 (43–94)	93 (66–100)	85
	MRE	94 (71–100)	80 (51–96)	92 (64–100)	84 (60–97)	87.5

S/CUS Small-intestine contrast US, *CE* Capsule endoscopy, *MRE* Magnetic resonance enterography, *SE* Sensitivity, *SP* Specificity, *NPV* Negative predictive value, *PPV* Positive predictive value, *ACC* Accuracy
[a]Consensus reference standard used as a criterion standard
[b]lleocolonoscopy used as a criterion standard

used as the reference for active SB involvement, CE had a higher specificity compared to MRE (83.3% vs. 50%). In patients with CD, those with an elevated PCDAI (>10) were more likely to have a positive CE as compared to those with a normal PCDAI (83% vs. 21%; $p = 0.018$) [36].

Inflammatory Bowel Disease Undetermined and Ulcerative Colitis

IBD undetermined (IBDU), is twice as common in pediatrics compared to adult-onset IBDU occurring in approximately 13% of pediatric cases and 6% of adults. One-fifth of pediatric cases younger than 6 years and one-third of cases aged under 3 years receive an initial IBDU diagnosis [37].

In a pediatric study, including 26 cases of IBDU, CE detected typical SB CD findings in 16 (62%), whereas SB imaging only detected 7 of those ($p < 0.05$) [38]. In another study of 18 subjects with a mean age of 13.8 years, two of four (50%) UC/IC patients were reclassified as having SBCD. In the four subjects with known CD, two (50%) had CE evidence of more proximal SB mucosal disease than previously recognized. In the 10 subjects with suspected IBD, 8 (80%) had SB ulcerations leading to a definitive diagnosis of CD. The treating physicians reported that CE helped to diagnose CD in 15 of 18 (83.3%) subjects and impacted medical decision-making in 13 of 18 (72.2%) leading to a change in medical management in 14 of 18 (77.8%) [4].

Pan-Enteric Capsule Endoscopy

A colon capsule was developed in 2006, with a second iteration released in 2009. This second-generation colon capsule (CCE-2) has a slightly larger size (11.6 × 31.5 mm) compared to SB capsule; the two cameras contain wider angles (up to 172°) enabling nearly 360° imaging of the colonic mucosa; and like the newest version of the SB (SB3), it has an adaptive image acquisition rate depending on the speed of capsule propulsion. CCE-2 captures 35 frames per second during active movement of capsule, while four frames per second are captured during the stationary period of capsule movement. The CCE-2 also has a battery saving system, with only 14 images per minute captured until SB images are recognized. High-resolution imaging below 0.1 mm, with a magnification of about 1 to 8, and a color enhancement feature improve the detection rate of colon lesions [39].

While the system was originally designed to more readily detect colon cancer, which has little applicability in pediatrics, it has led to pan-enteric capsule endoscopy (PCE), which can be used to evaluate both the small and large intestine in a single procedure. The disadvantages are that the capsule is larger than the SB3 capsule (though the same size as the colon capsule); bowel cleansing resembles that for a colonoscopy with an additional booster dose needed during the actual procedure; and procedure and reading times are understandably longer.

The first published study of 40 pediatric patients (age 13.1 ± 3.1 years) with known CD underwent protocolized, comparative procedures as part of disease course re-evaluation. The sensitivity of PCE to detect colon inflammation was 89% and the specificity was 100%. The positive predictive value (PPV) and negative predictive value (NPV) of PCE for colon inflammation were 100% and 91%, respectively. In the small bowel PCE showed 90% sensitivity, 94% specificity, with PPV and NPV of 95% and 90%, respectively. Accuracy parameters for SICUS (sensitivity 90%, specificity 83%) and MRE (sensitivity 85%, specificity 89%) were lower than those for PCE. No serious adverse events related to PCE procedure or preparation were reported [30].

Subsequently, the results of PCE and ileocolonoscopy (IC) in 66 adult subjects with known CD were reported. The diagnostic yield for active CD lesions was 83.3% for PCE and 69.7% for IC (yield difference, 13.6%; 95% confidence interval 2.6%–24.7%) and 65% of subjects had active CD lesions identified by both modalities. Of the 12 subjects who were positive for active CD by PCE only, 5 had active CD lesions in the terminal ileum. Of note, 3 subjects were positive for active CD by IC only [40]. Two other larger studies of 99 and 93 adult patients, respectively, subsequently reached similar conclusions also showing the superiority of PCE over MRE and found that raised C-reactive protein and fecal calprotectin were poorly sensitive in detecting active disease (0.48 and 0.59, respectively) [41, 42].

Monitoring the Mucosa

Mucosal healing (MH) defined endoscopically is predictive of decreased disease activity, hospitalizations, and surgery [43]. CE's diagnostic precision and minimally invasive nature makes it a logical tool to provide the information on MH and several studies have borne that out. The first was a cohort of 40 subjects with known or suspected non-penetrating and non-stricturing CD who underwent CE before treatment and after they clinically improved (after at least 1 month). The parameters used were the number of aphthous lesions and large ulcers and the presence of any endoscopic lesions [44]. Since only the number of large ulcers improved significantly with treatment, the authors concluded that the clinical response did not seem to correlate with the MH in patients with CD of the SB.

A small, prospective pediatric study utilized sequential CE to evaluate the mucosal response and PCDAI as one of the parameters to evaluate clinical improvement during a trial of a specific carbohydrate diet in ten patients with active CD (PCDAI ≥15). Nine patients completed the initial 12-week trial, with PCDAI decreasing from 21.1 ± 5.9 to 7.8 ± 7.1 (p = 0.011). CE showed improvement using the Lewis Score (LS), which declined from 2153 ± 732 to 960 ± 433 (p = 0.012). Seven patients continued the SCD up to 52 weeks; the PCDAI (5.4 ± 5.5) remained improved (p = 0.027) compared to baseline with mean LS at 1046 ± 372, which was similar to the 12-week score. Two patients showed sustained MH. Subsequent studies have confirmed the feasibility and safety of using CE as a minimally invasive method to evaluate mucosal response to treatment [45–48].

Even more exciting is the prospect of taking monitoring to the next level where the capsule is used to modify therapy for CD. This was first shown as a possibility in adult study by Efthymiou et al. [44] and in pediatrics by Gralnek et al. [4]. The effectiveness of this strategy has been demonstrated in a cohort of 48 pediatric patients with CD, first over 24 and then 52 weeks. PCE detected inflammation in 34 patients (71%) at baseline, 22 patients (46%) at week 24, and 18 patients (39%) at week 52 (p for comparison among time points <0.05). Findings from PCE led to a change in therapy for 34 patients (71%) at baseline and 11 patients (23%) at 24 weeks, whereas only two patients with negative results on PCE (4%) changed therapies based on findings from imaging. When the treat-to-target strategy was applied, proportions of patients with MH and deep remission (DR, clinical, and mucosal normality) increased from 21% at baseline to 54% at week 24 and 58% at week 52 (p for comparison among baseline and 52 weeks <0.05), while two patients (4%) did not respond to treatment. The DR and MH rates increased over time (21% to 58%) using treat-to-target strategy [49, 50]. Of note, comparisons were made to other modalities at each of the time points. The overall diagnostic yield of PCE, MRE, and biomarkers were 54%, 37%, and 33%, respectively ($p < 0.05$). PCE showed DR in 28 (58%) patients with the detection of new lesions in four and a complete MH in six (with previous partial MH at 24 weeks). MRE and SICUS had good concordance in evaluating DR (24/28, 86%), but did not identify mucosal improvements after therapy ($p < 0.05$). Fecal calprotectin and C-reactive protein were not able to accurately evaluate DR in either groups at 24 and 52 weeks (BR in 65% and 69%, respectively).

A 104-week PCE evaluation of the 42 subjects left in the cohort (two developed an ileocecal valve stricture at 52 weeks; four were lost to follow-up) was performed. There was only 7% drop-off in MH compared with one-year assessment. In intention-to-treat (ITT) analysis complete MH at 52 weeks was associated with decreased clinical relapse rate ($p < 0.003$), reduced steroid use ($p < 0.0005$), fewer treatment escalation ($p < 0.0003$), and diminished hospitalization rates ($p < 0.0001$). There was a trend toward decreased need for surgery, but this did not reach statistical significance ($p = 0.065$) (Fig. 23.3).

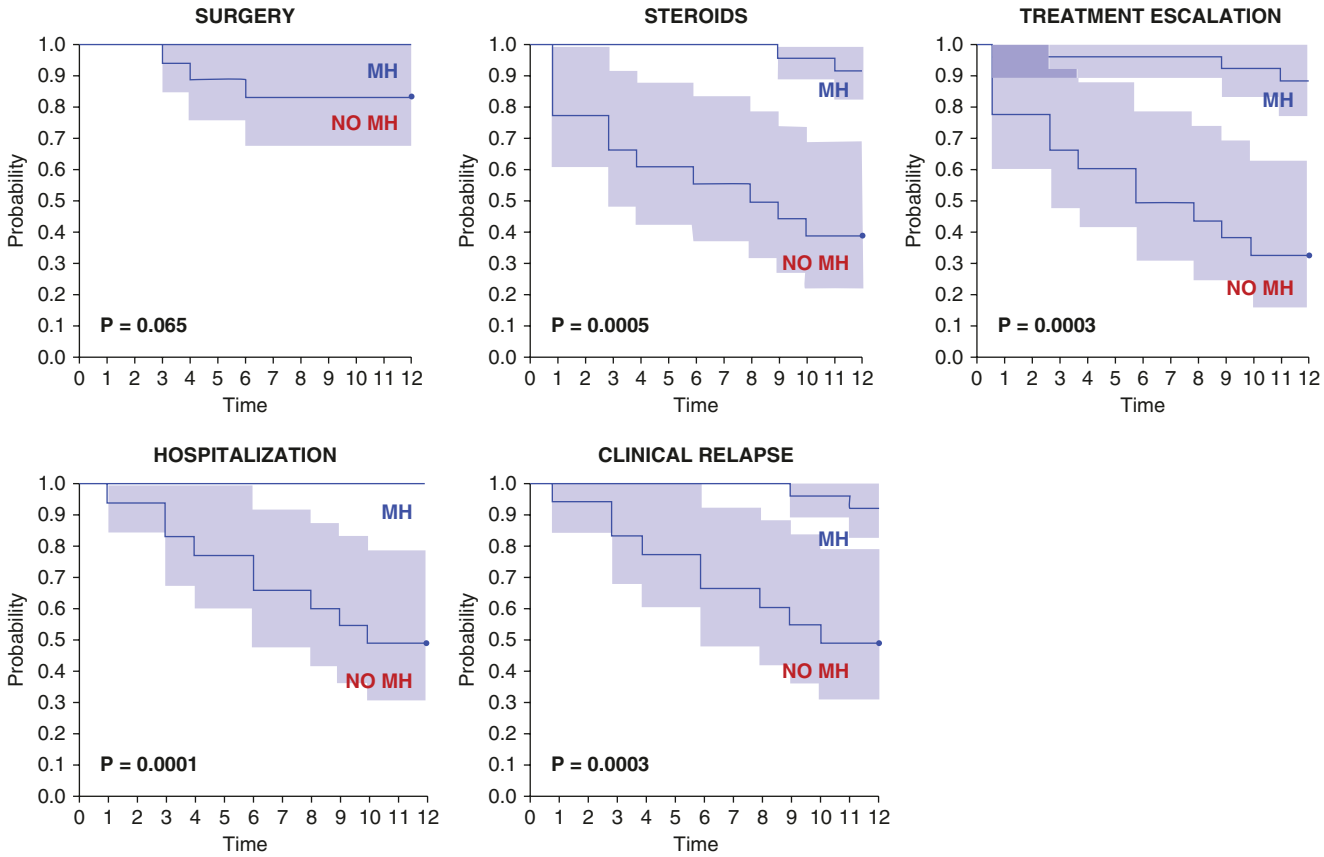

Fig. 23.3 Two-year outcomes when employing pan-enteric endoscopy in a treat-to-target strategy [50]

Capsule Topics of Interest

While much has evolved over the nearly two decades since CE has been in clinical use several issues remain, especially in pediatrics [51]. Therefore, the following topics need to be considered:

- Contraindications
- Capsule swallowing versus endoscopic placement
- Bowel preparation
- Interpretation consistency and scoring methods
- Capsule retention

Contraindications to Capsule Endoscopy

Many of the initial concerns and contraindications have been reevaluated and addressed over the years; however, certain precautions still need to be considered. Known stenosis of the gastrointestinal tract is the most obvious contraindication for CE, but even that is obviated if surgery is scheduled or recognized as the potential treatment. In at least one case [52], CE was performed specifically to help the surgeon identify the stricture intraoperatively. In patients with CD those who have had intestinal resection or have undergone radiation to the abdomen clinical signs of obstruction are a contraindication unless the passage of self-dissolving patency capsule within timed guidelines (discussed below) and radiographic evidence of patency is proven, or surgery is considered pre-procedure.

Although CE is approved for use in children over 2 years of age, there have been reports of younger children who have safely undergone the procedure with endoscopic capsule placement. Initially, swallowing and motility disorders were considered contraindications. However, endoscopic placement of the capsule can be considered in patients with swallowing disorders. For those with esophageal or gastric motility disorders endoscopic capsule placement and/or application of prokinetic agent could be considered.

CE should be restricted to urgent cases in pregnant females where diagnosis cannot be postponed after delivery, since safety data are not available. The capsule manufacturers state that the study is contraindicated in patients with implanted cardiac devices such as a pacemaker, cardioverter,

or left heart assist device, though theoretical and clinical evidence suggest that CE can be performed safely. Although video capsules are not proven safe with magnetic resonance imaging (MRI), incidents of patients undergoing MRI with a capsule in the abdomen have been reported, showing susceptibility artifacts, but no clinical harm [53].

Swallowing the Capsule/Endoscopic Placement for Those Who Cannot Swallow

Patients of any age may be unable to swallow the capsule similarly to the inability or unwillingness to ingest pills. These patients can use stimulus fading to learn and practice swallowing, first small and then progressively larger gelatin capsules or candies with water, other liquids, or even a small amount of yogurt, pudding, or applesauce [54]. For those unable or unwilling to swallow a capsule and those with motility disorders, a capsule can be placed endoscopically into the stomach, or preferably the duodenum, under direct vision. This should be performed under general anesthesia, since there are instances where capsules have been placed in the trachea when deep sedation was used. The front-loading capsule delivery device (AdvanCE TM, US Endoscopy) can be used for older SB2 capsules. However, the newer SB and PCE capsules have cameras at each end, so launching them with the extruder that pushes them out may impair the lens cover and eventually interfere with image interpretation. The alternative, a Roth Net (US Endoscopy) use has been shown to be associated with mucosal trauma in 50% of placements, and it may be difficult to launch in the duodenum [20].

A recent pediatric study compared the success rates and the differences between 51 swallowed and 53 endoscopically placed CEs. The median age was 12.8 years (range 1.6–18.5) among the 88 subjects. Children requiring endoscopic placement were significantly younger (9.8 vs. 14.2 years; $p < 0.001$), lighter (34.5 vs. 54.9 kg; $p < 0.0001$), and had longer small intestinal transit time (308 vs. 229 min; $p < 0.0001$). Positive findings were more likely in those who swallowed the capsule (50% vs. 30%, $p = 0.017$). Poor views were found in 30% (16/53) of patients in the endoscopic placement group due to iatrogenic bleeding from biopsies taken during concurrent procedures, but that was not thought to affect outcome or subsequent patient management [55].

Bowel Preparation

Due to the inability to flush or suction fluids or gas, adequate bowel cleaning is essential for successful CE. Debris, biliary secretion, bubbles and blood, especially in the distal SB, and failure of the capsule to reach the cecum have the potential to limit the diagnostic yield [56] So far, the optimal preparation regimen has not been established. A clear liquid diet the evening before CE and an overnight fast appear to be associated with poor visibility of the terminal ileum in most patients [57]. Since simethicone seems to improve mucosal visualization by reducing air bubbles and gas, a combination of simethicone and polyethylene glycol (PEG) has frequently been promulgated as an effective means to increase the visibility of the small intestine [58, 59]. The only pediatric study to date prospectively evaluated 198 patients with five different preparation regimens [60]. The least amount of PEG solution tested, 1.75 g/25 mL per kg (up to 1 L) of PEG solution (70 g/1000 mL) the night before the procedure plus 20 mL (376 mg) of oral simethicone 30 min before capsule ingestion, appears to be the preparation of choice for SB CE in children. Discomfort was lessened and mucosal visualization improved significantly in the distal ileum, which is the portion most often affected by debris.

A specific score to evaluate cleansing for CE has recently been developed and validated by 20 readers who independently read 1233 images in duplicate, 4 weeks apart. Each individual image was scored on two domains: visualized mucosa (VM) defined as the percentage of mucosa visible in the image and degree of obstruction (DO) defined as the percentage of the image obscured by debris, bubbles, and bile. Each domain was assigned a score between 0 and 3, and the overall score was the mean of the two domain scores. Almost perfect inter-rater and intra-rater reliability was observed for what is to be known as the KODA score and used for clinical trials [61].

A similar effort has been occurring for colon capsule cleansing. In this grading scale (CC-CLEAR), the colon is divided into three segments: right, transverse, and left colon. Each segment is classified according to an estimation of the percentage of mucosa clearly visualized (0: less than 50%; 1: from 50 to 75%; 2: more than 75%, and 3: more than 90%). The overall cleansing classification is a sum of each segment scores with grading defined as inappropriate (0 to 5 points); good (5 to 7 points) and excellent (8–9 points). If any segment presents a classification of 1 or less, the overall classification given was considered inappropriate independently of the overall score. This scale was considered superior to a previously developed score, the Leighton scale, on 58 consecutive colon capsules, with excellent inter- and intra-observer agreement [62].

The regimen devised for pediatric pan-enteric cleansing is based on what was used for the treat-to-target studies achieving an adequate cleaning level in >80% of cases [49]. This regimen is based on PEG and sodium phosphate (NaP) as boosters to speed up the capsule during the exam (Table 23.3). This scheme was able to obtain completion and excretion rates higher than 95% and 84%, respectively.

Table 23.3 Bowel cleansing technique for pan-enteric capsule endoscopy [30]

Day	Hours	Action
−1	All day	Liquid diet
	6–9 pm	50 mL/kg up to 2 L of **PEG**
0	6–7 am	50 mL/kg up to 2 L of **PEG**
0	8:00 am	**Ingestion of CCE**
0		**Domperidone** 20 mg (or metoclopramide when unavailable) If capsule remained in stomach >1 h
0	Upon SB detection	30 mL **NaP** + 1 L water
0	3 h later	30 mL **NaP** + 1/2 L water
0	3:30 h later (if necessary)	10 mg **bisacodyl** suppository

Table 23.4 Capsule endoscopy–Crohn Disease Score

Capsule endoscopy-Crohn diease (CE-CD) Score and Simple endoscopic score for Crohn disease (SES-CD)				
Variable	0	1	2	3
Size of ulcers	None	Aphthous ulcers (0.1–0.5 cm)	Large ulcers (0.5–2 cm)	Very large ulcers (>2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowing (stenosis)	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Interpretation and Scoring Methods

The diagnosis of CD in the SB is difficult to establish consistently by any single test. Certain features may be present: granuloma on histology, bowel wall thickening on imaging, or severe ulcerations throughout SB on CE, but even these can be non-specific if infectious or other inflammatory conditions are present. As a result, several endoscopic scoring systems have been implemented to standardize the assessment of endoscopic findings. Two main CE scores have been developed for CD: the Lewis score (LS) and CE Crohn Disease Activity Index (CECDAI) [63, 64]. Both indices have been used in small pediatric series, but remarkable discrepancies between the two were reported, with CECDAI better reflecting intestinal inflammation than LS [65]. LS is currently the most widespread and known CE score with well-defined cutoff values for disease activity. The LS total value is largely driven by stenosis and also includes villous edema, which is not considered a major feature of CD, and it leads to the risk of errors in the assessment of MH. Many endoscopists are not familiar with the current available CE scores since they mostly use scoring for standard colonoscopy, which uses different items in assessing inflammation [66]. This difference makes objective evaluation of CE lesions using available scores more complicated.

To rectify the situation and to create a seamless CE score for both the small and large intestine that aligns with colonoscopy scoring the Capsule Endoscopy–Crohn Disease (CE-CD) index was devised adapting the Score and Simple endoscopic score for Crohn disease (SES-CD), which is validated for ileocolonoscopic findings [67]. Similar to SES-CD, CE-CD considers ulcers as elemental lesions of CD and takes into account the number of ulcers, size of the largest ulcer, percentage of affected surface, and the presence of stenosis in both the small and large intestine (Table 23.4) [68]. To date, the CE-CD has proven to be simple, reliable, and reproducible in the evaluation of SB inflammation in 312 pediatric patients with CD. This score seems also predictive of disease outcomes over time. There appeared to be a good correlation between PCDAI and CE-CD (r: 0.624), LS (r: 0.633) and CECDAI (r: 0.651). PCDAI appears to be a moderately accurate classifier of SB inflammation (CE-CD ≥ 9; AUC: 0.779) with a high specificity (90.1% for PCDAI ≥ 15) and low sensitivity (60.5%). In accordance with this, we observed that 35 out 132 (26.5%) patients in clinical remission (PCDAI < 10) had a surprisingly severe endoscopic patterns (CE-CD > 13), suggesting that CE-CD might be a useful pre-clinical predictor of CD exacerbations rather than overestimating disease severity [66]. However, all interpretation is subject to the experience and skill of the reader. As a result, the American Society of Gastrointestinal Endoscopy (ASGE) recommends that the use of CE be limited to practitioners already competent and privileged to perform standard upper and lower endoscopy and who have extensive experience viewing gastrointestinal mucosa. ASGE guidelines 2006 recommended additional specific training in CE, as well as review of the initial 10 procedures to verify competence [69], while the newer European Society of Gastrointestinal Endoscopy (ESGE) recommends at least 30 CE readings [70].

Capsule Retention and Incomplete Procedures

A meta-analysis of 1013 pediatric procedures documented capsule retention in SB in 18, and gastric retention in four procedures, producing a pooled retention rate of 2.3% ($n = 22/1013$; 95% CI: 1.5%–3.4%) [2]. Endoscopy was used to remove five capsules, including four from the stomach and one from an ileal pouch; 13 were retrieved surgically while taking appropriate measures to mitigate the cause of the retention. A retained capsule was successfully evacuated by bowel prep at 22 days post-ingestion.

The greatest risk factors for capsule retention include known IBD (5.2% risk), previous SBFT demonstrating SBCD (35.7% risk), and a body mass index below the fifth percentile combined with known IBD (43% risk), although retention has occurred despite the absence of stricture on

SBFT [12]. Among four patients with CD having capsule passage lasting longer than 5 days (with three continuing on to retention), age was significant (18.8 ± 0.9 vs. 14.6 ± 3.5), but not height or weight, compared to patients who did not have retention [14]. Retention rates for OGIB, CD, and neoplastic lesion indications were 1.2% (95%CI: 0.9%–1.6%), 2.6% (95%CI: 1.6%–3.9%), and 2.1% (95%CI: 0.7%–4.3%), respectively, with a pooled rate of 1.4% (95%CI: 1.2%–1.6%) [69]. On a per-procedure basis, this pattern is similar in adults, where retention in OGIB, CD, and polyps occurs at rate of 1.4%, 2.2%, and 1.2%, respectively [24]. Thus, it appears that the risk of retention is dependent on the clinical indication, with a higher incidence in patients with a suspected chronic SB obstruction [71]. Rare cases of perforation, aspiration, or SB obstruction have been reported in adults, but none have been reported in children.

In a recent meta-analysis of 35 papers and 4219 adult and pediatric patients with CD, retention rates were 3.32% (95% confidence interval [CI], 2.62%–4.2%) with 4.63% (95% CI, 3.42%–6.25%) and 2.35% (95% CI, 1.31%–4.19%) in established CD and suspected CD, respectively. Retention rates were 3.49% (95% CI, 2.73%–4.46%) and 1.64% (95% CI, 0.68%–3.89%) in adult and pediatric CD, respectively. Retention risk in adults with established CD was 3.4 times higher than suspected CD, but there was no difference in retention risk in pediatric established CD compared with suspected CD. Retention rates in established CD were decreased after patency capsule (2.88%; 95% CI, 1.74%–4.74%) and MR/CT enterography (2.32%; 95% CI, 0.87%–6.03%) [72].

Patency Capsule

The majority of SB capsule retentions have occurred in patients with normal SB radiological studies, yet functional patency may be present in patients with radiologically documented strictures. To avoid this concern, a patency capsule (PC) identically sized to SB capsule was developed containing a mixture of barium, lactose, and a radiofrequency identity tag. The first version had a single timer plug that degraded at 40 h. The currently available version has dual timer plugs that gradually disintegrates if passage does not occur within 30 h.

Both a retrospective [2] and a prospective study [73] have been performed in pediatric IBD using the first iteration of the PC prior to SB CE. Of the 19 patients who were evaluable in the retrospective analysis, patency was established, and subsequent CE was performed successfully in all but 1 patient who had a retained capsule the following week. The prospective trial of 18 patients (age 10–16 years) who ingested the PC showed that 15 excreted an intact PC (mean 34.5 h) without any PC or CE retention or adverse events [71]. CD was eventually diagnosed in all patients having PC transit of more than 40 h and in nine out of 12 who passed the patency capsule in 40 h or less. There were no capsule retentions or adverse events. Thus, the PC can serve as a useful guide and may lessen the likelihood of CE retention, particularly in known CD where the risk of retention is greatest.

Conclusion

Capsule endoscopy provides a useful tool in the diagnosis and management of pediatric IBD. Although CE is often seen as an adjunctive procedure rather than the test of choice, with the advent of the Crohn capsule, there is a potential for more widespread use, especially when employing a treat-to-target strategy. Perhaps the best indicator of this is a recently released study designed to identify a cost-effective treatment strategy in CD, considering the patient outcomes and cost impact of PCE in the English National Health Service (NHS), utilizing a protocolized CD care pathway, informed by guidelines and expert consensus on 4000 simulated CD patients. Costs were taken from the NHS and Payer Provided Services (PSS) 2016–17 tariffs for England. The results showed PCE costs less and delivers a higher quality of life compared to colonoscopy ± MRE when looking over 20 years, as well as a lifetime time horizon [74].

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Bone Health in Pediatric Inflammatory Bowel Disease

24

Dale Lee and Edisio Semeao

Introduction

Throughout childhood and adolescence, bone mineral accrual results in ethnic-, gender-, maturation-, and site-specific increases in bone dimensions and density. During the critical two-year interval surrounding the time of peak height velocity, approximately 25% of skeletal mass is laid down, with 90% of peak bone mass is established by 18 years of age [1]. This rapid accumulation of bone mass correlates with the rate of growth and requires the coordinated actions of growth hormone, insulin-like growth factor-I (IGF-I), and sex steroids in the setting of adequate biomechanical loading and nutrition. Individuals with higher peak bone mass in early adulthood have a protective advantage against fracture when the inexorable decline in bone mass associated with older age or menopause occurs. Accordingly, the National Institutes of Health (NIH) Consensus Statement on Osteoporosis Prevention, Diagnosis and Therapy concluded "bone mass attained early in life is perhaps the most important determinant of life-long skeletal health" [2]. Furthermore, the Consensus Statement specifically called for research to determine the impact of chronic diseases and glucocorticoid therapy on bone accrual in children and to determine the effects of bisphosphonates on the growing skeleton.

Children and adolescents with inflammatory bowel disease (IBD) have multiple risk factors for impaired bone development, including poor growth, delayed maturation, malnutrition, decreased weight-bearing activity, chronic inflammation, genetic susceptibility, and glucocorticoid exposure. The impact of these threats to bone health may be immediate, resulting in fragility fractures during childhood and adolescence [3–5], or delayed, due to suboptimal peak bone mass accrual [6]. Numerous studies have demonstrated the effects of IBD on bone accrual during childhood and adolescence. Although the short- and long-term implications for fracture risk in pediatric IBD have not been characterized prospectively, a retrospective database study found that prepubertal children with IBD had an increased risk of fracture compared with controls [7].

This chapter summarizes the normal changes in bone density and structure during growth, as well as the risk factors for poor bone accrual in childhood IBD. The classification of bone health in children and adolescents is discussed, as are the advantages and disadvantages of available technologies for the assessment of bone in children and adolescents. The difficulties in assessing and interpreting bone measures in pediatric IBD are underscored in a review of selected studies, and an example is provided for a stepwise approach to identify discrete determinants of bone deficits in pediatric IBD [8]. Finally, potential therapies are described and discussed.

Skeletal Modeling and Bone Accrual During Childhood

Skeletal development is a complex process that is sensitive to the hormonal, mechanical, cytokine, and nutritional milieu of the bone. The bones are continuously modified and renovated by the two processes of modeling and remodeling: both result in the replacement of old bone with new bone. Remodeling is the major process in adults and does not result in a change of the bone shape. Remodeling takes place in the basic bone multicellular units on the trabecular surface and within the cortical bone. Normally, bone resorption by osteoclasts is followed by bone formation by osteoblasts; teams of osteoclasts and osteoblasts are juxtaposed in the bone multicellular units and bone resorption and formation are tightly

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coupled. For example, treatment of postmenopausal women with bisphosphonates (an antiresorptive agent) resulted in significant reductions in bone resorption within 6 weeks, followed by a reduction in bone formation in 3 months [9, 10]. Skeletal remodeling is vital to microdamage repair. However, after mid-adulthood, the amount of resorption exceeds formation, resulting in a negative bone balance.

In contrast, modeling during growth and development results in new bone formed at a location different from the site of bone resorption; formation and resorption are not coupled within a bone multicellular unit. For example, a small study of bisphosphonate therapy in children reported significant reductions in bone resorption markers with no changes in formation markers [11]. Modeling results in an increase in bone diameter and modification of bone shape. Figure 24.1 summarizes the complex interplay of site-specific bone resorption and formation activities that are necessary to achieve bone growth from length A to B [12]. Growth in the diameter of the cortical shaft is the result of bone formation at the outer (periosteal) surface and bone resorption at the inner (endosteal) surface. Simultaneously, the growth plate moves upward and the wider metaphysis is reshaped into a diaphysis by continuous resorption by osteoclasts beneath the periosteum.

Changes in Cortical and Trabecular Bone with Growth

Cortical and trabecular bone do not respond in the same way to diseases, medications, or mechanical loading and should be considered two functional entities. Cortical bone forms the outer shell of most bones, while trabecular bone is more porous and filled with marrow and blood vessels. Trabecular volumetric bone mineral density (BMD), as measured by three-dimensional quantitative computed tomography (QCT), does not increase before puberty [13, 14]. During puberty trabecular BMD increases significantly in healthy children due to increases in trabecular thickness. The increase in BMD is comparable in girls and boys [15], but the increase is significantly greater in black adolescents than in white adolescents [16].

Sex differences in cortical dimensions are established during puberty (Fig. 24.2): [17] cortical width increases by periosteal bone formation in boys and by less periosteal bone formation but more endocortical apposition in girls. Androgens stimulate periosteal apposition, while estrogens inhibit periosteal apposition and stimulate endosteal apposition. These sex differences have important implications for

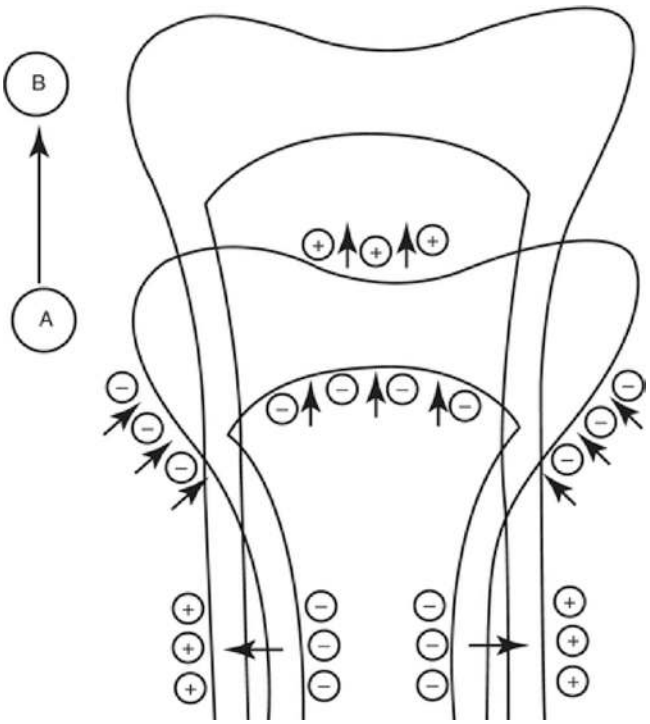

Fig. 24.1 Bone formation (+) and resorption (−) during growth (From: Baron [12])

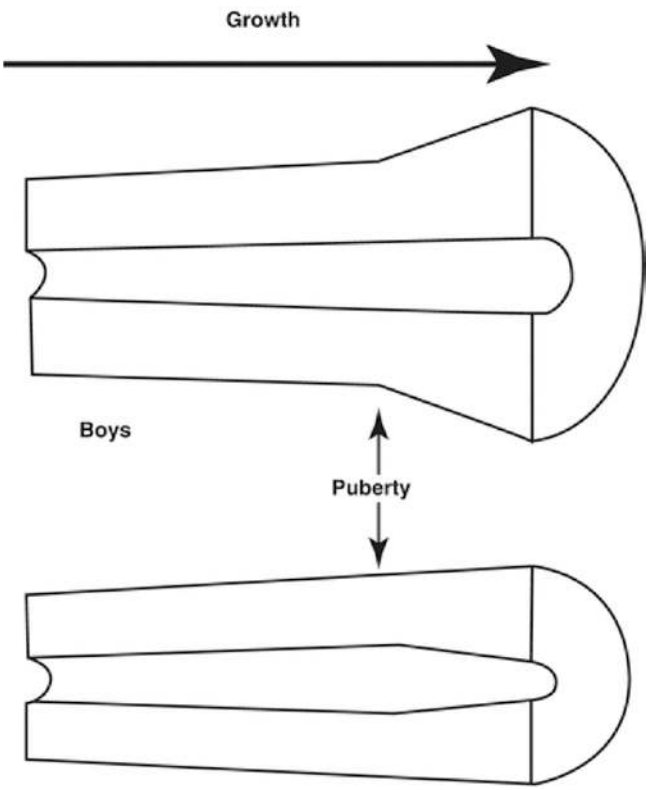

Fig. 24.2 Sex-specific increases in cortical bone dimensions during growth and maturation (Adapted from: Seeman [17])

bone strength; the greater periosteal radius (R_p) in males results in greater bone strength. The long bones are tubular structures that are loaded mainly in bending. The resistance of long bones to bending (i.e., bone strength) is represented by the cross-sectional moment of inertia (CSMI) = $\pi/4$ ($R_p^4 - R_e^4$); R_p and R_e indicate the periosteal and endosteal radius, respectively [18]. These power relationships indicate that small increases in R_p result in marked increases in bone bending strength.

Because the patterns of modeling on the periosteal and endocortical envelopes during growth produce changes in cortical geometry that impact life-long fracture risk [19, 20], the long-term effects of chronic childhood diseases, such as IBD, likely depend on the stage of skeletal maturation at disease onset and the disease effects on the periosteal and endosteal surfaces. Children further from peak bone mass at Crohn disease onset may have irreversible deficits not seen in adult-onset Crohn disease.

Biochemical Markers of Bone Metabolism

Biochemical markers of bone metabolism are released into the circulation during the process of bone formation and resorption, providing information about the dynamic process of bone metabolism. Biomarkers of formation, such as bone-specific alkaline phosphatase (BSAP) and osteocalcin, are by-products of osteoblast activity. Biomarkers of bone resorption are related to collagen degradation products, including pyridinium cross-links and C-telopeptide of collagen cross-links (β-CTX) [21]. In adults, biochemical markers of bone turnover correlate well with formation and resorption, as measured by bone biopsy, and are independent predictors of fracture risk [22]. Further, bone biomarkers can be used to monitor the effectiveness of bone therapies [9]. Because formation and resorption are tightly coupled in adults, drugs that increase bone formation (e.g., teriparatide, which is a synthetic form of parathyroid hormone) increase markers of formation and resorption, while drugs that inhibit resorption (e.g., bisphosphonates) decrease markers of formation and resorption [23].

In adults, bone metabolism is primarily due to remodeling. However, in children biomarkers of bone metabolism in children represent the aggregate turnover due to (1) endochondral bone formation (longitudinal growth of bone), (2) increase in bone circumference, and (3) bone remodeling [24]. The pubertal growth spurt is reflected by marked increases in bone biomarkers [25]. Therefore, the use of bone biomarkers in children and adolescents requires consideration of gender, pubertal maturation, and growth velocity [25] and is most appropriately limited to short-term longitudinal studies to assess the impact of specific interventions [24].

Potential Threats to Bone Health in Pediatric IBD

Osteopenia has been well documented in children and adults with IBD [26–30]. Vertebral compression fractures have been reported in children with IBD [3–5], and hip, spine, and forearm fracture rates are significantly increased in adults with Crohn disease [31–36]. Kappelman et al. found that children with IBD <12 years of age had an increased risk of fracture (odds ratio [OR] 2.2, 95% confidence interval [CI] 1.2–3.8) and children with Crohn disease (CD) had a trend toward an increased risk of vertebral compression fracture, both compared with controls [7]. The osteopenia in IBD is multifactorial; likely etiologies include growth failure, delayed maturation, anorexia, malabsorption, cytokine effects on bone cells, and glucocorticoid therapies.

Malnutrition

Children with IBD are at risk for inadequate intake of calories as well as micronutrients, including calcium, vitamin D, and zinc, secondary to anorexia due to active disease, malabsorption, increased metabolic demands, lactose intolerance, abdominal pain, or depression. Even in the setting of adequate caloric intake, malabsorption can cause deficiency states of the above micronutrients depending on location and severity of disease. Diarrhea can result in zinc deficiency, which has the potential to impact growth. Vitamin D deficiency may result from malabsorption as well as decreased exposure to sunlight due to disease flares. Vitamin K deficiency may result from malabsorption and altered bowel flora due to antibiotic use and IBD-associated dysbiosis, which may result in increased concentrations of undercarboxylated osteocalcin, which is associated with decreased bone turnover and fractures [37]. Nutrient deficiencies that may contribute to impaired bone acquisition in pediatric IBD include calcium, vitamin D, vitamin K, and magnesium [38].

Multiple studies have reported that vitamin D deficiency frequently complicates pediatric IBD [39–42]. For example, Pappa et al. examined vitamin D levels in 130 children and young adults with IBD, 94 with Crohn disease, and 36 with ulcerative colitis. The prevalence of vitamin D deficiency (serum 25 (OH) vitamin D concentration ≤15 ng/mL) was 34.6%, and the mean serum 25 (OH) vitamin D concentration was similar in patients with Crohn disease and ulcerative colitis, 52.6% lower among patients with dark skin complexion, 33.4% lower during the winter months (December 22 to March 21), and 31.5% higher among patients who were taking vitamin D supplements. Patients with Crohn disease and upper gastrointestinal tract involvement were more likely to be vitamin D deficient than those without it. A similar study reported that 45% of children with IBD had vitamin D levels

less than 20 ng/mL [39]. Of note, none of these studies detected a relation between vitamin D levels and spine BMD, as measured by dual-energy X-ray absorptiometry (DXA) [39–41]. A study by Augustine et al. demonstrated an association between greater inflammation and lower PTH and serum 1, 25 (OH) vitamin D concentration. Treatment with anti-TNF resulted in higher PTH levels and higher 1, 25 (OH) vitamin D concentrations, suggesting the negative role of inflammation on PTH and thus decreased renal conversion of 25 (OH) vitamin D to 1,25 (OH) vitamin D [43].

Decreased Muscle Mass and Biomechanical Loading of the Skeleton

Bone adapts its strength in response to the magnitude and direction of the forces to which it is subjected. Mechanical forces on the skeleton arise primarily from muscle contraction. This capacity of bone to respond to mechanical loading with increased bone size and strength is greatest during growth, especially during adolescence [44]. Numerous studies have documented the beneficial effect of physical activity and biomechanical loading on bone geometry in healthy children [45–50]. These relationships dictate that studies of bone health in chronic childhood diseases consider the effects of alterations in muscle mass and strength.

Weight-bearing physical activity and biomechanical loading of bone are critical determinants of bone mass in growing normal children [51]. The influence of skeletal loading on bone accretion is illustrated in two exercise trials in healthy children. An easily implemented school-based jumping intervention augmented cortical thickness in the femoral neck of healthy children [52]. A randomized clinical trial of physical activity and calcium supplementation in prepubertal children resulted in a significant, positive interaction between calcium supplements and physical activity in both cortical thickness and cortical area [53]. Harpavat et al. reported that none of the subjects in a small series of children with IBD were participating in weight-bearing physical activities [54]. Werkstetter et al. compared 39 children with quiescent or mild IBD to 39 healthy controls and found decreased physical activity and lean mass in the children with IBD despite no differences in the measurements in quality of life or energy intake [55]. We reported that in children with incident Crohn disease, both muscle cross-sectional area and muscle strength are independently associated with cortical section modulus, a summary measure of cortical bone dimension and strength [56]. The reports of decreased lean mass and muscle strength in pediatric IBD suggest that decreased biomechanical loading of the skeleton may contribute to impaired bone accrual in this disorder, but additional studies are needed.

The relations between bone and muscle mass have been demonstrated in multiple studies in children and adolescents with Crohn disease. Burnham et al. reported that Crohn disease was associated with a 0.50 SD deficit (p = 0.006 compared with controls) in whole body bone mineral content (BMC) relative to height in males, adjusted for age, race, and Tanner stage [8]. Adjustment for whole body lean mass attenuated this deficit to 0.19 SD (p = 0.13 compared with controls). The authors noted that the absence of a bone deficit after statistical adjustment for lean mass does not imply that the bones are normal or adequate. In a similar study, deficits in DXA estimates of femoral neck subperiosteal width were not statistically significant after adjustment for lean mass [57]. Our study of children with newly diagnosed Crohn disease found that cortical section modulus was 6.8% greater than predicted compared to healthy controls, given muscle cross-sectional area and strength deficits [56]. A prospective cohort study using tibia peripheral QCT in children with newly diagnosed Crohn disease reported that muscle mass improved significantly over 1 year following diagnosis, but cortical section modulus worsened significantly [58]. This apparent disconnect between changes in bone and muscle mass over time illustrates the limitations of the functional muscle bone unit paradigm in chronic inflammatory disease. In addition to lean mass and muscle strength, the role of inflammatory cytokines, physical activity, and therapeutic agents on bone outcomes must be further studied.

Glucocorticoid-Induced Osteopenia

Glucocorticoids are widely used in the treatment of IBD and impact bone formation and resorption. Decreased bone formation is the primary mechanism for bone loss in glucocorticoid-induced osteopenia [59]. Mesenchymal stem cells, which also give rise to adipocytes, myoblasts, and chondrocytes, differentiate into osteoblasts. Glucocorticoids shift the cellular differentiation away from osteoblasts and toward adipocytes, and prevent the termination differentiation of osteoblasts [60]. Osteoblast numbers are decreased further by glucocorticoid-induced increases in osteoblast apoptosis [61]. In addition, glucocorticoids inhibit osteoblast production of bone matrix components [62]. Finally, glucocorticoids suppress the synthesis of insulin-like growth factor-I (IGF-1), a hormone important in bone formation [63]. The cellular response to glucocorticoids also includes an early phase of increased bone resorption, probably a result of the increased expression of receptor activator of nuclear factor-κ-B ligand (RANKL) and decreased osteoprotegerin (OPG)—increased RANKL and decreased OPG both promote osteoclastogenesis, as detailed below [64]. However, typically a more chronic state of decreased bone resorption develops due to loss of cell signaling to osteoclast progenitors and apoptosis [65].

Patients treated with glucocorticoids have an underlying disease, which frequently also carries a risk of osteoporosis. Therefore, the independent effects of glucocorticoids on bone turnover and bone structure during growth are not readily apparent from clinical studies. However, recent animal models demonstrate that glucocorticoid administration during growth resulted in decreased bone formation, decreased bone resorption, reductions in the age-dependent increases in trabecular thickness, and reductions in linear growth and accrual of cortical thickness in the femur [66, 67]. These deficits were associated with decreased bone strength in the vertebrae and femur in mechanical testing [66, 67]. Of note, it is unclear if the reductions in femoral cortical thickness were proportionate to the significant reductions in bone length. That is, did the bones have normal cortical thickness and strength relative to the shorter length?

Inflammation and Bone Loss

Cellular inflammatory pathways in Crohn disease activate the protean transcriptional regulatory factor nuclear factor-κB with increased production of a variety of cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [68]. Three groups of cytokines are particularly important in bone physiology: interleukin-6 (IL-6), TNF-α, and IL-1 [64]. Inflammatory cytokines promote osteoclastogenesis and accelerated bone resorption. TNF-α induces the expression of receptor activator of NF-κB ligand (RANKL). RANKL stimulates osteoclast differentiation and activation and inhibits osteoclast apoptosis, thereby dramatically prolonging osteoclast survival and increasing bone resorption [69, 70]. Additionally, TNF-α decreases expression of OPG, a decoy receptor that blocks RANKL [71, 72]. Inflammatory mediators, including IL-1 and IL-6, also increase RANKL secretion and contribute to bone loss [73]. TNF-α also has direct effects on bone formation; it inhibits osteoblast differentiation, inhibits osteoblast collagen secretion, causes increased resorption by inducing osteoblasts secretion of IL-6, and induces osteoblast apoptosis [74, 75]. These effects on bone formation are strikingly similar to the effects of glucocorticoids [59, 60].

Assessment of Bone Status in Children and Adolescents

Classification of Bone Health and Relation to Fracture Risk

DXA is widely accepted as a quantitative measurement technique for assessing skeletal status. DXA scans involve the use of two X-ray beams and measurement of X-ray penetration through bone. The radiation exposure from a conventional DXA examination is less than 10 microsieverts (μSv), while a two-view chest X-ray would be 60 μSv, and a CT exam of the pelvis 5000 μSv [76]. In elderly adults, DXA BMD is a sufficiently robust predictor of osteoporotic fractures that it can be used to define the disease. The World Health Organization criteria for the diagnosis of osteoporosis in adults is based on a T-score, the comparison of a measured BMD result with the average BMD of young adults at the time of peak bone mass [77]. A T-score ≤ -2.5 SD below the mean peak bone mass is used for the diagnosis of osteoporosis, and a T-score ≤ -2.5 SD with a history of a low-impact fracture is classified as severe osteoporosis. While the T-score is a standard component of DXA BMD results, it is clearly inappropriate to assess skeletal health in children through comparison with peak adult bone mass. Rather, children are assessed relative to age or body size, expressed as a *Z*-score. In adults, low-impact fractures are defined as fractures that occur after a fall from standing height or less. This definition is often difficult to apply to fractures in children that occur during play or sports activities.

While there are no clear evidence-based guidelines for the definition of osteoporosis in children. The International Society for Clinical Densitometry has suggested that the diagnosis of osteoporosis in children and adolescents should include a history of clinically significant fracture and BMC or density *Z*-score ≤ 2.0 (adjusted for age, sex, and bone size) [78]. Fractures occur commonly in otherwise healthy children with a peak incidence during early adolescence around the time of the pubertal growth spurt [21]. Faulkner et al. recently reported that peak gains in bone area preceded peak gains in BMC in a longitudinal sample of boys and girls, supporting the theory that the dissociation between skeletal expansion and skeletal mineralization results in a period of relative bone weakness [79]. This may be due to increased calcium demands during maximal skeletal growth.

Several studies have compared the DXA BMD of normal children and adolescents with forearm fractures to that of age-matched controls without fractures. Most [80–84], but not all [85, 86], found that mean DXA BMD was significantly lower in children with forearm fractures than in controls. One study reported that 69% of fractures in healthy children were due to low-energy falls at home [85], illustrating the difficulties defining low-energy fractures in children. Studies using QCT or metacarpal morphometry to characterize cortical geometry showed that decreased cortical thickness was associated with significantly increased fracture risk [84, 87]. Finally, television, computer, and video viewing had a dose-dependent association with wrist and forearm fractures [88]. A recent prospective cohort study in over 6200 children in the United Kingdom reported a weak inverse relationship between whole body (less head) BMD at 9.9 years of age and subsequent fracture risk [odds ratio

(OR) per SD decrease = 1.12; 95% CI, 1.02–1.25] [89]. The association between fracture risk and BMD was much stronger when adjusted for bone and body size; fracture risk was inversely related to BMC adjusted for bone area, height, and weight (OR = 1.89; 95% CI, 1.18–3.04).

These data suggest that low DXA BMD can be a contributing factor for pediatric fracture in healthy children; however, bone geometry and non-skeletal factors, such as sports participation, body size, and sedentary activities, may have an independent contribution to fracture risk. Importantly, the relationships between DXA BMD, bone geometry, and fracture risk in children with chronic diseases, such as IBD, may be different than those observed in healthy children.

Limitations of DXA in Children and Adolescents

DXA is, by far, the most commonly employed method for the assessment of bone health in children. However, DXA has several limitations that are pronounced in the assessment of children (Table 24.1). A study highlighting the importance of these limitations evaluated children referred for enrollment in a childhood osteoporosis protocol based on low DXA spine BMD and found 80% had at least one error in interpretation of the DXA scan [112]. The most common error was the use of T-scores, and ultimately, only 26% retained the diagnosis of low BMD.

The significant limitation of DXA is the reliance on measurement of areal rather than volumetric BMD (vBMD). DXA provides an estimate of BMD expressed as grams per anatomical region (e.g., individual vertebrae, whole body, or hip). Dividing the BMC within the defined anatomical region (g) by the projected area of the bone (cm^2) then derives "areal BMD" (g/cm^2). This BMD is not a measure of volumetric density (g/cm^3) because it provides no information about the depth of bone. Bones of larger width and height also tend to be thicker. Since bone thickness is not factored into DXA estimates of BMD, reliance on areal BMD inherently underestimates the bone density in individuals with short stature. Despite identical volumetric bone density, the child with smaller bones appears to have a mineralization disorder (decreased areal BMD). This is clearly an important artifact in children with chronic diseases, such as IBD, that are associated with growth delay and short stature [113]. An analysis by Zemel et al. found that adjustment of age-specific BMC and BMD *z*-scores for age-specific height *Z*-scores were the least biased methods to correct for the confounding effect of height [114].

Table 24.1 Limitations of DXA techniques in infants and children

Scan acquisition	Fan beam results in magnification error with apparent differences in bone area and BMC as body size varies [90]
Scan analysis	Difficult to define landmarks and region of interest in the immature hip [91]
	Software developed to improve bone detection in the infant and child result in significantly different results for BMC and body composition [92–94]
Reference data [95–108]	Limited data in young children
	Analysis methods not standardized
	Variable hardware and software across published reference data sets
	Some are not gender specific [109] Some presented relative to age, others relative to height, Tanner stage, and weight
Interpretation	Underestimates volumetric density in children with short stature [110, 111]
	Unable to distinguish between changes in bone dimensions and density
	Unable to distinguish between cortical and trabecular bone

The confounding effect of skeletal geometry on DXA measures is now well recognized and multiple analytic strategies have been proposed to express DXA bone mass in a form that is less sensitive to differences in skeletal size [95, 96, 115–117]. The technique developed by Carter et al. is based on the observation that vertebral BMC scaled proportionate to the projected bone area to the 1.5 power [115]. Therefore, vertebral volume is estimated as $(\text{area})^{1.5}$ and bone mineral apparent density (BMAD) is defined as $\text{BMC}/(\text{area})^{1.5}$. Kroger et al. proposed an alternative estimate of vertebral volume: the lumbar body is assumed to have a cylindrical shape and volume of the cylinder is calculated as $(\pi)(\text{radius}^2)(\text{height})$, which is equivalent to $(\pi)((\text{width}/2)^2)(\text{area/width})$ [118, 119]. This approach was validated by comparison with MR measures of vertebral dimensions in 32 adults [116]; DXA-derived vBMD correlated moderately well with BMD based on MR-derived estimates of vertebral volume ($R = 0.665$). Although these methods provide estimates of vertebral volume, the BMC includes the bone content of the superimposed cortical spinous processes.

A study by Wren et al. sought to evaluate the usefulness of DXA spine correction factors based on published geometric formula and anthropometric parameters, compared with three-dimensional QCT [120]. Subject height, weight, body mass index, skeletal age, and Tanner stage were assessed in 84 healthy children. While DXA and QCT measures of BMC were highly correlated ($r^2 = 0.94$), DXA areal BMD only moderately correlated with CT vBMD ($r^2 = 0.39$), illustrating the potential confounding effects of bone size on DXA areal BMD. The correlations between QCT vBMD and DXA estimates were particularly poor for subjects in Tanner stages 1–3 ($r^2 = 0.02$ for areal BMD), but multiple regression accounting for the anthropometric and developmental parameters greatly improved the agreement between the DXA and CT densities ($r^2 = 0.91$). These results suggest that DXA BMC is a more accurate and reliable measure than

DXA BMD for assessing bone acquisition, particularly for prepubertal children and those in the early stages of sexual development. The use of DXA BMD would be reasonable if adjustments for body size, pubertal status, and skeletal maturity are made, but these additional assessments add significant complexity to research studies, and to clinical interpretation.

An additional shortcoming of DXA is that the integrated measure of bone mass in a given projected area does not allow distinction between cortical and trabecular bone. DXA-based measures provide no information on bone architecture and are limited in their usefulness to differentiate the spectrum of bone accrual during growth.

Comparisons to appropriate pediatric reference data are essential to describe accurately the clinical impact of childhood disease on bone development, to monitor changes in bone mineralization, and to identify patients for treatment protocols. Multiple sources of pediatric DXA reference data are now available for the calculation of DXA *Z*-scores. These include varied approaches, such as gender-specific centile curves, age- and height-specific means and standard deviations, Tanner- and weight-specific percentiles, age-, sex-, weight-, and height-adjusted curves, and *Z*-score prediction models [95–108]. Differences in reference data have a significant impact on the diagnosis of osteopenia in children with chronic disease [109]. For example, the use of reference data that are not gender-specific results in significantly greater misclassification of males as osteopenia [109]. In addition, the use of published pediatric reference ranges has been complicated by differences in scanner manufacturers, and frequent changes in hardware and software technology, including fan-beam technology, low-density software analysis modes and specialized pediatric software. These technical changes result in clinically significant alterations in DXA results [92]. The use of adequate reference data and validated classification schemes is important in the study of bone health in children.

Peripheral Quantitative Computed Tomography

A three-dimensional structural analysis of trabecular architecture and cortical bone dimensions can be obtained by computed tomography (CT). This technique offers an opportunity to overcome the limitations of two-dimensional imaging with DXA and advance our understanding of bone mineralization in children. CT provides an image unobscured by overlying structures [121]. The CT attenuation of different bone tissues provides quantitative information, referred to as quantitative CT (QCT). In contrast to DXA, this technique describes authentic vBMD, accurately measures bone dimensions, and distinguishes between cortical and trabecular bone. In order to minimize radiation exposure, special high-resolution scanners were developed for the peripheral skeleton (pQCT), specifically, the radius or tibia. The distal site is largely trabecular bone, while the mid-shaft is almost entirely cortical bone. The volume of each component is calculated from the scan thickness and cross-sectional area, and the density by attenuation of the X-ray beam. Bone strength can also be estimated by pQCT from the total bone area, and cortical thickness and density [122]. QCT studies of bone mineral accretion and bone strength demonstrated gender, maturation, and ethnic-specific patterns of development of bone strength during childhood and adolescence [123]. A study longitudinal in children with Crohn disease comparing QCT measured vBMD versus DXA-derived measures of BMD demonstrated greater BMD deficits at diagnosis and greater improvements over 12 months with the PQCT vBMD approach [124].

Clinical Studies of Bone Health in Pediatric IBD

Accounting for Body Size Differences

Numerous studies have reported decreased DXA BMD in children with IBD [39]. However, as detailed above, DXA studies are frequently confounded by disease effects of growth. For example, two studies reported that DXA BMD for age *Z*-scores were significantly correlated with height for age *Z*-scores in children with IBD [39, 125]. Furthermore, expression of DXA results as BMAD (an estimate of volumetric BMD) eliminated the correlation with height *Z*-scores [125]. Another study addressed the confounding effect of short stature by expressing the spine DXA results as percent predicted BMC for bone area for age and gender in 73 children with Crohn disease or ulcerative colitis [126]. The percent predicted bone area for age and gender was decreased in IBD, compared with controls, consistent with shorter stature. While the median BMD for age and gender *Z*-score was significantly decreased in IBD (mean *Z*-score in spine = −1.6, in whole body = −0.9), the percent predicated BMC for bone area, age, and gender was normal. The authors concluded that children with IBD have small bones for age due to growth retardation, but adequate bone mass relative to bone size. Finally, Herzog et al. reported that BMD *Z*-scores were less than −2.0 in 44% of children when expressed relative to chronologic age, but were less than −2.0 in only 26–30% when expressed relative to bone age of height age [127].

The above studies illustrate the varied approach used to adjust for the confounding effects of poor growth. Leonard et al. reported that whole body BMC relative to height predicted bone strength (estimate by stress–strain index) as measured by QCT [117]. From the same group, Burnham

et al. assessed whole body BMC, lean mass, and fat mass (as measured by DXA) relative to height in 104 children and young adults with established Crohn disease, and 233 healthy controls, 4–26 years of age. The studies demonstrated significant bone and muscle deficits [8, 128]. Individuals with Crohn disease had significantly lower height-for-age, body mass index (BMI)-for-age, and whole body lean mass-for-height *Z*-scores than healthy controls (all $p < 0.001$). Table 24.2 summarizes four sequential models in males and females. The least adjusted models assessed whole body BMC in Crohn disease, compared with controls, adjusted for age and race, and revealed substantial deficits. Assessment of BMC without consideration of the decreased skeletal size for age in subjects with Crohn disease group may overestimate bone deficits. Accordingly, the second model was also adjusted for height. Figure 24.3 demonstrates that the marked BMC deficits relative to age (A) are less pronounced when assessed relative to height (B). Adjustment for height attenuated the Crohn disease effect in the multivariate regression model; however, significant BMC deficits persisted in males and females with Crohn disease, compared with controls. In the third model in Table 24.2 Tanner stage was added to determine if delayed pubertal maturation for age contributed to the decreased BMC in Crohn disease. Adjustment for delayed pubertal maturation did not appreciably change the estimate of BMC deficits in Crohn disease. The fourth and final model, adjusted for lean mass, eliminated significant BMC deficits in Crohn disease.

None of the glucocorticoid measures were significantly correlated with BMC-for-height *Z*-scores. However, height *Z*-score was negatively and significantly associated with duration of glucocorticoid therapy ($r = -0.24$, $p = 0.02$), and cumulative (mg/kg) glucocorticoids ($r = -0.36$, $p < 0.001$). Parenteral nutrition, isolated upper tract disease, hypoalbuminemia, nasogastric feeding, and decreased BMI *Z*-scores were associated with decreased BMC-for-height *Z*-scores, but these factors have the potential to be confounded by greater disease severity. Whereas BMC and BMD *Z*-scores for age may overestimate bone deficits, bone *Z*-scores for height have the potential to underestimate bone deficits. This can occur because children and adolescents with IBD may be of more advanced pubertal status than their comparators of similar height. As such, adjusting age-specific BMD or BMC *z*-scores for age-specific height *Z*-scores may be a more accurate approach [114].

Table 24.2 Hierarchical models of whole body BMC *Z*-scores in Crohn disease [8]

	Males		Females	
Models	*Z* (95% CI)	*p*	*Z* (95% CI)	*p*
1. Age, race	−1.16 (−1.51, −0.82)	<0.001	−0.61 (−0.95, −0.27)	0.001
2. Height, age, race	−0.63 (−0.95, −0.30)	<0.001	−0.44 (−0.81, −0.06)	0.02
3. Height, age, race, tanner	−0.50 (−0.85, −0.15)	0.006	−0.35 (−0.72, 0.02)	0.06
4. Height, age, race, tanner, lean mass	−0.19 (−0.43, 0.06)	0.13	−0.05 (−0.34, 0.25)	>0.2

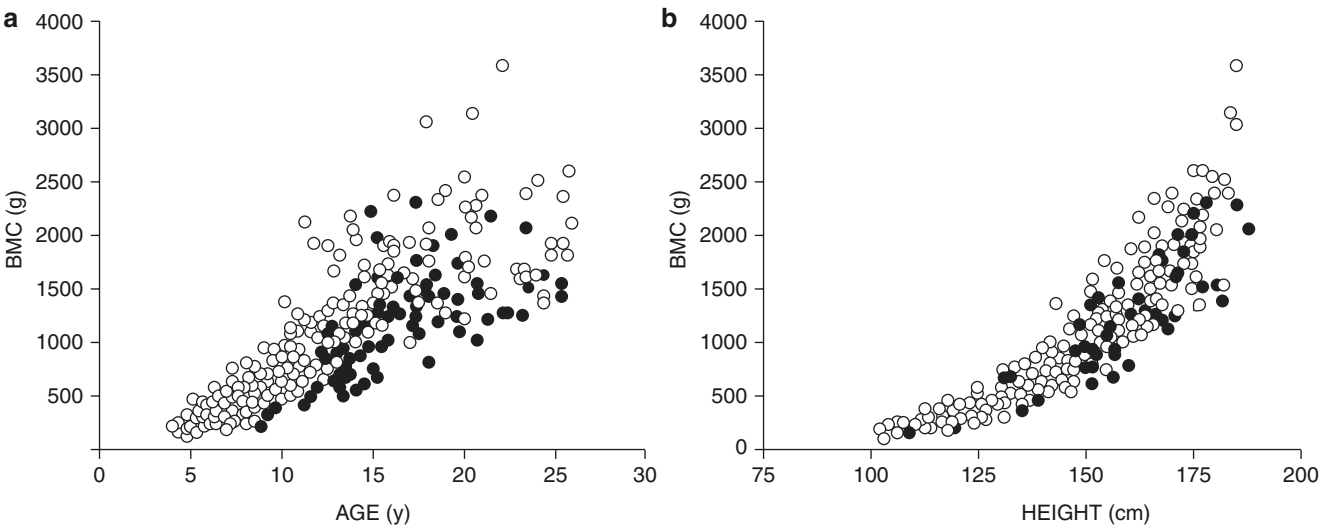

Fig. 24.3 Distribution of whole body BMC relative to age (**a**) and relative to height (**b**) in children and young adults with Crohn disease, compared with healthy controls (From Burnham et al. [8])

Glucocorticoid Effect

Over 90% of the children and young adults in the prior study had a history of glucocorticoid exposure; therefore, it was not possible to distinguish between disease and glucocorticoid effects on bone. The impact of the underlying IBD process is best assessed in subjects with newly diagnosed disease. The largest study of DXA BMD in newly diagnosed subjects was reported by Gupta et al. [129]; however, the study was complicated by the observation that BMD was markedly decreased in controls, compared with the DXA reference database. Overall, DXA spine BMD was comparable in the 41 children with ulcerative colitis and the controls, while results were significantly lower in the 82 subjects with Crohn disease. Laakso et al. reported on a longitudinal study of children and adolescents followed over a median of over 5 years and found greater lifetime glucocorticoid exposure to be associated with lower lumbar spine BMD [130]. The authors conclude that the findings may likely reflect both glucocorticoid effect and glucocorticoid exposure as a surrogate of more severe disease. In steroid-sensitive nephrotic syndrome, a condition without underlying inflammation but involving glucocorticoid therapy, no deficits in BMC are seen, but this may be related to the increase in skeletal loading associated with increases in BMI [131]. This demonstrates the complex interaction between medication exposures, side effects of therapy, and underlying disease pathophysiology.

Impact of Disease Activity

Walther et al. recently compared lumbar spine BMAD *Z*-scores in 34 steroid-naïve and 53 steroid-treated children with IBD in order to obtain information about the influence of non-steroidal factors [125]. Overall, 56 had Crohn disease and 30 had ulcerative colitis. Reference data were obtained in 52 controls. The mean BMAD *Z*-scores in the subjects with Crohn disease were −0.76 ± 1.25 in females and −0.79 ± 0.92 in males. The mean BMAD *Z*-scores in the subjects with ulcerative colitis were −0.30 ± 0.75 in females and −1.08 ± 1.23 in males. Among the steroid-naïve subjects, the duration of treatment ranged from 0 to 8 years, but the majority (approximately 80%) were within the first 5 weeks of therapy. Among the steroid-treated subjects, the cumulative steroid exposure averaged 4600 mg (range 0.05–25,000 mg) over the treatment duration of several days to 7.6 years. The mean BMAD *Z*-scores were comparable in steroid-naïve (−0.74 ± 1.08) and steroid-treated (−0.66 ± 1.08) subjects. The 19 subjects that had been treated with calcium and/or vitamin D supplements were all within the steroid-treated group. The study is limited by the small number of controls and the lack of data on disease activity between the steroid-naïve and steroid-treated groups. Nonetheless, these data demonstrate bone deficits in the absence of steroid therapy. The studies listed above were all based on DXA estimates of BMC and BMD and did not distinguish between cortical and trabecular bone.

Sylvester examined DXA BMD and bone biomarkers in 23 children with newly diagnosed Crohn disease [132]. Although BMD *Z*-scores did not differ between Crohn disease subjects and controls in this small sample, bone biomarkers were significantly lower in Crohn disease. This may be due to reduced bone remodeling, or reduced growth velocity. Importantly, activated T cells produced greater concentrations of interferon-γ, which may contribute to lower bone turnover. DeBoer et al. found that IGF-1 levels increased significantly over 10 weeks after initiating anti-TNF-alpha therapy and greater improvements in IGF-1 level predicted superior gains in DXA and pQCT measures of BMD and BMC [133].

Longitudinal Studies

Dubner et al. performed tibia pQCT in 78 CD subjects (ages 5–18 year) at diagnosis and followed them for 12 months [58]. At diagnosis, CD subjects had significant deficits in trabecular vBMD (*Z*-score: −1.32 ± 1.32, $p < 0.001$), section modulus (a summary measure of cortical bone dimensions and strength) (−0.44 ± 1.11, $p < 0.01$), and muscle cross-sectional area (−0.96 ± 1.02, $p < 0.001$), compared with controls. Over the first 6 months, trabecular vBMD and muscle *Z*-scores improved significantly (both $p < 0.001$); however, section modulus worsened ($p = 0.0001$) and all three parameters remained low after 1 year. Improvements in muscle were associated with improvements in section modulus and improvements in trabecular vBMD were greater in prepubertal subjects. Werkstetter et al. in a longitudinal study using forearm pQCT of 102 pediatric IBD patients (82 CD, 30 newly diagnosed) showed similar findings at diagnosis and median follow-up interval of 2.6 (0.9–5.8) years [134]. In a study from Sweden following children with IBD over 2 years, at baseline mean disease duration was 41.3 months and mean lumbar spine BMD *Z*-score of −0.9 ± 2.8 and this did not change significantly over the 2 years [135]. The authors note that corticosteroid and azathioprine exposures were not significantly associated with changes in BMD. A study from Italy evaluated children with Crohn's receiving 8 weeks of therapy with exclusive enteral nutrition (EEN) and continuing either aminosalicylate or azathioprine for a year. This study demonstrated improvement, but not normalization, in whole body (less head) DXA BMD over the course of a year [136]. Whereas the role of anti-TNF-alpha agents was not evaluated in the studies from Sweden or Italy, Griffin et al. described the

changes occurring over 12 months using QCT in children and adolescents initiating therapy with anti-TFN-alpha [137]. In this study, 74 subjects with median disease duration of 2.1 years (range 0.2–9.7) had baseline trabecular BMD *Z*-score −1.44 ± 1.11, cortical BMD *Z*-score 0.19 ± 1.08, and cortical area *Z*-score −0.97 ± 1.35. After 12 months, trabecular BMD and cortical area increased significantly (0.45 ± 0.76 and 0.29 ± 0.65, respectively, both $p < 0.001$), but cortical BMD decreased. Bone biomarkers were significantly increased over the first 10 weeks of anti-TNF therapy and the authors hypothesize that the decline in cortical BMD is a consequence of rapid increase in periosteal bone formation necessary in catch-up growth. This study highlights the value of QCT distinction of cortical versus trabecular bone and also demonstrates the role of anti-TNF-alpha therapy in the bones of children with IBD.

Finally, the impact of childhood IBD on peak bone mass and risk of osteoporosis is not yet clear but has been described. Bernstein et al. assessed spine, proximal femur, and whole body BMD in 780 premenopausal adult women (age <45 year) who were diagnosed with IBD prior to 20 years of age [138]. The mean BMD T-scores were normal in the spine (−0.14 ± 1.05), femoral neck (−0.15 ± 1.04), and whole body (0.09 ± 1.04) and results did not differ between the 12 subjects with disease onset before puberty, and the 58 subjects with disease onset after puberty. Alternatively, Azzopardi et al. recently described 83 adult subjects with Crohn disease (mean age 39) and found that age of diagnosis <17 years was significantly associated with lower BMD ($p = 0.0006$) [139].

Potential Therapies for Bone Health in Pediatric IBD

Physical Activity

Physical activity is an important determinant of bone mass accretion during growth; simple loading exercises promote bone accretion in healthy children. Numerous studies have documented the beneficial effect of physical activity and biomechanical loading on bone geometry in healthy children [45–47, 49, 50, 140]. Bone adapts its strength in response to the magnitude and direction of the forces to which it is subjected. This capacity of bone to respond to mechanical loading with increased bone size and strength is greatest during growth, especially during adolescence [44]. Physical activity affects the skeleton via two distinct mechanisms, which function as osteogenic stimuli: (1) "muscle pull" involves the force of contracting muscles upon their bony attachments and (2) weight-bearing exercise results in the mechanical loading of the bone with compressive forces. A physical intervention trial in adults with CD utilizing a home-based program of low-impact dynamic muscle conditioning exercises did not show a statistically significant difference in BMD of the lumbar spine and hip between cases and controls; however, analyses limited to those subjects achieving 100% adherence to the program did show a significant increase in trochanteric BMD [141]. A recent systematic review on the influence of physical activity on bone strength in children and adolescents concluded that physical activity has a significant positive impact on bone strength in the growing skeleton (36/37 studies) and that weight-bearing activity specifically enhances bone strength [142]. These findings were in healthy children, and the potential for physical activity to modulate the relationship between disease and bone metabolism will require further study. Based on existing evidence, a program consisting of resistance training (muscle-building) activity in addition to high-impact weight-bearing activity may result in positive impacts on skeletal health. The protocol for a multicenter, randomized controlled study on the effect of physical activity on whole body BMD as assessed by DXA has been published and will potentially be the first study to assess the role of physical activity in pediatric bone health in a children with IBD in a prospective randomized fashion [143].

Vitamins and Minerals

Multiple prospective randomized double-blind intervention trials have documented that calcium supplementation promotes bone accretion in normal children and adolescents [144–149]. Subjects with Crohn disease involving the small bowel are at increased risk for calcium oxalate kidney stones. Normally dietary calcium binds with oxalate in the gut to form a complex that is poorly absorbed. In small bowel disease, fat malabsorption results in increased binding of fatty acids with calcium to form insoluble soaps, thereby increasing the soluble oxalate for absorption [150]. Calcium supplements result in decreased urinary oxalate without increasing urinary calcium above normal; therefore, calcium is recommended to prevent enteric hyperoxaluria [151]. To our knowledge, no calcium balance studies or calcium supplementation trials have been conducted in children with chronic illness.

Vitamin D is essential for the maintenance of adequate calcium levels for bone mineralization and functioning of the immune functioning and all pediatric IBD patients are at risk for vitamin D deficiency. In 1997, the Institute of Medicine concluded that the adequate intake of vitamin D in children and young adults in 200 IU per day [152]. However, in the years following the Institute of Medicine report, a series of publications have argued that 200 IU is not adequate in healthy children and adults [153–160]. A study of the serum 25-hydroxyvitamin D (25(OH)D) response to oral cholecal-

Table 24.3 Institute of medicine 2011 dietary reference intakes for calcium and vitamin D

	Calcium (mg/day)		Vitamin D (IU/day)	
Age (year)	RDA	UL	AI	UL
4–8	1000	2500	600	3000
9–18	1300	3000	600	4000
19–30	1300	3000	600	4000

ciferol reported that each additional 100 IU of cholecalciferol resulted in a 0.7 ng/mL increase in serum 25(OH)D over a two–three-month period, then plateaued [155]. The exact dose required to achieve adequate serum 25(OH)D levels is children with IBD is unclear, but Weaver et al. reported that 863 IU/day would be required in healthy adolescent girls, on average to achieve a serum 25(OH)D of 32 ng/mL [157].

In 2011, the Institute of Medicine updated Recommended Daily Allowances (RDA) and Tolerable Upper Intake Levels (UL) for calcium and vitamin D, and these values are summarized in Table 24.3 [161]. These recommendations reflect the need for increasing calcium intake with age in order to accommodate the calcium needs for the rapidly growing skeleton, especially during the years of the adolescent growth spurt. A national dietary intake survey showed that calcium intake of children declines in all ethnic groups at the ages when calcium requirements increase [162]. Additional practice guidelines from the Endocrine Society propose that patients at risk for vitamin D deficiency require higher doses of vitamin D, specifically, 600–1000 IU/day for patients 4–18 years of age (UL 4000 IU), and 1500–2000 IU/day for patients 19–30 years of age (UL 10,000 IU) [163]. Pappa et al. conducted a six-week trial in children with IBD and found supplementation with cholecalciferol (D3) 2000 international units daily to be superior to ergocalciferol dosed similarly at raising 25 (OH) vitamin D levels [164]. Serum 25-hydroxyvitamin D levels should be measured and optimized, especially in subjects at northern latitudes in the winter months. Future studies will need to further evaluate the role of inflammation on decreased PTH and decreased renal conversion of 25(OH)D to $1,25(OH)_2D$ as has been described by Augustine et al. [43].

Bisphosphonates

The beneficial effects of bisphosphonates in adults with postmenopausal osteoporosis and corticosteroid-induced osteoporosis are well recognized. However, concerns regarding the impact on the structure of the modeling skeleton initially tempered enthusiasm for these medications in children, in particular in IBD where secondary bone deficit can be addressed by treating underlying inflammation. Bisphosphonate therapy results in distinctive radiographic metaphyseal bands in children; the significance of these bands is unclear. Furthermore, some have suggested drug holidays for those receiving bisphosphonate therapy due to concern for over suppression of bone turnover and risk of avascular necrosis of the jaw [165]. Pamidronate proved effective in uncontrolled observational studies of children with osteogenesis imperfecta; bone density and size increased and the incidence of fractures decreased [166–168]. The treatment did not alter fracture healing, growth rate, or growth plate appearances. A report of osteopetrosis in a child treated with a cumulative pamidronate dose approximately seven-fold greater than recommended raised concerns regarding the safety of this treatment in growing children [169, 170]. Similar complications have not been observed in children on lower doses [171].

Numerous case series and case reports have been published describing bisphosphonate therapy in children with disparate chronic diseases [172–180]. The two largest studies conducted in children with chronic inflammatory conditions are summarized in Table 24.4. Both of these studies demonstrated significant improvements in DXA BMD; however, only one was a randomized trial [11]. The trial had many important limitations. First, the study population included 22 children with highly disparate conditions, including juvenile arthritis, lupus, dermatomyositis, IBD, renal transplantation, autoimmune anemia, and cystic fibrosis; only 18 completed the protocol. Second, baseline height *Z*-scores and subject age differed significantly between the intervention and placebo group. Third, the spine and femur BMD was assessed using DXA and was likely confounded by bone size. These data highlight the growing use of bisphosphonates in children, and the need for controlled trials using three-dimensional imaging techniques.

Insufficient data are available on the long-term effects of bisphosphonates to recommend its routine use in pediatric IBD, especially in patients at risk for low bone turnover due to cytokine effects [132, 182]. Furthermore, a recent study has demonstrated improvements in BMD and bone metabolism in IBD using anti-TNF-alpha therapy and controlling inflammation [137]. This suggests that addressing underlying inflammation should be the focus in addressing bone deficits in IBD. A recently published position paper from Australia did not give guidance on usage of bisphosphonates in IBD, instead focusing on primary etiologies of bone fragility or secondary etiologies without specific remedy [183]. However, future studies may demonstrate an important role for bisphosphonate treatment in patients requiring long-term glucocorticoid therapy.

Table 24.4 Bisphosphonate studies in children and adolescents with chronic inflammatory disease

Study/subjects	Intervention/outcome	Comments and results
Bianchi et al. [181] *Chronic rheum disorder and ↓ spine BMD* $N = 39$[a], age 5–18	*Design*: 12-month case series Oral alendronate Weight <20 kg: 5 mg q day Weight >20 kg: 10 mg q day Instructed to ↑ calcium to RDA *Outcome*: DXA spine areal BMD	Serum alkaline phosphatase levels decreased by 16.5 ± 10.8%. Urinary excretion of NTX decreased by 17 ± 16.5%. Mean spine areal BMD *Z*-scores (adjusted for sex, age, body surface area) increased from a mean of −2.7 at baseline to −1.9 at 6 months ($p < 0.01$ compared with baseline) and to −1.05 at 12 months ($p < 0.001$ compared with baseline).
Rudge et al. [11] *Chronic glucocorticoids* $N = 22$[b], age 4–17	*Design*: 12-month RCT Oral alendronate vs. placebo 1–2 mg/kg weekly No calcium supplements Rx Vit D if level <20 ng/mL *Outcome*: DXA of spine and femur shaft	Baseline height *Z*-score significantly greater in placebo group (−0.2 vs. −2.0). 18 completed study. Significant ↓ in bone resorption markers in alendronate group ($p < 0.01$) Lumbar spine: significant ↑ in BMAD in alendronate group ($p = 0.013$) compared with baseline, but not in placebo group ($p = 0.16$) Femur mid-shaft: marginal ↑ in CSMI in alendronate group ($p = 0.08$) compared with baseline, but not in placebo group ($p = 0.18$)

[a]16 juvenile arthritis, 11 systemic lupus erythematosus (*SLE*), 6 dermatomyositis, 2 Behcet's syndrome, 2 granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), and 2 undefined
[b]7 juvenile arthritis, 6 SLE, 4 dermatomyositis, 2 IBD, 1 renal transplant, 1 autoimmune anemia, and 1 cystic fibrosis

Summary

In conclusion, children with IBD are at risk for impaired bone mineral accrual. However, additional studies are needed to fully appreciate the magnitude of bone disease in pediatric IBD, as well as the implications for lifetime fracture risk and targeted therapies. Currently, the prevention of bone disease is best accomplished by controlling inflammation, providing adequate calcium and vitamin D supplementation, and encouraging physical activity. Prospective trials of therapeutic agents need to be performed to assess efficacy and safety in the developing skeleton.

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Part IV

Medical Therapy

5-Aminosalicylate Therapy

25

Michelle Gonzalez and Michael Stephens

Introduction

Aminosalicylates are a class of medications commonly used as first-line therapy for induction and maintenance of remission in mild to moderate inflammatory bowel disease (IBD) [1]. Although their use in ulcerative colitis (UC) is well established, their role in Crohn disease (CD) remains controversial. Aminosalicylates were derived from sulfasalazine (SASP, salicylazosulfapyridine), a sulfa drug originally developed for the treatment of rheumatoid arthritis. The SASP molecule comprises two moieties with antimicrobial and anti-inflammatory properties, sulfapyridine and 5-aminosalicylic acid (5-ASA), respectively [2, 3]. In the colonic lumen, bacteria metabolize the azo bond that joins the subunits, thereby releasing the therapeutically active 5-ASA and the inactive sulfapyridine [4]. Although effective for the treatment of IBD, the dose-related adverse effects and hypersensitivity reactions associated with sulfapyridine led to the development non-sulfa aminosalicylates. These modern formulations have similar efficacy as their predecessor and have improved side effect profiles.

Although the use of 5-ASAs in adults with IBD is well established, there is limited evidence for their safety and efficacy in the pediatric IBD population. This shortcoming is further accentuated by mounting evidence that suggests important differences between adult and pediatric IBD. Nonetheless, 5-ASAs are commonly used in pediatric IBD patients. More recently, prospective pediatric data have emerged regarding mesalamine therapy response, specifically in pediatric UC [5].

Mechanism of Action

The exact mechanism of action of aminosalicylates in IBD remains unclear. The primary therapeutic effect of 5-ASA over the gastrointestinal mucosa is thought to be topical rather than systemic [6]. Colonic epithelial cells absorb 5-ASA and its effectiveness is in turn related to colonic mucosal concentrations. Systemic exposure remains low after oral and rectal administration. Current data suggest that 5-ASA induces the expression of a class of nuclear receptor genes, with resulting increased peroxisome proliferator-activated receptors (PPARs) in colonic epithelial cells. PPAR expression is particularly high in the colonic epithelium, and activation is largely driven by intestinal bacteria [7, 8]. PPAR-γ is involved in the control of inflammation, cell proliferation, apoptosis, and modulation of cytokine production. It has also been shown to have antitumorigenic effects [9]. As a result of these interactions, PPAR-γ may be the basis for future chemopreventive strategies against colorectal cancer (CRC) [10]. In turn, PPAR-γ expression has been shown to be downregulated in patients with active UC [11]. One randomized placebo-controlled clinical trial of a PPAR-γ ligand (rosiglitazone) demonstrated efficacy in treating mild to moderate UC [12]. Cardiovascular side effects, however, have dampened enthusiasm for rosiglitazone.

Other proposed mechanisms of action of 5-ASA have been described. One includes the inhibition of cyclooxygenase (COX) and 5-lipoxygenase pathways of arachidonic acid metabolism, resulting in a decrease in pro-inflammatory prostaglandins and leukotrienes, and inhibition of interleukin-1, interleukin-2, and tumor necrosis factor (TNF)-alpha [13]. Furthermore, 5-ASA has also been described as a potent antioxidant and free radical scavenger [6, 13]. Furthermore, data support the role of 5-ASA in restoration of the imbalance between angiogenic (VEGF) and antiangiogenic factors (endostatin and angiostatin) in experimental UC, potentially by modulation of metalloproteinases (MMP2 and MMP9), and again implicating TNF-alpha [14].

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Pharmacokinetics

5-ASA is absorbed in the stomach and small intestine unless bound as a prodrug or combined with another delivery system [2]. As 5-ASA is thought to act topically, the clinical goal is to maximize delivery of the active drug to the site of inflammation in the colon while minimizing systemic absorption in the small intestine. Rectal gels, liquids, and foam enemas have been formulated to this effect [15]. However, these formulations have the undesirable side effects of leakage and abdominal bloating and many patients find them impractical. As a result, adherence to the dosing regimen is often poor, limiting their use as an adjunct therapy in many cases [16].

Oral 5-ASA agents are much better tolerated and are thought to be more practical and patient friendly. SASP was the first prodrug that delivered 5-ASA to the colon via an azo bond linked to sulfapyridine. This bond is cleaved by bacteria in the colon to release the active drug [2]. 5-ASA is primarily excreted in the stool, as it is poorly absorbed in the colon. The sulfapyridine component, however, is absorbed from the colon and then metabolized in the liver, with excretion through the urine. Due to the multiple dose-limiting side effects of sulfapyridine, newer formulations of 5-ASA have been created, with specific compositions to ensure delivery to the targeted area of inflammation. Some are bound to other prodrugs, while others are time-release preparations and pH-dependent release formulations [17–19]. The other prodrug formulations are olsalazine and balsalazide, which are bound by distinct azo bonds, and, like SASP, are then cleaved by intestinal bacteria, releasing the active medication into the colon. Olsalazine is a 5-ASA dimer linked by a diazo bond and balsalazide is 5-ASA linked to an inactive carrier molecule by a diazo bond.

The pH-dependent delivery systems have been developed to target release of the active medication into the small bowel and colon. An acrylic-based resin, Eudragit, is used to coat these tablets. Asacol® and its newer bioequivalent, Delzicol® (mesalamine), are examples of such medications, and have been designed to release 5-ASA at a pH of 7 or higher in the terminal ileum and colon. Other preparations have been formulated to release 5-ASA at a lower pH of 6 or greater (Apriso®), which are released more proximally in the ileum and through the colon.

Pentasa® (mesalamine) is a time-dependent release formulation in which the active drug is packaged into microgranules that are coated by ethylcellulose. The ethylcellulose coating dissolves when hydrated and the drug is released throughout the small intestine and colon.

Luanda® is a once-daily, high-strength formulation of mesalamine, utilizing a Multi Matrix System (MMX) technology designed to deliver the active drug throughout the colon. The matrix is enclosed within a resistant coating which also disintegrates at a pH of 7.0 or greater, releasing the active medication within the terminal ileum and colon. Once the matrix is exposed to gut fluid, it expands and forms a viscous gel mass that is slowly released throughout the colon.

Most of the older formulations are limited by the amount of 5-ASA that can be delivered per capsule, which required that patients take multiple doses per day and several tablets per dose. However, the newer formulations allow for less frequent once to twice a day dosing and fewer pills. Table 25.1 and Fig. 25.1 outline the formulations more commonly used in the United States, sites of action, and delivery system.

Table 25.1 Preparations of 5-ASA

Drug	Formulation	Delivery System	Dosage Form	Release Location
Azo-bonded Formulations				
Sulfasalazine (Azulfidine®)	Azo bond of 5-ASA to sulfapyridine	Broken down by colonic bacteria to release active 5-ASA moiety	Tablet 500 mg	Colon
Olsalazine (Dipentum®)	Diazo bond of 5-ASA dimer	Broken down by colonic bacteria to release active 5-ASA moiety	Capsule 250 mg	Colon
Balsalazide (Colazal®)	Azo bond of 5-ASA and inactive carrier	Broken down by colonic bacteria to release active 5-ASA moiety	Capsule 750 mg	Colon
Mesalamine Formulations				
Pentasa®	Controlled release	Time release	Capsules 250 mg, 500 mg	Small intestine, colon
Asacol®	Enteric coated; delayed release	pH-dependent (≥7)	Tablet 400 mg	Terminal ileum, colon
Asacol HD®	Enteric coated; delayed release	pH-dependent (≥7)	Tablet 800 mg	Terminal ileum, colon
Lialda®	Delayed release	pH-dependent (≥7)	Tablet 1200 mg	Terminal ileum, colon
Delzicol®	Delayed release	pH-dependent (≥7)	Capsule 400 mg	Terminal ileum, colon
Apriso®	Delayed and extended release	pH-dependent (≥6)	Capsule 375 mg	Terminal ileum, colon
Rowasa®	Topical		Rectal suspension 4 g/60 mL	Left colon
Canasa®	Topical		Suppository 1000 mg	Rectum

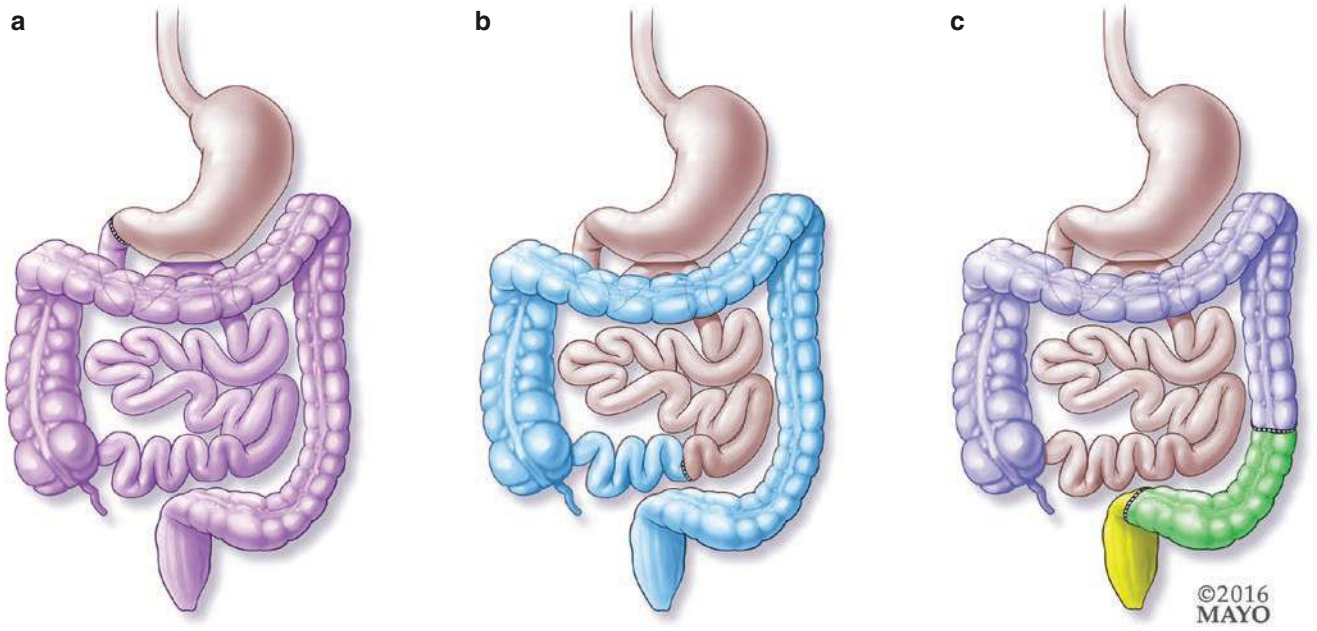

Fig. 25.1 (**a**) Purple shading: Pentasa (**b**) Blue shading: Asacol, Asacol HD, Lialda, Apriso (**c**) All three shaded areas (purple, green and yellow): Azulfidine, Colazal, Dipentum; Green shading only: Rowasa; Yellow shading only: Canasa

Indications and Efficacy

Ulcerative Colitis

The efficacy of aminosalicylates for the induction and maintenance of remission of UC is well established in the adult literature and these medications remain the first-line treatment for mild to moderate disease [20, 21]. Although there is very little pediatric UC data, oral 5-ASA formulations are recommended as the first-line induction therapy for mild to moderately active pediatric UC as well [22].

In a recent systematic review and meta-analysis, both oral and rectal preparations of 5-ASAs were found to have modest efficacy at inducing remission in mild to moderate UC compared to placebo with no statistically significant difference between the preparations [23]. There is no standardized dosage or frequency of dosing for rectal preparations in inducing remission of UC. In the most recent Cochrane Review, rectal 5-ASA was superior to rectal steroids for inducing remission of UC [24]. There is improved efficacy with combined rectal and oral 5-ASA therapy compared with oral 5-ASA therapy alone [25]. In fact, in a recent prospective open label study, 42% of children with mild to moderate UC that had been previously refractory to oral mesalamine obtained clinical remission on addition of rectal mesalamine (Pentasa enemas), with a 71% clinical response rate at week 3 [26]. Although there is no standard dosing of oral 5-ASA for inducing remission, doses of 1.5–4.8 g/day have been shown to be effective depending on disease severity and mesalamine preparation in adults. The result of the ASCEND I and II trials shows a statistically significant higher rate of mucosal healing in UC at 6 weeks with a dose of 4.8 g/day of delayed-release oral mesalazine over 2.4 g/day dosing [27]. However, a recent randomized control trial in pediatric UC patients showed equal effectiveness of high- and low-dose oral delayed-release mesalamine for achievement of clinical remission [28]. The reduction in fecal biomarkers, calprotectin and lactoferrin, was not statistically significant between the groups. Despite improved efficacy of combined oral and rectal 5-ASA therapy for inducing remission over oral 5-ASA alone, the remission rates are still significantly lower than with corticosteroids alone [24]. In UC, mesalamine has similar efficacy to SASP at equimolar doses.

Both oral and rectal mesalamine are more efficacious in preventing relapse of quiescent UC than placebo [21]. There are many randomized control trials that show topical 5-ASAs have comparable efficacy at preventing relapse of quiescent UC. On the other hand, in one recent meta-analysis, intermittent rectal mesalamine was superior to oral 5-ASAs with a NNT of 4 [25, 29]. In another recent meta-analysis, topical (rectal) mesalamine was more effective at preventing relapse of quiescent UC compared to placebo with a NNT of 3 [30]. This study also showed a trend toward a greater effect size with continuous topical therapy compared with intermittent topical therapy. The analysis showed lower relapse rates when an overall higher total weekly dose of topical mesalamine was used, similar to the occurrence with higher doses of oral 5-ASA therapy for preventing relapse of quiescent

UC. However, the majority of the patients in this study had only left-sided disease or proctitis.

In the adult population, oral 5-ASA has modest efficacy in maintaining remission of quiescent UC with good adherence, but there is no standardized dosing regimen. Some studies assessed not only efficacy in maintaining remission in UC but also adherence to the prescribed treatment. In a study of MMX mesalamine at 2.4 g/day, there was only a 30% recurrence rate at 12 months for patients who were adherent to the medication more than 80% of the time, as compared to a 53% relapse rate at 12 months for patients who were less than 80% adherent to the medication regimen [31]. A meta-analysis showed that once-daily dosing of oral mesalamine was equally as effective as conventional dosing in preventing relapse in quiescent UC over 12 months of therapy [32, 33]. Although 5-ASA has proven to be effective in maintaining remission in quiescent ulcerative colitis, adherence must be considered when developing an individual's treatment plan.

There are a few studies evaluating the efficacy of 5-ASA for the treatment and maintenance of remission in pediatric UC. One recent multicenter prospective study (PROTECT) aimed to determine initial response to oral mesalamine in treatment-naïve pediatric UC patients. Overall, 34% of children achieved the 12-week outcome of corticosteroid-free remission (PUCAI <10). Initial treatment solely with mesalamine was reserved for patients with mild UC (PUCAI <35) with an observed corticosteroid-free remission of 48%, whereas the moderate and severe groups were initially started on oral or IV corticosteroids, respectively, and with a 33% and 21% achieving the 12-week outcome as previously stated. The most significant clinical predictor of corticosteroid-free remission was clinical remission at week 4. Histological features were also predictive of response with baseline rectal biopsy peak eosinophil count of >32 cells per high-power field associated with better outcomes, and surface villiform changes associated with worse outcomes. Worse outcomes also were observed in patients with increased disease activity, as well as laboratory markers suggestive of increased disease severity (i.e., lower initial serum albumin). Per the study, age, sex, ethnicity, BMI, pANCA positivity, and baseline fecal calprotectin were not associated with outcome.

A study on the efficacy of mesalamine 500 mg suppositories for the treatment of ulcerative proctitis in children showed a statistically significant decrease in the disease activity index at 3 weeks for the 49 patients enrolled. 41 patients had a mild or an unrelated adverse event [34]. Another pediatric study compared the efficacy of oral beclomethasone dipropionate (BDP) to oral 5-ASA in the treatment of mild to moderate pediatric UC. The results of the study showed clinical remission was achieved after 4 weeks in 12 of 15 patients treated with BDP but only 5 of 15 patients treated with 5-ASA, suggesting BDP may be more efficacious at inducing remission in mild to moderate pediatric UC than 5-ASA [35].

In general, the preparation of 5-ASA used is dependent on the location and severity of disease. In addition, particularly in the younger age groups who may have greater difficulty in swallowing pills, the mode of delivery is also crucial. There are currently no 5-ASA liquid formulations. However, certain capsule formulations, namely, Pentasa® and Colazal®, may be opened and the contents are emptied into foods, such as yogurt and peanut butter. Data on the efficacy of this practice, have not been published to date.

Rectal formulations are usually a reasonable starting choice in patients with mild disease limited to the rectum or left colon [36]. Adherence needs to be considered when using these formulations. Patients with more extensive disease involving the transverse and ascending colon may require the addition of an oral preparation.

Dosing of oral 5-ASA in the pediatric population is variable, but the dosages usually fall in the range of 30–100 mg/kg/day. Guidelines established by ESPGHAN and the European Crohn's and Colitis Organisation (ECCO) suggest a dose of 60–80 mg/kg/day in 2 daily doses up to 4.8 g daily for mesalazine, and 40–70 mg/kg/day in two divided doses with a maximum of 4 g per day for SASP. Higher doses have been used, although it is not evidence based. For rectal dosing, 25 mg/kg up to a maximum of 1 g may be used once daily [37].

Crohn Disease

The efficacy of 5-ASA in the induction and maintenance of remission in Crohn disease (CD) is controversial. Currently, their use in treatment of pediatric CD is limited and only recommended in selected patients with mild disease [38]. In a Cochrane review consisting of adult studies, SASP showed only a modest effect over placebo in inducing remission in mild to moderate CD at a dose of 3–6 g/day [39]. It showed a 38% higher chance of inducing remission compared to placebo-treated patients. However, this effect was limited to patients with Crohn colitis. SASP was 34% less effective at inducing remission than corticosteroids alone and it was less effective than combination therapy with corticosteroids and SASP. Two studies, the Trial of Adjunctive Sulfasalazine in Crohn disease (TAS) and the European Cooperative Crohn Disease Study (ECCDS), showed that SASP was not a useful adjunct to corticosteroid therapy in achieving remission [40, 41].

A systematic review and meta-analysis of randomized controlled trials that excluded the Crohn's III trial data also suggest a modest effect of 5-ASA drugs inducing remission of active CD over placebo-treated patients with a number needed to treat (NNT) of 11 to prevent one patient's disease

remaining active [42]. The effect was based on a mean reduction in CDAI scores. Had the data from the Crohn's III trial been available, the authors suspect there would have been no statistically significant difference between the 5-ASA-treated group and the placebo-treated group. According to the latest Cochrane review, low-dose controlled-release mesalamine (1–2 g/day) was less effective at inducing remission in active CD compared to placebo-treated patients [39]. As with sulfasalazine, delayed-release mesalamine (2 g/day) was less efficacious than corticosteroids [43]. Trials evaluating higher doses of mesalamine (3–4.5 g/day) show inconsistent results. The majority of the studies show no difference in induction of remission in mild to moderately active Crohn disease relative to placebo [39]. Two of the studies showed statistically significant changes in CDAI scores, but they were found to be clinically insignificant. In a single trial, high-dose mesalamine was less effective than budesonide [44]. Many of these studies were small and had several methodological weaknesses, which may limit the generalizability of the effects of mesalamine at inducing remission in mild to moderately active Crohn disease.

Nonetheless, another more recent network meta-analysis did show that at doses above 2.4 g/day there was some benefit in induction of remission of Crohn disease over placebo, although this effect is not as significant as budesonide or corticosteroids [45]. This study attempted standardization in the definition of clinical remission as defined by a CDAI score of <150.

One pediatric study reviewed disease activity at diagnosis in 43 patients and treatment provided. Ten of 25 patients in the mild group and 3 of 18 patients in the moderate to severe group received 5-ASA monotherapy immediately after diagnosis. These patients tended to have more exacerbations, shorter duration of the first remission, and longer total duration of systemic steroid use than patients receiving combination therapy, immunomodulators, or systemic steroids [46].

The role of 5-ASAs in maintaining remission in quiescent CD was also assessed in the review by Ford et al. No statistical significant benefit over placebo was found, although subgroup analysis of trials with low risk of bias showed mesalamine to be of benefit in preventing relapse with a NNT of 13 [42, 47]. This was the same result when a more conservative protocol analysis was completed, in which dropouts from individual studies were not considered treatment failures. There is one pediatric study evaluating maintenance of remission in CD patients after successful flare-up therapy with either nutrition or medications that showed that the relapse rate was similar with mesalazine and placebo [48].

Overall, evidence does not support the use of mesalamine for maintenance treatment in pediatric CD.

Many gastroenterologists continue to use aminosalicylates in CD despite multiple studies showing at best a modest benefit over placebo [39]. The dosing of oral 5-ASA for pediatric CD is similar to that for pediatric UC with 50–80 mg/kg/day up to 4 g daily [38].

Surgically Induced Remission of Crohn Disease and Prevention of Postoperative Recurrence

Surgical resection can induce remission in CD. However, endoscopic and clinical relapse of CD after surgical resection is common and has been reported to be as high as 75–90% and 20–30%, respectively, within 1 year [49, 50]. There is currently no standard therapy for preventing relapse postoperatively. Aminosalicylates in the postoperative setting have been extensively studied, but their effectiveness at preventing relapse after surgical resection remains controversial. In a systematic review and meta-analysis of 11 randomized controlled trials, the effect of mesalamine appears to be modest with a NNT of 13 compared to placebo or not treating after surgery [51]. The previously referenced Cochrane review on the effectiveness of mesalamine in surgically induced remission in Crohn disease published their updated study to include more recent RCTs up to 2018 [52]. They suggest benefit of mesalamine over placebo in the maintenance of clinical remission with a NNT of 13 patients to prevent one relapse. There continues to be little evidence to support maintenance of endoscopic remission. Similar to the previous review, this potential benefit was not seen with the use of sulfasalazine.

There is heterogeneity in all of these studies, including the dosage and preparation, the length of treatment post-surgery, and the definition of remission. In another network meta-analysis comparing different pharmacologic interventions in preventing relapse of CD after surgery, mesalamine was shown to reduce the risk of clinical relapse (RR 0.60; 95% credible interval 0.37–0.88), but not endoscopic relapse (RR 0.67; 95% CrI 0.39–1.08) when compared to placebo [53].

Chemoprevention of Colorectal Carcinoma

Due to their structural similarity to aspirin, which has been shown to reduce the risk of colorectal cancer (CRC) and adenomas in patients without IBD, it was believed that 5-ASAs had a similar effect on patients with a diagnosis of IBD [54]. However, more recent studies suggest that they may not provide much, if any, chemoprophylaxis for CRC. A population-based study including more than 8000 patients found that there was no protective effect of 5-ASA against CRC [55, 56]. This study evaluated the cumulative use of 5-ASA at 1, 5, and 7.5 years. Adherence to 5-ASA therapy was based on the frequency of prescription refills. It is possible that the cumulative use for longer than 7.5 years could be chemopreventive, but this has not been studied. In con-

trast, one small case-controlled study found that cumulative mesalamine doses decreased the risk of CRC in patients with IBD [57]. There are also several studies that have observed a significant chemopreventive effect of mesalamine compounds, especially at doses of >1.2 g/day. However, these have been criticized because of the design, outcomes measured, and variables controlled for [58]. A more recent meta-analysis did show a chemopreventive effect of mesalamine, and not sulfasalazine, against CRC only in clinical-based studies, but not population studies [59]. Furthermore, this effect was only seen in UC but not in CD, and was more pronounced in doses of ≥1.2 g/day. Results of these studies are again limited by the heterogeneity of the studies included. A chemopreventive effect was not seen in patients who received sulfasalazine regardless of setting (referral versus non-referral).

As noted above, the exact mechanism of action of 5-ASA in the treatment of IBD is unknown, and the same can be said regarding chemoprophylaxis. One retrospective cohort study attempted to determine the precise moment in the dysplasia-carcinoma sequence where mesalamine would potentially exert its protective effect. The study identified patients with UC with no dysplasia, indefinite dysplasia, or flat low-grade dysplasia (LGD) and followed them for the development of high-grade dysplasia (HGD) or CRC. The data suggest that if mesalamine has any chemopreventive effect, it may act early in the neoplastic process before the development of LGD [58]. There are many in vivo and in vitro studies currently looking at the anti-inflammatory and anti-neoplastic effects on different proposed mechanism of action pathways, including inhibition of cyclooxygenase activity, enhanced apoptosis through inhibition of NF-κB and MAP kinases, improvement in the DNA replication process, inhibition of reactive oxygen species, and downregulation of oncogenes and transcription factors [54, 60]. 5-ASA is now thought to be involved in inhibition of protein synthesis, which may contribute to its anti-inflammatory and anti-neoplastic properties [61]. A recent observational study utilizing colonic biopsy specimens from UC patients undergoing long-term 5-ASA therapy studied gene expression levels of 5-ASA targets. Basically, specimens were collected at initial colonoscopy and at a follow-up colonoscopy at 2–6 years in patients with mild to moderate UC on 5-ASA for their maintenance. They observed significant reduction in the transcript levels of inflammatory and CAC-associated 5-ASA targets after prolonged 5-ASA therapy, including Ki-67, p53, CEACAM-1, BCL2L1, NF-kB, and PPARγ [62].

Side Effects

Sulfasalazine (SASP) therapy is usually accompanied with more side effects than the 5-ASA formulations due to the sulfapyridine moiety [2]. Up to 80–90% of patients who cannot tolerate sulfasalazine tolerate 5-ASA preparations [63]. In addition, patients who experience adverse reactions to a particular 5-ASA formulation often tolerate a different preparation.

Side effects of 5-ASA are listed in Table 25.2. The most common side effects of both SASP and 5-ASA are nausea, abdominal pain, diarrhea, dyspepsia, rash, and fever [64, 65]. Some of these effects, such as diarrhea, can be mitigated by a gradual increase in the dose [66]. Rare, but more serious side effects include interstitial nephritis, pancreatitis, pericarditis, pneumonitis, hepatitis, neutropenia, and rarely, worsening colitis [63–65]. The risk of interstitial nephritis and pancreatitis is higher with 5-ASA, while the risk of hepatitis is higher with SASP. Agranulocytosis, hemolytic anemia, and oligospermia have also been reported with SASP [65].

The safety profile of these medications in the pediatric literature is similar in adults [34, 67, 68]. As there are reports of hypersensitivity to 5-ASA causing worsening colitis, it can be challenging to clinically differentiate the gastrointestinal symptoms of diarrhea and abdominal pain as medication side effects from worsening underlying disease. There are no standard guidelines for monitoring these medications and the possible hypersensitivities. However, most studies and literature suggest regularly monitoring renal function.

5-ASA appears to be safe in pregnant and breastfeeding women [69–71]. Only a small amount of the drug is transferred to breast milk. There are reports of allergic reactions in nursing infants in the form of acute watery diarrhea [72, 73]. This usually resolves with cessation of the drug.

Table 25.2 Side effects of 5-ASA and sulfasalazine

5-ASA	Sulfasalazine
Common	*Common*
Headache	Headache
Diarrhea	Nausea
Nausea	Vomiting
Flatulence	Abdominal pain
Abdominal pain	Diarrhea
Rash	Anorexia
	Dyspepsia
	Rash
	Fever
Less common	*Less common*
Nephritis	Pancreatitis
Interstitial pneumonitis	Hepatitis
Worsening of colitis	Drug-induced connective tissue disease
Pancreatitis	Bone marrow suppression
Myopericarditis	Nephrotoxicity
	Interstitial nephritis
	Oligospermia
	Hemolytic anemia
	Folate deficiency
	Alveolitis

Adherence

Adherence to long-term 5-ASA therapy is of great concern in clinical practice. Approximately 40–60% of patients with UC do not take their oral 5-ASA therapy as prescribed [74]. Despite the benefits, the lowest adherence rates are in patients with quiescent UC, who may not understand the importance of continuing treatment when they are in clinical remission. Patients who are non-adherent have an increased risk of disease relapse than those patients who are adherent at least 80% of the time. Many factors contribute to non-adherence including dosing frequency, the number of pills, fear of side effects, and disease extent and duration [75, 76]. Before the introduction of delayed-release and high-dose formulations, 5-ASA was given in three to four divided doses per day. However, these newer formulations require twice daily or daily dosing with the same efficacy of conventional dosing. In a study looking at the persistency of oral 5-ASA therapy, patients receiving Lialda (MMX mesalamine) had significantly higher persistency at 12 months compared with patients receiving other oral 5-ASA formulations [77]. This study was from a large pharmacy database, but correlates with the understanding that simpler treatment plans lead to improved adherence in a number of chronic diseases, including UC [75]. There are few studies on adherence to medical regimens in the pediatric IBD population. Limited data suggest that patient age and emotional and behavioral functioning make a substantial contribution toward predicting adherence to oral 5-ASA [78]. Adolescents in the older age group (15–18 years old), for example, have been found to have lower rates of adherence than younger age groups. Further analysis of the previously mentioned PROTECT study (pediatric UC patients) utilized pill bottles with electronic caps to measure adherence and found that declining adherence over time strongly predicted treatment escalation [79].

A retrospective analysis on long-term mesalamine maintenance in adult patients with UC suggests that adherence, rather than daily dose, reduces long-term flare risk [80]. Thus, it is essential to take the time and discuss with each patient the importance of compliance and persistency.

Conclusion

5-ASA is a well-established first-line therapy for mild to moderate UC in the adult population. This remains an important option for children with mild to moderate UC. Its role in pediatric CD is limited given the lack of data supporting its efficacy. Few studies have addressed the use of 5-ASA in the pediatric population. An important step forward was observed following the Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) Study. Overall, 5-ASA are deemed effective in specific scenarios and considered generally safe.

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Antibiotic Therapy

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Jessica Breton and Lindsey Albenberg

Introduction

The pathogenesis of inflammatory bowel disease (IBD) is thought to involve an inappropriate inflammatory response to commensal gut microbes in a genetically susceptible individual [1]. Many genetic risk alleles for IBD involve regulation of the epithelial barrier or innate host immune responses to microbial invasion [2]. A multitude of animal studies show that bacterial colonization of the gut is critical for the development of intestinal inflammation [3, 4]. Observations in patients with IBD also support a role for the gut microbiota as IBD usually affects intestinal regions with the highest abundance of bacteria [5] and diversion of the fecal stream can be effective in the management of Crohn disease (CD) [6]. Furthermore, over the past decade, molecular analysis of the human intestinal microbiome using culture-independent DNA sequencing methods has accelerated our understanding of the alteration in microbiota composition and function that contributes to intestinal inflammation [7]. With these advances, dysbiosis characterized by a decrease in community richness, reduced proportions of Bacteroides and Firmicutes thought to have anti-inflammatory properties, and a relative increase in Enterobacteriaceae, including *Escherichia coli* and Fusobacterium, has been described in IBD [7]. Based on our current knowledge of IBD pathogenesis, antibiotics could therefore benefit patients with IBD through different mechanisms, including reducing luminal bacterial content, altering the composition of the gut microbiota, favoring beneficial bacteria, reducing bacterial invasion of intestinal tissue and translocation, as well as targeting an unknown specific pathogen in IBD.

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There is clear evidence for the effectiveness of antibiotics in the treatment of inflammation in multiple animal models of IBD [3]. Unfortunately, the evidence for the effectiveness of antibiotics in the treatment of humans with IBD has been inconsistent. This may be partially explained by the various antibiotics trialed, treatment duration, outcome measures, and potentially also by variable level of antibiotic resistance [8]. Nonetheless, recent meta-analyses of randomized controlled trials, all performed in adult populations, have documented a small but statistically significant benefit of antibiotics to induce remission in both CD and UC [9, 10]. Since then, accumulating evidence from uncontrolled and controlled studies, including two important RCTs performed in pediatric IBD [11, 12], have provided additional data to support the role of antibiotics in treating IBD.

We aim to review the current evidence relating to antibiotics in IBD management, evaluating both the available data from previously published adult and pediatric studies, while focusing on specific clinical scenarios. Taken together, this summary of the currently existing efficacy and safety data may help pediatric gastroenterologists integrate antibiotics in current IBD practice.

Antibiotic Use in Crohn Disease

Despite the aforementioned theoretical basis for the role of the microbiome in CD and supportive animal models, the therapeutic role of antibiotics in CD remains controversial. Evidence points towards use of antibiotics in perianal CD, utilizing ciprofloxacin with or without metronidazole as an adjunct to biological therapy, and perhaps post-operative therapy following ileal resection to prevent or delay recurrence, although long-term benefits remain unknown. Recent pediatric studies, including a RCT, also suggest a modest role for antibiotics in luminal CD. We summarize here the evidence for the use of antibiotics in CD, focusing on specific clinical scenarios.

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Active Crohn Disease

Several human studies, including RCTs and uncontrolled studies, have been carried out over the last 30 years evaluating the use of antibiotics to induce remission in active CD using different antibiotic combinations, course duration, and end points. Overall, studies have either used antimycobacterial agents targeting Mycobacterium avium subspecies paratuberculosis (MAP) or broad-spectrum antibiotics.

While there are conflicting results for many of these studies, a meta-analysis of 15 randomized controlled trials, all performed in adult populations, demonstrated a small but statistically significant benefit of antibiotics in the treatment of CD (RR 1.33, 95% CI 1.17–1.51, $P < 0.00001$) [13]. Notably, all RCTs utilized clinical indices as the primary outcome measure. More commonly used antibiotics were ciprofloxacin, rifaximin, metronidazole, and clarithromycin. Rifaximin, a minimally absorbed, non-systemic antimicrobial agent showed significant benefit (RR 1.28, 95% CI 1.02–1.62, $P = 0.03$). In the largest study evaluating this antibiotic, Prantera et al. demonstrated that rifaximin for 12 weeks induced clinical remission with few adverse events in patients with moderately active CD (45). The meta-analysis also showed a significant difference in clinical improvement between antibiotic-treated patients and controls, especially in the rifaximin and metronidazole groups. Clarithromycin showed a signal of minimal clinical benefit (RR 1.29, 95% CI 1.03–1.63, $P = 0.03$), hampered by conflicting results among the 2 RCTs included. Among the ciprofloxacin trials, subgroup analysis conducted for treatment of active CD showed a significant difference in the clinical remission or response rate in patients treated with ciprofloxacin for no more than 10 weeks (RR 2.84, 95% CI 1.46–5.52, $P = 0.002$). Indeed, longer treatment duration did not result in any clinical benefit.

Pediatric studies evaluating the use of antibiotics in active luminal CD are limited; however, three recent studies have suggested a modest signal for clinical and biochemical benefits, all using combination antibiotics [11, 14, 15]. In the only available pediatric RCT [11], Levine et al. evaluated if azithromycin-based therapy could improve response and induce remission compared with metronidazole alone. Here, 35 children were randomized to azithromycin 7.5 mg/kg, 5 days/week for 4 weeks, and 3 days/week for another 4 weeks with metronidazole 20 mg/kg/day and 38 children to metronidazole alone, daily for 8 weeks. The combination of azithromycin and metronidazole was superior to metronidazole alone for induction of remission (66% vs. 39% ($P = 0.025$), as defined by a Pediatric Crohn Disease Activity Index (PCDAI) <10, though it did not reach superiority for response. Moreover, significant reduction in calprotectin ($P = 0.003$) in combination therapy only was also observed. These results replicated the success reported in a previous retrospective study ($n = 32$) using the same antibiotic combination [15]. Finally, in a recent retrospective study published by Breton et al. [14], benefit of combination of three–four antibiotics used as salvage therapy in refractory colitis was demonstrated in a cohort of 63 children, including 27 (43%) with colonic or ileocolonic CD. Use of combination antibiotics led to significant decrease in mean Pediatric Ulcerative Colitis Activity Index (PUCAI) from 52 ± 17 to 23 ± 25 ($p < 0.0001$), with 25/63 (39.7%) patients achieving clinical remission (PUCAI <10 points). Clinical benefits of oral antibiotics were independent from IBD diagnosis (CD vs. UC) as shown in multilinear regression analysis.

Anti-MAP Therapies

The association between CD and infection with MAP dates back to the 1930s. MAP causes Johne's disease in ruminants, a granulomatous enteritis which shares clinical and pathological features with CD. These observations suggested a positive causative role for MAP in CD and consequently, led to the hypothesis that a specific anti-MAP therapy would benefit patients with CD [16]. However, multiple groups have tested thousands of IBD tissue samples for MAP without reaching a definitive conclusion [17]. Despite this, some uncontrolled studies have documented a favorable therapeutic response to anti-MAP antibiotics [18–20], and three trials utilizing anti-MAP therapy showed a small but significant signal for prevention of relapse in quiescent CD during prolonged treatment of 8–24 months (RR, 0.62; 95% CI, 0.46–0.84; number needed to treat (NNT), 4) [9]. It should be noted that not all patients had documented MAP infection.

Recently, RHB-104, a novel oral formulation containing a fixed-dose combination of clarithromycin, clofazimine, and rifabutin and showed encouraging in vitro data with synergistic inhibitory activity on MAP strains isolated from CD patients. This antibiotic combination is currently being investigated in a randomized, placebo-controlled phase III trial aimed at evaluating its efficacy and safety in CD [21]. Preliminary analysis, including 331 randomized patients with active luminal CD treated with either corticosteroids or immunosuppressives (50%) or anti-TNF (20%), showed promising results. After 26 weeks of treatment, 36.7% of patients in the RHB-104 group had attained clinical remission (primary endpoint) as compared with 23.0% of the placebo group (P = 0.007). Additionally, 42.2% of the RHB-104 group achieved early remission (week 16) vs. 29.1% of the placebo group ($P = 0.015$). Moreover, in a subgroup of 35 patients assessed endoscopically at 26 weeks, 35.7% of the RHB-104 group had at least 25% improvement in the Simple Endoscopic Score versus 9.5% for the placebo group ($P = 0.048$) [22]. Data on documented MAP infection were not provided in this abstract.

Overall, results from previous adult studies evaluating the therapeutic role of anti-MAP therapy in luminal CD have demonstrated clinical improvement, with some preliminary data suggesting endoscopic recovery. However, additional studies, particularly in pediatrics, are needed before this antibiotic combination take a relevant position in the therapeutic armamentarium for CD management.

Perianal Disease

Population-based studies indicate that 25–40% of patients with CD will develop perianal fistulas during their disease course [23], while the specific prevalence in pediatric patients has been estimated to be between 10 and 15% [24, 25]. One of the primary therapies for perianal fistulizing disease has been antimicrobial treatment, more commonly ciprofloxacin and/or metronidazole. A total of three RCTs have been performed in active perianal fistulizing CD, all in adult populations, and were analyzed in a recent meta-analysis [26]. Only one included antibiotics alone ($n = 25$) [27], while the other two compared the efficacy of ciprofloxacin vs. treatment with a TNF-α antagonist and placebo ($n = 96$) [28, 29]. Thia et al. provided data on remission and response in patients assigned to treatment with ciprofloxacin, metronidazole, or placebo [27]. However, despite trend to response to ciprofloxacin, the study was underpowered to detect statistical significance. Two trials [28, 29] compared combination therapy with a TNF-α antagonist and an antibiotic to TNF-α antagonist monotherapy. The pooled RR demonstrated that a TNF-α antagonist coupled with an antibiotic was more effective than a TNF-α antagonist administered alone for induction of fistula response (RR, 1.58; 95% CI, 1.09–2.28; $P = 0.01$) and healing (RR, 1.94; 95% CI, 1.14–3.29; $P = 0.01$). In summary, these results suggest that antibiotics, in particular ciprofloxacin, may be used as an adjunctive induction treatment in active perianal CD, but not as monotherapy.

Postoperative Recurrence of Crohn Disease

A large proportion of patients with CD require surgery at some point during the course of their disease, and a majority of these patients will eventually develop recurrence of disease requiring additional surgery [30]. Previous studies have suggested that bacteria may play a role in the recurrence of disease as inflammation recurs when the mucosa is reexposed to luminal contents and bacteria [31]. Based on these observations, antibiotics may be beneficial in the prevention of postoperative recurrence of Crohn disease.

A total of five RCTs have evaluated the efficacy of antibiotics in preventing postoperative recurrence of CD, predominantly using metronidazole or nitroimidazole [32–35]. In a meta-analysis of medical therapies used to prevent recurrence of postoperative CD [36], nitroimidazoles (e.g., metronidazole) alone (two RCTs, $n = 81$) showed no improvement compared to placebo in preventing postoperative endoscopic recurrence of CD at 12 months according to a Rutgeerts score of ≥i2. However, nitroimidazole combination therapy with an anti-TNF-α or a thiopurine was more effective than placebo ([RR 0.22; 95% CI 0.07–0.72] and [RR 0.56; 95% CI 0.40–0.80], respectively). When evaluating the efficacy of medical therapies at preventing clinical recurrence at 12 months postoperatively, combination therapy with anti-TNF-α and a nitroimidazole (1 RCT, $n = 45$) was ranked as the most effective treatment and was significantly more effective than placebo [RR 0.06; 95% CI 0.01–0.42]. Thiopurine and nitroimidazole combination therapy (2 RCTs, $n = 80$), and nitroimidazole monotherapy (three RCTs, $n = 111$) were also more effective than placebo. One additional RCT ($n = 33$), not included in this meta-analysis, showed a non-significant trend to reduced endoscopic recurrence with ciprofloxacin monotherapy when compared to placebo [35].

Taken together, a moderate signal for effectiveness in preventing postoperative recurrence has been shown with antibiotics, particularly nitroimidazoles/metronidazole; however, long-term effects are unknown.

Antibiotics in Active Ulcerative Colitis

A number of RCTs and uncontrolled studies have been performed in patients with acute severe colitis (ASC) or chronically active ulcerative colitis (UC) with varying results. Two meta-analyses have demonstrated a higher rate of remission in patients with active UC treated with antibiotics [9, 37]. Since then, data to support the role of antibiotics in treating patients with refractory UC have been accumulating. The heterogeneity of studied regimens and treatment protocols, however, have limited our ability to formulate recommendations for clinical practice. While current adult guidelines [9, 10] recommend the use of antibiotics only if infection is considered, or immediately prior to surgery, the recently published pediatric guidelines for management of ASC specify that a short course of antibiotics may be considered in selected patients refractory to conventional therapies while preparing for colectomy [11]. Here, we focus specifically on pediatric studies illustrating the role of antibiotics as salvage therapy in refractory colitis.

Two Japanese RCTs using a combination of oral antibiotics, amoxicillin, tetracycline, and metronidazole (ATM) against Fusobacterium varium (F. varium) for 2 weeks showed improvement in clinical and endoscopic remission rates in patients with chronic relapsing UC [5, 6]. Likewise, almost

half of the 15 included children (7/15) with moderate to severe refractory UC responded to a two–three-week course of an oral broad-spectrum antibiotic cocktail (including metronidazole, amoxicillin, doxycycline, and—in hospitalized patients—also vancomycin; hereafter referred as the "Jerusalem cocktail") in a pediatric cohort study by Turner and colleagues [7]. Subsequently, a smaller pediatric case series showed similar benefit when using the same antibiotic cocktail in children with refractory UC, reporting a 38% clinical remission rate (3/8 children) [8]. Further, data from a retrospective study of 63 children treated with various versions of the "Jerusalam cocktail" showed a 40% clinical remission rate at 3 weeks. Twenty-six individuals were hospitalized with ASC, of whom seven (27%) entered remission at 3 weeks, with response seen typically within 5 days. Importantly, in this cohort, including patients with either UC, IBD-U, or colonic or ileocolonic CD, with previous or current loss of response to anti-TNFα therapy at the time of antibiotic initiation, clinical benefits of oral antibiotics were found to be independent from anti-TNFα therapy optimization [14].

The results of the only available pediatric RCT evaluating the effectiveness of antibiotic combination in ASC, the PRASCO trial (Pediatric Randomized trial of Antibiotics in acute Severe Colitis), were recently published [12]. Here, pediatric patients (n = 28) hospitalized with ASC were randomized to receive intravenous corticosteroids (IVCS) alone versus IVCS plus the "Jerusalem cocktail." Day-5 PUCAI was significantly lower in the combination antibiotics+IVCS arm vs. IVCS alone (25 ± 16.7 vs. 40.4 ± 20.4, P = 0.037). It should be noted that the trial was not powered to detect differences in need for second-line therapy or colectomy and there were only 2 children in the IVCS arm and 3 children in the antibiotics + IVCS arm who required colectomy during 1-year follow-up (P = 0.89). Interestingly, microbiome data at time of admission showed a decreased in diversity in those with day-5 response in the IVCS arm. Taken together and in agreement with the recently published guidelines for management of pediatric UC [11], a short course of combination antibiotics may be considered as salvage therapy in this refractory population left with limited therapeutic options. Clinical response should be assessed frequently and therapy discontinued if no improvement is documented. Further studies leading to an understanding of the changes in the composition and functions of the gut microbiome in responders and non-responders to combination antibiotic therapy are needed to develop better antimicrobial-based strategies.

Antibiotics in Extra-Intestinal Manifestations of IBD

Limited data exist on the use of antibiotics for extra-intestinal manifestations associated with IBD. Oral vancomycin has shown some promise in treating the subset of pediatric IBD patients with primary sclerosing cholangitis (PSC). Davies et al. treated 14 IBD patients (11 UC) diagnosed with PSC with 50 mg/kg/day of oral vancomycin for 14 days. All showed significant improvement in their alanine aminotransferase, gamma-glutamyl transpeptidase, erythrocyte sedimentation rate, and clinical symptoms. Three patients who were rebiopsied demonstrated reversal of their fibrosis [38]. While this initial study was promising, further studies are needed to verify whether oral vancomycin is an effective long-term treatment in preventing the progression of PSC to cirrhosis in IBD patients.

Additional Considerations

While generally well tolerated, antibiotics can lead to adverse effects that may require discontinuation and should be monitored closely. Ciprofloxacin has been noted to cause arthropathies in immature animals, and long-term use is generally avoided among very young children. There is also one pediatric study which evaluated the side effects associated with long-term metronidazole use. Duffy et al. reported on their experience among 13 patients with pediatric Crohn disease who received metronidazole for 4–11 months [39]. The authors reported that 85% (11 of 13) had peripheral neuropathies based on abnormal nerve conduction velocities or neurological examinations, although only 6 of 11 were symptomatic. Complete resolution of the neuropathy occurred in five children, improvement occurred in three children, and there was no change in one child.

Concerns regarding development of antibiotic resistance with antibiotic exposure have also been raised. Previous data have demonstrated higher prevalence rates of methicillin-resistant Staphylococcus Aureus (MRSA), vancomycin-resistant Enterococcus (VRE), and extended-spectrum beta-lactamases (ESBL) are significantly higher among IBD patients [40, 41]. Certain antibiotics are also associated with increased dysbiosis, resulting in relatively higher fungal abundancy, as shown in an observational pediatric CD cohort initiating therapy for induction of remission [42]. The long-term effects of these antibiotics on the microbiome remain to be studied. Finally, a theoretical increased risk for infection with C. difficile exists and should be considered in patients with prolonged antibiotic use. Interestingly though, a previous study [43] has reported a lower C. difficile infection rate in patients chronically exposed to antibiotics.

Summary

In summary, the current literature, including recent meta-analyses, supports a modest clinical effect of various antibiotics classes in luminal, perianal disease and postoperative prevention in CD, as well as in ASC and refractory

UC. However, much remains unclear, including which antibiotic(s), the duration of therapy, and long-term benefits. When integrated into clinical practice, the use of antibiotics should be judiciously balanced against potential adverse effects and resulting alterations of the microbiome for which the long-term sequelae are unknown.

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Nutritional Management of Inflammatory Bowel Disease

27

Anthony Otley, Andrew S. Day, and Mary Zachos

Introduction

While similar in many respects, the inflammatory bowel diseases (IBD) can be classified based on certain distinctive endoscopic and histological characteristics. Clinical manifestations also vary between Crohn disease (CD) and ulcerative colitis (UC), including their impact on nutritional status. A history of weight loss or poor weight gain is a very common symptom at presentation particularly with CD and severe UC [1, 2]. Linear growth impairment is reported even before the onset of intestinal symptoms in almost half of children with CD [3]. Given the early age of onset, such impairment of growth is particularly problematic, with subsequent impact on onset of puberty, self-esteem, and quality of life.

In the treatment of IBD in children, nutrition and growth outcomes are critical indicators of overall well-being and therapeutic success in addition to other therapeutic targets of symptom resolution and mucosal healing. In addition to a multitude of pharmacologic approaches to therapy, there is extensive evidence supporting the efficacy of nutritional therapy in CD. Current guidelines support exclusive enteral nutrition (EEN) as the first-line therapy to induce remission in children with active CD [4]. Despite the obvious advantages, including the direct impact on growth and nutrition and the avoidance of adverse drug effects, nutritional therapy has not been as widely accepted in North America as other parts of the world [5, 6].

Since anemia, linear growth and bone disease have been addressed in alternate chapters, this chapter will focus on nutritional deficiencies and the role of nutritional management in the treatment of IBD, highlighting updates since the last edition.

Nutritional Impairment in Pediatric Inflammatory Bowel Disease

Malnutrition is common in IBD. In a recent systematic review, the main nutritional consequences of pediatric IBD included growth stunting, slower pubertal development, underweight, and vitamin deficiencies. Nutritional impairments were more significant in CD, while overweight and obesity were more common in patients with UC [7]. Several cohort studies have demonstrated weight loss or poor weight gains at the time of initial diagnosis of CD. Griffiths et al. [8] reported that 80% of the 386 children diagnosed with CD over a period of 10 years had a history of weight loss. A registry cohort of 261 patients in northern France found that 27% of children were underweight and 32% had BMI below two standard deviations of normal at diagnosis. At maximal follow-up, 15% continued to suffer from malnutrition. A Danish prospective population-based cohort study reported that children with CD had poor nutritional status at diagnosis compared with the general pediatric population [9]. Among Australian children, a case–control study by Aurangzeb et al. [10] assessing nutritional status found that children with newly diagnosed IBD had lower mean body mass index (BMI) Z scores and weight-for-age percentiles than controls.

Weight loss is seen less commonly, particularly through the course of established UC, but has been seen in up to 65% of children at diagnosis [1]. Kugathasan et al. [11] conducted

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a systematic review of 783 children with newly diagnosed IBD from two prospective inception cohorts to examine BMI status at presentation. Most children with CD and UC had a BMI in the normative range (5–84%). Low BMI (<5%) was seen in 22–24% of children with CD and 7–9% of children with UC.

Several interrelated factors contribute to growth impairment in IBD. Chronic suboptimal nutrition has long been implicated as a cause of growth retardation [1, 12–16]. In addition, direct growth-inhibiting effects of pro-inflammatory cytokines (such as Tumor Necrosis Factor (TNF)-α) released from the inflamed intestine have been more recently recognized for their role in growth impairment, as well as indirectly resulting in anorexic effects and early satiety [17]. Symptoms, including nausea, abdominal pain, or diarrhea in association with meals, also limit caloric intake. Localization of disease in the small bowel may lead to partial obstruction and early satiety. Small intestinal involvement may also lead to disaccharide intolerance resulting in shorter gut transit times, pain, and exacerbation of diarrhea. Malabsorption of food components and the diversion of calories to sites of gut inflammation may also lead to impaired weight gain and growth [18]. Thus, enhancement of growth is best achieved through control of intestinal inflammation and assurance of adequate nutrition [19, 20].

Dietary Intake and Body Composition in Children with IBD

Dietary Intake

The impact of CD on growth and body composition is determined by an interaction between the duration and severity of the inflammatory disease process, genetic predisposition, and the extent to which the demands for energy and nutrients are met. It is imperative that the management of children and adolescents with CD combines the control of inflammation while providing optimal nutrition support with adequate protein and sufficient calories to support growth.

The mean energy intake of patients with CD is less than age-matched controls particularly during symptomatic relapses [13] but also while asymptomatic [8]. Pons et al. [21] evaluated the dietary intake of 41 children with CD (18 active, 23 in remission) and compared them with the intakes of 22 age-matched control children without IBD. The energy intakes of the children with CD were less than the estimated energy requirements regardless of disease activity. Fat and carbohydrate intake were found to be lower in patients with CD than in controls, while protein intake was similar in patient and control groups [21].

A recent study from Brazil found that total energy intake was lower than the daily recommended intake (DRI) in 50% of the adolescents with active CD compared to 3.5% in inactive CD and 5.7% in the control group. Protein intake was found to be low in all three groups but significantly lower in the active CD group than in the inactive CD and control groups (68.2% vs. 17.2% and 14.3%, below the DRIs, respectively) [22].

Body Composition

A systematic review, reporting on a total of 1479 children with IBD (1123 CD, 243 UC), attempted to define the alterations in non-bone tissue compartments in children with IBD [23]. Data were highly heterogeneous, in terms of methodology and patients. In this systematic review, six studies were prospective and 11 cross-sectional in design. Body composition methodologies included whole-body dual X-ray absorptiometry (DXA) most commonly, as well as peripheral quantitative computerized tomography (p-QCT), skinfold thickness, isotope dilutional studies, whole-body potassium measurement, total body potassium counting (n = 30), and bioelectrical impedance. Overall, the review concluded that almost all children with CD (~94%) and half with UC (~47%) have reduced lean mass; however, body fat alterations are not well defined. Deficits in female children persisted well after disease treatment.

Deficits in protein-related compartments were reported with lean mass deficits documented in 93.6% of patients with CD and 47.7% of those with UC when compared with healthy control populations. Several studies have confirmed that children with CD have significant deficits in lean body mass (or fat-free mass), which is consistent with cachexia [24–27]. Wiskin [26] found that fat-free mass was related to disease activity regardless of changes in weight and concluded that weight or BMI may mask deficits in lean tissue in the presence of normal or increased proportions of body fat.

Lean mass deficits can persist for many years despite improvements in disease activity and improvement in fat mass [20, 28]. In a study evaluating the role of physical activity and dietary intake on lean mass and muscle torque in 138 children and adolescents with CS, time in moderate to vigorous physical activity was found to be positively associated with both lean mass and muscle torque. Neither caloric intake nor protein intake was associated with either lean mass or muscle torque. Thus, physical activity may play a role in lean mass, muscle torque, and the management of inflammation in CD [29]. Further studies on the role of diet and physical activity on lean mass and disease activity are required.

Body fat composition findings have been inconsistent [23]. Some studies report reductions in body fat in new diagnosis or active CD. For example, Boot et al. [30] suggest proportional reductions in lean and fat mass, as shown by

percentage body fat that did not differ significantly from zero in their combined IBD cohort. In contrast, in an all CD cohort, Burnham et al. [24] report that fat mass adjusted for age and fat mass adjusted for height were not significantly different from controls. Similarly, in 42 children with CD, weight gain over a two-year period was explained by gains in fat mass raising concerns regarding the long-term impact of disease on growth and bone health [31].

In addition to circulating inflammatory cytokines, there are several other factors that are likely to contribute to the reduction in protein compartments in patients with IBD (Table 27.1).

Body composition studies have often been limited by the large proportion of participants that had received concomitant systemic corticosteroids at the time of body composition assessment. Glucocorticoids instigate remission but also promote muscle proteolysis and alter whole-body adiposity [32]. Variations in the glucocorticoid treatment the participants received may have influenced some of the discrepancies in the fat-related data across the studies in this review. Future studies should attempt to differentiate between the effects of therapy and the disease process itself.

There is conflicting data from studies reporting resting energy expenditure (REE) in children with CD. Azcue et al. [25] demonstrated that per unit of lean body mass, there was no difference between REE in patients with CD and controls, whereas patients with anorexia nervosa had significantly reduced REE. In contrast, Zoli et al. [33] found elevated REE in growing children with CD. Surprisingly, the latter study did not reveal any further increase in REE with relapse of disease and suggested that energy may be "diverted" from growth to disease activity during relapse. Varille et al. [34] showed that a lower fat-free body mass in pediatric IBD was associated with higher REE. Thus, these energy imbalances may explain the cachectic changes seen in children with IBD even when disease is in remission. This REE imbalance is most likely driven by nutritional insufficiencies and chronic inflammation.

Height, age, and pubertal status may also influence body composition. Puberty affects fat and muscle compartments and should be accounted for in analysis of body composition. In children with IBD, height is reduced, and bone age and puberty are delayed when compared with healthy children of the same age, possibly explaining some of the body compositional deficits seen [23].

Table 27.1 Factors affecting body composition

Circulating inflammatory cytokines
Medications, particularly glucocorticoids
Malnutrition
Resting energy expenditure
Height, weight, and pubertal status
Sex
Physical activity

Sex differences can also influence body mass composition, as reported by Thayu et al., [27] who studied the body composition of 74 children with CD at diagnosis. They found that boys with CD at diagnosis had significant fat-free mass deficits consistent with cachexia, whereas girls demonstrated both fat mass as well as fat-free mass deficits consistent with wasting. In a recent systematic review, lower lean mass was common to both sexes in CD and UC, but deficits in females persisted for longer, possibly because males are known to accumulate lean tissue at puberty, while females reach peak lean mass before puberty [23].

The effect of malabsorption may lead to reduction in protein compartments due to protein-losing enteropathy that result in fluid shifts [25]. In addition, physical activity is important for muscle and bone strength in growing children and may be limited in children with IBD even when their disease is asymptomatic. Werkstetter [35] compared 39 patients with IBD in remission (or with only mild disease activity) with 39 healthy controls. Muscle function assessed by measuring handgrip strength was reduced in children with CD, which corresponded to deficits found in muscle cross-sectional area of the upper limb. In addition, individuals with IBD tended to take fewer steps per day and engage in shorter periods of physical activity, particularly among females and patients with mild disease. Exercise studies in adolescents with CD have shown impaired fat metabolism during activity with a greater reliance on carbohydrates to meet the energy demands of submaximal exercise [36].

The clinical significance of muscle deficits in children with CD is not known; however, lean mass deficits may be associated with poor physical functioning and greater infection risk during childhood and compromised peak bone mass by young adulthood. Adult studies suggest that body fat composition predicts infectious complications following bowel resection in CD [37]. In adults, low muscle mass and sarcopenia are common and may be predictive of osteoporosis [38]. Further study of the long-term impact of altered body composition in children with IBD is required, as this may have clinical importance in terms of nutritional and pharmacological management, even when disease is in remission.

Because of the difficulty ensuring adequate energy and nutrient requirements of children with IBD, particularly during flares, active monitoring of nutritional status must be undertaken throughout childhood but especially in adolescence. Hannon et al. [39] demonstrated that in stable adolescents with CD, enteral nutrition promotes anabolism by suppressing proteolysis and increasing protein synthesis. Thus, where indicated, aggressive nutritional intervention should be initiated before puberty, whether disease is active or in remission, to correct the energy deficits and maximize growth potential.

Micronutrient Deficiencies

Low concentration of plasma micronutrients is commonly reported in patients with IBD. Dietary intakes of children and adolescents with IBD may be compromised in micronutrient content in addition to protein and energy due to many factors, including decreased food intake, intestinal losses, malabsorption, and drug effects [40].

Specific micronutrient and vitamin deficiencies are encountered more commonly with CD than with UC. Hendricks et al. [13] compared a group of adolescents with CD and growth failure with a control group of adolescents with CD who were growing normally. Mean serum ferritin levels were significantly decreased in both groups, and mean plasma zinc levels were borderline low in the growth failure group and low in the control group. Dietary zinc intake was below the recommended dietary allowance (RDA) in 88% of the group with growth failure and 44% of controls (64% combined) and less than 75% of the RDA in 41% of all adolescents with CD. Dietary iron intake was also below the RDA in 24% of all adolescents with CD, with one adolescent in the growth failure group consuming less than 75% of the RDA. One-third of adolescents were consuming less than 75% of the RDA for calcium. In evaluation of 41 children with CD compared to age-matched controls, calcium intake was significantly less than the Australian recommended daily intake (RDI), and iron intake approached less than RDI [21]. Vitamin D is a key factor in both bone mineralization and immunomodulation. Levin et al. [41] retrospectively assessed vitamin D in a group of 78 Australian children with IBD (70 CD, 5 UC, 3 IBDU) and explored associations between vitamin D status and clinical factors. Using a level of 50 nmol/L or less to indicate deficiency and 50–75 nmol/L to indicate insufficiency, 19% of children were vitamin D deficient and 38% were insufficient, respectively. Levels were not found to be associated with disease location or use of immunosuppressive drugs. Children with vitamin D deficiency had significantly greater corticosteroid exposure than those with normal status. In Canadian children with newly diagnosed IBD, vitamin D deficiency was seen in 52% ($n = 44$) of children, and correlated with the greatest frequency of sarcopenia in children younger than 13y with CD [42].

Alkhouri et al. [43] investigated the prevalence of vitamin and zinc deficiencies in 61 children with newly diagnosed IBD (80% with ileal inflammation) compared to age- and sex-matched controls. Sixty-two percent had vitamin D deficiency (vs. 75% in the controls). In contrast to other studies, this report did not demonstrate folate or vitamin B12 deficiency in any subjects with IBD suggesting no reason for routine monitoring. However, vitamin A (16% deficient) and zinc (40% deficient) deficiencies were statistically more prevalent among those with IBD than controls, suggesting that levels should be assessed at the time of diagnosis. In addition, since vitamin D deficiency was so common in the population tested, routine screening and supplementation are warranted [43].

Older studies of micronutrient intakes in CD have found mean intakes of zinc, copper, iron, calcium, folic acid, vitamin C, and vitamin D to be significantly ($P < 0.05$) lower than age-matched controls and RDAs [17]. Essential fatty acid status may also be altered, in association with low body mass index and disease activity [44]. Malabsorption of fat-soluble vitamins can be an issue in patients with ileal disease [45, 46]. Gerasimidis et al. [47] looked at the impact of Exclusive Enteral Nutrition (EEN) on body composition and circulating micronutrients in plasma and erythrocytes of 17 children with active CD. At baseline, several children presented with suboptimal concentrations of carotenoids, trace elements, vitamins C and B6, and folate in plasma but not in erythrocytes. The same group later reported anemia in 72% of children with IBD at diagnosis. Children with CD at diagnosis had significantly shorter diagnostic delay and a lower BMI than those who were not. After EEN, the frequency of severe anemia decreased (32–9%; $P = 0.001$). Extensive colitis was associated with anemia in UC [48]. Several additional studies have evaluated the prevalence of anemia in children with IBD, both at diagnosis and follow-up. Using the WHO definition of anemia, prevalence ranges from 44% to 74% at diagnosis and 25% to 58% at one-year follow-up [49]. Anemia should therefore be routinely monitored and treated as it is the most common extraintestinal manifestation of IBD (refer to Chap. 10 for further details).

Fritz et al. [50] recently performed a systematic review to critically analyze the current research on micronutrient deficiency in children with IBD and synthesized these data to provide evidence-based guidelines for nutritional surveillance in this population. From the 39 studies included in the final review, the data demonstrated iron and vitamin D as the most common deficiencies in children with IBD. Vitamin B12 and folate deficiency are rare. Zinc deficiency, while uncommon, occurs at a higher rate in patients with CD than in healthy controls. There were limited data on vitamins A, E, and C, and selenium, but deficiency of these micronutrients seems rare.

In a recent study by Ehrlich et al., [51] the status of trace elements, minerals, and vitamins was retrospectively evaluated in a large cohort of children with IBD. Out of 359 children with IBD with a median age at diagnosis 14.1 years, 240 (67%) were diagnosed with CD and 119 (33%) with UC. Median follow-up time was 7 years (IQR 5–10). The prevalence of deficiencies in patients with CD at diagnosis and last follow-up, respectively, were iron (88% and 39.5%), zinc (53% and 11.5%), vitamin D (39% and 36%), and folic acid (10% and 13%). In patients with UC, frequencies were as follows: iron (77% and 40%), vitamin D (49% and 33%), zinc (31% and 10%), and folic acid (3.8% and 9.7%).

Deficiency of magnesium or vitamin B12 was rare. For both diseases, iron deficiency was associated with hypoalbuminemia. Deficiencies in iron and zinc were more common in patients with CD than those with UC [51]. They concluded that deficiencies in iron, zinc, and vitamin D are common at diagnosis of IBD in childhood and persist during follow-up requiring ongoing assessment throughout the course of disease.

Vitamin B12 (cobalamin) is selectively absorbed in the distal ileum, bound with gastric-derived intrinsic factor. Patients with ileal CD and/or ileal resection and/or clinical deficiency features should be screened yearly for B12 deficiency [52] . Patients with clinical deficiency should receive 1000 mg of vitamin B12 by intramuscular injection every other day for a week and then every month for life [53] . Patients with more than 20 cm of ileum resected should receive 1000 mg of vitamin B12 prophylactically also every month and indefinitely [54].

Despite recognition of the occurrence of potential nutritional deficiency in individuals with IBD, only ESPEN has recommended nutritional deficiency screening in this population [54, 55] stating that patients with IBD should be checked for micronutrient deficiencies on a regular basis and specific diets should be appropriately corrected. The extent of micronutrient deficiency screening and whether or not to supplement a child's diet should be considered on an individual basis, following dietary assessment, as firm recommendations for vitamin and mineral supplementation await future studies [19]. Kleinman and colleagues [56] have suggested that patients should be recommended a multivitamin/mineral to meet 100–150% of the RDA when dietary intake is less than expected. Santucci et al. [57] also suggested that a daily multivitamin supplement may correct most deficiencies but is no guarantee of adequacy and iron, zinc and Vitamin D are likely to require specific replacement regimens.

Vitamin and mineral supplement adherence has been examined by two studies. In a cross-sectional study examining self-reported adherence to IBD maintenance medications as well as supplements, an average adherence rate of 80% was reported across all medications and supplements combined [58]. More recently, adherence specifically to vitamin and mineral supplements was assessed in 49 youth with IBD aged 11–18 years using a validated interview [59]. Mean adherence rates ranged from 32 to 44% across supplements, which included multivitamins, calcium, or iron. Youth who did not know the reason for supplementation (approximately 25% of the sample) displayed substantially poorer adherence than did those with moderate or high levels of knowledge, across all supplements. Poor compliance, particularly in adolescents, is common with multivitamin supplements and patient education about the rationale behind their use is important [59].

Elevated Body Mass Index in Inflammatory Bowel Disease

Although most emphasis of the nutritional aspects of IBD is focused upon impaired nutritional status, the increasing rate of childhood obesity is also relevant in children presenting with acute IBD. Several cohorts have found that children with IBD are at comparable risk of overweight and obesity as the general population. Observations by Kugathasan et al. [11] from two large multicenter North American cohorts revealed that 10% of children with CD and 20–30% of children with UC had a BMI at diagnosis consistent with overweight or risk for overweight. A large multicenter cohort of 1598 children with IBD found that approximately one in five children with CD and one in three with UC are overweight or obese [60]. Rates of obesity in UC are comparable to the general population. Attempts to evaluate whether overweight and obese status is associated with patient demographics or disease characteristics found that sociodemographic risk factors for obesity in the IBD population were similar to those in the general population. Prior IBD-related surgery was the only disease characteristic associated with overweight and obesity in children with CD (OR 1.73, 95% CI 1.07–2.82) [60]. In a multicenter retrospective study of 675 patients there were no differences in age, weight, height, and disease activity between the 368 children with CD and the 307 with UC. [61] The prevalence of overweight and obesity in newly diagnosed children with IBD was 8.4% and was higher in patients with UC than in patients with CD.

Obesity is associated with a pro-inflammatory state that may be involved in the etiology of IBD. However, a prospective cohort study conducted on a sample of 300,724 participants recruited for the European Prospective Investigation into Cancer and Nutrition study found no association in obesity, as measured by the BMI with the onset of incident UC or CD [62]. However, obesity has been found to be independently associated with worsening disease activity [63]. In this adult cohort study of the impact of obesity on disease activity and Patient-Reported Outcomes Measurement Information System (PROMIS), 7296 patients with IBD were included in a much larger cross-sectional and longitudinal study of an Internet-based cohort of >15,000 patients living with CD and UC. Obesity prevalence was 19.5% in 4748 patients with CD, and 20.3% in 2548 patients with UC with intact colon. Obesity was independently, and in a dose-dependent fashion, associated with an increased risk of persistent disease activity or relapse in both patients with CD (class II or III obesity vs. normal BMI: adjusted odds ratio, 1.86; 95% confidence interval, 1.30–2.68) and UC (adjusted odds ratio, 2.97; 95% confidence interval, 1.75–5.17). Obesity was also independently associated with higher anxiety, depression, fatigue, pain, and inferior social function scores in patients with CD and

UC at baseline and with worsening depression, fatigue, pain, and social function in patients with CD on longitudinal assessment [63]. Similar detrimental effects have been reported in a study of 152 children, 85 with CD and 67 with UC, where BMI in the lower and upper quartiles was significantly associated with higher risk of disease exacerbation in the year following diagnosis [64].

General Management of Nutrition in Inflammatory Bowel Disease

Monitoring Nutritional Status

Assessment for under- (or over-)nutrition is an essential component of medical care of children with IBD. According to ESPEN guidelines [54], patients with IBD are at risk and therefore should be screened for malnutrition at the time of diagnosis and thereafter on a regular basis.

At a minimum, screening should include measurement of body weight and height for age, with calculation of BMI. Although a variety of screening tools exists, the tools have poor ability to discern different levels of nutrition risk for children with IBD [65].

Nutritional status can be expressed in terms of the degree of height deficit (shortness), weight deficit (underweight or lightness), or relative weight for height or BMI for age (thinness). Each component captures a different aspect of growth, and interpretation is further complicated during puberty when differences in measures for thinness can be driven by changes in lean muscle and/or fat [26]. Growth parameters should be routinely collected and graphically recorded on standardized charts. It is important to obtain information on familial growth patterns, particularly parental heights, as well as pre-illness measurements to assess growth potential and the impact of disease on growth, respectively.

Ongoing assessment of nutritional status includes history, physical examination, and laboratory testing. History should attempt to obtain information on appetite, weight changes, and dietary intake (often with the assistance of a registered dietician), as well as identification of medications and nutritional or herbal supplements, including vitamins and minerals. Review of psychosocial factors such as economic and cultural or environmental influences may be useful.

Physical examination, in addition to growth parameters and BMI, should include anthropometric assessment of body habitus along with recordings of sexual maturation by Tanner staging. Examination may reveal signs of generalized malnutrition or specific nutrient deficiencies.

Laboratory tests are valuable in assessment of specific nutrient deficiencies; however some measures of nutritional status can also be affected by inflammation (e.g., serum albumin and ferritin). Serum pre-albumin has a much shorter half-life (2 days) than albumin (18–20 days) and may be more useful in the assessment of nutritional status changes with nutritional support [66].

Other potential tests of nutritional status are urinary creatinine/height ratio or 3-methylhistidine determinations which reflect somatic (muscle) protein status and 24-h urine urea nitrogen which reflects protein catabolism. However due to the difficulty obtaining accurate specimens and assumptions required for interpretation, these lab tests are not used in routine clinical practice. Additional research techniques for assessment of nutritional status are dual-energy X-ray absorptiometry [24], bioelectric impedance analysis, and total body electrical conductance to determine total body water and fat mass and isotopic labeling of various molecules to determine energy expenditure and metabolic turnover rates [19].

Serum leptin may also have a role in nutritional assessment as a marker of fat stores [67–69] and has been found to be lower in children with severe protein energy malnutrition [70]. Controversy exists in the literature regarding the correlation of leptin levels with inflammation or whether it simply reflects nutritional status regardless of underlying disease. Hoppin et al. found no difference in serum leptin levels between children with IBD and controls and concluded that serum leptin levels depend on BMI and sex and not on disease activity or severity [71].

Aurangzeb et al. [10] explored the relationship between leptin and BMI in newly diagnosed children with IBD in comparison to controls. Significantly lower mean serum levels were found in 28 newly diagnosed patients compared to 56 controls (2.32 pg/mL ± 1.88 vs. 5.09 pg/mL ± 4.86, p +0.009). In this group of children with IBD, leptin levels did not correlate with the degree of inflammation, as defined by serum markers of inflammation. Further studies are required to elucidate the role of leptin in nutritional assessment of patients with IBD.

Following diagnosis of IBD, there are numerous ongoing aspects of nutritional management to address. Nutritional issues relating to therapy may arise. The use of steroids often leads to increased appetite and commonly alters fluid balance with initial fluid retention and weight gain that only partially reflects improvements in underlying nutritional status. Steroids are clearly linked with impaired bone mineralization, with enhanced resorption, and with decreased new bone formation [72, 73]. Adequacy of calcium and vitamin D intake must be reviewed regularly. Inhibition of linear growth and altered final height, due to suppression of insulin-like growth factor-1 (IGF-1), is also a feature of daily corticosteroid therapy [74].

Other medications may interfere with the absorption of specific micronutrients. Sulfasalazine may interfere with folate metabolism by reducing absorption; however, daily supplementation does not appear necessary [75]. In con-

trast, folate supplementation is required when the immunosuppressive drug methotrexate is used, as this drug acts to inhibit the conversion of folate to the active moiety tetrahydrofolate [76].

Questions related to nutrition and which foods to avoid are among the commonest raised by families both at diagnosis and in routine follow-up. The current consensus from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) is that diets of children with CD should be well balanced, based on the Food Guide Pyramid, and follow dietary reference intakes [19]. Brown et al. [77] created a "global practice guideline," which attempted to consolidate the existing information regarding diet and IBD proposed by medical societies or dietary guidelines from patient-centered, IBD-related organizations. The dietary suggestions included nutritional deficiency screening, avoiding foods that worsen symptoms, eating smaller meals at more frequent intervals, eliminating dairy if lactose intolerant, limiting excess fat, reducing carbohydrates, and reducing high-fiber foods during flares. Enteral nutrition was recognized as being recommended for CD in some parts of the world more often than others (e.g., more in Japan than in the USA). According to the most recent ESPEN guidelines [54, 55], no specific diet needs to be followed during remission phases of IBD. Dietician counseling as part of the multidisciplinary care is recommended to improve nutritional status and avoid malnutrition and nutrition-related disorders [54, 55]. General advice on healthy eating can be given to patients with UC and Crohn, aiming for a Mediterranean-style diet is supported by recent studies [78].

Overall, CD, in contrast to UC, can have a tremendous and long-lasting impact upon nutritional status but can also be successfully treated with nutritional therapy. Minimal evidence exists for the treatment of UC with enteral nutrition. Wedrychowicz et al. [79] evaluated the effect of EEN on vascular endothelial growth factor (VEGF) and transforming growth factor beta 1 (TGF-β1) in both UC and CD. However, due to the concomitant use of antibiotics and 5ASA in this study, the role of EEN in UC is impossible to determine from this study. Although there is not yet definitive data illustrating a role for EEN in the management of active UC, there are several lines of evidence that suggest a potential benefit for dietary interventions, including the effects on the microbiome in CD that are likely also relevant to UC. Furthermore, the use of EEN in children with UC may improve bone health [80]. Prospective studies are needed to evaluate the role of EEN and other dietary interventions in UC in children. However, given the current paucity of data, the remainder of this chapter will focus on the nutritional impact and management of CD.

History of the Use of EEN in CD

The effectiveness of elemental diets was originally identified in 1973 by Voitk [81] when it was used in adults with CD to provide preoperative nutritional support. The first controlled study of an elemental diet in adults with CD determined that an elemental diet was equally effective in the induction of remission as corticosteroids [82]. The role of EEN in pediatrics, where EEN had the important additional benefit of supporting growth, was first reported by Sanderson and colleagues in 1987 [83].

The type of EEN utilized has evolved from the initial use of elemental feeds by nasogastric tube toward using polymeric feeds, which have better palatability, lower cost, and the option of oral administration. Although still the subject of some debate, practice has moved toward the use of EEN for any disease location in the gastrointestinal tract. Ongoing research continues to explore the mechanism of action of EEN and strategies to optimize acceptance and utility of nutritional therapy.

Postulated Mechanisms of Action of EEN in CD

Our understanding of the mechanisms by which the beneficial effects of EEN are achieved in active CD remains incomplete. Various mechanisms have been proposed over time, including relative gut rest, avoidance of allergenic elements, nutritional mechanisms, alteration of the intestinal microflora, and specific anti-inflammatory effects. Gut rest does not appear to be a complete explanation as complete gut rest, with total parenteral nutrition and nil by mouth, does not lead to enhanced rates of remission. Avoidance of dietary protein allergens also does not seem to explain the effects of EEN fully as the benefits of EEN are shown to the same whether an elemental or polymeric formula is utilized. Recent studies have focused upon changes in the intestinal microbiota, direct anti-inflammatory activities, and effects upon gut barrier function.

The Intestinal Microbiota

The intestinal microbiota plays a central role in the pathogenesis of IBD, although current data does not indicate any one species as being causative on its own. The impact of EEN upon the intestinal microbiota has been examined in human settings and in an animal model of IBD.

Two early studies used molecular techniques to examine the impact of EEN upon the flora in the context of IBD [84, 85]. These reports illustrated changes in the flora consequent

to the introduction of the enteral formula. A more recent study employed a more comprehensive molecular approach (denaturing gel gradient electrophoresis or DGGE) with a wider selection of probes, enabling a broader profile of the changes [86]. This study showed a reduction in the diversity of the bacterial species and changes within all the main bacterial groupings. These changes were sustained, with effects well beyond the period of EEN alone.

A subsequent study utilized 16S rRNA and whole genome high-throughput sequencing to ascertain additional understanding of the impact of EEN upon the microbiota [87]. All five children included in this study had dysbiosis at diagnosis of CD. EEN resulted in a prompt reduction of the number of operational taxonomic units (OTUs), which correlated with induction of disease remission. Subsequent exacerbation of disease leads to an increase in the number of OTU. Furthermore, six specific *Firmicutes* families were shown to correlate closely with disease activity during and after exposure to EEN [87]. Further studies from the UK [88] and the USA [89] have utilized advanced molecular tools to further define changes in the intestinal microbiota consequent to EEN.

These reports (and others) were further summarized in a recent systematic review [90] . In addition, Pigneur and colleagues [91] demonstrated that EEN induced high rates of mucosal healing and that this was associated with a particular change in the microbiome. Although each of these reports indicates the impact of EEN, they do not yet fully illustrate whether these changes result solely from the difference in the nutrients supplied in the formulae or how these changes then influence mucosal inflammation.

Data from an animal model of CD complements these human data. Using an IL-10 knockout model of gut inflammation, a Japanese group assessed changes after the administration of elemental formula [92]. The bacterial diversity and bacterial number were both reduced in those animals given the formula compared to a control group with normal mouse diet.

Two studies have also assessed patterns of the intestinal flora consequent to enteral feeding in non-IBD contexts. Smith et al. [93] assessed changes in bacterial composition in the stomach and duodenum of adults receiving enteral formulae via a gastrostomy for various non-inflammatory indications. Higher levels of bacterial DNA were found in the upper gut after enteral feeding. The fecal flora was not examined in this patient group. A second study examined the fecal microflora in a small group of adults requiring exclusive nasogastric feeding for a variety of medical indications [94]. Individuals with IBD were excluded from this study. The subjects provided stools at the start of, during, and at the end of a 14-day period of enteral feeds. Molecular methodology was employed to assess the flora (fluorescence in situ hybridization). Overall the investigators did not observe consistent changes in the microflora during this short period. However, they did note changes in particular groups of organisms in the individuals who developed diarrhea secondary to the enteral feeds. However, these effects differed to those seen consistently in individuals with IBD.

Anti-Inflammatory Activities of Enteral Formulae

Meister et al. [95] demonstrated in vitro anti-inflammatory activities of formulae in a series of experiments using explants (short-term culture of colonic tissue samples obtained endoscopically). These samples were incubated directly with an elemental formula or maintained in a control situation. The production of interleukin (IL)-1-β, IL-1-receptor antagonist (RA), and IL-10 was used as an indicator of cell responses. The cells incubated with formula lead to an increase in the ratio between IL-1RA and IL-1-β, compared to the control cells ($P < 0.05$). These changes were also evident when full protein-based formulae were employed. Further, these changes were not observed in biopsies taken from individuals with UC or with non-inflamed IBD tissue.

An in vitro model of intestinal cells has been used extensively to elucidate the anti-inflammatory effects of formulae [96]. These experiments utilized established colonic epithelial cells lines, which were stimulated with one or more pro-inflammatory cytokines to replicate intestinal inflammatory events. Polymeric formulae (PFs) were then used to rescue or to prevent the cellular response to this inflammatory insult, with interleukin (IL)-8 utilized as an indicator of epithelial response. The effect of adding PF to this model was assessed in a series of different ways, with particular use of a two-compartment model, whereby the PF was separated from the inflammatory cytokine. Experiments using this model demonstrated that PF leads to alteration of the inflammatory effects of TNF-α (reduced levels of IL-8) and suggested alteration of cellular signal transduction pathways as a mechanism for this finding [96].

A similar model was utilized to show that the application of PF resulted in modulation of nuclear factor (NF)-κB activity, thereby modulating the production of pro-inflammatory cytokines [97]. Subsequent studies showed that vitamin D and two specific amino acids (arginine and glutamine) mediated the effects of PF in this setting [98]. These findings suggest that active components within the nutritional products used for EEN may explain the anti-inflammatory effects seen in vivo. More recently, an animal model has again shown that EEN mediated reduced gut inflammation via inhibition of NF-κB activation, in conjunction with regulation of the p38/MSK1 pathway [99].

Other investigators have examined the impact of EEN upon other mucosal responses. Teng et al. [100] demonstrated that EEN utilized in an animal model of gut inflammation contributed to decreased expression of IL-17A along with concomitant reduction of IL-17A protein production. Variable patterns of mucosal cytokines were noted in a small group of six children managed with EEN [101]. Together, these data indicate mucosal anti-inflammatory effects consequent to EEN.

Epithelial Barrier Function

Disruptions to barrier function, measured as altered intestinal permeability, are demonstrated in individuals with CD [102]. It is unclear whether these are primary events or are consequent to inflammation. Data showing similar alterations in permeability in asymptomatic first-degree relatives of people with IBD suggest that these could be primary changes, which could thereby predispose to the development of inflammatory changes in some individuals [103]. Intestinal permeability improves with resolution of inflammation [104], including following EEN [105].

In vitro studies have explored these mechanisms further [106] . These studies employed an in vitro model of inflammation similar to that described above, whereby intestinal epithelial cell monolayers were stimulated with pro-inflammatory stimuli and then rescued with PF. Using an Using chamber, these experiments demonstrated that PF leads to complete reversal of cytokine-induced changes in transepithelial resistance, short-circuit current, and horseradish peroxidase flux. In addition, PF was shown to correct cytokine-induced changes in tight junction proteins and key mediators of tight junction function. A subsequent series of confirmatory experiments were conducted using an animal model of colitis. Colitis induced in interleukin-10 knockout mice resulted in altered barrier function. These changes were reversed by the administration of a PF to the affected animals. PF in this setting also had reversal of mucosal inflammatory changes [107].

Further support for nutritional modulation of barrier dysfunction comes from another animal study [108]. The administration of a multi-fiber mix to the mice in these experiments enhanced barrier function and ameliorated inflammatory changes.

Although the molecular mechanisms of these observations are not yet defined, these findings provide significant clues to the activity of EEN in vivo. More work is required to clearly define the molecular events behind these important observations and also to translate these findings to the in vivo situation.

Effectiveness of Exclusive Enteral Nutrition Therapy in Crohn Disease

Induction of Remission

Multiple pediatric studies have indicated that approximately 60–90% of children fed an exclusive liquid diet will enter clinical remission. As shown in several studies and a meta-analysis [109] updated with the most recent randomized study [110], high remission rates with EEN are achieved irrespective of the type of enteral feed (14/15 93% achieved remission with elemental diet vs. 15/19 73% on polymeric diet, n.s.). In addition, a number of pediatric retrospective studies have found that EEN is more effective than corticosteroids in improving disease severity and growth deficiency. Among these is a large retrospective study from Canada, including 229 patients, where EEN has been commonly used as induction therapy [111]. In addition, a recent retrospective study from China where the incidence of CD is much lower, EEN was also found to more effective than corticosteroids (90% vs. 50% $P < 0.05$) [112]. Another large Canadian cohort found equal efficacy to corticosteroids [113].

In addition, there have been numerous open and comparative studies evaluating the use of EEN versus corticosteroids in adults [114–117] (and children [83, 118, 119] with CD. Recently, patients enrolled at diagnosis into the growth relapse and outcomes with therapy in Crohn disease (GROWTH CD) study were evaluated for disease activity, CRP, and fecal calprotectin for 1 year. Clinical remission at 12 weeks with EEN was superior to corticosteroids both when considering remission by PCDAI (OR, 2.07; 95% CI, 1.8–18.3) or combined normal PCDAI and CRP (OR 3.4; 95% CI, 1.3–9) [120]. The latest studies continue to show the effectiveness of EEN either in comparison to medications or partial enteral nutrition (PEN) combined with novel dietary approaches.

In the original meta-analyses investigating the use of EEN in CD, including both pediatric and adult studies, steroids were found to be more effective in the induction of remission [121–124]. However, these analyses involved predominantly adult studies of varying quality and many confounding factors. There have now been four pediatric meta-analyses combining data from studies with EEN [124–127] showing no difference between steroids and EEN. Swaminath et al. [124] included 8 studies and 451 patients and demonstrated no difference between corticosteroids and EEN (OR 1.26, 95% CI 0.77–2.05). When only those patients who completed the treatment were compared by per-protocol analysis, a slightly [but statistically significant] larger proportion of patients on EEN reached clinical remission. Most recently, Yu et al. [127] analyzed 13 stud-

ies, including 349 patients treated with exclusive elemental diet and 311 pediatric patients treated with corticosteroids and also found no difference in remission rates between groups. Additional subgroup meta-analysis of only RCTs showed that EEN was more effective than corticosteroids (OR 2.62 90%CI 0.86–7.94; $p = 0.09$). In addition, the most recent meta-analyses examined mucosal healing and found that patients who received EEN were more likely to achieve both endoscopic and histologic mucosal healing than those who received corticosteroids [124, 127].

Day et al. [128] have identified poor compliance resulting in inadequate volume of EEN received as a major reason why some patients did not achieve remission. The effect of compliance was explored in a recently updated Cochrane meta-analysis by performing a sub-analysis of the data on a per-protocol basis, excluding patients who withdrew due to lack of acceptability of nasogastric tube feeding or palatability of the enteral feed. When comparing those who completed EEN therapy to the corticosteroid group, efficacy was equivalent for induction of clinical remission [109]. Since the effectiveness of EEN in inducing remission in CD is now well established, but is felt to be poorly accepted over a prolonged period as the sole source of nutrition, Levine et al. [129] chose tolerance as the primary endpoint of a novel study comparing PEN with the Crohn disease exclusion diet (CDED). They defined the patient's tolerance to the diet by week 6 by withdrawal from the study because of patient's refusal to continue the diet. Four patients randomized to EEN withdrew within 48 hours with refusal to continue to take Modulen orally. The primary endpoint of tolerance was significantly different, favoring CDED+PEN over EEN: 39 of 40 (97.5%) vs. 28 of 38 (73.7%), $P = 0.002$ (Delta 23.8%; 95% Confidence Interval [CI] 9.0%–38.6%); odds ratio (OR) 13.92 (95% CI 1.68–115.14). Compliance with both regimens showed no significant difference (CDED+PEN 82.5%, EEN 76.5% $p = 0.52$) indicating that the majority of children have very good adherence to the different types of nutritional therapy.

In summary, existing studies and meta-analyses demonstrate high remission rates with EEN therapy depending on adherence. With efficacy to corticosteroids being similar, the advantages in mucosal healing, lack of corticosteroid side effects, and improvements in nutritional status strongly support the use of exclusive enteral nutrition over corticosteroid therapy for induction of remission. Current guidelines support EEN as the first-line therapy to induce remission in children with active CD [4, 130].

Comparative Effectiveness of Nutritional and Biological Therapy

In a recent prospective study of 90 children with CD, clinical outcomes of disease activity, quality of life, and mucosal healing estimated by fecal calprotectin were compared between PEN ($n = 16$), EEN ($n = 22$), and anti-TNF therapy ($n = 52$). Clinical response (PCDAI reduction ≥15 or final PCDAI ≤10) was achieved by 64% on PEN, 88% EEN, and 84% anti-TNF (test for trend $P = 0.08$). FCP ≤250 μg/g was achieved with PEN in 14%, EEN 45%, and anti-TNF 62% (test for trend $P = 0.001$). Improvement in overall quality of life was not statistically significantly different between the three groups [131]. Further clinical and cost-effective studies are required to aid in the therapeutic decision pathway of pediatric CD.

Adult studies [132] also suggest a role for EEN for anti-TNF refractory Crohn disease.

Maintenance of Remission

Following the induction of remission, the use of EN as maintenance therapy may have additional benefits to prolonging remission, including delaying the requirement for further therapy (i.e., corticosteroids) and optimizing growth and nutrition. Most often maintenance EN is practiced in combination with maintenance medical therapy, but limitations of adherence may similarly impact enteral therapy as it does medical therapy.

To date the majority of the literature on maintenance of remission of CD with EN therapy has been in adult patients, mostly arising from multiple centers in Japan. A recent meta-analyses [133] to assess the remission maintenance effect of EN ($n = 857$) included 8 studies. The remission or response maintenance effect in the EN group was 203/288 (70.5%), which was higher than 306/569 (53.8%) in the non-EN group. The odds ratio for long-term remission or response using fixed effects model and random effects model were 2.23 (95% CI 1.60–3.10) and 2.19 (95% CI 1.49–3.22), respectively. There is a smaller and older body of work in pediatrics.

While EEN is often used as an adjunct to medical and surgical therapy in complex pediatric Crohn disease, further study is required to better define its indications, efficacy, and mechanism of action in complex clinical phenotypes or disease complications.

Maintenance of Remission with EN in Adults

Akobeng and Thomas [134] conducted a Cochrane review of enteral nutrition for maintenance of remission in CD. They identified only two maintenance studies in adult patients which were randomized controlled studies, one where the comparison groups were two types of formula (elemental vs. polymeric) [135] and another where a maintenance EN regimen was compared with regular diet [136]. Verma and colleagues [135] studied 33 adult steroid-dependent patients

with CD in remission, who were randomized to elemental ($n = 19$) versus polymeric ($n = 14$) formula, and followed for maximum of 12 months. Fourteen or 43% of the total population remained in remission and off corticosteroid at 12 months, with no significant difference in relapse rates noted between the two formula groups. They did not identify any disease- or patient-related factors that predicted response to enteral nutrition; however, their sample size was small limiting their ability to make meaningful comparisons. Although no "toxicity" was encountered per se, 6 (18%) of patients withdrew within 2 weeks of study start due to intolerance to feeds related to smell or taste problems.

Takagi [136] studied 51 adult patients in remission who were randomized to receive a half-elemental diet ($n = 26$) or a free diet group ($n = 25$). The half-elemental diet group was required to take half the daily caloric allowance as an elemental formula (either orally or via a nasogastric tube). While there were some restrictions placed on the caloric intake of the other "half" of their diet (aided through use of semi-weighed food diaries), there were no specifications for its composition. This was one of many Japanese studies which has looked at the question of maintenance EN, however, and as such, the unrestricted free diet is likely different from the equivalent Western diet. The authors in the Takagi study chose a primary outcome of relapse over a two-year period [136]. The study was stopped before achieving the two-year follow-up for all participants because the relapse rate in the half-elemental diet group was significantly lower than that in the free diet group (34.6% vs. 64%) after a mean follow-up of 11.9 months.

Yamamoto [137] carried out a systematic review examining EN for the maintenance of remission in CD. They included studies where EN was compared with another therapy; thus, the study by Takagi [136] was included, but not the study by Verma and colleagues [135]. They did not limit their review to RCTs, so three prospective non-randomized trials [138–140] and six retrospective studies [141–145] were included. The number of patients included in most of these studies was small. One of the ten studies included pediatric patients alone [142]. Eight of ten studies were conducted in Japan. Knowledge of the country of origin for a study is important when interpreting the results and assessing generalizability. In Japan, EN has a central role in the management of CD. In all but one of the eight Japanese studies included in the systematic review, an elemental formula was used, and also in a majority of studies, the oral component of the diet was a low-fat diet. The impact of this dietary approach, compared with a maintenance PF and/or traditional Western diet, has not been directly studied. The contribution of the low-fat diet, and elemental formula with a relative low-fat component, may be a relevant factor in light of the work by Bamba et al. [146] who suggested that a lower-fat diet may be an important factor related to the efficacy of EN in CD. Another factor, when reviewing EN studies from Japan, is that virtually all participants with CD are on a 5ASA preparation, as this is viewed as a standard of care for maintenance [137]. Because all participants are exposed to this intervention, it would not be expected to bias the findings relative to the EN outcomes. Additionally azathioprine was used by a number of study participants, but as is the case with 5ASA, overall its use seemed to be balanced between the treatment and comparison groups in the studies, thereby limiting the bias this concomitant therapy might have introduced.

In the systematic review by Yamamoto [137], the authors broke down the studies by whether the patients had achieved a medically or surgically induced remission. Interestingly, different from what would be seen in studies conducted in North America, for those studies with patients who entered from a medically induced remission, the majority of patients went into remission with total parenteral nutrition or EEN. Regardless of the method of induction of remission (medical or surgical), the outcomes for the ten included studies showed benefit of EN for maintenance of remission (48–95%) over the non-EN comparison groups (21–65%) [137]. In four studies the impact of dose of EN on remission rates was evaluated [141, 143, 145]. They found that higher amounts of enteral formula were associated with higher clinical remission rates. Another interpretation of these findings could be that patients with less active disease tolerated the enteral feeding better and, therefore, reached greater intakes than those with more active disease. Thus, patients with milder disease may tolerate the nutrition better, rather than the higher intake being a predictor of maintenance of remission. As well, because there was no standard approach to "dosing" used in these studies, at this time no clear recommendations can be made regarding the minimum dose of EN required to optimally maintain remission.

Maintenance of Remission with EN in Pediatrics

Maintenance EN programs have been provided in various forms: overnight NG feeds in conjunction with normal daytime eating, short intervals of exclusive NG feeds every few months interspersed with regular diet, or as oral supplements in addition to oral eating through the day. Two Canadian groups have considered the first two approaches [142, 147]. Researchers from Toronto, Canada, reported on 28 children who after entering remission with EEN had subsequently continued overnight supplementary NG feeds in addition to normal diet in the daytime [142]. They were compared with 19 children in whom EEN successfully induced remission but who opted to discontinue nocturnal elemental feeding. At 12 months, 43% (12/28) of those receiving nocturnal EN had

relapsed compared with 79% (15/19) who had discontinued supplemental elemental feedings ($P < 0.02$). A second group, from Montreal, Quebec, published a report utilizing a different approach to EN feeds, with intermittent intensive periods of nutritional therapy (EEN) [147]. This small study included eight children with CD and associated growth failure who were given intensive exclusive periods of formula for 1 month out of every 4 months. Disease activity markers fell in this group over time and in comparison to a control group who did not receive this intensive therapy. These eight children managed with intensive nutritional therapy also had significant catch-up growth [147].

EN in Combination with Medical Therapy

Thus far, the majority of studies investigating the role of EN with medical therapy have focused on concomitant use with infliximab. A meta-analysis of four adult studies, which were all from Japan, showed that specialized enteral nutrition therapy with infliximab resulted in 109 of 157 (69.4%) patients reaching clinical remission compared with 84 of 185 (45.4% with infliximab monotherapy [OR 2.73; 95% confidence interval 1.73–4.31, $P < 0.01$]. Maintenance of remission was also achieved in the combination treatment group [148].

In children, there have been minimal studies conducted to examine the use of immunomodulators and EEN in children with newly diagnosed CD, but Buchanan et al. reported that patients found it difficult to continue supplemental nutrition as maintenance or remission and therefore used a strategy of early introduction of azathioprine for maintenance of EEN-induced remission [149]. The relative importance of choice of initial induction therapy on two-year outcomes in the setting of early thiopurine use was recently evaluated. In the setting of early thiopurine commencement, choice of EEN over corticosteroid induction was associated with reduced linear growth failure (7 vs. 26%, $P = 0/02$), steroid dependency (7 vs. 43%, $P = 0.002$), and improved primary sustained response to infliximab (86 vs. 68%, $P = 0.02$) [150].

The effect of supportive short-term partial enteral nutrition (SPEN) on the treatment of children with severe CD along with unspecified conventional therapy was recently explored in a Korean cohort [151]. Patients with active CD were divided into mild, moderate, and severe categories according to PCDAI. The severe group was given the option of receiving SPEN, and 17 of 34 patients opted in. The remaining 17 patients were considered to be the non-SPEN group. Changes in nutritional status and PCDAI were significantly higher in the SPEN group ($P < 0.05$).

Further long-term study of the combination and synergistic effects of enteral nutrition and medical therapy particularly for maintenance of remission and mucosal healing is needed.

Repeated EEN and Long-Term Outcomes of Therapy

Despite the convincing results regarding immediate benefits of nutritional treatment, the efficacy of EEN for disease exacerbation and duration of remission is poorly studied.

The efficacy of repeated EEN therapy as a treatment for flares of disease tends to decrease with the second course. In a recent retrospective study, 26/52 patients received a second EEN course. The first compared to the second EEN tended to a higher remission rate (92% remission for the first course vs. 77% n.s.). Duration of the second EEN therapy was shorter compared to the first (mean days 50 vs. 43, $P < 0.05$). It was possible that non-adherence increased with the second course of EEN and contributed to the lower effectiveness. Disease activity measured by the mathematically weighted PCDAI (wPCDAI) was higher for the first course of EEN therapy (59 vs. 40, $P < 0.0001$) [152]. Remission rates ranging from 57 to 80% have been reported by other retrospective studies evaluating a consecutive course of EEN [128, 153, 154].

In terms of 1–2-year outcomes, approximately half to two-thirds of patients will relapse [152, 154, 155]. Predictors of higher relapse rates include the type of induction therapy (corticosteroids have higher relapse rates than EEN induction) [154, 155] and the type of NOD2 genotypes (92% R702W or G908R vs. 50% 1007 fs vs. 60% wild type, $P < 0.01$) [152].

Further data on the impact of induction therapy on clinical course from Grover et al. [150] demonstrated superiority of EEN over corticosteroids as initial induction therapy when comparing two-year corticosteroid-dependency (EEN, 7% vs. CS, 43%) and primary response to anti-TNF therapy (EEN, 86% vs. CS, 68%) in a retrospective study. Similarly, Connors et al. [156] demonstrated that the choice of EEN over CS for induction was associated with avoidance of corticosteroids over a six-year follow-up period which was most pronounced at 2 and 4 years post-diagnosis with 47.3% and 39.6% of EEN patients remaining steroid naive, respectively. Cohen-Dolev et al. [157] prospectively evaluated the outcomes of patients with mild to moderate disease in an inception cohort from the GROWTH CD study, treated with either EEN or CS at presentation, in order to evaluate if early use of EEN might reduce early complication rates and improve growth. A total of 147 children, treated by EEN [$n = 60$] or CS [$n = 87$] were included. They found similar relapse and complication rates in new-onset mild to moderate pediatric CD. However, the use of EEN was associated with higher remission rates (41/87 [47%] in CS and 38/60 [63%] EEN, $p = 0.036$) and a trend toward better growth (mean height Z scores decreased from Week 0 to Week 78 with CS [-0.34 ± 1.1 to -0.51 ± 1.2, $p = 0.01$], but not with EEN [-0.32 ± 1.1 to -0.22 ± 0.9, $p = 0.56$] [157].

Additional Effects and Proof of Efficacy of EEN

EEN and Mucosal Healing

For some time the treatment goals for the management of active CD have focused on the induction of remission, judged clinically (resolution of symptoms) and biochemically (normalization of altered inflammatory markers). More recently it has become clear that the goal of treatment should be the achievement of mucosal healing. Mucosal healing in both CD and UC is clearly associated with improved long-term outcomes [158]. Persisting inflammatory changes are likely to contribute to poor growth in children and are also associated with an increased risk of subsequent disease relapse [159]. Mucosal healing may also influence disease progression and extraintestinal disease patterns.

Both EEN and infliximab lead to high rates of mucosal healing in CD: more so than other therapies used to induce remission (such as corticosteroids) [160].

At the turn of the century, Fell and colleagues [161] undertook a prospective assessment of mucosal healing in a group of children treated with EEN. These 29 children with active CD were treated with a PF. In addition to baseline endoscopic assessment, repeat colonoscopy was completed after 6–8 weeks time in order to judge endoscopic and histologic changes. EEN leads to clinical remission in 79% of these children. Overall there was significant endoscopic improvement in these children. A one-point improvement in the colonoscopy grading score was seen in the ileum and colon ($P < 0.0001$ and $P < 0.001$, respectively). Eight of the children achieved mucosal healing in the ileal region, while eight also had colonic mucosal healing.

More recently the results of two prospective Italian studies and an Australian study show the enhanced rates of mucosal healing following EEN comparing to corticosteroids [162–164]. Berni-Canani and colleagues [162] evaluated the responses in children managed with EEN or corticosteroids. Thirty-seven children were treated nutritionally for 8 weeks with various different formulae (polymeric, semi-elemental, and elemental), while ten received corticosteroids. Clinical remission rates were similar in the two groups (86.5% vs. 90%, respectively), but mucosal healing rates were quite different. Twenty six of the 37 children treated nutritionally had mucosal improvements, and seven of them had complete mucosal healing. In contrast, just four of the steroid group had improvement noted, and none had mucosal healing.

In a second Italian study, children with active CD were allocated to receive either EEN (PF) or corticosteroids. Baseline colonoscopic assessment was followed by repeat colonoscopy at 10 weeks. Fourteen (74%) of the 19 children treated with EEN had mucosal healing. In contrast, mucosal healing was achieved in just six (33%) of the 18 children treated with corticosteroids ($P < 0.05$) [163]. Grover et al. evaluated the effects of 6 weeks of EEN in a cohort of 26 children. Paired endoscopic assessments showed that 58% of the group had complete or near-complete MH following EEN [164]. Subsequent work by this group in a larger group of children demonstrated that complete MH (seen in 18 of 54 children) after EEN resulted in sustained remission for up to 3 years [165]. A further recent report showed MH in 89% of a small group of 13 French children with CD managed with 8 weeks of EEN [91]. In comparison, only one of the six children treated with corticosteroids for the same duration was noted to have achieved MH.

Data from adult patients also clearly demonstrate high rates of mucosal healing consequent to EEN. Yamamoto et al. [166] assessed the mucosal changes following an elemental formula in 28 adults with active CD. In this series of patients treated with EEN, clinical remission was seen in 71%. Furthermore, endoscopic healing or improvements were documented in 44% and 78% of patients, respectively. Chen et al. [167] noted a MH rate of 79% in a group of patients of average age of 28.9 years managed with EEN. Despite this, however, only 17% of the group were noted to have transmural healing (noted sonographically).

Mucosal healing with EEN does not appear to be dependent on the type of formula utilized. Benefits have been documented with elemental [162, 166, 168] or polymeric formulae [161, 163].

Coincident with promoting healing of the inflamed mucosa, EEN is also shown to lead to changes in levels of inflammatory mediators. Several reports published in the final decade of the last century demonstrated that EEN lead to reduced mucosal production of pro-inflammatory cytokines (especially TNF-α and interleukin-2) [168, 169] and prompted downregulation of pro-inflammatory genes measured within the intestinal mucosa [161, 170]. In addition, Fell et al. [161] also demonstrated increased levels of TGF-β mRNA, consistent with increased production of this anti-inflammatory cytokine. Yamamoto and colleagues [166] also showed that the mucosal levels of multiple pro-inflammatory cytokines fell to control levels consequent to treatment with an elemental formula. The ratio between IL-1β and IL-1ra within the mucosa was also normalized.

Overall these data clearly show alterations in levels of inflammatory mediators within the mucosa following treatment with EEN. The full implications of achieving mucosal healing with EEN in children are not yet well defined. Maintenance EN may have a role in maintaining the levels of mucosal healing. It is also not clear if mucosal healing with one therapy (such as EEN) is different to that achieved by another agent (e.g., steroids). Furthermore, treatment protocols have not yet evolved to stratify maintenance therapy upon the level of mucosal healing.

EEN and Changes in Fecal Markers of Inflammation

Various proteins measured in the stool are valid markers of the level and extent of gut inflammation [171]. The most well-known markers are calprotectin and lactoferrin, but others include S100A12 and osteoprotegerin.

In a study by Gerasimidis et al., [172] fecal calprotectin (FC) levels were measured on multiple occasions during and following a course of EEN in 15 children. The children received a PF, and clinical disease activity was defined by determination of PCDAI scores, with a score of 10 or less being judged as clinical remission. FC levels fell only in the children who were in clinical remission by the end of the period of EEN, but FC levels were normalized in only one child. Interestingly, the FC level after 1 month of EEN was associated with clinical response at the end of EEN, suggesting a predictive value at this time. In contrast, a subsequent study evaluated serial measurement of FC in a group of 38 children with CD [173]. An early reduction in FC at week 2 of EEN did not predict clinical response. The authors suggested that a lack of reduction in FC at week 2 should not be seen as a signal to cease EEN. A composite of CRP, FC, and PCDAI was suggested in an Australian study as a non-invasive end point for assessment of the response to treatment [174].

Logan et al. [175] demonstrated reductions in FC after 4 and 8 weeks of EEN in a group of 66 children with CD. This work also noted a subsequent rise in FC levels within 17 days of food reintroduction following the end of the course of EEN. Interestingly, the use of ongoing maintenance enteral nutrition provided some protection against this increase in FC.

The levels of S100A12 (a protein related to calprotectin) were evaluated in a small group of Australian children managed with EEN for active CD [176]. Levels fell in the subset of children who achieved clinical remission and normal CRP.

Recent work showed that EEN treatment also led to reductions in levels of another fecal inflammatory marker, osteoprotegerin (OPG) [177]. Levels of OPG fell to around 25% in response to 6–8 weeks of EEN (1994 ± 2289 pg/g at baseline to 406 ± 551 pg/g after EEN: $P = 0.002$). The value of this marker in predicting response to EEN or in correlating with mucosal healing has not yet been determined.

EEN: Nutritional Status and Growth

Along with improvements in disease activity, weight and growth improvements are also commonly seen with EEN. Numerous studies show improved weight gains, while some have illustrated changes in specific nutritional markers. Several studies have suggested that nutritional improvements occur at different times to changes in specific inflammatory markers. These studies demonstrate that improvements in nutrition do not correlate with the timing of normalizing inflammatory markers [66, 178]. It is not clear whether the nutritional changes are essential to achieve anti-inflammatory improvements. However, satisfactory weight gains are associated with response to EEN, illustrating the importance of these events [128].

Insulin-like growth factor (IGF)-1 is a key mediator of growth hormone signaling. Alterations in this protein occur due to the effects of cytokines (reduced hepatic production secondary to interleukin-6) and are commonly observed in active CD. A number of studies illustrate early increases in IGF-1 and its related binding protein (IGF-BP3) after commencement of EEN [179]; unpublished data, Day et al. [128]. IGF-1 levels rose after just 7 days of EEN in a small group of 12 children [178].

Detailed nutritional assessments, including body composition analysis, have been conducted in individuals receiving EEN. One key study evaluated body composition using multiple direct methods to define fat, water, total body protein, and potassium [180]. A group of 30 individuals with CD were assessed before and after 3 weeks of EEN. Within this short time, increased weight was linked with proportionate increases in body fat, protein, and water. Another study documented changes in body compartments in a group of Canadian children [25]. Body water, lean body mass, and height increases were observed in the children who had received EEN, but not in a comparison group treated with corticosteroids. EEN has been shown by other authors to promote anabolism consequent to suppression of proteolysis and enhanced protein synthesis [18, 39].

These changes in nutrition manifest in weight gains during EEN. The average weight gain in a group of Australian children treated with 6–8 weeks of EEN was 4.7 ± 3.5 kg [128]. In addition, weight Z scores increased over the duration of EEN from −0.2767 ± 0.9707 to 0.1866 ± 0.8024 ($P = 0.0016$). Weight standard deviation scores increased after 8 and 16 weeks ($P < 0.05$) in a small cohort of 14 UK children with a mean age of 12.5 years [179]. However, studies do report variable weight gains [163, 181].

EEN is also noted to have a positive benefit upon linear growth, with improved height velocity even within a short period of time [17, 83]. In a meta-analysis, Newby and colleagues [182] illustrated a significant improvement in height velocity Z scores with EEN compared to outcomes after treatment with corticosteroids. In the aforementioned Australian study, children receiving EEN gained up to 3 cm during the eight-week course of EEN; however, there was no change in height Z scores across the whole group [128].

EEN and Bone Health

CD is associated with reductions in bone mineral density, which can lead to osteopenia and increased fracture risk. EEN appears to have benefits upon bone health. Whitten et al. [183] evaluated serum markers of bone turnover in a group of children with active newly diagnosed CD who were treated with PF as sole therapy to induce remission. Serum levels of bone resorption and bone production were measured at baseline and then again after 6–8 weeks of EEN. Control data were obtained from a group of children without IBD with normal growth patterns. Serum levels of C-terminal telopeptides of type-1 collagen (CTX), a marker of bone resorption, were elevated at baseline and fell during therapy ($P = 0.002$). In addition, levels of bone-specific alkaline phosphatase (BAP), a marker of new bone formation, were low at baseline but rose significantly during therapy ($P = 0.02$). This study did not include evaluation of other aspects of bone health or bone densitometry.

Other work has evaluated the impact of EEN upon vitamin D, an important factor involved in bone health [41]. This study retrospectively evaluated levels of vitamin D in 78 children with CD. A subgroup ($n = 38$) had been treated with EEN at diagnosis. These children treated with EEN had higher levels of vitamin D than a comparison group of 17 children treated with corticosteroids after diagnosis ($P = 0.04$), suggesting that EEN provided a protective effect for this aspect of bone health.

Further information supporting the role of EEN in bone health was shown in a small German study. In this report, ten children with CD managed with EEN had repeated assessments of bone densitometry. The administration of EEN lead to improved trabecular and cortical density by 3 months after starting EEN, although further improvements were not seen subsequently [184]. Strisciuglio et al. [185] assessed bone mineral density (BMD) in 18 children before and after 8 weeks of EEN. BMD scores at week 52 were improved from baseline. A more recent assessment of bone health evaluated markers of bone formation, bone resorption and bone mineral density in children before and after nutritional interventions [186] A serum marker of bone formation increased with nutritional therapy at week 12; however, BMD at week 26 was no different to baseline. This study included some subjects managed with EEN for 6 weeks and others managed with CDED and PEN. In addition, the timing of follow-up assessments differed. Another recent study assessed the impact of PEN alone upon bone health [187]. Bone health did not improve in the group of 22 children managed with PEN for 12 months: however, the children's growth was enhanced.

Together, these data clearly demonstrate that EEN provides significant beneficial effects upon bone metabolism in children with CD.

EEN and Quality of Life

Impaired QOL is well recognized in children with CD. The IMPACT questionnaire was developed and validated as a disease-specific tool to measure QOL in pediatric IBD [188]. Given the importance of eating and food in many cultures and the disruption of these usual patterns during treatment with EEN, there has been some concern that EEN could further impair QOL in these children. The influence of EEN upon QOL has been examined in just a small number of studies in children and adults.

An initial report on the effects of EEN upon QOL and functioning was published by a French group [189]. This study involved 30 children with active CD: half of the group was treated with EEN via an NG tube, while the other half of the group was given corticosteroids. The children were assessed by an adaptation of the IBD Questionnaire and underwent a series of psychological assessments, including a psychological interview. A disease-specific pediatric scoring tool was not utilized in this cohort. The authors showed that the children managed with EEN overall had improvements in their well-being. Several reported concerns about feeling different, disruptions to family routines, and the cosmetic effects of the NG tube itself. The children managed with EEN had better scores of anxiety and depression measures than those treated with corticosteroids. Both groups had disruptions to daily activities, such as school absences. A study from the UK looked specifically at QOL in a group of 26 children with active CD who were all managed with EEN [190]. This study reported remission rates and measured QOL using the IMPACT II questionnaire. Almost 90% of these children entered remission with EEN. Overall, 24 of the 26 children had improved QOL scores during this therapy. In this group of English children, the use of NG tubes to provide the formula did not impact adversely upon QOL.

In contrast to these findings, Hill et al. [191] found that the use of EEN was associated with lower QOL scores in their evaluation of children in their Australian center. This study involved the repeated assessment of various variables, including QOL and disease activity, at diagnosis and then six monthly in 41 children (with 186 assessments in total). Nine children had assessments while receiving EEN: these children were noted to have lower QOL scores than other children on no treatments or those on other medical therapies. However, the group treated with EEN was also those with the highest disease activity scores and lowest nutritional parameters. Furthermore, multiple regression analyses showed that the only independent factor for prediction of QOL in the overall group was disease activity.

These data relate to the use of EEN as therapy for active disease. The ongoing influence of maintenance EN upon QOL has also been assessed in a large group of Japanese adults with known CD [192]. Ninety five of the 126 patients

included were receiving EN as maintenance therapy at the time of the assessment. The investigators used the adult IBD Questionnaire to assess QOL scores. In addition to QOL, other parameters were evaluated. Overall, this study showed that disease activity affected QOL, while nutritional treatment improved QOL. Overall scores and sub-scores for bowel and systemic symptoms were better in the patients with long-standing disease who were receiving maintenance EN. In a pediatric study, Wall et al. (2019) showed in a small cohort that the effects of EEN on improving HRQOL could be seen quite quickly, with significant improvements in HRQOL ($p < 0.0001$) and anxiety scores ($p = 0.002$) observed after 2 weeks of EEN. These were sustained such that at 6 months significant improvements in HRQOL, as well as anxiety and depression measures were observed in this cohort, while a comparator cohort from the same center with standard of care induction at diagnosis noted an improved HRQOL at 6 months, but not with anxiety or depression outcomes [193].

In the PLEASE study discussed above, comparing anti-TNF therapy, EEN, and PEN, with assessment of outcomes at 8 week of therapy, a secondary outcome of QOL was assessed [131]. While clinical response (PCDAI reduction ≥15 or final PCDAI ≤10) was obtained in 64% of PEN, 88% EEN, and 84% anti-TNF, improvement in overall QOL was not statistically different between the three groups ($P = 0.86$). However, QOL improvement in the body image domain was greatest in the EEN group ($P = 0.03$) and with anti-TNF in the emotional functioning domain ($P = 0.04$).

At present, the overall impression of the available data is that the net benefits of EEN upon QOL are positive, likely consequent to improved energy and improved disease control. However, these data are not yet comprehensive, and further study is required to more fully understand the relationships between nutritional therapies and QOL in children with CD.

Pre-/Postoperative Effects

Grass et al. [194] conducted a systematic review on preoperative nutritional support in adult CD patients. They found that EEN prior to surgery may improve preoperative nutritional status and reduce inflammation (CRP) and reduce the risk of postoperative complications and infections. Two recent adult studies from China have examined the role of EEN in the preoperative setting. Li et al. [195] retrospectively reviewed the influence of preoperative three-month EEN on the incidence of intra-abdominal septic complications (IASCs) after bowel resections for enterocutaneous fistulas (ECFs). The EEN group had a significantly higher serum albumin level and lower CRP at operation and suffered a lower risk of IASCs (3.6% vs. 17.6%, $P < 0.05$). In addition, another Chinese report. Demonstrated that preoperative optimization of CD following immunosuppressive therapy by EEN prolongs the immunosuppressant-free interval, reduces the risk of urgent surgery and reoperation, and decreases complications after abdominal surgery [196]. Both these studies by Li et al. were included in a meta-analysis of five studies by Brennan and colleagues examining whether preoperative enteral or parenteral nutrition reduce postoperative complications in CD patients [197]. The remaining three studies looked at use of TPN, and found that postoperative complications occurred in 15.0% of patient receiving preoperative TPN compared with 24.4% in the group who did not ($P = 0.43$). In this meta-analysis preoperative EN was superior to preoperative TPN in reducing postoperative complications. Supporting these findings, a recent case-matched study from Yamamoto et al. [198] showed that an elemental diet (1800–2400 kcal/day) for at least 2 weeks prior to surgery, compared with a group who did not receive preoperative EN or parenteral nutrition, did reduce postoperative complications. The incidence of postoperative septic complications was significantly lower in the EN group (4%) compared with the control group (25%, $p = 0.04$). The occurrence rate of overall complications was lower in the EN group (21% vs. 29%, $P = 0.51$), but this difference did not achieve statistical significance.

In an adult case–control study of 51 patients, EEN was found to down stage the need for surgery in patients presenting with stricturing or penetrating complications of CD with 25% [13/51] patients treated with EEN avoiding surgery. It was also associated with a reduction in systemic inflammation, operative times, and the incidence of postoperative abscess or anastomotic leak [OR 9.1; 95% CI (1.2–71.2), $P = 0.04$] [199].

There is limited data from Japan on the impact of enteral nutrition on postoperative recurrence of CD. Initial intraoperative enteroscopic evaluation suggested prophylactic effects of enteral nutrition on postoperative recurrence of small intestinal CD [145]. Yamamoto et al. [140] studied the impact of long-term enteral nutrition on the clinical and endoscopic recurrence rates in a prospective, non-randomized, parallel, controlled study of 40 adults who underwent resection for ileal or ileocolonic CD. Twenty patients continuously received enteral nutritional therapy (EN group) overnight via nasogastric tube and had a low-fat diet during the day. The 20 controls had neither nutritional therapy nor food restriction (non-EN group). Six months after operation, five patients (25%) in the EN group, and eight (40%) in the non-EN group developed endoscopic recurrence, but the difference did not achieve significance. At 1 year a significant difference was found in both clinical recurrence (5% in the EN group vs. 35% in the non-EN group) and endoscopic recurrence rates (30% in the EN group vs. 70% in the non-EN group). The authors subse-

quently published the five-year extension of this prospective cohort study [200]. Using an intention to treat analysis the end point selected for the five-year follow-up study was recurrence requiring biologic therapy or reoperation. In the EN group, 4/20 could not continue with the elemental diet long term. Two patients (10%) in the EN group and nine patients (45%) in the non-EN group developed recurrence requiring infliximab therapy ($P = 0.03$). One patient (5%) in the EN group and five patients (25%) in the non-EN control group required reoperation for recurrence, but this difference was not statistically significant ($P = 0.18$). This preliminary work in the postoperative setting supports the effectiveness of enteral nutrition, but additional studies are required to replicate this effect or determine regimens of postoperative EN use that would optimize long-term compliance and outcomes.

Adverse Effects of Enteral Nutrition

There are very few adverse effects associated with the use of EN. Loose stools may be reported, particularly in those with predominantly colonic disease distribution. Nausea and constipation are less commonly reported [161].

A cross-sectional Japanese study in adults has reported a risk of selenium deficiency in patients with CD being treated with EN. Selenium concentrations were measured and compared in 29 patients with CD treated by EN, 24 patients with CD who were not being treated with EN, and 21 healthy controls. Selenium levels were only decreased in patients with CD receiving EN and were inversely correlated to the duration and daily dose of EN. Clinical manifestations of selenium deficiency were only found in one patient [201]. A European study examining the effect of exclusive EN on antioxidant concentrations in childhood CD reported conflicting results with respect to selenium. Mean selenium concentrations of the cohort increased significantly from 0.82 μmol/l to 1.14 mmol/L ($P < 0.001$). There were, however, significant reductions in mean concentrations of vitamins C and E [202]. A recent study on the impact of EEN on circulating micronutrients resulted in improved concentration for several nutrients, but interestingly, more than 90% of patients had depleted concentrations of all carotenoids, which later improved on normal diet [47]. Multiple factors, including differences in age groups, disease activity, nutritional status, and EN formulae, may all impact on vitamin and antioxidant levels and the disparate results of the above studies. Further investigation of potential adverse effects at the micronutrient level is required.

Another potential biochemical side effect reported to occur with EEN is transient elevation of transaminase enzymes. Schatorje et al. [203] performed prospective follow-up of liver enzymes in 11 new consecutive children who were primarily treated with total enteral nutrition (TEN) for 6 weeks. Liver enzymes were measured before starting TEN and after 3, 6, and 12 weeks. Overall, nine of 11 patients developed a marked elevation of aspartate transaminase (AST), and ten had an elevated alanine transaminase (ALT) peaking at 3 and 6 weeks. GGT was slightly elevated in three patients during therapy, including two boys with either pre-existing or persistent raised transaminases. Alkaline phosphatase and bilirubin remained normal. The mean follow-up period was 2.1 years (1.0–3.5 years). None of the patients developed liver disease during follow-up, and liver biopsy was therefore not performed [203]. However, subsequent to this publication, a letter to the editor by Lemberg et al. [204] reviewing transaminase results in their published cohort of 12 children with newly diagnosed CD managed with 8 weeks of EEN showed conflicting data. ALT levels were borderline elevated in only two of their patients at 3 weeks of EEN and one patient at 8 weeks of EEN therapy. At diagnosis, all of the markers were within normal ranges. After 2–3 weeks of EEN, the average AST levels were 26.2. Subsequent means were 25 at 8 weeks and 16.8 at 1–2 months after EEN. Average ALT levels rose initially to 21.9 U/L and were subsequently 21.2 at 8 weeks and 14.2 at 1–2 months after EEN. ALT levels were above the upper range of normal (45 U/L) at 2–3 weeks in only two children (51 and 48, respectively) and at 8 weeks in one child (48 U/L). GGT levels did not change and liver disease did not develop in any of the patients.

In a retrospective study exploring liver enzyme elevation in pediatric IBD, EEN therapy was strongly associated with the first episode of abnormal LEs in patients with IBD without PSC/ASC (hazard ratio [HR] 4.2; 95% confidence interval [CI], 1.6–11.3). The effect of EEN on the liver is unclear from existing data. Further prospective investigation is required to clarify the effects of EEN on transaminase levels.

Severe adverse events related to EN are rare. To date there are three case reports of refeeding syndrome consequent to the use of EEN in CD [205, 206]. The two cases reported by Akobeng et al. occurred within days of starting EEN in severely malnourished children [206]. Although rare, it is important for clinicians to be aware of refeeding syndrome and to identify and monitor patients at risk [207].

Factors Affecting Response to EEN

Disease-Related Factors

Disease Duration

Several studies suggest higher efficacy of EEN in children with newly diagnosed CD over those with established disease duration. A multicenter North American study using a semi-elemental formula showed a remission rate of 83% in children newly diagnosed with CD [208], compared to a response rate of 50% in children with previously diagnosed

CD. An Australian retrospective study found 12 of 15 (80%) children with newly diagnosed CD entered remission, defined by PCDAI, compared to 7 of 12 (58%) children, who had been diagnosed with CD for a mean of 3.2 years [128]. The latter study also showed that although some children in this group did not enter remission, each had reductions in PCDAI scores and each had nutritional improvements. The recent meta-analysis by Swaminath did not show a difference in efficacy based on newly diagnosed versus relapsing disease [124].

As previously discussed, the efficacy of repeated EEN therapy as a treatment for flares of disease tends to decrease with the second course [152], but the contribution of non-adherence in this setting versus disease duration is unclear.

Disease Location

Disease location has often been considered to potentially influence the effectiveness of EEN. Several early reports suggested increased efficacy when there is small bowel involvement [143, 153] and a trend toward earlier relapse in those with isolated colonic involvement [153]. Yet, Afzal et al. [181] demonstrated, in a prospective study of 65 children with acute intestinal CD treated with exclusive polymeric diet, that even the patients with disease limited to the colon had remission rates of 50%, albeit much lower than those with ileocolonic (82% remission rate) or ileal disease (91.7% remission rate).

Buchanan and colleagues [149], using carefully defined phenotypic classification in 110 patients on EEN, found no significant differences in the remission rates based on disease location. This is supported by a retrospective study by Rubio et al. who recently compared remission rates according to route of administration and found that the site of disease activity had no impact on response to nutritional therapy [209]. Disease location could not be examined by the meta-analysis by Narula and Zachos et al. due to insufficient data [109, 123]. The most recent randomized trial evaluating elemental versus PF also did not identify any difference in remission rates based on disease location [110]. Additional studies exploring EEN in the last 5 years have included all disease locations but do not report on response according to disease location. Thus, until the influence of disease location on response to EEN is more clearly delineated, it is reasonable to recommend it for all patients with CD regardless of disease site.

EEN-Related Factors

Polymeric Versus Elemental/Semi-Elemental Diets

Nutritional therapy is classified by the nitrogen source derived from the amino acid or protein component of the formula. Elemental diets are created by mixing of single amino acids and are entirely antigen free. Oligopeptide or semi-elemental diets are made by protein hydrolysis and have a mean peptide chain length of four or five amino acids, which is too short for antigen recognition or presentation. Polymeric diets contain whole protein from sources, such as milk, meat, egg, or soy. They can be classified more simply as elemental (amino acid based), semi-elemental (oligopeptide), and polymeric (whole-protein) diets.

Although elemental diets were used in the initial studies focusing upon the nutritional treatment of CD, subsequent studies in both children and adults have compared these elemental diets to polymeric diets [110, 161, 210, 211] Comparisons between any combination of the different protein sources when combined in meta-analysis [109, 123] have shown no significant difference in effectiveness. Similarly, one study comparing polymeric diets differing in glutamine enrichment showed no difference in remission rates [212].

Fat Composition

Several trials have been conducted to investigate the importance of fat composition [146, 213–215], building on the hypothesis that the proportion or type of fat in an enteral feed could affect the production of pro- or anti-inflammatory mediators. Two trials, Leiper et al. [214] and Sakurai et al. [215], investigated the effect of low versus high long-chain triglyceride (LCT) content and differing amounts of medium-chain triglycerides, respectively, in adult patients and showed no difference in effect. Another study by Bamba et al. [146] comparing diets of low-fat (3.06 g/day), medium-fat (16.56 g/day), or high-fat (30.06 g/day) contents showed higher remission rates in the lowest fat group. By intention to treat analysis, remission was achieved in eight of 11 patients (72.7%) of the low-fat group, four of 13 (30.8%) in the medium-fat group, and two of 12 (16.7%) of the high-fat group. However, all of these studies were flawed by either small sample sizes, high dropout rates, or unvalidated activity indices used to define remission. When studies evaluating fat composition were combined by meta-analysis [109, 123], a non-significant trend favoring very low-fat and low LCT content has been demonstrated. However, these results should be interpreted with caution due to statistically significant heterogeneity and small size, which may have lacked statistical power to show differences should they exist. In addition, subgroup analyses could not be performed based on the n6 or n9 fatty acid composition in the feeds due to significant heterogeneity. Ajabnoor et al. [216] recently conducted a systematic review attempting to assess the effects of individual dietary oils and their fatty acids. Their results suggest trends supporting diets with a high n-6 to n-3 ratio and perhaps from avoidance of monounsaturated fatty acids (MUFA). However, definitive conclusions once again were

not possible due to incomplete comparative information and a lack of robust clinical trials in this area.

The possibility that fat composition influences immunomodulatory or anti-inflammatory effect in active CD warrants further exploration with larger trials. In summary, no specific formula composition of EN diets has been conclusively shown to influence induction of remission in active CD.

Exclusive Versus Partial EN (PEN)

The question of whether supplementary EN could be considered instead of EEN was explored in a randomized controlled pediatric trial by Johnson et al. [217]. This study showed that the combination of partial EN (50% of energy requirements) with normal diet leads to a substantially lower rate of remission compared to the use of EEN (100% of energy requirements) (15% in PEN vs. 42% in EEN; $P < 0.035$).

Gupta et al. [218] retrospectively examined a novel protocol providing patients with 80–90% of caloric needs by EN and allowing consumption of remaining calories from a normal diet. Fifteen of twenty three (65%) of the patients receiving the novel partial EN protocol achieved remission [218]. However, subsequent work from this group, as part of the PLEASE study [131], would suggest that although patients/families are instructed to consume 10–20% of calories from a normal diet, it would seem that in many patients, the overall caloric consumption is increased. Close monitoring of intake by dietitians revealed that the PEN group consumed 150.8% ± 36.2 of their estimated energy requirement from a combination of formula (77.7% ± 14.2) and food (72.9% ± 25.5) so that 47.0% ± 13.5 of their caloric intake was from food. While PEN plus ad lib diet improved clinical symptoms in this study, EEN and anti-TNF therapies were superior for inducing remission. Overall, data suggest that EEN is effective due to the exclusion or at least a significant reduction of certain components of normal diets. In the past decade, emerging data and further efforts have been underway to study the effect of restricted table food-based diets (e.g., AID, CDED, specific carbohydrate diet (SCD), CD-TREAT) on CD, often in conjunction with PEN. These specialized diets will be addressed in another chapter.

Duration of Therapy

The duration of EEN therapy ranges from 2 to 12 weeks but the majority of studies use EEN for 6–8 weeks [219]. The early effects of EEN on the microbiome have been achieved over the first 4 weeks of therapy. Additional later effects in the fourth to eighth weeks of therapy may include further anti-inflammatory and nutritional benefits [128].

Predicting the Response to EEN

Several reports have focused on early indicators of the likely success of a course of EEN in children with active CD. Moriczi et al. [220] examined predictors of better response to EEN in 22 children treated with EEN. Ileal location and several markers of disease activity at diagnosis (including FC <500 or a weighted PCDAI score less than or equal to 57.5) were associated with superior outcome. A recent report further highlighted changes in the microbiome in the prediction of remission with EEN [221] Modeling that included microbial abundances, disease location, and bacterial species richness provided a strong association with sustained remission in a group of children managed with EEN. Although not yet assessed in a pediatric cohort, Xu et al. [222] recently developed and validated a nomogram to predict the response to EEN with ROC curve of 0.906. This tool included colonic involvement, the pattern of colonic ulceration, endoscopic severity score, BMI, and CRP value.

Delivery of EEN

Route of Administration of EEN

EEN can be administered by various different routes, such as oral and nasogastric (NG), or via a gastrostomy tube. The choice of route of administration will often be dependent on clinical judgment and reflects local practice, tolerance of formulae, and patient choice [223]. An international survey of pediatric practitioners found that oral administration was the preferred route, with 66% of respondents always starting oral, and switching to NG only if oral route not tolerated [219]. Nine percent of respondents always start NG and switch to oral only if the patient is unwilling/unable to tolerate NG route, while 24% of respondents present both routes and let patient/family decide [219]. Elemental or semi-elemental formulae may be more difficult to take orally. Since PFs have the same clinical benefits, lower cost, and better palatability (allowing for oral administration), they may be associated with increased interest, tolerance, and adherence of EN therapy, which remains the greatest challenge of this form of therapy. However, while generally, children will accept the oral route more than the NG route, oral feeding may lead to greater difficulties over time as the child tries to maintain sufficient volume over a longer period of time. Rubio et al. [209] retrospectively reviewed 106 patients treated with either fractionated oral or continuous enteral feedings and found that both routes were efficacious in inducing remission and mucosal healing. After 8 weeks of EEN, 34/45 (75%) achieved remission in the oral group and 52/61 (85%) in the enteral nutrition (via NG) group ($P = 0.157$). All patients showed a significant decrease in disease severity assessed by PCDAI and significant improvements in anthropometric measures and inflammatory indices. Weight gain was greater in the enteral group ($P = 0.041$) [209]. Similarly a Croatian group reporting their single center retrospective cohort results noted no significant differ-

ence in terms of efficacy (induction of remission) in either the oral or NG routes of administration of EEN [224].

Some reports refer to the practice of routine placement of a NG tube at the start of the course of EEN and then encouragement of oral intake so that children end up with removal of the tube and ongoing oral feeds [110, 219]. On the other hand, children who struggle with tolerance soon after commencing a period of EEN orally can subsequently be switched to NG administration [149].

Approach to Reintroduction of Normal Diet

Following the completion of the course of EEN, the next step will be the recommencement of normal regular diet. An international review of protocols in different units illustrated the range of approaches [225]. Overall, the time taken to reintroduce a normal diet (following a 6–8-week period of EEN) at these pediatric units varied from 1 to 12 weeks.

One of the most accepted approaches to reintroduce normal diet is a gradual introduction of food quantity, while formula volume is progressively decreased [225]. This approach entails the introduction of a meal every 2–3 days while reducing the volume of formula with the introduction of each meal, so that the adjustment takes place over 7–10 days time [128, 149]. Although not formally evaluated in this setting, this approach has been well accepted with very few children having disruptions to the reintroduction of normal diet [personal observations, A. Day].

One group has reported the immediate introduction of food, while formula volume is decreased to overnight feeds [226]. A further approach has involved the use of a low-allergen diet, with new low-allergen foods (initially lamb, potato, chicken, or rice) introduced every 2 or 3 days, followed by the progressive reintroduction of other foods and food groups [227]. This method of returning to a normal diet was evaluated by Shergill-Bonner et al. in 100 patients, and no clear benefits were demonstrated [228]. Similarly Faiman et al. reported a retrospective cohort study where 20 patients had reintroduction of food using the low-allergen approach, while a comparison group (n = 19) followed a low-residue diet for 3 days before reestablishing their usual unrestricted diet, with their EEN being weaned over a 2-week period. As with other studies which have looked at this issue, no significant differences were noted between the two groups with respect to relapse rate and duration of remission [229].

Geographic Variability and Barriers to Utilization of EEN

There is significant geographic variation in the practice and recommendations for EEN as primary therapy in the management of children with CD [77]. In Europe and Japan, guidelines recommend EEN as the first-line therapy for induction of remission in children with CD [230, 231]. The variation in use is noted between and within different countries across the world [5, 232–234]. In an early study by Levine et al. [5], significant variations in the use of EEN were reported in a trans-Atlantic survey of 167 physicians from the USA, Canada, Western Europe, and Israel. In that study, while 4% of North American pediatric gastroenterologists used EEN regularly, 62% of European practitioners reported regular use. These European numbers were echoed in a report from a survey of Swedish pediatric GI units, which showed that 65% of the units used EEN as their primary therapy in newly diagnosed CD [233]. The variation in practice among North American pediatric gastroenterologists was revisited in a survey of 326 NASPGHAN members from North America (86% USA, 14% Canada) [234]. They reported that 31% of respondents never used EN, 55% reported sparse use, and 12% reported regular use. Physicians in Canada reported significantly more use than in America ($P < 0.001$). Variations in EN use within a country were also demonstrated in a study of Australian pediatric gastroenterologists by Day et al. [232]. In both the North American and Australian studies, currently working and previously working in a center where EEN was used were important factors for both the perceived appropriateness of EEN and the regularity of its use. North American pediatric gastroenterologists reported that concerns about adherence were the main disadvantage of EEN and provided a barrier to wider usage. Australian respondents also commented that adherence was a concern but cited other issues, including cost and resource demands. Both of these surveys noted that experience with EEN during gastroenterology training related to current use and confidence with EEN.

While this preliminary work has attempted to explore physician factors to explain the use of EEN, currently only one pilot study has been published which assesses factors influencing patient or parent acceptance [235]. Individual qualitative interviews were conducted with 11 pediatric CD patients and their parents from various clinics across Canada to explore the experience of choosing (or not choosing) a treatment option. Of the 11 patients, seven had received some form of EN as part of their initial treatment. Issues raised during the qualitative interviews were grouped into six themes, and for each of these themes, considerations and impacts on practice were derived (see Table 27.2). Patient, family, and societal/cultural factors undoubtedly play a role in the acceptance and use of EEN. The fear of corticosteroid-related side effects, the cost of EEN (which is rarely covered by insurance plans in many countries), concerns over giving up conventional foods, poor palatability of formulae, and fear of tube feedings are some of the reasons patients and/or parents give for not choosing EEN [236].

Another potential barrier to the incorporation of EN as a realistic therapeutic option is adequate resources to support an EN program. There are no published studies which have delineated the optimal resources required. A recent clinical

Table 27.2 Thematic summary of patient and family interviews

Factor/themes (with examples)	Considerations and impact on practice after discussion in workshop
Messaging from healthcare team	
"Pharmacist said incidence of most side effects from steroids was 10% or lower" Family opted for the steroid because they did not feel the efficacy of the EEN was explained	Need for multidisciplinary education and conviction; ensure accurate and consistent messaging Written information to ensure accurate recall by families
Parental assumptions and expectations	
"At 14, no way would she do that" "12 is a difficult, in-between age. Maybe if he was younger or older, he would (been convinced to) have tried the [formula]."	Importance of connecting parents with experienced parents Involve social work or health psychology
Social concerns	
Integration into school, activities, not eating "EEN would be socially isolating" "Patient became emotional about not eating (worried about missing the food he like, being different from his friends)"	Importance of connecting patients to youth with EEN experience; use available resources (videos, camp/social experience)
Guilt	
Parents felt that he had already been through so much that they did not want to upset him further "At 10 or 11, it was hard to imagine that he could only drink, when his friends were eating"	Focus on benefits of EEN, not only challenges Importance of connecting parents with experienced parents Involve social work or health psychology
Child as the decision maker	
"Parents have to respect the wishes of their children (even very young children). The option of a steroid was the only one our son wanted to look at, so we had to go with his wishes." (patient was 10 years old when EEN was offered) "You can't make your teen do what they don't want to do"	Be sure child is present and actively engaged in discussions regarding treatment The child is a key player in the decision making, but they are not the only player—parental involvement is also important; it is a difficult decision to make alone Engage supports—such as peers—and connect with patient who has been on EEN
Adaptation	
"It seems so traumatic at first, but you have to look ahead. There are so many possibilities for a good outcome." "It is hard, but it will get a lot better" "Nervous but relieved [at decision to place NG tube]." "The tube was in for 10½ weeks, stayed in, and was changed three times. Very successful. She gained weight."	Have families share their experiences and strategies

Taken from Johan Van Limbergen et al. [235]
EEN Exclusive enteral nutrition, *NG* Nasogastric

report on EN as primary therapy in pediatric CD from the NASPGHAN highlighted several issues of importance [236]. Attitudes among the healthcare staff that promote the use of EN and the center's experience appear to play a large role [234]. Dedicated dieticians are fundamental to an EN program, determining appropriate nutrient intake, and in administration of the program. Nursing support with experience in administering and teaching care of tube feedings and use of the feeding pumps is necessary for those who are unable to tolerate oral formula. Formula cost is also an important consideration, particularly when semi-elemental or elemental formulae are chosen, and they are providing sole source of nutrition during the period of exclusive EN feeding. Also, formula costs may not be covered by the relevant health system or drug insurance plans. In some jurisdictions, coverage may be obtained if formula is delivered by a tube, either NG or gastrostomy tube. The high cost is likely to be a barrier to utilization of this therapy.

Conclusion

Nutrition is an important component of the management of IBD in children and adolescents. Successful use of EEN as a form of therapy, specifically for CD, requires a dedicated multidisciplinary team of nurses, dieticians, social workers, and medical staff to support children and families during therapy. Pediatric gastroenterologists must consider EEN in the therapeutic decision process since it yields all of the target outcomes of interest in the management of CD, including alleviation of symptoms, mucosal healing, correction of nutritional deficiencies, optimization of growth, and normalization of quality of life, without adverse effects encountered with most pharmacologic therapies.

With a renewed interest in the role of nutrition in the treatment of IBD, a remaining challenge is the difficulty in maintaining remission as many patients do not welcome repeated restrictions on normal eating. The combination of enteral

and drug therapy with immunomodulators, or other therapies, to maintain remission requires further study. Avenues of investigation will likely include further exploration of specific oral diets and nutrients that have anti-inflammatory and pharmacologic properties, such as the ability to induce immunomodulation. Although the influence of nutrition on the pathogenesis of IBD and the role of nutrition in the therapy of IBD remain unclear, future investigation of the potential interactions among nutrition and the genome, microbiome, and immune system will enhance our understanding of pathogenesis and have an important clinical impact on the treatment of pediatric IBD.

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2021 Corticosteroids

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Introduction

Glucocorticosteroids (GCs) have been used since about 60 years ago as a first-line treatment to induce remission in Crohn disease and ulcerative colitis in children and adults. The first randomized trial demonstrating their efficacy in active IBD was conducted in 1965 by Truelove et al. [1]. Systemic corticosteroid treatment causes disfiguring cosmetic side effects during short-term use and bone demineralization as well as growth failure in long-term treatment, therefore limiting its use in children and adolescents. In addition to the side effects, corticosteroid resistance and dependence are common. The current trend is to minimize or even avoid corticosteroid use in pediatric as well as adult inflammatory bowel disease (IBD). In mild pediatric Crohn disease, enteral nutrition as primary therapy is a safe and effective alternative to prednisolone in mild disease. In moderate-to-severe pediatric Crohn disease, specifically in patients that are at risk of complicated disease, first-line anti-TNF treatment is preferred over corticosteroids [2]. In this chapter, the working mechanism, efficacy, side effects and pharmacokinetics of "classic" (systemic) as well as topical corticosteroids, such as budesonide, will be reviewed.

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The Working Mechanism of Corticosteroids

Under homeostatic conditions, activation of the innate and adaptive immune system is counteracted by endogenous glucocorticoids [3, 4]. At lower dosages, steroids may well follow these physiological pathways, whereas at higher concentrations other mechanisms may be involved.

Upon binding of the high affinity glucocorticoid receptor, a cascade of events takes place starting with the dissociation of molecular chaperones followed by nuclear translocation. At this location, specific DNA sequences in the promoter region of steroid-responsive genes (glucocorticoid response elements) are bound leading to suppression of the genes encoding for the transcription of inflammatory proteins, such as those involved in the mitogen-activated protein kinase (MAPK) pathway. Subsequently, the production of inflammatory mediators, such as prostaglandins, is reduced. The major anti-inflammatory effects of glucocorticoids appear to be due largely to interaction between the activated glucocorticoid receptor and transcription factors, notably nuclear factor-kappa B (NF-kappaB) and activator protein-1 (AP-1), that mediate the expression of inflammatory genes [5]. Inflammation may also become suppressed by increasing the synthesis of the anti-inflammatory mediators, such as interleukin-10, and of Inhibitor of kappa Ba (IκBα), which is regarded as an inhibitor of the key inflammatory transcription factor NFκB. Inhibition of non-genomic mechanisms may also be involved. An example is the activation of endothelial nitric oxide synthase by glucocorticoids leading to the production of nitric oxide (NO). NO is an important modulator of the inflammatory cascade in IBD by affecting leukocyte–endothelial interactions, leukocyte infiltration, and vasodilatation. In summary, it has become clear that glucocorticoids interact with wide range of molecules and therefore exert their immunosuppression by affecting various inflammatory pathways.

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Systemic Corticosteroids

Placebo-controlled trials on the safety and efficacy of prednisolone have not been performed in children with Crohn disease or ulcerative colitis. Multiple studies, however, as reviewed by Heuschkel et al. [6], have compared the results of enteral nutrition versus a course of steroids in the treatment of active Crohn disease in children and reported clinical remission in 85% of children treated with predniso(lo)ne. However, it has long been known that corticosteroids do not heal the mucosa in IBD [7] and are not effective for the maintenance of remission [8–10]. From recent excellent data, drawn from a multicenter observational registry in the USA, we are now informed about the natural history of corticosteroid therapy in children with Crohn disease [11] as well as ulcerative colitis [12]. Despite the use of immunomodulators, 31% of children with CD and 45% of children with UC were found to be corticosteroid dependent at 1 year after diagnosis [11, 12]. This is in accordance with data from adults [13–15]. A recent randomized controlled trial in children with moderate-to-severe Crohn disease showed that first-line infliximab induction treatment combined with azathioprine (AZA) was more effective to achieve and maintain clinical remission without treatment escalation at week 52 compared to conventional induction treatment (by predniso(lo)ne or exclusive enteral nutrition) combined with AZA [13]. Furthermore, propensity score-matched analysis of the RISK study suggested that early anti-TNF monotherapy had higher corticosteroid- and surgery-free remission rates at 1 year than induction with predniso(lo)ne or exclusive enteral nutrition followed by immunomodulator therapy [14]. These and other studies have resulted more and more in corticosteroids being a less preferable first choice in the treatment of pediatric Crohn disease, specifically in children with high risk of complicated disease, where first-line anti-TNF is recommended [2].

In children with severe acute ulcerative colitis, current guidelines recommend intravenous methylprednisolone as first-line treatment [16], with response rates of 71% as reported from a prospective trial in this group of patients [17].

One of the major drawbacks of corticosteroids is the range of side effects that may emerge during treatment, being cosmetic (acne, moonface, weight gain), psychological (mood swings, insomnia, depression), metabolic (bone demineralization, diabetes) or a risk of infections as a result of immune suppression. In children, the effect of systemic corticosteroids on growth is a special concern [18].

Topical Corticosteroids

For targeting local and systemic inflammatory processes in IBD therapeutic agents of first choice (e.g., aminosalicylates, corticosteroids) have been developed in special galenic forms to accomplish the topical delivery of the active compounds to the terminal ileum (Crohn disease) and/or the colon (Crohn disease and ulcerative colitis).

For over 10 years, non-systemic corticosteroids, such as budesonide, beclomethasone dipropionate, fluticasone, and hydrocortisone thiopivalate, have been of interest for the targeted therapy of IBD. Budesonide is a GC with a weak mineralocorticosteroid activity. It has a favorable ratio between anti-inflammatory activity and systemic GC effect. This is explained by a high local GC activity and an extensive first-pass hepatic degradation to metabolites with very low GC activity. Due to these circumstances the well-known GC adverse effects are less frequent than with the conventional corticosteroids.

Pharmacokinetics

The absolute bioavailability of budesonide is very low, which results from gastrointestinal afflux mediated by P-glycoprotein, the product of the multidrug resistance 1 (MDR1) gene, and from biotransformation via cytochrome p450 3A (CYP3A) in gut and liver. After this extensive first-pass metabolism, the metabolites 6β-hydroxybudesonide and 16α-hydroxyprednisolone are formed. Glucocorticoid activity of these metabolites amounts to only 1–10% of the parent drug.

Two pharmacokinetic studies have been performed in children with Crohn disease [19, 20]. Absolute bioavailability of budesonide (Entocort®) was found to be similar in children (9 ± 5%) compared to healthy adults (11 ± 7%) [20]. Consistently, overall systemic elimination of budesonide (Budenofalk®) reflected by clearance and half-life was not different in children and adults [19]. Conversion to 6β-hydroxybudesonide was shown to be 1.5-fold higher in children than in adults, suggesting enhanced biotransformation via CYP3A enzymes in children [19]. Corrections in dosing of budesonide based on body weight or body surface may not adequately reflect differences in pharmacodynamics. Therefore, the dose of budesonide (9 mg, once daily) decided on in both pediatric clinical trials [21, 22] was the same as used in adults with Crohn disease.

Topical Steroid Formulations

There are two oral formulations of budesonide used for treatment of Crohn disease: controlled ileal release (Entocort®) and pH-dependent release (Budenofalk®). The controlled ileal release capsules contain 3 mg of budesonide distributed in approximately 100 pellets that have an outer coating of Eudragit L100-55 that dissolves at pH of 5.5 or higher.

Absorption of Entocort® in the ileocaecal region ranges from 52 to 79 percent. The pH-dependent Budenofalk® capsules also contain 3 mg of budesonide in 400 pellets of a 1 mm diameter and are coated with eudragit, resistant to pH below 6.

For rectal treatment of left-sided ulcerative colitis, budesonide is available as enemas containing 2 mg per 100 mL of enema (Entocort® enema) and a foam containing 2 mg per dose of enema (Uceris® foam or Budenofalk® foam) has been developed with a goal of optimizing drug retention and providing uniform drug delivery to the rectum and distal colon with a mean spread of 25 cm [23]. Also, an oral controlled release system, MMX® extended-release budesonide 9 mg tablets (Uceris®; Cortiment®), characterized by a multimatrix structure, has been developed. This new formulation has a gastro-resistant outer layer that dissolves as the luminal pH increases over 7.0 [24, 25]. It aims at a homogeneous distribution of budesonide through the ascending, transverse, and descending colon, in order to treat colonic IBD, more specifically ulcerative colitis.

Efficacy of Oral Budesonide Treatment in Crohn Disease

Two randomized clinical trials have been performed comparing safety and efficacy of budesonide versus prednisolone in children with active ileocecal Crohn disease [21, 22]. In the non-blinded study by Levine et al., 33 patients (mean age 14.3 years) with active mild-to-moderate pediatric Crohn disease were randomized to 12 weeks of treatment with pH modified release budesonide (Budenofalk® 9 mg, once daily) or prednisone (40 mg, once daily) [26]. The groups treated with budesonide and prednisone did not differ by age, onset of disease, location of disease, or disease activity. Remission (defined as Pediatric Crohn Disease Activity Index PCDAI ≤10) at 12 weeks was reported in 9/19 patients (47%) of the budesonide treatment group and in 7/14 patients (50%) of the prednisone treatment group (difference not statistically significant). Side effects occurred in 32% and 71% of patients treated with budesonide and prednisone, respectively ($p < 0.05$). Severity of cosmetic side effects was significantly lower in patients treated with budesonide ($p < 0.01$).

The study by Escher et al. was a randomized, double-blinded, double-dummy, controlled multicenter clinical trial. In a joined effort by the IBD working group of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), 36 centers located in eight European countries took part [22]. Planned sample size was 120, but the study was terminated prematurely due to low enrolment numbers, with 48 patients (mostly new patients) with active Crohn disease involving ileum and/or ascending colon completing the 12-week study. Patients (mean age 13 years) were randomized to budesonide (Entocort 9 mg, once daily for 8 weeks, tapered to 6 mg for 4 weeks) or prednisolone (1 mg per kg bodyweight, once daily for 4 weeks, followed by 4 week tapering down to a 2.5 mg daily dose). Primary outcome parameter was clinical remission (modified Crohn Disease Activity Index CDAI ≤150) at 8 weeks. Clinical remission was reported within 2 weeks of treatment in about 50% of the patients in both groups. At week 8, 12/22 patients in the budesonide group (55%) and 17/24 patients in the prednisolone group (71%) were in clinical remission ($p = 0.25$). The observed 16% difference in remission rate in favor of prednisone was statistically not significant. In case of planned enrolment of 120 patients, the extrapolated difference in remission rates would still not have reached significance. Mean CDAI of the patients was 239 (budesonide group) and 268 (prednisolone), representing mild to moderate disease. It is unknown whether prednisolone may be more effective than budesonide in patients with severe disease. Data from the North American prospective Pediatric IBD Collaborative Research Group Registry show that oral budesonide was used in 13% of children with newly diagnosed Crohn disease, mostly combined with 5-ASA (in 77%) or immunomodulators (43%). Despite the fact that oral budesonide is designed for controlled ileal release, less than 50% of these patients had disease located in the terminal ileum and/or ascending colon [27].

In adults, a Cochrane systematic review demonstrated that budesonide is more effective than placebo and although inferior to conventional corticosteroids in mild to moderately active Crohn disease in the terminal ileum and/or ascending colon, the likelihood of adverse events and adrenal suppression with budesonide is lower [28]. Four trials comparing budesonide versus prednisolone in adults showed less corticosteroid-related adverse events in the budesonide group [29–32]. Based on the above evidence, ECCO guidelines state that oral budesonide (9 mg once daily) for mild-to-moderate ileocaecal Crohn disease is an alternative to systemic corticosteroids for induction of remission in children [2].

Side Effects of Budesonide in Children

Glucocorticosteroid-associated side effects, such as moon face and acne were shown to occur significantly less in children treated with budesonide compared to prednisolone [22]. In the randomized clinical trial by Escher et al., moon face was almost three times as common in the prednisolone group. All short-term GC-associated side effects of budesonide versus prednisolone are listed in Table 28.1. Adrenal suppression, expressed as a decrease in mean morning plasma cortisol levels, was evident during budesonide remission induction while being significantly less compared to prednisolone treatment. Headache was reported in both treatment groups in

Table 28.1 Glucocorticosteroid-associated side effects of budesonide versus prednisolone in children with ileocaecal Crohn disease

	Budesonide $n = 22$	Prednisolone $n=26$[a]	p-value
Moon face	5	15	0.01
Buffalo hump	0	1	NS
Acne	1	7	0.033
Hirsutism	2	3	NS
Skin striae	0	1	NS
Bruising easily	1	1	NS
Swollen ankles	0	1	NS
Hair loss	1	3	NS
Mood swings	3	2	NS
Depression	2	1	NS
Insomnia	5	4	NS
Any such sign[b]	11	20	0.030

RCT by Escher, et al. [20], with permission
NS Not statistically significant
[a]One of these had no on-treatment data regarding possible glucocorticosteroid side effects
[b]Some patients had more than one sign

4/22 (budesonide group) and 4/26 patients (prednisolone group) and may be associated with benign intracranial hypertension as reported by Levine et al. [33].

A retrospective review of 6 prepubertal children with Crohn disease showed linear growth to be subnormal (2 cm/year) during budesonide maintenance treatment [34]. It remains unclear, however, whether impaired growth in these children (with PCDAI's of 15–27.5, indicating active disease) was due only to budesonide treatment or to ongoing mucosal inflammation.

Maintenance Treatment in Crohn Disease

Maintenance treatment with budesonide has not been studied prospectively in children. Systemic corticosteroids, however, have not been shown to be effective in prolonging clinical remission. A Cochrane review based on four placebo-controlled randomized trials in adults with Crohn disease [31, 35–37] concluded that maintenance treatment with oral budesonide at 6 mg/day is not effective in preventing relapses of Crohn disease in adults [38]. In view of this evidence, and the concerns on longitudinal growth in children, maintenance treatment with budesonide should not be recommended.

Budesonide in Ulcerative Colitis

In children, no studies have been performed on the efficacy of budesonide enemas. In adults, topical steroid treatment with budesonide foam enemas is more efficacious than placebo in inducing remission in patients with mild to moderate left-sided colitis as demonstrated in two randomized, double-blinded studies and has demonstrated a favorable safety profile [39, 40]. However, budesonide enema was less effective in left-sided UC compared to 5-ASA [41]. In adults with mild–moderate active mesalazine-refractory ulcerative colitis, two recent studies have each shown a modest effect of budesonide MMX formulation for inducing remission compared to placebo and is well tolerated [42, 43]. In children with active ulcerative pancolitis, budesonide MMX was reported not be effective though side effects were not observed during a median treatment time of 5.2 months [44]. The role of these medications in maintenance of remission in ulcerative colitis has not been studied.

Conclusion

Corticosteroids have been primary induction treatment in Crohn disease for many years, but early, first-line biological treatment is now preferred in most pediatric patients due to their high risk of complicated disease. The inability to heal mucosa and disfiguring acute and serious long-term side effects, such as growth retardation and bone demineralization, further limit their use. The current trend in pediatric as well as adult Crohn disease is to minimize and avoid repeated corticosteroid use by introducing immunomodulators and biological treatment early in the course of disease. In mild active Crohn disease, primary treatment by a 6–8-week course of enteral nutrition is favored over remission induction by prednisolone. Systemic or topical corticosteroids are not effective as maintenance treatment.

Adrenal suppression is less during budesonide treatment compared to prednisolone, and GC-associated side effects, such as acne and moon face, occur less frequently.

Corticosteroids do not heal the mucosa, prevent relapse, and alter the course of disease. In the current era, confidence with early immunomodulator and biological treatment is growing, with a tendency towards top-down instead of step-up treatment. It is now clear that corticosteroids are losing their position as first-line treatment of pediatric IBD.

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Mercaptopurine Therapy

29

Darja Urlep and Erasmo Miele

Introduction

Thiopurines (azathioprine and its prodrug 6-mercaptopurine (6-MP)) have been widely used as the first-line immunosuppressive drugs for maintenance of remission in patients with Crohn disease (CD) and ulcerative colitis (UC) [1]. Their role in combination therapy with anti-tumor necrosis factor (anti-TNF)-alpha agents is also established [2, 3]. However, their use is limited, mainly due to toxicity and the increased risk of lymphoproliferative disorders (LPDs) [4, 5]. Withdrawal of thiopurines associated with adverse events has been reported in about a quarter of patients with IBD [6]. Given the aforementioned increased risk for adverse events and malignancy, some pediatric gastroenterologists avoid using thiopurines in their everyday clinical practice. Recently, differences in use of thiopurines between the North American and European clinical practice have been reported [7]. In North America, anti-TNF drugs are frequently used as first-line treatment, while in Europe, they are more commonly used as second-line treatment in patients who do not respond adequately after at least 3 months of treatment with an immunomodulator [7]. These differences are reflected in the current European [8] and Canadian [9] guidelines on medical management of pediatric CD.

Currently, the prognostic factors for thiopurine effectiveness and their side effects mostly remain unknown. This is in part due to large interindividual pharmacokinetic differences and differences in genetic polymorphisms of enzymes involved in the complex thiopurine metabolism [10].

In this chapter, we review the metabolism of thiopurines and mechanisms of their action, their effectiveness in pediatric CD and UC, current clinical indications, the use of thiopurine methyltransferase (TPMT) enzyme testing and monitoring of thiopurine metabolites, thiopurines' toxicity, and adverse events, including the risk of malignancy.

6-Mercaptopurine Metabolism

Thiopurines are prodrugs and must be converted intracellularly to 6-thioguanine nucleotides (6-TGNs) to exert their therapeutic effect. After oral intake, azathioprine (AZA) is rapidly converted, predominantly by glutathione-S-transferase, to 6-MP. 6-MP can then be metabolized via three competing pathways: xanthine oxidase (XO), TPMT, and hypoxanthine-guanine phosphoribosyltransferase (HGPRT). In the first pathway, thiopurine metabolism via the XO pathway leads to production of 6-thiouric acid, an inactive metabolite excreted in urine. In the second pathway, TPMT converts 6-MP to 6-methylmercaptopurine (6-MMP) and 6-methyl-mercaptopurine ribonucleotides (6-MMPRs), which are inactive metabolites. Finally, metabolism via HPRT followed by inosine monophosphate dehydrogenase and guanosine monophosphate synthase leads to the production of 6TGNs, which are thought to be the active metabolites [11]). The complete metabolism of thiopurines leading to the production of 6TGNs and their mechanism of action are illustrated in (Fig. 29.1).

Thiopurines modulate immune responses through several mechanisms, which ultimately lead to apoptosis and inactivation of T-lymphocytes [12]. Firstly, 6TGN is incorporated into DNA replacing guanine and adenosine, leading to strand breakage and cell cycle arrest. Secondly, 6TGNs that are incorporated into DNA show reduced stability, leading to changes in DNA structure and activation of the mismatch repair system. Thirdly, the GTPase Ras-related C3 botulinum toxin substrate 1 (*Rac1*) bound to 6TGN (instead of guanosine-5′-triphosphate) blocks the *Rac1* activation pathway. The suppression of *Rac1*-target genes, such as mitogen-activated protein kinase, *NF*-k*B* and *bcl-x(L)*, causes a mitochondrial apoptosis [13]. Further mechanisms of action

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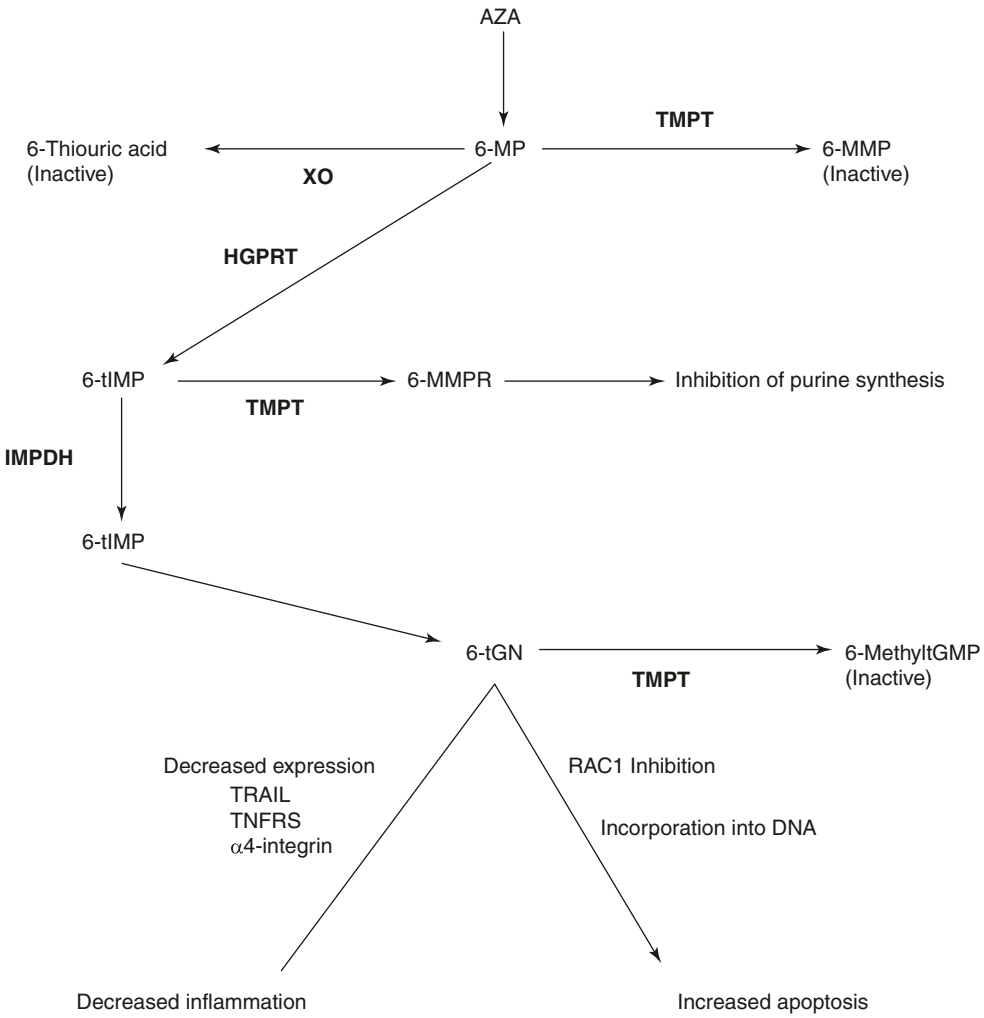

Fig. 29.1 Metabolic pathways of Azathioprine (AZA azathioprine; XO xanthine oxidase; 6-MP 6-mercaptopurine; 6-MMP 6-Methylmercaptopurine; TPMT thiopurine S-methyltransferase; HGPRT hypoxanthine guanine phosphoribosyltransferase; 6-tIMP 6-thiomercaptopurine; 6-MMPR 6-Methylmercaptopurine ribonucleotide; IMPDH inosine monophosphate dehydrogenase; 6-tXMP 6-thioxanthosine; 6-tGN 6-thioguanine nucleotides; 6-MethyltGMP 6-Methylthioguanine monophosphate) [With permissions from Wolters Kluwer Health, Inc]

include inhibition of several genes involved in intestinal inflammation and trafficking of leukocytes to the gut, such as tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), TNF receptor superfamily member 7 (TNFRS7), and alpha-4-integrin in the presence of T-cell activation [14]. Similarly, anti-TNF-alpha therapy was also shown to suppress activation of Rac1-GTP. This may contribute to the synergistic effects of thiopurines and anti-TNFα agents [15].

Efficacy of Thiopurines in Crohn Disease

6-MP was shown to be an effective immunomodulator (IM) agent in the management of CD as early as in the 1980s. In a randomized controlled trial (RCT) published in 1980, 6-MP was more effective than placebo in stopping or reducing steroid therapy [16].

In a landmark pediatric RCT by Markowitz et al., early use of 6-MP was shown to be highly effective in pediatric CD patients with newly diagnosed moderate to severe CD. Fifty-five children, initially placed on a prednisone weaning therapy, were randomized into 6-MP or placebo groups. After 18 months of follow-up, 91% and 47% of patients in the 6-MP and placebo groups maintained clinical remission, respectively ($p = 0.007$) [17]. This is the only pediatric RCT on 6-MP effectiveness that has been published; however, subsequent observational pediatric studies did not confirm such high efficacy of early thiopurine use [18–21]. In a retrospective pediatric French study, steroid-free remission (SFR) was maintained in only 40% of CD patients at 12 months, and in 33% and 31% at 18 and 24 months of AZA monotherapy, respectively [21]. Lower success rates were also implied by Boyle et al., in a prospective multicenter study on thiopurine effectiveness in maintaining clinical remission based on real-life clinical practice. The observed rate of SFR was 47% at 6 and 23% at 12 months [22].

A large meta-analysis of AZA/6-MP effectiveness, a 2015 Cochrane review of nine studies, comparing AZA/6-MP with placebo, showed only modest superiority over placebo for maintenance of remission (relative risk (RR) 1.28) [23].

Until recently, no pediatric studies on use of dose optimization via therapeutic drug monitoring to bolster thiopurine efficacy have been published. In the first such study, published by Atia et al., interestingly, SFR at 12 months was comparable to those previously reported, with SFR found in 39% (37/96) of patients with CD. The study also underlined the importance of the normalization of inflammatory markers (C-reactive protein, erythrocyte sedimentation rate) as an outcome of treatment. At 12 months, SFR with a normalization of inflammatory markers was found only in 21% (20/96) of CD patients [24]. Further larger studies, preferably of RCT design, using optimized thiopurine therapy via monitoring of metabolites, are needed in the future.

Efficacy of Thiopurines in Ulcerative Colitis

The evidence for thiopurine use in UC is not as robust as in CD. In 2006, an adult open-label study in patients with UC demonstrated significant superiority of AZA over 5-aminosalycilic acid (5-ASA) in achieving clinical and endoscopic SFR [25]. A further 2016 meta-analysis showed thiopurine to be significantly superior to placebo in maintaining remission [26]. In pediatrics, an important prospective multicenter study by Hyams et al. found that 49% (65/133) of patients were in SFR, without the need for biologics or calcineurin inhibitors 1 year after initiating thiopurine therapy [27].

A multicenter Italian study compared SFR between early (0–6 months) and late (6–24 months) AZA initiation, with no statistically significant difference observed. At year 1, SFR was found in 50% and 57% of UC pediatric patients in the early and late groups [28].

In the previously mentioned study by Atia et al. with optimization of thiopurine treatment, in the UC arm, SFR was achieved in 39% (13/33) and SFR with a normalization of inflammatory markers in 27% (9/33) of UC patients at 12 months [24].

Thiopurines and Mucosal Healing

Thiopurines have also been shown to induce mucosal healing (MH), which has recently been put in the foreground as a main goal of treatment. An adult CD study by D′ Haens et al. demonstrated complete endoscopic healing of the colon in 70% and ileum in 54% of patients with CD after at least 9 months (24 ± 14 months) of AZA monotherapy [29]. However, the SONIC study reported that only 15% of adult CD patients treated with AZA monotherapy achieved MH at week 26 [2]. In another adult study by Qiu et al., MH was reported in 38% and 46% of CD patients on thiopurine monotherapy, after 12 and 36 months of thiopurine initiation [30].

A recent Italian pediatric multicenter study reported endoscopic healing in 77% of UC and 48% of CD patients after 52 weeks of AZA monotherapy; however, no association between histologic and endoscopic scores was observed [31].

Interestingly, in a recent observational study of 269 CD patients receiving anti-TNF biologics, combination therapy with thiopurines resulted in higher rates of MH at 12 months, compared to methotrexate co-therapy (58% vs. 17%, $p < 0.01$), while there were no significant differences in adverse events [32].

Clinical Indication

According to the current European pediatric clinical guidelines on CD, in patients who have reached remission, thiopurines can be used as maintenance therapy. Instead of thiopurines, methotrexate can also be used to maintain clinical remission as a first choice IM, or after thiopurine failure or intolerance [8]. The European pediatric guidelines on UC recommend thiopurines as first-line maintenance therapy, precisely in children with moderate-severe UC, who are steroid dependent or relapsing (≥ 2 relapses per year) despite optimal 5-ASA treatment and in UC children who are intolerant to 5-ASA [33]. However, in the Canadian recommendations on management of pediatric luminal CD, thiopurine use to maintain remission is recommended only in females, while the consensus group did not issue a recommendation regarding its use in male patients [9]. Reasons behind this decision were the concerns regarding increased conferred risk of LPDs [4, 5]. However, larger RCTs, comparing the effectiveness of thiopurines and methotrexate head to head are currently lacking. A smaller RCT comparing the effectiveness of these drugs in adult CD did not find any statistical differences in remission rates after 6 months (methotrexate 56%, azathioprine 63%; $p = 0.39$) [34]. However, in children, no RCTs on methotrexate effectiveness exist, and in almost all existing observational studies on methotrexate effectiveness, children mostly received methotrexate after thiopurine failure [35]; therefore, comparing the efficacy of thiopurines and methotrexate in children is difficult. Given the differences in recommendations, each pediatric gastroenterologist should consider the benefits and risks of prescribing thiopurines in each individual patient, considering their characteristics, and disease severity.

Thiopurines in Combination with Anti-TNF

Thiopurines, when used concomitantly with anti-TNF drugs, have been shown to decrease the likelihood of development of anti-drug-antibodies (ADAs) [2, 3].

In the SONIC study, the adult double-blind RCT, significantly more anti-TNF and AZA naïve CD patients on combination therapy (AZA + IFX) achieved SFR at week 26 (57%) in comparison with patients receiving IFX (44%; $p = 0.02$) or AZA alone (30%; $p < 0.001$) [2]. Using AZA with IFX improved serum IFX trough titers and decreased prevalence of ADA [2]. Similarly, in the UC SUCCESS study, superior efficacy of IFX in combination with AZA was shown in patients with steroid-refractory UC [3]. Quite surprisingly, in the DIAMOND study, no differences in clinical efficacy were found when AZA was used in combination with adalimumab or as monotherapy [36].

In pediatrics, most of available data are based on retrospective studies. A retrospective pediatric study which included 195 patients, treated for ≥30 weeks with IFX (monotherapy or combination with IM), showed a significant decrease in loss of response in patients who were treated with combination therapy [37]. Additionally, in a prospective observational study by Grossi et al., patients on combination therapy had a greater likelihood of remaining on IFX over time [38]. In agreement with these data, a recent systematic review of pediatric real-world observational studies (with an observation period of >1 year) reported that combination therapy with an IM improves the durability of IFX therapy [39].

A lot of uncertainty remains regarding the optimal duration of combination therapy. In an open-label pediatric trial by Kierkus et al., patients with CD who had achieved clinical response after induction treatment with IFX were randomized to groups, receiving either combination therapy for 54 weeks or 26 weeks, followed by 26 weeks of IFX monotherapy in case of the latter. At the end of year 1, there were no differences in terms of the clinical response loss rates, and clinical and endoscopic scores [40].

Contribution of thiopurines to the superiority of combination therapy with IFX is linked partially to their impact on IFX pharmacokinetics (formation of antibodies) [2]; however, thiopurines have also been shown to exert the additional synergistic effect with anti-TNF agents [41]. It was also demonstrated that the addition of a thiopurine in some patients who have lost response to anti-TNF monotherapy was an effective strategy to recapture anti-TNF response [42].

The European guidelines on pediatric CD recommend combination therapy with an IM (thiopurines or methotrexate) in patients starting with IFX [8]. The guidelines suggest stopping concomitant immunomodulator therapy after 6–12 months of combination therapy in cases when drug through levels are within the target levels and both endoscopic and transmural healing have been achieved [8]. The European recommendations on pediatric UC state that discontinuation of AZA may be considered after 6 months of combination therapy if satisfactory trough IFX levels are ensured (>5 μg/mL). The use of thiopurines with adalimumab, golimumab, and vedolizumab remains controversial due to a lack of randomized studies [33].

Contrary to the European guidelines on pediatric CD, the Canadian guidelines suggest against using infliximab or adalimumab in combination with thiopurines in males [9], but for females, the consensus group has not issued a recommendation [9]. Indeed, in a meta-analysis by Kotylar et al., assessing relative risk of lymphoma in patients with IBD exposed to thiopurines, the risk was lower in women compared with men, with the highest risk in younger men (<35 years) [4].

As it has become clear that combination therapy is associated with increased risk of lymphoproliferative disease, the risk of combination therapy must be always weighed against its benefits [43]. The risks of combination therapy may perhaps be lowered by a reduction in the dose of AZA, a strategy that has been shown not to affect immunogenicity [44]. Another strategy is to shorten the period of combination therapy, as it was shown that most immunogenicity develops in the beginning of biologic treatment [45].

Postoperative Prophylaxis

Studies from referral centers reported that symptomatic postoperative recurrence (POR) occurred in 20–37% of CD patients, whereas endoscopic lesions (Rutgeerts' endoscopic score ≥1) were found in 48–93% of patients within one year after surgery [46]. Risk factors for POR include extensive disease, short disease duration from diagnosis to surgery, recurrent surgery, long resected segment, surgery for fistulizing disease, disease complications, impaired growth, pubertal delay, perianal disease, or smoking habits [46, 47]. The current European guidelines on surgical management of pediatric CD state that thiopurines may be used for prevention of POR in children with moderate risk of CD recurrence. However, when thiopurines have failed preoperatively, careful risk–benefit analysis prior their postoperative use is recommended [47]. The use of thiopurines for prevention of POR in pediatric CD remains controversial, as all existing data come from adult studies [47]. The RCT by Hanauer et al. showed benefit of 6-MP (50 mg/day) over placebo (hazard ratio (HR) 0.52; $p = 0.045$) [48]. A RCT on 142 adult CD patients receiving AZA (2 mg/kg/day) or mesalazine (3 g/day) for 24 months did not find any difference in clinical

and surgical POR. Nevertheless, a subgroup analysis showed a favorable effect of AZA for patients with previous intestinal resections [49]. In a RCT by D'Haens et al., patients at high risk of POR received metronidazole (250 mg three times daily for 3 months) and additional AZA or placebo for 12 months. The endoscopic recurrence rate at 12 months was significantly lower in those receiving concurrent AZA (44%) compared to placebo (69%) [50].

Reinisch et al. randomized 78 CD patients with postoperative CD and moderate to severe endoscopic recurrence to receive AZA (2–2.5 mg/kg) or mesalazine (4 g/ day). Even if AZA treatment was associated with a significant decrease in the endoscopic score (decrease Rutgeerts' score ≥1) and lower rates of severe endoscopic lesions (Rutgeerts' score ≥i3), no difference in treatment failure between the two groups was observed [51]. However, three meta-analyses showed that thiopurines, although with more adverse events, were more effective than 5-ASA in preventing endoscopic POR at 12 months, but not severe recurrence or clinical recurrence at 12 or 24 months [52–54]. Nevertheless, evaluating only studies with a placebo arm, they demonstrated that thiopurines reduced clinical and severe endoscopic recurrence at 12 months [48, 50].

Finally, three RCTs comparing thiopurines and anti-TNF (adalimumab) also showed conflicting results. The first randomized study by Savarino et al., evaluating CD patients with ileocolonic resection receiving adalimumab, AZA, or mesalazine, starting 2 weeks after surgery, with follow-up for 2 years, demonstrated that the rate of endoscopic recurrence was significantly lower in adalimumab (6.3%) compared with AZA (64.7%) or mesalazine groups (83.3%). Furthermore, there was a significantly lower proportion of patients with clinical recurrence in the adalimumab group (12.5%) compared with AZA (64.7%) or mesalazine group (50%) [55]. In agreement with these data, the POCER study reported superiority of adalimumab over azathioprine [56]. However, the more recent APPRECIA trial demonstrated equivalent efficacy of the two drugs in terms of clinical, combined endoscopic/magnetic resonance enterography and surgical rates of recurrence [57].

Testing for TPMT Deficiency

Testing for TPMT deficiency has an important role in determining a safe initial dose of thiopurines [58]. The recommended pediatric AZA dose is 2–2.5 mg/kg once daily. The dose for its prodrug 6-MP is 1.0–1.5 mg/kg once daily [8]. Children aged six and younger may require higher doses of 6-MP/AZA per body weight to achieve clinical remission [59]. Dose reduction is necessary in patients who are heterozygous in the S-methyltransferase (TPMT) gene or with intermediate enzyme activity. Thiopurines are contraindicated in patients who are TPMT homozygotes, with extremely low enzymatic activity, as these patients are at increased risk of developing severe and even life-threatening myelotoxicity [58]. European clinical guidelines both on CD and UC and Canadian guidelines on pediatric CD recommend TPMT activity testing (phenotype or genotype) prior to thiopurine treatment [8, 9, 33]. However, as normal TPMT activity does not fully eliminate the risk of thiopurine toxicity, monitoring of complete blood count (CBC) and liver enzymes is mandatory. The aforementioned tests should be initially preformed once every 1–2 weeks during the first month of thiopurine treatment and later at least once every 3 months [8, 9, 33].

TPMT polymorphisms account for only 10–25% of overall thiopurine toxicity [10]. In 2014, Yang et al. discovered a missense variant in the NUDT15 gene (encoding p.Arg139Cys), strongly associated with thiopurine-induced early leukopenia in patients with CD. Although more common in Asians, the missense variant in the NUDT15 gene was also associated with thiopurine-induced leukopenia in patients with IBD of European descent [60]. Subsequent studies have reported several novel NUDT15 variants found in Asians (9.8%) and among Hispanics (3.9%), but rarely in Europeans (0.2%). Additionally, a NUDT R139C variant was shown to be significantly associated not only with early leukopenia but also with severe hair loss in patients with IBD [61]. Some authors have suggested to consider testing for NUDT15 variants, particularly in patients of Asian origin [62].

Monitoring of Thiopurine Metabolite Levels

Measurement of 6-TGN and 6-MMP levels during treatment with thiopurines has been suggested to facilitate safer and more effective thiopurine therapy. The correlation between 6-TGN levels and both clinical response and myelotoxicity was confirmed in several studies [63–67]. The adequate levels of 6-TGN to ensure efficiency while avoiding leukopenia are 230–450 pmol/8 × 108 RBC), and for 6-MMP <5700 pmol/8 × 108 RBC to avoid hepatotoxicity [43]. Interpreting the level of 6-TGN as low (<230) or high (>450) depends on the clinical features. In cases of active disease**,** a low or absent 6-TGN level may indicate underdosing or nonadherence [68]. A change in treatment should be considered in patients with active disease despite adequate 6-TGN levels after at least 12 weeks of thiopurine treatment [33]. In patients with hyperactive TPMT (hypermethylators) who present with low 6-TGN and high 6-MMP (often associated with elevated transaminases), concomitant use of allopurinol)50 mg once daily in patients <30 kg and 100 mg once

daily in patients ≥30 kg, maximum 5 mg/kg) with reduced dose of azathioprine (to approximately 25–30% of initial dose) may provide a valid therapeutic option [8, 33]. The current pediatric European clinical guidelines on CD [8] and UC [33] recommend measuring thiopurine metabolites (6-TGN and 6-MMP) in patients with suboptimal response, elevated liver enzymes, cytopenia, for compliance monitoring and for optimizing drug dosing.

Thiopurine Toxicity

Adverse reactions may occur in 10–28% of patients, including gastrointestinal intolerance, pancreatitis, hypersensitivity, and life-threatening bone marrow suppression, which often result in withdrawal of treatment [69–71]. Indeed, a thiopurine withdrawal rate due to adverse events has been observed in 2–30% of children [69]. Among dose-independent minor adverse events, rash, arthralgias, nausea, vomiting, diarrhea, and flu-like reactions represent common manifestations in patients receiving AZA or 6-MP; pancreatitis, neutropenia, hepatotoxicity, and malignancy represent major adverse events [69]. Pancreatitis has been reported in approximately 4% of patients treated with thiopurines, usually within weeks of beginning treatment, and is considered an idiosyncratic, dose-independent drug reaction [6]. Mild leukopenia ($3.0–4.0 \times 10^9$/L) is the most common hematological side effect occurring with standard doses of AZA. In children, leukopenia has been reported in about 10% of children receiving AZA or 6-MP and resolves either spontaneously or with dose reduction or drug discontinuation [72]. However, severe myelosuppression is the most common serious and occasionally fatal adverse event of treatment with AZA, more likely to occur in patients with absent or decreased TPMT activity [73]. An increased rate of serious infection, including opportunistic infections, has been described even in the absence of neutropenia [74].

As thiopurines prevent lymphocyte proliferation and increase apoptosis of activated lymphocytes, a primary infection with EBV or CMV may lead to development of hemophagocytic lymphohistiocytosis (HLH), a rare but life-threatening disorder of excessive macrophage activation and cytokine production [75]. A prospective registry of long-term outcomes in 5766 pediatric IBD patients identified five patients with HLH, all of whom were exposed to thiopurines [76].

Thiopurines may also cause mild elevations in transaminases that are transient or reversible with dose reduction, as well as, albeit rarely, nodular regenerative hyperplasia and portal hypertension, which can be progressive [77].

Thiopurines and Risk of Malignancy

In a large prospective observational French study that included 19,486 adult IBD patients, the multivariate-adjusted HR of LPDs between patients receiving thiopurines and those who had never been exposed to thiopurines was 5.28 [78]. Similarly, in a nationwide cohort study on 36,891 patients with UC, including 4734 UC patients treated with thiopurines, the adjusted HR of developing lymphoma for those treated with thiopurines was 4.2 [79]. Men with IBD taking thiopurines were found to be at higher risk for development of LPD, compared with women (SIR = 4.50 for men and 2.29 for women) [4]. Patients younger than 30 years had the highest relative risk (SIR = 6.99). Importantly, an elevated risk of lymphoma was found in current, but not former thiopurine users [4]. Interestingly, in a recent large cohort study, including 189,289 IBD patients, the risk of lymphoma did not differ between patients on thiopurine monotherapy (adjusted HR = 2.60), compared with patients on anti-TNF monotherapy (adjusted HR = 2.41). The risk was greatest in patients on combination therapy with thiopurines and anti-TNF agents (adjusted HR = 6.11) [5]. Similarly, in a recent systematic review and meta-analysis, using specific generalized linear mixed models appropriate for meta-analyses for rare events, the risk of lymphoma did not differ between exposure to thiopurine monotherapy and anti-TNF monotherapy, but was higher in those with combination therapy, as expected [80].

Among LPDs associated with thiopurines, the most concern is focused on hepatosplenic T-cell lymphoma (HSTC), a rare but mostly incurable form of non-Hodgkin lymphoma. The first cases of HSTCL were reported in 2007 in patients treated with thiopurines alone or with combination therapy with IFX [81]. In 2011, Kotylar et al. reported that the main risk factors for the development of HSTCL are male gender, age <35 years, and at least 2 years of thiopurine exposure [82]. In a recent systematic review that included data from the Food and Drug Administration (FDA) Adverse Event Reporting System, 62 patients with HSTCL were identified among IBD patients on biologic therapy (median age of 28 years; range 12–81) and only five of them did not have thiopurine exposure. All cases of HSTCL were exposed to anti-TNF, at least before exposure to other biologic agents. Eighty-four percent of them were male and 88 percent of them died, with a median survival of 5 months [83].

Due to higher risk of EBV-associated lymphoma in patients on thiopurines, the European Crohn's and Colitis Organisation stated that EBV IgG screening should always be considered before initiation of thiopurine therapy [84].

Thiopurine use has also been associated with risk of non-melanoma skin cancer, especially after several years of therapy [85]. European evidence-based consensus on malignancy in IBD recommends that patients being treated with thiopurines should be instructed on the lifelong use of sun protection measures and have regular full-body skin examinations [86].

Conclusion

Thiopurines have been proven to have a steroid-sparing effect, reduce likelihood of relapse, and improve efficacy of anti-TNF agents. However, their use should always be weighed against their potential risks, especially of LPDs. All current guidelines on pediatric IBD recommend TPMT enzyme activity or genetic testing prior to initiation of thiopurine therapy. Nevertheless, adverse effects may occur and pediatric IBD patients on thiopurine therapy should be carefully monitored. The purpose of thiopurine metabolite measurement (6-TGN and 6-MMP) is to achieve appropriate therapeutic response, assess for non-compliance or underdosing, and to minimize toxicity. Future discovery of new pharmacogenetic variants in the complex metabolism of thiopurines may elucidate the predictors of thiopurines effectiveness and help prevent their short-and long-term adverse events.

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Methotrexate

30

Joel R. Rosh

Introduction

In treating inflammatory bowel disease (IBD), the short-term goal remains the relief of clinical symptoms, while the long-term goal is to improve quality of life, as well as changing the natural history of the disease by decreasing the incidence of adverse outcomes, such as the need for hospitalization and surgical intervention. The long-term goals have undergone a paradigm shift over the last decade, embracing a model that emphasizes the induction and then maintenance of not only a clinical but also a biologic remission evidenced by mucosal healing [1, 2].

Glucocorticosteroids have both anti-inflammatory as well as immunomodulatory effects. As such, steroids have been the most commonly used immune-modifying agent in the treatment of pediatric IBD. Historically, it was recognized that when corticosteroids were started as an induction agent, more than 30% of pediatric patients with Crohn disease remained dependent on glucocorticosteroids 1 year after diagnosis, while almost 10% underwent surgery, thereby demonstrating steroids' inability to alter the course of Crohn disease [3]. In addition to this lack of long-term efficacy, chronic corticosteroid use is associated with a legion of side effects. As a result, approximately 60% of pediatric patients are placed on immune-modifying therapy within the first year of diagnosis [4].

The thiopurines, 6-mercaptopurine (6MP) and azathioprine (AZA), were shown to be effective as well as steroid sparing in the first pediatric IBD prospective multi-center trial which was led by Markowitz, et al. [5]. In addition to bone marrow suppression, pancreatitis, and idiosyncratic reactions, including fever and gastrointestinal toxicity, concerns with regard to hemophagocytic lymphohistiocytosis (HLH) and lymphoma, especially hepatosplenic T-cell lymphoma (HSTCL), drove clinicians to look for other potential immune-modifying agents [6, 7].

Methotrexate has emerged as an effective and overall well-tolerated alternative for the treatment of adults with Crohn disease [8–10]. While a prospective pediatric trial has not yet been performed, there are now ample published data regarding the efficacy of this agent in pediatric Crohn disease as well [11]. Notably, the clinical trial data in ulcerative colitis have not been positive [12].

Mechanism of Action

Methotrexate is a folic acid derivative originally designed as an analog of dihydrofolic acid. As a competitive antagonist of folic acid, methotrexate inhibits folate-dependent enzymes, such as dihydrofolate reductase (DHFR), which is critical to both purine and pyrimidine synthesis. In relatively high doses, methotrexate inhibits DNA production and exerts anti-proliferative as well as cytotoxic effects and has been used for many years in this manner as a cancer treatment [13].

When given for immune-mediated diseases, low-dose methotrexate is used. At these doses, methotrexate does not exert such a profound anti-metabolite effect. This is an important clinical distinction since at low dose, there is a relative absence of otherwise common side effects, such as hair loss and folate supplementation, may decrease the toxicity but not the apparent of efficacy of low-dose methotrexate [14].

The mechanism of action of low-dose methotrexate still needs to be fully elaborated. While not anti-proliferative, low-dose methotrexate may induce T-cell apoptosis [15, 16] although there are studies that do not agree with this finding [17]. Other potential mechanisms of action include methotrexate's effect on intra-cellular and extra-cellular concentrations of adenosine and the effects of adenosine on the adaptive immune response [18] (See Table 30.1). Methotrexate has also been shown to have a more direct effect on a variety of regulatory cytokines [19, 20]. Therefore,

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Table 30.1 Effects of adenosine-related pathways on adaptive immune response

Increased interleukin (IL)-10
Increased IL-2
Inhibition of neutrophil chemotaxis
Decreased leukotriene B_4 (LTB_4)
Decreased tumor necrosis factor alpha
Decreased IL-6
Decreased IL-8
Decreased selective adhesion molecules (SAMs)

there are multiple effects of low-dose methotrexate and it should be considered as a nontargeted, nonspecific, immune-modulating agent.

Improved understanding of methotrexate's mechanism of action and pharmacokinetics may also affect the recommended dosing. As has become appreciated with the thiopurines, metabolites of the parent drug may be the more clinically important compounds. There is now evidence that intra-cellular methotrexate polyglutamates are the active immune-modifying compounds [19] and that there are genetic polymorphisms that have been shown to affect intracellular methotrexate polyglutamate levels. Therefore, pharmacokinetics and pharmacogenetics may play a large role in the efficacy and potential toxicity of methotrexate in any individual [20]. The importance of methotrexate polyglutamate levels in IBD patients has not yet been fully studied.

Efficacy

In 1995, Feagan et al. published their 16-week placebo-controlled induction study demonstrating that 25 mg of intra-muscular methotrexate delivered weekly is an effective, steroid-sparing, induction strategy in adult patients with active Crohn disease with a number needed to treat of five [9]. Those who achieved remission with methotrexate were then offered enrollment in a 40-week double-blind placebo-controlled maintenance trial of 15 mg of methotrexate administered intra-muscularly on a weekly basis. Seventy-six patients participated and demonstrated a methotrexate remission rate of 65% compared to 39% with placebo. No serious adverse events were noted [10]. In addition, there have been head-to-head trials suggesting that the effect of methotrexate is similar to that seen with thiopurines [21, 22].

There is now a true published experience with methotrexate in pediatric Crohn disease [23–33]. Mack et al. first reported on 14 patients with a mean age of 10.6 years who had active Crohn disease and received subcutaneous (SQ) administration of methotrexate and showed clinical improvement by as early as 4 weeks [25]. Steroid sparing was also demonstrated. Another single center experience [27] demonstrated a 12-month steroid-free remission rate of about 33% which is similar to that seen in reports of adult patients with Crohn disease. Good tolerance of the methotrexate therapy was reported. Two larger, multi-center retrospective reports [17, 26] demonstrated a 40–45% one-year steroid-free clinical remission rate with methotrexate. Again, overall good drug tolerance was demonstrated as were a steroid-sparing effect and a positive effect on linear growth [24]. Similar retrospective reports have been published from several European countries showing a 12-month remission rate of 25–52% and these studies are well summarized elsewhere [28]. Along with this growing evidence of the efficacy of methotrexate as monotherapy in treating pediatric Crohn disease, the concern regarding the potential toxicities of thiopurine therapy, especially in the pediatric population likely led to a much higher rate of methotrexate use in treating pediatric Crohn disease. In fact, a multi-center report from the Pediatric IBD Collaborative Research Group demonstrated that the number of patients exposed to methotrexate quadrupled from 2002 to 2010 (14% to 60%) [32].

Two prospective studies in ulcerative colitis (UC) investigated whether methotrexate was effective in adult UC. METEOR [34] was a randomized placebo-controlled trial that showed parenteral methotrexate to not be superior to placebo for the induction of steroid-free remission in adults with UC. Additionally, the multi-center MERIT-UC trial, a 48-week, double-blind, placebo-controlled trial demonstrated that methotrexate was both numerically and statistically inferior to placebo at preventing clinical relapse. Taken together, the METEOR and MERIT-UC studies have demonstrated a lack of efficacy for methotrexate in the treatment of adult UC [12, 35]. There are very limited published data on the use of methotrexate in pediatric UC and consensus guidelines state that this can be considered in rare cases [36, 37]. However, updated guidelines that consider the evidence from both METEOR and MERIT-UC are awaited.

In addition to its use as monotherapy, the use of methotrexate in combination with monoclonal antibodies directed against tumor necrosis factor alpha (TNF) has been explored. While the prospective COMMIT trial did not show improved efficacy of infliximab dosed in combination with methotrexate compared to infliximab monotherapy in adults with Crohn disease [38], many factors, including high rates of corticosteroid use at baseline, may have been critically confounding [39]. Notably, there were significantly higher infliximab levels and lower rates of antibodies to infliximab in patients who received methotrexate. Thus, a one-year trial may not have been long enough to see clinical difference between the two arms. Retrospective data from the Pediatric IBD Collaborative Research Group demonstrated improved infliximab durability when administered in combination with methotrexate [40]. It has been shown that the methotrexate dose may be critical to fully achieve this effect and a weekly dose of 12.5–15 mg weekly may be optimal when methotrexate is used as a concomitant agent [41, 42].

Dose and Administration

Methotrexate is administered once a week. The route of administration can be parenteral (subcutaneous or intramuscular) or oral. For parenteral dosing, the SQ route is better tolerated and, therefore, preferred. Since there are no head-to-head prospective trials comparing the efficacy of oral and parenteral methotrexate for IBD, it remains controversial whether there is a preferred route of administration. Retrospective reports have provided some data related to this question. Two uncontrolled, observational studies published within a year of each other differed in their conclusions with one showing no difference between oral and parenteral methotrexate [43] and the other showing clear advantage to the parenteral route [44]. Pharmacokinetic studies have been performed to see if there is a clinically significant difference in absorption between the two routes as it is recognized that oral absorption is individually variable and subject to a saturation effect with decreasing rates of absorption at higher doses, especially above 15 mg per dose [45].

In IBD, studies of adult [43] as well as pediatric patients [44] have demonstrated a wide individual range of methotrexate bioavailability. Interestingly, a study in adult patients showed the oral route to provide about 73% of the bioavailability that was seen with the parenteral route, while no such difference was seen in the pediatric study. Both of these pharmacokinetic studies were performed on subjects who were clinically stable on methotrexate maintenance therapy. Therefore, neither provides bioavailability data on patients being induced with methotrexate and there are retrospective data to suggest the parenteral route may induce a more rapid remission [45]. Additionally, it has recently been pointed out that any difference in bioavailability between these two routes of administration still falls within the FDA's definition of bioequivalence [46].

The question as to whether there is a clinically important difference in efficacy based upon the route of administration was investigated in a more direct, albeit retrospective manner, in the 2015 study by Turner et al. who used a propensity score analysis to look at outcomes in pediatric CD patients treated with oral vs. parenteral (subcutaneous) methotrexate [24]. This study demonstrated that any superiority of SQ over an oral route of administration was quite modest and the authors suggest that a change to oral MTX can be considered in those patients successfully induced with parenteral MTX. It is notable that a recent meta-analysis of the use of MTX in rheumatoid arthritis patients offered a different approach. This study demonstrated that efficacy and toxicity are related to an individual's absorbed dose rather than route of administration and the authors concluded that it is best to start patients on a relatively high oral dose and convert to the parenteral route in those who fail to respond [26].

In addition to the ongoing questions with regard to the optimal route of administration, the actual ideal dose of methotrexate for pediatric IBD patients has not been studied. The usual recommended dose is 15 mg/m^2 once weekly to a maximum weekly dose of 25 mg [47]. All patients are supplemented daily with folic acid 1 mg orally to avoid the development of medication-related nausea and subsequent anticipatory intolerance [28]. It has also been shown to be beneficial to recommend oral ondansetron as pre-medication before each of the first 8 doses to prevent drug-associated nausea [29]. In our Center, we often continue pre-medication with oral ondansetron indefinitely.

Toxicity and Monitoring

In patients with inflammatory bowel disease, low-dose methotrexate has been shown to be a well-tolerated agent with more than 90% of clinical trial patients able to complete study drug [20]. Reported side effects are usually transient or respond to dose reduction and, less commonly, drug withdrawal (the potential side effects of low-dose methotrexate are summarized in Table 30.2).

Table 30.2 Side effects and toxicities of low-dose methotrexate

- Teratogenicity:
  - Contraindicated in women of child-bearing potential
  - Contraindicated in breastfeeding women
- Gastrointestinal—folate related
  - Nausea and behavioral/anticipatory intolerance—most common
  - Abdominal pain, diarrhea
  - Stomatitis, including esophagitis
- Bone Marrow Suppression
  - Monitor with CBC (Table 30.3 for schedule)
  - Increased with trimethoprim–sulfamethoxazole
- Hepatic
  - Monitor with routine liver chemistries (Table 30.3 for schedule)
  - Increased risk with obesity, concomitant hepatotoxic medications
  - Routine liver biopsy not recommended
  - Possible role for elastography
- Infections
  - Upper respiratory most common
  - Rarely herpetic as well
  - Rarely clinically serious
- Pneumonitis
  - Immune mediated
  - Rare
  - Suspect if prolonged non-productive cough
  - Preliminary evaluation = chest radiograph and pulmonary function tests
- Dermatologic
  - Hypersensitivity reactions
- Renal excretion
  - Avoid in the face of renal impairment

There were early reports from the rheumatology literature that pediatric patients may have fewer methotrexate induced side effects compared to adult patients [48]. An exception to this may be the development of learned associations and anticipatory intolerance to the medication [49]. Nausea has been correlated with inhibition of folate-dependent enzymes. As a result, folic acid supplementation may help limit this side effect, which has been reported in more than 20% of the adult patients who participated in clinical IBD trials [50]. Use of ondansetron as a pre-medication for the first 4–8 weeks can effectively mitigate against the development of nausea [49]. Other gastrointestinal side effects include abdominal pain, diarrhea, and stomatitis that may even evolve into mucositis involving the esophagus [51].

In light of the potential for hepatic toxicity with high-dose methotrexate, liver-related complications have been well studied with low-dose methotrexate. There may be a disease-related rate of liver complications following therapy with low-dose methotrexate. Patients with psoriasis were shown to have a 7% rate of hepatic fibrosis [52] as compared to the 1% rate in rheumatoid arthritis [53]. The low rate of hepatic fibrosis and cirrhosis in RA has led to the official recommendation of the American College of Rheumatology that routine, surveillance liver biopsies not be performed [53]. Studies in juvenile idiopathic arthritis (JIA) patients have shown at least as good hepatic tolerance [50]. Similarly, negligible rates of drug-related hepatotoxicity have been seen in adult patients with IBD treated with prolonged low-dose methotrexate [54]. This may actually occur at a higher rate in pediatric patients with a meta-analysis demonstrating a rate of elevated liver chemistries as high as 10% with 6% requiring dose reduction [55].

Rather than biopsy, routine liver chemistry monitoring should be performed as shown in Table 30.3. Elastography is a promising tool to noninvasively monitor for drug-induced hepatic fibrosis and it may be more sensitive than measuring liver chemistries. More recent data using elastography have been quite reassuring as liver fibrosis was not seen in Crohn disease patients on low-dose methotrexate therapy [56].

Due to the risk of liver toxicity, it seems prudent to avoid methotrexate use in significantly overweight and obese patients as the risk of therapy is increased in the presence of fatty liver disease. In addition, since it is renally excreted, methotrexate should also be avoided in patients with known kidney disease.

Bone marrow suppression leading to leukopenia or thrombocytopenia occurs in about 1% of low-dose methotrexate treated patients [20]. This is usually transient and responds to dose reduction or holding of the drug. Routine monitoring of complete blood counts should be performed to look for bone marrow suppression (Table 30.3). Concomitant medications, especially anti-folate agents, such as trimethoprim–sulfamethoxazole should be avoided with methotrexate therapy as these can exacerbate potential bone marrow suppression. Theoretically, this may be true of sulfasalazine as well although the combination of low-dose methotrexate and sulfasalazine has been utilized without increased toxicity [57].

Table 30.3 Methotrexate (MTX)—dosing and Monitoring

- **Supplemental oral folic acid 1 mg/day to be given to all patients**
- **Consider pretreatment with ondansetron at least for first 4–8 doses of MTX**
- **Dose** (subcutaneous injection on a weekly basis)
  - 15 mg/m^2 (body surface area) to a maximum dose of 25 mg once a week
- **Maintenance**
  - Consider conversion to oral dosing if stable >3 months
  - If clinical remission for >3–6 months consider decreasing dose to 10 mg/m^2 to a maximum of 15 mg once a week
- **Patient monitoring**
  - Complete blood count (CBC) with differential and platelets, Erythrocyte Sedimentation Rate (ESR) and/or C-reactive protein (CRP), and liver chemistries weekly for the first month and then every 2–3 months if stable.
  - The dose should be reduced by 50% for elevation in alanine aminotransferase (ALT) >twice baseline
  - The dose should be reduced by 50% for white blood count (WBC) <4000, absolute neutrophil count (ANC) <1500, or platelet <120,000 and held for 2 weeks for WBC <3000, ANC <1000, or platelets <100,000.

MTX should be held for 2 weeks for nonproductive cough >1 week and discontinued for pneumonitis or serious infections

An immunologically mediated pneumonitis can also rarely be seen with methotrexate therapy. Screening asymptomatic pediatric patients does not seem warranted and in fact, the rarity of this condition when methotrexate is used for inflammatory disease has recently been further characterized [58]. Clinically, a persistent cough or other symptoms should prompt a chest radiograph and pulmonary function studies with suspension of methotrexate therapy until clarification of the clinical picture is achieved.

The most important toxicity of methotrexate is related to its teratogenicity. Methotrexate is completely contraindicated in pregnancy as well as during breastfeeding. All patients and their families must be educated about this prior to starting methotrexate therapy. Previous concerns about the use of methotrexate for males considering conception have recently been called into question [59].

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Infliximab Therapy for Pediatric Crohn Disease and Ulcerative Colitis

31

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Introduction

Both Crohn disease (CD) and ulcerative colitis (UC) are chronic inflammatory conditions of the gastrointestinal tract characterized by a relapsing and remitting course that requires treatment to prevent disease-related complications. The goal of therapy in pediatric inflammatory bowel disease (IBD) should be to induce and maintain clinical remission, prevent delays in growth and puberty, and improve quality of life while minimizing the adverse effects of medications [1]. Since the onset of IBD peaks in early adolescence in children, there exists a very narrow therapeutic window before growth retardation and developmental deficiencies may become permanent. These goals are often not achieved with previous (historic) therapeutic strategies (sulfasalazine, 5-aminosalicylates, immunomodulators [IMMs], and corticosteroids [CSs]). Prior to use of biologics, the short-term clinical response with historic management strategies was only 60% with CS resistance seen in 17% and CS dependency noted in 30–45% of children with IBD with an overall unfavorable safety profile [2–5]. For maintenance of remission, IMM, including thiopurines (TPs) and methotrexate (MTX), had long been the mainstay of therapy for pediatric IBD. Historically, IMMs were considered first to second-line therapy despite an overall poor long-term response rate, ranging from 49 to 80% for TPs and 27% for MTX [6–9]. In addition to a high incidence of side effects [10], the IMMs are often paired with CS given the slow onset of action of IMM.

Additional therapeutic options prior to the development of biologics also included dietary therapy, specifically exclusive enteral nutrition, which is associated with response rates >80% [11]. Exclusive enteral nutrition has an important role in the management of IBD, especially in CD, including prevention and correction of malnutrition, prevention of osteoporosis, and the promotion of optimal growth and development with long-term non-adherence as the leading cause of treatment failure [12, 13].

With homage to historic approaches to manage IBD, it is clear that the advent of biologic therapies has revolutionized the treatment landscape for both adult and pediatric IBD. Infliximab was the first anti-TNF medication approved for use in children in 2006 followed by approval of adalimumab for treatment of moderate to severe pediatric IBD (discussed in Chap. 32). Infliximab is a chimeric monoclonal IgG1 antibody to tumor necrosis factor (TNF)-α. It is composed of a (±75%) human constant and (±25%) murine variable region. TNF is a prominent pro-inflammatory cytokine with the number of TNF-producing immune cells significantly increased in the lamina propria of the bowel of patients with IBD and increased concentrations of TNF have been found in the stool of children with IBD [14–16]. Infliximab binds to both soluble and bound TNFα to neutralize TNF, inhibit leukocyte migration and induce apoptosis of T lymphocytes and monocytes [17–21]. An additional mechanism of action for infliximab to neutralize TNF includes complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) [22].

In this chapter, we will review the current evidence for the role of infliximab as a first-line biologic in pediatric CD and as second-line for moderate to severe UC, including review-

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ing the current evidence for combination therapy vs. monotherapy and a review the role of therapeutic drug monitoring (TDM) to optimize dosing strategies to improve drug durability.

Crohn Disease

Current evidence suggests CD develops as the result of a dysregulated immune response to the intestinal microbial flora in a genetically susceptible host [23]. Targan et al. showed that more than 80% of adult CD patients had a clinical response 4 weeks after a single infusion (5 mg/kg) of infliximab [24]. This study was followed by the randomized ACCENT 1 clinical trial in which 58% of adult CD patients (335/573) had a clinical response after the first infusion and were randomized to either placebo or infliximab (dosed as 5 or 10 mg/kg) [25]. Both doses of infliximab were more effective in achieving clinical remission at week 54 compared to placebo, while there was no statistical difference in clinical response or remission between the 5 and 10 mg/kg groups. Early pediatric studies [26, 27] also demonstrated high clinical response (94%) and remission (48%) rates after a single dose of infliximab. These small clinical reports along with the landmark adult clinical trials paved the way for the first randomized clinical trial with infliximab in children with CD.

Infliximab Is Within REACH for Pediatric CD

The Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF Chimeric Monoclonal Antibody in Pediatric Subjects with Moderate to Severe Crohn Disease (REACH) enrolled pediatric CD (PCD) patients with a Pediatric CD Activity Index (PCDAI) >30 [28]. Notably, all children enrolled were receiving concurrent, stable doses of an IMM (TP or MTX). All subjects received the same induction regimen of 5 mg/kg at 0, 2, and 6 weeks with clinical response (defined by a decrease in the PCDAI by 15 points from baseline) evaluated at week 10. Subjects meeting clinical response criteria were then randomized to receive infliximab either every 8 or 12 weeks. Overall, 112 children were enrolled and 103 (92%) were randomized. Hyams et al. found that 88.4% had a clinical response by week 10 and 55% in clinical remission (PCDAI ≤10). At week 54, 63.5% of subjects allocated to every eight-week infusions had a clinical response with 55.8% in clinical remission compared to a clinical remission rate of 23.5% for those who received infliximab every 12 weeks ($p < 0.001$). Not only did the subjects receiving infusions every 8 weeks have improvement in gastrointestinal symptoms, but they also had significant improvements in their mean height *z*-score by week 54 as well [28].

While REACH established infliximab efficacy and set the precedent for maintenance dosing in PCD, this landmark study may not reflect current practices in PCD treatment algorithm with infliximab. As discussed, all children in REACH were receiving and continued concomitant IMM therapy throughout the trial. While REACH demonstrated efficacy of combination therapy with infliximab (predominantly TP) [28], there is a serious safety concern with this dual therapy approach given the association of hepatosplenic T-cell lymphoma (HSTCL) in patients receiving this specific combination (infliximab and TP), especially in young (<35 years old) males [29]. Recent data from an Inflammatory Bowel Disease Multicenter, Prospective, Long-term Registry of Pediatric Patients (the DEVELOP Registry) confirmed that both malignancies and hemophagocytic lymphohistiocytosis (HLH) were associated with TP either used as monotherapy or in combination with biologic therapy and not with infliximab monotherapy itself [30]. While we await the results of the comparative effectiveness clinical trial of ant-TNF monotherapy vs. combination therapy with lose-dose MTX in PCD (The COMBINE Study, ClinicalTrials.gov, NCT02772965), Feagan et al. found that infliximab in combination with MTX was safe but no more effective (similar treatment failure rate, 30.6% vs. 29.8%) than infliximab monotherapy in a 50-week double-blind, placebo-controlled trial of 126 adults with CD [31].

Early Use of Infliximab

In contrast to UC, CD-specific phenotypes (severe growth failure, stricture, and/or fistula formation) and a poor overall response to 5-aminosalicylates [32] combine to present unique challenges toward the successful management of this progressive disease. The pivotal studies by Markowitz et al. [7]. showed that early induction with TP improved rates of sustained clinical remission and reduced CS use compared to placebo in PCD. Unfortunately, TP showed no effect on linear growth and subsequent studies have not been able to replicate these early results [7]. With the success of REACH in PCD, and the Study of Biological and Immunomodulator Naïve Patients in Crohn Disease (SONIC) [33] in adult CD, many pediatric gastroenterologists started to adopt early introduction of anti-TNF therapy with or without an IMM in a select group of patients who were judged by their physicians to be at increased risk of disease complications. The speculation was that early anti-TNF would improve rates of intestinal healing and result in less structural damage leading to fewer complications (strictures or fistula) and subsequently, a decrease in rates of CD-related abdominal surgery.

In order to better evaluate if early anti-TNF was associated with improved outcomes, Walters et al. [34]. evaluated early anti-TNF therapy in a well-defined inception cohort of PCD subjects who were enrolled in the RISK Stratification study (RISK; Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn Disease). RISK is the largest prospective inception cohort of PCD and enrolled their first patient in 2008 and overall included 913 children <17 years of age with newly diagnosed, inflammatory (non-penetrating and non-stricturing) CD from 28 centers in the USA and Canada [35]. In the Walters et al. study, which included a subset of the RISK cohort (552/913), the authors separated the cohort into triads (those who initiated anti-TNF therapy within the first 3 months of diagnosis, subjects who received an IMM within 3 months, and a group who did not receive either an IMM or anti-TNF therapy within the first 3 months of diagnosis) and evaluated the one-year clinical outcomes. The physician global assessment (PGA) and PCDAI were used to document response. Patients receiving a combination of anti-TNF and IMM (n = 12) were not included in the analysis. Sixty-eight of the 552 subjects received anti-TNF within the first 3 months of the initial diagnosis which led to a propensity score analysis to match the subjects in each triad and reduce the risk of selection bias. In this study, 67/68 early anti-TNF subjects received infliximab. The IMM group (n = 68) included 14/68 patients on azathioprine, 40/68 on 6-mercaptopurine, and 14/68 on MTX. Overall, there was no difference in complete response (as defined by the PGA) at 3 months (50% on anti-TNF, 45.5% on IMM, 42.5% on IMM/anti-TNF). However, at 1 year, 85.3% of those receiving early anti-TNF were in remission compared to 60.3% receiving an IMM (P = 0.0003) and 54.4% in the no IMM/anti-TNF group [34]. The authors did not find any patient-specific characteristics (age, gender, albumin, or C-reactive protein) or disease phenotype (deep ulcerations at diagnostic colonoscopy) that affected the probability of surgery-free remission. Similar to REACH, they found the mean height z-score increased by 0.14 in the early anti-TNF triad compared to the other two triads [36].

Early infliximab therapy in treatment-naïve CD patients was also compared in a head-to-head trial versus CS or exclusive enteral nutrition (EEN) in an open-label, parallel-arm RCT [37]. In this Top-down Infliximab Study in Kids with Crohn disease (TISKids) trial, the biosimilar infliximab-dyyb was administered for the first 5 infusions as a modified induction to the first group and CS or EEN was given as an induction regimen in the second group of newly diagnosed, treatment-naïve moderate–severe (PCDAI >40) PCD patients. In this European trial, subjects also received azathioprine in combination from the start of treatment in both groups and continued throughout maintenance therapy. The primary endpoint was clinical remission (PCDAI <12.5) without the need for additional treatment escalation beyond TP maintenance therapy or surgery by 52 weeks. Among the top-down group, 41% (19/46) were in clinical remission at week 52, while only 15% (7/48) were in remission in the step-up group (P = 0.004) [38]. In a secondary analysis, top-down patients had a higher rate of mucosal healing than step-up patients at week 10 [38].

Combination Therapy Versus Infliximab Monotherapy

As noted, the hallmark studies of infliximab in PCD and adult CD, (REACH and SONIC), demonstrated efficacy of infliximab in combination with an IMM. In the SONIC trial, 56.8% of subjects receiving the combination of infliximab and TP achieved CS-free clinical remission at week 26 compared to 44.4% of those receiving infliximab monotherapy (P < 0.02). Although combination therapy was associated with higher rates of clinical remission compared to infliximab monotherapy in SONIC, there was a trend but not statistically significant difference in mucosal healing at week 26 between the two groups (43.9% vs. 30.1%, p = 0.06). With a growing, concerning list of IBD patients diagnosed with HSTCL, especially in young, male patients who had received combination TP and anti-TNF therapy, many pediatric gastroenterologists are hesitant to prescribe this combination [39].

With additional studies suggesting the benefit of combination infliximab therapy is secondary to improved pharmacokinetics (PK), Colombel et al. performed a post hoc analysis of the SONIC cohort in those who had infliximab trough concentrations available at week 30 [40]. When they re-evaluated the rates of CS-free clinical remission at week 26 by quartiles of infliximab concentrations, they found there was no difference in rates of remission between combination therapy and monotherapy [40]. These results led Colombel et al. to conclude that the benefit of combination therapy was likely secondary to the improvement in infliximab PK properties and to suggest future studies to evaluate whether sustaining therapeutic drug concentrations with biologic monotherapy could achieve the same desired clinical outcomes as combination therapy [40].

Grossi et al. [41] evaluated the real-world experience of concomitant use of IMM and infliximab in PCD. The study population included 502 PCD patients in the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry who had received infliximab. They included all children with CD younger than 15 years old who had received a minimum of three induction doses of infliximab. The primary outcome was continuation of infliximab after initiation of therapy. The probability of remaining on infliximab was evaluated using the Kaplan–Meier curve analysis. They

found 84% of patients remained on infliximab at 1 year, 76% at 2 years, 69% at 3 years, and 60% at 5 years. Overall, they found that clinical factors, including disease extent, age at diagnosis, perirectal involvement, or starting infliximab within 2 years of diagnosis, did not affect durability of infliximab response. They further showed that patients receiving concomitant IMM for >6 months were much more likely to remain on infliximab over time as compared to both no IMM exposure and IMM use <6 months. Overall, 47% of patients receiving infliximab required an intensification (increased dose or frequency), which was delayed if infliximab was combined with IMM for greater than 6 months ($P < 0.05$).

An additional significant finding from the Grossi et al. registry is that male patients receiving MTX for more than 6 months demonstrated a significant greater likelihood of remaining on infliximab (similar for females but a smaller cohort size) [41]. Furthermore, they showed that a combination of MTX and infliximab durability was superior to TP/infliximab. For comparison, in an RCT with adult-onset CD patients, Feagan et al. failed to show any differences in one-year clinical outcomes between combination infliximab and MTX compared to infliximab monotherapy. However, the combination group had a lower likelihood of developing immunogenicity (4% vs. 20%, $p = 0.01$) and had a higher median serum trough infliximab concentration (6.35 μg/mL) compared to those on infliximab monotherapy (3.75 μg/mL, $P = 0.08$) [31]. In addition, an analysis of pediatric data found that when IMMs were added following the development of anti-drug antibodies, patients receiving combination MTX had improved outcomes compared to those who were maintained on monotherapy [42].

As noted, a prospective pediatric RCT, the Low-Dose Oral Methotrexate in Pediatric Crohn Disease Patients Initiating Anti-Tumor Necrosis Factor Therapy (COMBINE) trial, is currently testing the long-term efficacy of combination MTX in comparison to anti-TNF monotherapy (NCT02772965).

Proactive Therapeutic Drug Monitoring and Treat-to-Target in CD

The defining feature of CD is its relapsing and remitting course. The overarching treatment goal is to induce and sustain remission while minimizing secondary complications. SONIC and other studies have shown that infliximab heals the gut lining (absence of ulcerations) with intestinal healing evolving as a "target" of CD management [33, 43]. Although the United States Food and Drug Administration (FDA) will continue to mandate documentation of intestinal healing in future drug trials, there has been an increased interest in evaluating patient reported outcome (PRO) measures and pharmacodynamic biomarkers, such as C-reactive protein and fecal calprotectin to inform biologic dosing [44]. In clinical practice, pediatric gastroenterologists are left to debate the safety and utility of repeat endoscopy to document intestinal healing versus using surrogate biomarkers or disease activity scores to guide treatment strategies. Until surrogate markers are further validated and cutoff values are better established (such as for fecal calprotectin) in those receiving infliximab, pediatric gastroenterologists will need to develop best practices to utilize therapeutic drug monitoring (TDM) as multiple studies have found that a detectable serum trough concentration correlates with clinical response and mucosal healing [45–48], while loss of response to infliximab largely results from increased clearance of the drug (high inflammatory burden, diarrhea) and/or presence of antibodies to the drug [49, 50].

Similar to TDM for TP metabolite concentrations, regular monitoring of infliximab serum concentrations is predicted to improve drug efficacy by tailoring dosing regimens to an individual's PK [51, 52]. An initial retrospective study suggested that proactive TDM, as an alternative to reactive TDM (testing with clinical symptoms), may be associated with improved clinical outcomes as proactive TDM allows for dosing adjustments to a target range when the patient is asymptomatic [53]. While future clinical trials of proactive TDM are needed for infliximab, Assa et al. found that proactive monitoring of adalimumab trough concentrations and subsequent dose optimizations were associated with an increase in clinical remission compared to the strategy of reactive TDM [54].

While the therapeutic target range for infliximab maintenance has been controversial, Ungar et al. showed in adults that an infliximab trough of 6–10 μg/mL was associated with mucosal healing [55]. More recent evidence suggests a target range of 10–15 μg/mL may be required for complicated CD as the median infliximab trough for perianal fistula healing was 12.7 μg/mL (IQR, 6.6–15.5) [56]. Finally, in a large adult and pediatric cohort study (PANTS), a subtherapeutic drug concentration prior to the start of infliximab maintenance was the only independent factor associated with both primary non-response and year-one non-remission [57]. The group found post-induction concentrations >7 μg/mL were associated with lower fecal calprotectin and protective against immunogenicity [57].

Despite a high clinical response rate during infliximab induction, the use of the as-labeled (5 mg/kg) infliximab dosing regimens in children with IBD has been associated with a high rate of subtherapeutic trough concentrations during induction as well [58]. These observations have led to renewed interest in achieving therapeutic targets at the start of treatment with higher infliximab doses guided by disease severity [59] and biomarkers of increased infliximab clearance [60].

As suggested by the findings in the post hoc analysis of the SONIC trial [40], anti-TNF monotherapy in combination with proactive TDM may minimize the need for combination therapy with IMM and infliximab [61]. Arguments for proactive TDM include preventing undetectable or subtherapeutic trough concentration (consequently also decreasing the risk of immunogenicity) and potentially preventing future morbidity by using dose intensifications prior to the development of symptoms or CD-related complications. In their retrospective review, Vaughn et al. showed that in adult CD patients, a strategy of proactive TDM vs. a standard of care group (where drug level monitoring was symptom based), achieving an infliximab trough of ≥5 μg/mL resulted in >90% probability of maintaining infliximab over 5 years. Importantly, they found with proactive monitoring only 29% of the cohorts were within the target range of 5–10 μg/mL, which is similar to a PCD study that found 24% had undetectable levels and 38% were <3 μg/mL following reactive TDM [46, 53]. Interestingly, Vaughn et al. found that small-dose adjustments (median escalation of 100 mg, range 50–250 mg) were enough to improve the trough levels in contrast to common methods of infliximab intensification in clinical practice of doubling from 5 to 10 mg/kg or decreasing the frequency of infusions from 8 to 6 weeks [53]. An analysis of a real-world practice change from reactive to proactive TDM among pediatric IBD patients demonstrated that proactive TDM was associated with a higher odds of achieving CS-free remission (clinical and biochemical) and decreased infliximab failure due to immunogenicity (Fig. 31.1) [62].

Two adult trials have attempted to study proactive monitoring prospectively; however, they did not find any clinical benefit when they studied this for the maintenance phase. In the Trough Concentration Adapted Infliximab Treatment (TAXIT) RCT, subjects with sub- or supratherapeutic doses were initially dose optimized to achieve levels between 3 and 7 μg/mL. Following dose optimization, subjects were then randomized into a reactive versus a proactive TDM group to maintain 3–7 μg/mL. While there were no differences in rates of achieving remission, the proactive group had fewer disease flares [48]. In a second study, a randomized controlled trial investigating tailored treatment with infliximab for luminal Crohn disease (TAILORIX), patients were randomized to different strategies of maintenance dose escalation based on a combination of clinical, biochemical, and trough level targets also using the 3 μg/mL cutoff [63]. At 1 year, the combination of strategies was no more effective in achieving remission than dose escalation based on symptoms alone. More recent evidence suggests that the cutoffs in these studies may have been suboptimal. A post hoc analysis of TAILORIX subsequently identified that a week-14 level of 7.8 μg/mL was associated with radiologic remission at 1 year [64], while a week-2 level >23 μg/mL and a week-6 level >10 μg/mL were associated with endoscopic remission at week 12 (which was prior to the randomization phase) [65]. In fact, a recent PCD study identified that an induction infusion level of ≥26.7 μg/mL at week-2 and a level of ≥15.9 μg/mL at week-6 were associated with clinical response [66]. Moreover, to achieve a higher week-14 level of >5 μg/mL, levels ≥29 μg/mL and ≥18 μg/mL should be targeted at week-2 and 6, respectively, and has been endorsed in the 2020 ECCO/ESPGHAN CD guidance on TDM [67].

There is an accumulating body of literature that has furthermore demonstrated that proactively monitoring trough levels as a proxy for exposure is important as there are several PK factors that can lower drug exposure, including weight <30 kg, younger patients, lower serum albumin, more extensive disease, immunogenicity, and possibly additional

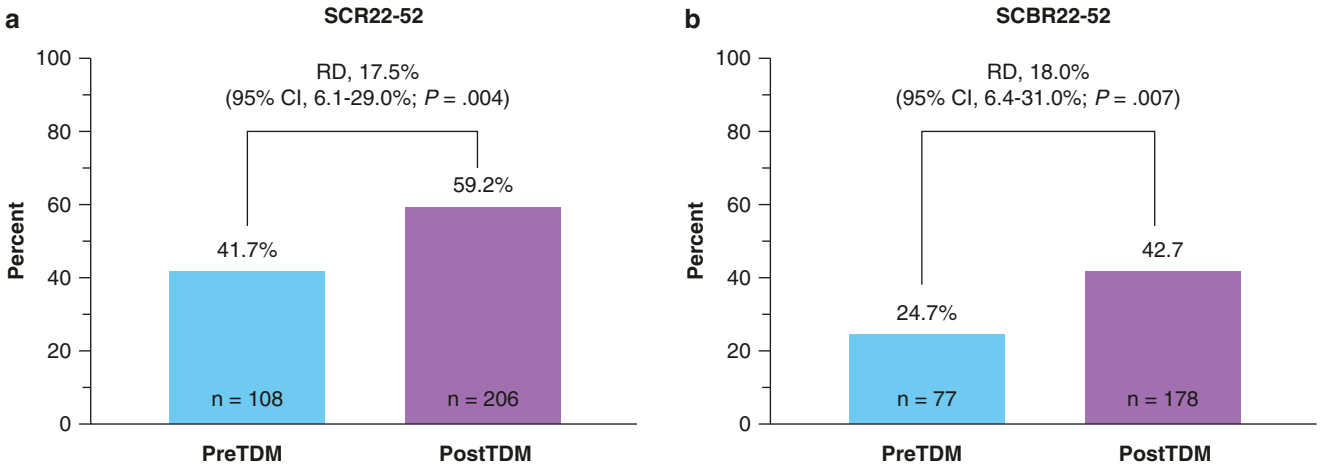

Fig. 31.1 Bar graphs comparing percentage of patients in (**a**) sustained clinical remission between 22 and 52 weeks (SCR22-52) and (**b**) sustained clinical and biochemical remission between 22 and 52 weeks (SCBR22-52) between pre-TDM and post-TDM groups. Used with Permission [62]

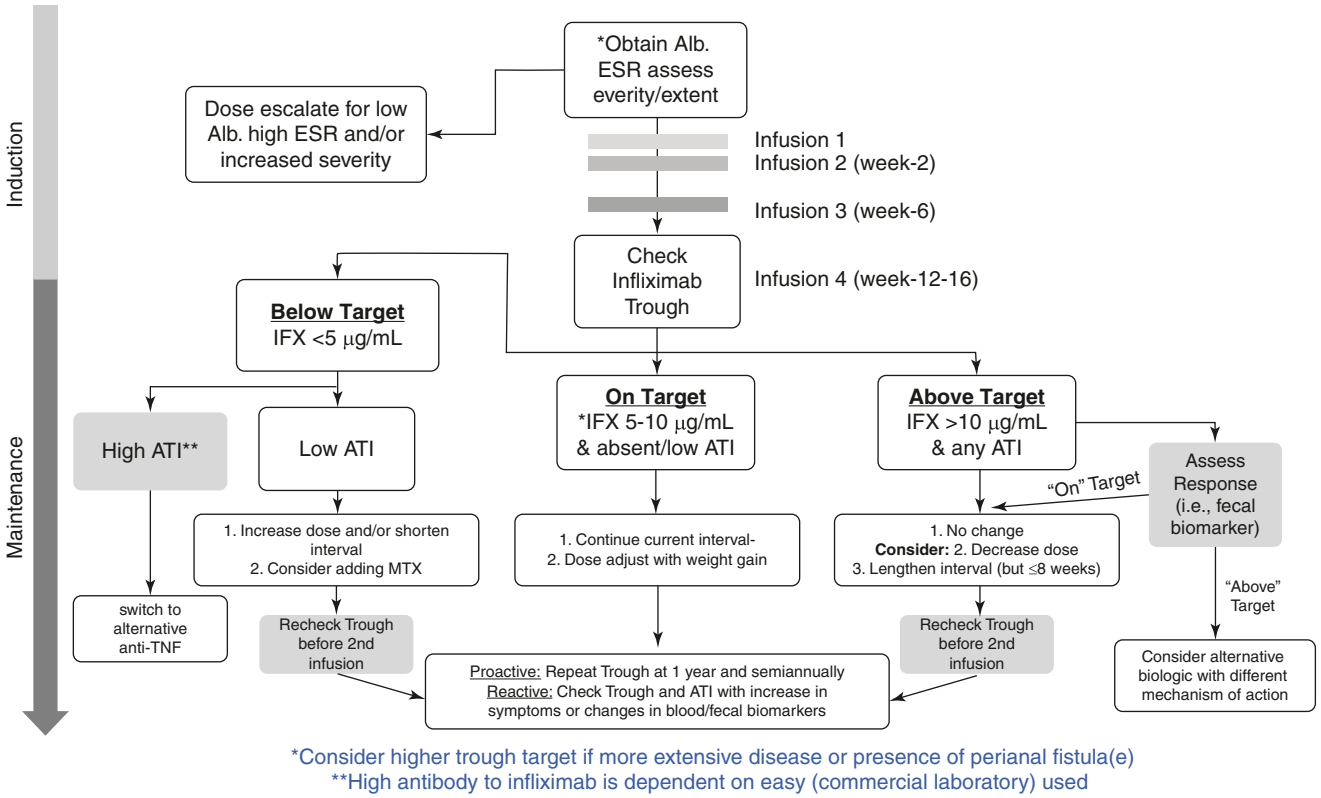

Fig. 31.2 Proposed Algorithm for Proactive Therapeutic Drug Monitoring in Children with IBD. The first infliximab trough concentration is to be obtained at the end of induction (prior to first maintenance dose). For patients predicted to have accelerated drug clearance during induction (high inflammatory burden, severe colitis, and/or low serum albumin), a higher dose (>5 mg/kg) should be considered as well as checking a trough concentration at infusion-3 (week-6) to guide future maintenance dosing. Alb, serum albumin; ATI, antibody to infliximab; ESR, erythrocyte sedimentation rate; IFX, infliximab; MOA, mechanism of action; MTX, methotrexate

composite markers of inflammation, such as erythrocyte sedimentation rate (ESR) and neutrophil CD64 surface expression. There is a need for a more systematic approach to biologic dosing and proactive TDM (Fig. 31.2) [60, 68–73]. Based on these observations, precision dosing guided by PK dashboards may be a more accurate way for clinicians to account for these individual factors in the real world [60, 69, 74, 75]. Preliminary data from a prospective adult trial found that dashboard-guided dosing was more effective in preventing relapse than labeled dosing, even when a target trough level of 3 μg/mL was used [76].

In addition to monitoring of PK factors, a better understanding of how infliximab exposure leads to mucosal healing and improvement in composite pharmacodynamic (PD) biomarkers is warranted. As close monitoring with serial endoscopies is impractical for adult-onset and PCD, the 2020 ECCO/ESPGHAN CD guideline recommends serial PD monitoring with fecal calprotectin to monitor biochemical response [77]. Moreover, a recent pediatric study demonstrated that higher exposure to infliximab was associated with a better improvement in fecal calprotectin and blood biomarkers [78].

Infliximab Concentration Detection Methods

Multiple assays have been developed to improve the monitoring for circulating infliximab levels, including the enzyme-linked immunosorbent assay (ELISA), the radioimmunoassay (RIA), a drug neutralizing (activity) assay (ARUP Laboratories, Salt Lake City, UT), and the homogenous mobility shift assay (HMSA) offered by Prometheus® (Prometheus Laboratories Inc., San Diego CA) [79–81]. Infliximab serum concentrations can be determined quickly and at low cost with the ELISA technique. However, due to infliximab drug interference, certain ELISA may not detect the presence of antibodies to infliximab (ATI) if circulating drug is present. Newer technologies have permitted commercial laboratories to offer novel assays that are drug tolerant and can detect both infliximab concentration and ATI in the presence of a detectable infliximab concentration using the HMSA or the electrochemiluminescence immunoassay (ECLIA, offered by LabCorp, Esoterix, Calabasas, CA and Mayo Clinic Laboratories, Rochester, MN). Moreover, it should be noted, that while infliximab levels are often comparable between these assays, there may be more disagree-

ment between ATI measurements (either in the reported unit of measure and whether total [neutralizing and non-neutralizing] or neutralizing ATI are reported) [82]. While these previously described techniques may be cost prohibitive and may take up to several weeks to result, with the increase use of proactive TDM and PK dashboard-assisted dosing, it is important to identify more rapid patient-centered and cost-effective methods optimized dosing and concentration monitoring [75]. Reliable point-of-care tests with instant turnaround times and more patient friendly methods (such as dried blood sampling by finger sticks at home) may revolutionize the current TDM practice [83].

Incidence of Primary and Repeat Abdominal Surgeries in the Infliximab Era

The cumulative incidence of surgery 10 years after diagnosis in CD ranges from 40 to 70% in adults [84, 85]. In a large pediatric cohort of 989 CD patients, Gupta et al. noted that 13% of children required intestinal resection after a median of 2.8 years, with 17% at 5 years and 28% at 10 years [86]. In a univariate regression analysis, infliximab use was associated with decreased risk of surgery (hazard ratio = 0.42, 95% confidence interval [CI] 0.23–0.76, $p < 0.004$). Park et al. [87] reported a similar decrease in risk of abdominal surgery in children receiving anti-TNF therapy (OR 0.57, 95% CI 0.46–0.7) in a large utilization review of anti-TNF therapy. The RISK study found patients who received early anti-TNFα were less likely to have a penetrating complication (hazard ratio 0.30, 95% CI 0.1–0.89) but no difference in stricturing complications (hazard ratio 1.13, 95% CI 0.51–2.51) [35]. It is important to note that only 21% of the RISK cohort received an anti-TNF within 90 days while drug levels and use of proactive TDM were not reported.

The postoperative recurrence of endoscopic inflammation following intestinal resection in PCD has been shown to be as high as 50%, 73%, and 77% at 1, 5, and 10 years, respectively [88]. The ECCO–ESPGHAN 2020 guidelines advocate for use of anti-TNF in high-risk patients to prevent recurrence [67].

Two adult RCTs described prophylactic anti-TNF use following intestinal resection. Regueiro et al., in a proof of concept randomized, double-blind, placebo-controlled trial, found that the 11 patients who were randomized to receive infliximab within 4 weeks of ileal resection had a significant reduction in endoscopic recurrence at 12 months compared to the 13 patients assigned to placebo (9% recurrence in infliximab treated vs. 85% in placebo group) [89]. In a subsequent multicenter randomized controlled trial, this group demonstrated that if infliximab was started within 45 days after ileocolonic resection, patients had 30% endoscopic recurrence compared to 60% in the group that was not treated postoperatively with infliximab [90]. The established risk factors for subsequent intestinal resection are a history of penetrating disease, cigarette smoking, and postoperative endoscopic recurrence of intestinal inflammation. Postoperative surveillance and prophylaxis are discussed in more detail in Chap. 43.

Ulcerative Colitis

In UC, the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2) were the first multicenter trials that evaluated efficacy of infliximab in adult UC patients [91, 92]. These studies showed that infliximab was superior to placebo in achieving induction and remission in patients with moderate to severe UC and further supported several single-center and retrospective studies in pediatric UC.

Infliximab in Moderate to Severe UC

Since the initial use of infliximab in the treatment of moderate to severe UC in adults with the ACT1 and ACT2 studies, six studies have been conducted in children, four retrospectively and two prospectively [93–96]. Hyams et al. published the first prospective study in 2010 [97]. A total of 52 children with UC were treated with infliximab. Of these, 63% were CS refractory and 35% were CS dependent. At the initiation of therapy with infliximab, 51% of patients were receiving a 5-aminosalicylates, 63% were on IMM, and 87% were on CS. The study showed that 38% of the patients had CS-free inactive disease at 1 year and 21% at 2 years, while 61% were colectomy free at 2 years [97]. Turner et al. evaluated the short-term response (clinical improvement based on the pediatric UC activity index [PUCAI] and laboratory parameters, including ESR, C-reactive protein, and serum albumin at days 3 and 5 of admission) to intravenous CS in 128 children hospitalized with acute severe UC (ASUC). Based on the PUCAI, they found that 29% (37 patients) did not respond to CS treatment. Of these 37 patients, 33 received infliximab with 55% maintaining clinical response at 12 months. Finally, the efficacy and safety of infliximab for inducing and maintaining response in children with moderate–severe UC was studied in a clinical trial of 60 patients with a similar study design as the REACH trial. At week 8, 73.3% had a clinical response. For the maintenance study, 44 patients were randomized to receive infusions either at 8- or 12-week intervals. Among these 44 responders, they found twice as many (8/21 vs. 4/22) were in clinical remission at week 54 ($P = 0.146$) with every eight-week infusions [98].

Infliximab in Refractory UC

Even though treatment with infliximab in moderate to severe UC has been widely proven, there are still many patients who fail to respond to conventional doses (5 mg/kg) or who are unable to maintain remission. These patients represent a therapeutic challenge. In the prospective study conducted by Turner et al., of CS refractory patients treated with infliximab, 12% still remained CS dependent at 12-month follow-up and 52% of the cohort studied required a colectomy [99].

The initial poor response rates to the as-labeled dosing (5 mg/kg) has led to clinicians and researches to alternatively treat ASUC with an escalated doses of infliximab (up to 10 mg/kg) to better maintain therapeutic exposure and overcome rapid drug clearance seen with a high inflammatory burden and/or significant infliximab stool losses. Driven by favorable data from adult-onset UC [100], Falaiye et al. reported a single-center retrospective experience in 29 patients who required hospitalization for active IBD and were treated with infliximab [91, 101]. Of the 29 patients in the study, 15 had UC, 12 CD, and 2 IBD unspecified (IBD-U) and all of the patients were anti-TNF naïve at the initiation of the treatment. Their results showed that 62% (18/29) needed infliximab dose escalation, while 41% (12/29) went on to a colectomy [101]. Importantly, the study identified an association between the need for dose escalation and lower body mass index (BMI) z-score, low serum albumin (median of 3.0 g/dL), and an elevated ESR (median of 53 mm/h) from baseline. More importantly, in a retrospective analysis, Church et al. found that in 73 patients who received standard infliximab induction (5 mg/kg) and 52 patients who received intensified infliximab induction (mean induction dose >7 mg/kg or interval ≤5 weeks between doses 1 and 3) for either CS-refractory or CS-dependent UC, the intensified regimen was associated with a higher chance of remission (hazard ratio 3.2, $P = 0.02$) and a lower chance of colectomy (hazard ratio 0.4, $P = 0.05$) [36].

Therapeutic Drug Monitoring and UC

Several studies in adults have demonstrated that fecal calprotectin, infliximab trough concentration, and clinical symptoms should be used to inform dose optimization in pediatric UC. Huang et al. concluded in their study of adults with UC that fecal calprotectin <250 μg/g was associated with a favorable infliximab response and concluded dose escalation could be considered for fecal calprotectin >250 μg/g [102]. They also demonstrated that infliximab trough levels of 3–7 μg/mL were indicative of good drug response, while levels <3 μg/mL should trigger a dose escalation and levels >7 μg/mL may require a dose de-escalation. Similar results were published by Vande Casteele et al. where they found that an infliximab trough level between 3 and 7 μg/mL was associated with improved drug efficacy [48]. Very few studies of proactive TDM in children with only UC have been published [52, 103], while multiple studies that include both adult and PCD and UC have found that proactive TDM improves clinical outcomes in comparison to reactive TDM [61, 62]. Similar to the induction targets established for PCD [58], Papamichael et al. found that short-term mucosal healing had higher median infliximab concentrations at weeks 2, 6, and 14 than those who did not achieve mucosal healing [104]. More specifically, using a receiver operating characteristic analysis, the infliximab thresholds associated with short-term mucosal healing at weeks 2, 6, and 14 were 28.3 μg/mL, 15 μg/mL, and 2.1 μg/mL, respectively [104].

Infliximab and the Incidence of Surgery in Pediatric UC

The long-term effect of infliximab and the incidence on colectomy in children with UC is not clear at this time. In adult-onset UC, the ACT1 and 2 studies showed a colectomy rate of 10% in patients treated with infliximab at 54 weeks compared to 17% in the placebo group [97]. In pediatric UC, Hyams et al. found 72% of the patients studied avoided a colectomy at 1 year and 61% at 2 years with infliximab use [98]. Colombel et al. also demonstrated that patients being treated with infliximab and achieved mucosal healing were more likely to achieve CS-free and colectomy-free remission at 54 weeks [105]. While early use of infliximab in CS-dependent patients is promising, a recent meta-analysis from the biologic era identified that a cumulative rate of colectomy was 12.9% at 5 years [106]. These data along with the accelerated infliximab drug clearance associated with ASUC [107] suggest the critical need for use of precision dosing (based on individual predicted drug clearance) to reduce the rates of colectomy in children.

Infliximab Biosimilars

Since the expiration of the infliximab reference product patent in Europe in 2015 and the US in 2018, several infliximab biosimilars have entered the market. While the exact definitions slightly differ between the EU and US, a biosimilar is a highly similar product of a biological reference product with no clinically meaningful differences and high similarity in physiochemical characteristics, efficacy (and potency), purity, and safety [108]. Biosimilars could potentially reduce the cost of the therapy, but currently there are limited data regarding real-world efficacy, safety, and immunogenicity

among the different products. Approval of the infliximab biosimilars has been based on adult data from non-IBD indications. More recently, however, an adult trial also included IBD patients and showed that the biosimilar CT-P13 (infliximab-dyyb, Celltrion Inc.) was non-inferior to the infliximab originator [109]. Since then, several real-world studies have reported the safety and efficacy of starting a biosimilar or switching from the originator to a biosimilar in their respective pediatric IBD cohorts [110–113]. There are a limited amount of data available with regard to PK, such as immunogenicity; however, current rates of anti-drug antibody formation are similar to the infliximab originator different [114–116]. At this time, no biosimilar has yet received the label of interchangeability, and thus switching between the currently available infliximab biosimilars more than once or reverse-switching is not recommended.

Infliximab Safety Profile

Infusion Reactions

Although relatively rare, an infusion reaction is a side effect of infliximab therapy which may limit longer-term use of the medication for some patients. *Acute infusion reactions* may resemble anaphylaxis with urticaria, blood pressure changes, respiratory symptoms, and chest pain. While a portion of acute infusion reactions may occur in the absence of anti-drug antibodies, prevention of anti-drug antibodies with proactive TDM protocols, avoidance of episodic infliximab therapy, and concomitant IMM appear to have a role in prevention of some of these reactions [10, 25, 117–119]. In pediatrics, infusion reactions have been reported in 5–16% of patients receiving infliximab, but it is not currently known if proactive TDM and early dose escalation in patients with greater disease extent or severity may improve durability of infliximab therapy by reducing subtherapeutic exposure and therefore lowering the rates of immunogenicity [28, 120–122]. Although controversial, some acute infusions reactions may be prevented in part by pretreatment with antihistamines or CS and has led to a wide variation of pretreatment use across centers [123, 124].

Management of an acute infusion reaction may vary based on the type of reaction and could include CS, antihistamines, slowing, or even stopping the infusion. It has been generally accepted that if an infusion reaction is severe, a change to alternative medication with the same mechanism of action is advised.

Autoimmune phenomena may occur as an additional side effect of infliximab therapy. *Delayed reactions* may happen days after an infliximab infusion and mimic a serum sickness reaction [123]. These reactions are more typical in patients with high antibody levels or in patients who have not had infliximab exposure for an extended period of time (i.e., episodic therapy or attempted resumption of infliximab after a period of time off the drug). These reactions are thought to result from deposition of ATI-induced immune complexes being deposited in the tissues and blood vessels and present with myalgia, arthralgia, and other systemic symptoms requiring treatment with CS and/or switching to an alternative biologic [123]. Autoantibody formation has been described in patients with IBD and other conditions receiving infliximab therapy, with up to half of patients with infusion reactions developing antinuclear antibodies (ANA) and about one-third developing antibodies to double-stranded DNA (anti-dsDNA) [125, 126]. Fortunately, only about 1% of patients with ANA or dsDNA develop drug-induced lupus, whether being treated for IBD or other conditions [125–127]. Development of coombs negative anemias, demyelinating lesions, and optic neuritis has also been described with infliximab use, but fortunately, these are rare phenomena and typically improve with CS or withdrawal of infliximab [127, 128].

Skin-related side effects have also been associated with infliximab therapy and may warrant discussion prior to initiating infliximab therapy. Development of new psoriasis or other skin conditions can occur in up to 30% of patients receiving infliximab [129]. In most instances, these conditions are not associated with ATI and may be treated with topical and sometimes oral therapy without necessitating discontinuation of the anti-TNF.

Rapid (One-Hour) Infusions

Time burden and costs associated with prolonged infliximab infusions have resulted in investigations of decreasing infusion time. Most infusions are given over a period of 2–4 h, but shorter one-hour infusions appear to be safe in adults, with no increased risk of infusion reactions even for those receiving larger drug doses up to 10 mg/kg [130, 131]. These shorter infusions have been shown to correlate with improvement in overall, social, and job-related quality of life as well [132]. More recent pediatric data have shown that that rapid (1-h) infusions are likely safe for pediatric patients if they have demonstrated repeated tolerance of several standard (long) infusions in the past [130, 133, 134]. The selection of which patients qualify and timing (induction or maintenance) of rapid infliximab infusions should be at the discretion of the treating physician with careful consideration of presence of anti-infliximab antibodies along with the personnel present and resources at the infusion facility (i.e., hospital center, infusion clinic at a satellite, home infusions or private infusion center) to manage a possible infusion reaction.

Infections

As with other immunosuppressive therapy, infections may occur more commonly in patients receiving anti-TNF. In the REACH study, 80% of reported serious infections (pneumonia, herpes zoster, and abscess) occurred in patients receiving infliximab every 8 weeks compared to the 20% that occurred in patients receiving infliximab every 12 weeks [28]. As a whole, many infections were respiratory in nature, but severe infections included sepsis and fever, pneumonia, colitis, and skin infections, such as MRSA adenitis or furunculosis. Ultimately, the rate of serious infections associated with both infliximab and adalimumab in pediatrics has been reported to be 352 per 10,000 patient years and is similar between both anti-TNF agents as well as the expected rate of infections associated with IMM use (estimated at 333 per 10,000 patient years) [139]. Systemic CS in use is associated with a significantly higher risk infections with about 730 infections per 10,000 patient years compared to infliximab [127, 139]. Moreover, pooled analyses of adults receiving long-term infliximab did not demonstrate a significant risk of infections or serious infections for infliximab monotherapy, and data from the adult "TREAT" registry (Crohn's Therapy, Resource, Evaluation, and Assessment Tool) suggest that active moderate to severe disease and the use of CS are much more likely to be associated with infection compared to infliximab alone [135, 136].

Although there are limited pediatric data, opportunistic infections remain a significant risk as described in the adult "TREAT" registry and may occur in 1.81 of 1000 patients [135, 137]. While respiratory infections remain the most commonly reported infection in pediatrics, opportunistic infections, such as *Candida albicans*, *Listeria monocytogenes*, *herpes simplex virus* (HSV), *cytomegalovirus* (CMV), and *Epstein-Barr virus* (EBV) have been reported and present a higher risk to elderly IBD patients in comparison to the pediatric IBD patient [135, 138]. Clinician awareness of regional opportunistic infections, such as histoplasmosis (Ohio and Mississippi river valley), blastomycosis (Ohio and Mississippi river valley), or coccidioidomycosis (Southwestern US), may warrant additional screening and treatment prior to initiating therapy [140].

Rare, but serious infections, such as tuberculosis (TB) reactivation, have been associated with anti-TNF therapy as well [141]. Although first described in the setting of infliximab, reactivation of TB is a concern for all anti-TNF therapies and has led to standard screening guidelines for latent TB prior to initiation of anti-TNF therapy and yearly screening during maintenance treatment [142–145]. Most recently, during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19) pandemic, there has been some concern from the community about contracting COVID-19 while receiving any immunosuppression. Preliminary data from the SECURE-IBD registry reported that among 1439 IBD patients with a confirmed COVID-19 infection, anti-TNF monotherapy was not associated with a more severe disease course. However, TP monotherapy and combination therapy with an anti-TNF and a TP were both associated with a four times increased risk of severe COVID-19 course [146].

Vaccination

Live attenuated vaccines are contraindicated for patients receiving anti-TNF therapy while all inactivated, attenuated viruses should be offered, particularly the annual influenza vaccine [142, 144]. Additional vaccinations that are important for those receiving immunosuppressant therapies include vaccinations for Hepatitis B and pneumococcal since these infections may pose serious health risks if reactivated or contracted during anti-TNF therapy. It is generally recommended that the patients serologic response to Hepatitis B be checked at diagnosis prior to initiating any immunosuppressive therapy, including anti-TNF biologics [143, 145, 147]. The Hepatitis B (if inadequate serologic response documented) and pneumococcal vaccines can be administered once infliximab has started. Additionally, protection against human papilloma virus (HPV) is indicated due to increased risk of cervical dysplasia in IBD patients on immunosuppression [148]. It is important to note that response to vaccines may be suboptimal in patients on biologic therapies, such as infliximab, or receiving CS.

In contrast, the varicella vaccines (Varivax®, the single-antigen varicella vaccine and ProQuad®, a combination measles, mumps, rubella, and varicella vaccine) contain live, attenuated varicella-zoster virus, and are *contraindicated* once a patient starts anti-TNF therapy or any immunosuppression. For patients found to be truly non-immune to varicella, the clinician must weigh the risks and benefits of delaying anti-TNF therapy to provide vaccination for a patient based on previously published guidelines [149].

Malignancy

Cancers, such as colorectal cancer, remain a risk for patients with IBD who have continued, active inflammation regardless of medication exposure [150, 151]. The additional risk of malignancy related to anti-TNF treatment remains a consideration for most patients and families starting a biologic. One of the most significant concerns has been for HSTCL, a rare malignancy associated with therapy for IBD and often universally fatal in most cases. In a recent systematic review (2020), Shah et al. found there have been 62 HSTCL reported cases in the literature. The median age of affected patient was 28 years (range 12–81), 83.6% were male and 84.7% had CD [152]. Only 5/62 of the cases had no prior (reported) TP exposure. They found 87.8% (43/49) of those patients

with a known (reported) outcome died with a median survival of 5 months [152]. Given the association between HSTCL and combination anti-TNF with a TP in the pediatric IBD population, it is recommended that a patient-centered (shared-decision) discussion be initiated before starting anti-TNF therapy in this demographic. A recent review found that combination therapy with anti-TNF and TP is declining and is not recommended in any male patient [153, 154].

Regarding other types of cancers, Lichtenstein et al. in a long-term safety registry of CD patients (TREAT registry), reported similar crude cancer incidences between infliximab and "other treatments only" exposed patients [155]. Furthermore, data from An IBD Multicenter, Prospective, Long-Term Registry of Pediatric Patients (the DEVELOP registry), found that infliximab exposure was not associated with an increased risk of malignancy or HLH when data were compared to the Surveillance, Epidemiology and End Results Program (SEER) database [30]. In contrast, pediatric IBD patients exposed to TP with or without infliximab do have an increased risk of malignancy compared to the reference population of the SEER database [30].

Other forms of malignancies, such as skin cancers, have been described during longer-term follow-up of patients on infliximab therapy, but the highest risk seems to be from older age and longer IBD duration rather than cumulative exposure to just infliximab [127]. Infliximab does not appear to increase risk for non-melanoma skin cancer after adjusting for TP therapy, but patients receiving infliximab may have an increased risk of melanoma skin cancer related to the disease itself and potentially related to anti-TNF therapy [156]. Cervical cancer remains a risk for women with IBD which may be unrelated to treatment but warrants appropriate vaccination for HPV in this high-risk population [157].

The discussion of malignancy risk for patients undergoing anti-TNF therapy represents a unique opportunity to include families in a shared decision-making approach to medical treatment. There is no single consensus about approach to anti-TNF monotherapy or combination therapy for young patients, so this particular aspect of treatment may call for a more customized approach to care, discussion of medications with presumed lower risk of cancers, such as MTX, and a clear communication between the patient (family) and the clinician about the potential benefits and side effects associated with starting infliximab.

Mortality

Mortality associated with anti-TNF use, particularly in pediatrics, is not common. Dulai et al. described seven deaths for patients on anti-TNFs, but two of these were felt to be unrelated to medication [139]. The five patient deaths receiving anti-TNF totaled a rate of 5.3 per 10,000 patient years during follow-up. Of the three patients who died on infliximab therapy, the cause of death was attributed to bone marrow transplant complication, cardiac complication (in the setting of a previously described arrhythmia), or azathioprine-induced neutropenia which led to sepsis [139]. Deaths due to lymphoma, particularly HSTCL, have also been described following infliximab use [127, 158].

Summary

The arrival of infliximab has revolutionized the treatment of moderate to severe IBD in both children and adults. It has shown to be effective in inducing and maintaining remission, is CS sparing, and restores growth. Varying practices in infliximab use has shown that scheduled dosing, rather than episodic, is not only more efficacious but also prevents ATI formation and thereby results in a more durable and sustained response. Newer data suggest that proactive TDM is more effective than reactive TDM in maintaining therapeutic trough concentrations, reduces IBD flares, and improves drug durability. The safety profile of infliximab is overall favorable although continued vigilance remains necessary for the occurrence of infrequent but serious events, including opportunistic infections and malignancies, especially in patients receiving concomitant immunosuppressive treatment. With more novel anti-cytokine and anti-integrin biologics available to the pediatric clinician (both on and off FDA label), it will be key to develop a multiomic approach to begin pairing the right drug (biologic or small molecule) for the right patient (based molecular, genetic, and/or IBD-specific phenotype). Once the right drug is selected, it is vital for clinicians to become familiar with precision dosing strategies and use of innovative PK dashboards that can quickly synthesize the predicted drug clearance and model individual PK profiles to simulate an optimized dose and dosing regimen for the individual patient.

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Anti-TNF Therapies Other Than Infliximab for the Treatment of Pediatric Inflammatory Bowel Disease

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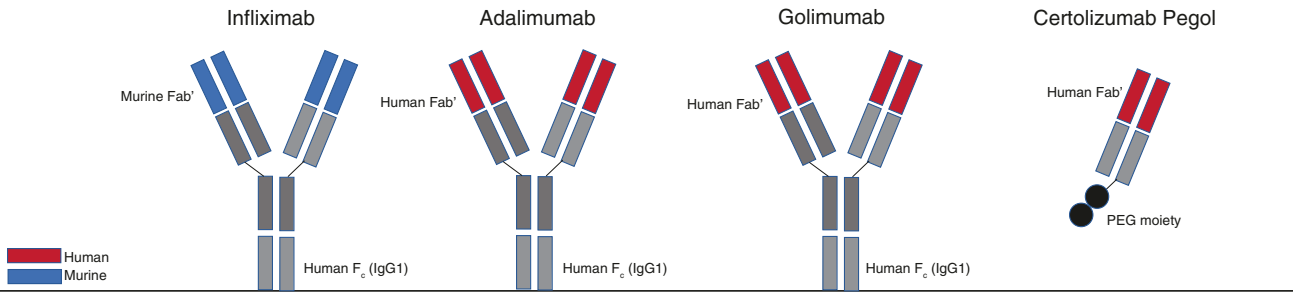
Introduction

The cornerstone of inflammatory bowel disease (IBD) therapy for the last 20 years has revolved around biologic agents targeting tumor necrosis factor alpha (TNFα). Since the approval of infliximab as the first anti-TNFα agent to treat Crohn disease (CD) and ulcerative colitis (UC), other agents also targeting TNFα have come to market including adalimumab, certolizumab, and golimumab. These agents differ in their route of administration, pharmacokinetics, mechanism of action, as well as antibody structure (Fig. 32.1). In this chapter we will review the clinical efficacy, safety, and future directions for this class of drugs. While all of these agents have been used to treat pediatric IBD, only infliximab and adalimumab are FDA as well as EMA approved [1]. To date, a number of randomized controlled trials evaluating the use of adalimumab, certolizumab pegol, and golimumab are quite low in pediatric patients; therefore, the majority of the recommendations supporting their use in pediatric CD and UC come from observational studies or extrapolation from the adult literature.



- Binds Soluble TNF	Yes	Yes	Yes	Yes
- Binds Membrane TNF	Yes	Yes	Yes	Yes
- FcR Binding	Yes	Yes	Yes	No
- ADCC (Fc mediated)	Yes	Yes	Yes	No
- FDA Approval: Pediatric IBD	Yes	Yes	No	No
- FDA Approved: Adult IBD	Yes(UC/CD)	Yes (UC/CD)	Yes (UC)	Yes (CD)
- Method of Delivery	IV q 4-8 wks	S.C. Injection q1-2 wks	S.C. Injection q4 wks	S.C Injection q2-4 wks

TNF: Tumor Necrosis Factor, ADCC: Antibody Dependent Cell Mediated cytotoxicity, IV: intravenous, S.C: subcutaneous, wks: weeks, IBD: inflammatory bowel disease, CD: Crohn disease, UC: ulcerative colitis

Fig. 32.1 Structure, mechanisms, and clinical indications for each anti-TNFα therapy

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Therapeutic Efficacy and Pivotal Trials

Adalimumab

Adalimumab is a fully humanized monoclonal antibody against TNFα, which, after infliximab, is one of the most commonly used biologics in pediatric patients with IBD [2]. Adalimumab was engineered using phase display technology and is indistinguishable in both structure and function from human immunoglobulin (IgG1) with no murine or other non-human components [3]. In adults and pediatrics adalimumab has been FDA approved for the treatment of CD and UC. In pediatrics, it is approved for CD ages 6–17 and UC approval was granted in February 2021 for ages 5–17. Adalimumab was the first anti-TNFα agent on the market after infliximab and offered an alternative route of administration as a subcutaneous injection. The recommended dosing of adalimumab in children with Crohn disease weighing more than 40 kg is 160 mg followed by 80 mg 2 weeks apart and then 40 mg every 2 weeks thereafter for maintenance. In children under 40 kg, the induction dosing is 80 mg and then 40 mg 2 weeks later, followed by 20 mg every 2 weeks for maintenance [4]. The pharmacologic half-life of adalimumab is 10–20 days. Although the exact mechanism of action is still incomplete the clinical efficacy of binding TNFα is believed to be secondary to decreased TNFα signaling as well as complement and antibody dependent cytotoxicity to TNFα-positive cells [5]. While there are no studies to date demonstrating a clear difference in the mechanism of action between adalimumab and infliximab, some researchers have suggested that structural differences in the molecules result in adalimumab's increased affinity for binding TNFα and that its recognition of a larger epitope compared to infliximab improves its ability to fully bind to the TNFα surface (Table 32.1) [6].

Efficacy of Adalimumab in Pediatric CD Patients

The pivotal trial supporting the efficacy of adalimumab induction therapy in pediatric CD patients was the IMAGINE 1 study published in 2012 [7]. This trial was an open-label induction trial of 188 patients aged 6–17 years with moderate to severe CD. All patients were given adalimumab at week 0 and 2 with either 160 mg and then 80 mg (weight ≥40 kg) or 80 mg and then 40 mg (weight <40 kg). After induction patients were randomized at week 4 to treatment with high-dose adalimumab (40 mg if ≥40 kg, or 20 mg if <40 kg every 2 weeks) or low-dose adalimumab (20 mg if ≥40 kg, or 10 mg if <40 kg every 2 weeks) and followed for 52 weeks. The primary endpoint of this study was clinical remission (defined as a decrease in Pediatric Crohn Disease Activity Index [PCDAI] of ≤10) at week 26. As a secondary endpoint, the trial looked at remission rates at week 52 as well as clinical response rates and steroid-free remission at weeks 26 and 52. At week 4 after induction 82.4% of patients had a clinical response and 27.7% were in clinical remission per PCDAI scores. The high-dose adalimumab group had a higher rate of clinical remission (38.7%) compared to the low-dose group (28.4%) at week 26, but this difference did not reach significance ($p = 0.075$). At week 52 there was again no significant difference in the percentage of patients who achieved clinical remission between high- and low-dose adalimumab ($p = 0.100$) though there was a significant difference in clinical response rates ($p = 0.038$). The study also compared the response to adalimumab in patients who were infliximab naïve and those who had previous infliximab exposure. Patients who were infliximab naïve had significantly higher rates of clinical remission compared to those with previous infliximab exposure at week 52 (45% vs. 19%, p value <0.001) [4, 7]. Of note, one of the limitations of the IMAGINE 1 trial was that there was no placebo comparison group for analysis.

As part of IMAGINE 1, patients who did not achieve a clinical response or those with loss of response by week 12 were allowed to dose escalate to weekly dosing. As part of this protocol, patients were continued on the blinded dose initially started in IMAGINE 1. After a minimum of 8 weeks of blinded weekly dosing, patients with ongoing flare symptoms or no response were allowed to enter into open-label weekly high-dose adalimumab (40 mg weekly if ≥40 kg and 20 mg weekly if <40 kg). 83 patients from IMAGINE 1 underwent dose escalation at week 12 [7, 8]. Among patients who received low-dose weekly adalimumab, 18.8% were in clinical remission at week 52 and 47.9% had a clinical response. Similarly, among patients on high-dose weekly adalimumab 31.4% of patients were in clinical remission and 57.1% had a clinical response. While the response and remission rates were higher among those on the high-dose weekly adalimumab, this difference did not achieve statistical significance ($p = 0.19$ for remission, $p = 0.41$ for response).

To understand the long-term efficacy and safety of adalimumab in pediatric patients with CD, the IMAGINE 2 study followed patients from the conclusion of IMAGINE 1 at week 52 through to week 240 [9]. In this open-label extension study, including 31 sites, 100 patients were included. Enrollment in IMAGINE 2 required successful completion of IMAGINE 1 and having achieved clinical response at any time point during the initial study. For the duration of the IMAGINE 2 trial, patients continued their original, blinded dosing from IMAGINE 1 (high- or low-dose adalimumab based on weight and either every other week or weekly injections). In this study, 41% of patients were in remission at week 240 and 48% had a clinical response. In a sub-analysis evaluating patients in clinical remission at the end of IMAGINE 1 (and therefore beginning of IMAGINE 2), 45% maintained this remission through week 240.

Table 32.1 Pivotal trials on the efficacy of adalimumab in pediatric and adult patients with inflammatory bowel disease

Study	Year	Study Type	Patients	Disease	Pediatric	Findings
IMAGINE 1 [7]	2012	Open label	188	CD	Yes	At week 4, 82.4% of patients had a clinical response and 27.7% were in clinical remission. At week 26, 33.5% were in clinical remission
IMAGINE 2 [9]	2016	Open-label extension	100	CD	Yes	At week 240, 48% of patients had a clinical response and 41% of patients were in clinical remission
Nobile et al. [11]	2014	Retrospective	48	CD	Yes	At 12 months, 50% of patients had endoscopic improvement and 25% had mucosal healing. 48% of patients had a clinical response and 36% in clinical remission
CLASSIC I [20]	2006	RCT	299	CD	No	At week 4, 12% of patients in placebo group in clinical remission compared to 18%, 24%, and 36%, respectively, for adalimumab dosed 40 mg/20 mg, 80 mg/40 mg, and 160/80 mg (week zero/week two doses)
CLASSIC II [21]	2007	RCT	276	CD	No	At week 56, 79% of patients who received adalimumab 40 mg every other week, 83% of patients who received adalimumab 40 mg weekly and 44% of those who received the placebo were in clinical remission
CHARM [22]	2007	RCT	854	CD	No	At week 26, 40% receiving every other week adalimumab, 47% receiving weekly adalimumab and 17% receiving placebo were in clinical remission
EXTEND [24]	2012	RCT	135	CD	No	At week 12, 27% of patients receiving adalimumab had mucosal healing compared to 13% receiving placebo. At week 52, 24% of patients treated with adalimumab had mucosal healing compared to 0% who received placebo
GAIN [25]	2007	RCT	301	CD	No	All patients infliximab exposed. At week 4, 21% of patients in the adalimumab group compared to 7% in the placebo group achieved clinical remission
ULTRA 1 [26]	2011	RCT	390	UC	No	At week 8, 16.5% of patients treated with adalimumab were in remission compared to 9.2% of placebo
ULTRA 2 [27]	2012	RCT	494	UC	No	At week 52, 17.3% of patients in the treatment group and 8.4% of patients in the placebo group were in clinical remission
Sandborn et al. [28]	2013	Post hoc analysis	248	UC	No	At week 52, 30.9%, 49.6%, and 43.1% achieved clinical remission, clinical response, and mucosal healing, respectively
ULTRA 3 [29]	2014	Open-label extension	199	UC	No	60% of the patients who had achieved remission as well as mucosal healing by year 1 were able to maintain these endpoints at year 4

CD Crohn disease, *UC* Ulcerative colitis, *RCT* Randomized controlled trial

The largest systematic review of clinical remission rates in pediatric CD patients treated with adalimumab included 14 studies (one randomized trial and 13 case series) and 664 patients. In this review the pooled clinical remission rates were 30% at 4 weeks, 54% at 3 months, 42% at 6 months, and 44% at 12 months [10]. In this study only 6% of patients were deemed primary non-responders to adalimumab.

To date there is only a single study evaluating endoscopic remission in pediatric patients with CD treated with adalimumab [11]. In this retrospective cohort study of 48 patients 7–18 years of age, 19 patients were treated with adalimumab and observed for a mean of 38.5 months (range 1–116 months). Adalimumab dosing in this study was 160 mg at week 0 and 80 mg at week 2 for induction in 84% of patients and 80 mg at week 0 and 40 mg at week 2 for induction in the remaining patients. All patients then received 40 mg every other week. Endoscopic remission in this study was defined as disappearance of lesions, whereas endoscopic response as defined as a significant reduction, but not disappearance of lesions. After 12 months of therapy 50% of patients on adalimumab had endoscopic improvement and 25% had endoscopic remission. In those who responded endoscopically to adalimumab the response was sustained for an average of 22.2 months. Likewise, in this study, clinical remission and response were seen in 36% and 48% of patients, respectively, after 12 months of therapy.

Efficacy of Adalimumab in Pediatric UC Patients

Only small retrospective studies have evaluated the use of adalimumab in pediatric UC. In one retrospective case series of 11 pediatric patients with UC treated with standard-dose adalimumab, 55% of patients achieved and maintained clinical remission after a median of 25 weeks [12]. All of the patients in this study had prior exposure to infliximab. Similarly, in a larger retrospective study of 31 pediatric patients with UC refractory to infliximab, 83% of those who transitioned to adalimumab had a clinical response and remained on adalimumab for the duration of the study [13, 14]. In the largest retrospective study to date utilizing data from a national registry, pediatric patients with UC who had previously failed infliximab were treated with standard-dose adalimumab (160 mg at week 0, 80 mg at week 2, and 40 mg thereafter every other week) for a median follow-up of 16 months. The primary endpoint of this study was corticosteroid-free clinical remission at week 52 (PUCAI <10). Of the 32 patients included, 41% achieved corticosteroid-free clinical remission after 1 year. Mucosal healing was evaluated as a secondary endpoint at month 0 and 12 using the Mayo Score. Mucosal healing in this study was seen in 28% of patients at 52 weeks [15].

Efficacy of Adalimumab in Pediatric Patients Exposed to Infliximab

While some of the studies described above included patients who were previously treated with infliximab and subsequently given adalimumab, there are studies that specifically aimed to understand the response to adalimumab after infliximab exposure. A nationwide observational cohort study from the Netherlands evaluated 53 pediatric patients with CD who were previously exposed to infliximab and subsequently treated with adalimumab [16]. Adalimumab induction dosing regimens varied in this study with 74% of patients receiving an induction doses prior to maintenance dosing which was weight based: 20–40 mg for patients <40 kg and 40–80 mg for patients >40 kg. 25% of patients required dose escalation which included shortening the interval of dosing and increasing the dose at the discretion of the treating physician. In this study, the primary endpoint was clinical remission and this was achieved in 64% of patients after a median of 3.3 months of therapy. Among patients who responded to adalimumab this response was maintained in 50% of patients for an average 2 years. 34% of patients were considered 'adalimumab failures' due to non-response (n = 4), loss of response (n = 11) or adverse events requiring termination of the drug (n = 3). Patients who were primary non-responders to infliximab tended to be less likely to achieve clinical remission with adalimumab (33%) compared to those who were secondary non-responders to infliximab (71%), however this difference did not achieve statistical significance (p = 0.24). Furthermore, patients with antibodies to infliximab had higher remission rates with adalimumab compared to those without antibodies (81% vs. 53%, p = 0.09). Of note, there was no difference in response rates to adalimumab based on concomitant immunomodulator use. A similar, however smaller, retrospective case series of 27 pediatric patients treated with adalimumab after infliximab loss of response or intolerance was published utilizing data from a population based registry [17]. In this study, treatment response was measured using the Physician Global Assessment (PGA); clinical remission was defined as a PGA of 1 and clinical response was defined as a decrease of at least 2 points in PGA score after 6 months of adalimumab therapy. After a median follow-up of 16 months, clinical response was seen in 70% of patients and was maintained in 52% of patients at 26 months. Primary adalimumab failure was seen in 30% of patients and loss of response in 19% of patients. While all patients initially received adalimumab subcutaneously every other week, 52% of patients in this study required 'dose optimization' which included dose escalation in 6 patients, a reduced dosing interval in 1 patient and a combination of the two techniques in 7 additional patients. Among these patients [10], 71% had a clinical response after dose optimization.

One of the first studies to demonstrate the efficacy of adalimumab in pediatric CD patients previously exposed to infliximab was the Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) study. This was a retrospective multicenter study at 12 sites as part of a pediatric IBD collaborative research group [18]. This study included 115 patients with pediatric CD who received at least one dose of adalimumab and were evaluated for clinical response as measured by the Physician Global Assessment (PGA). 95% of the patients in this study had prior exposure to infliximab with the majority of patients discontinuing the infliximab due to loss of response or infliximab intolerance (secondary non-responders). In this study clinical remission rates at months 3, 6, and 12 were 65%, 71%, and 70%. Steroid-free remission was seen in 22%, 33% and 42% of patients at months 3, 6 and 12.

Efficacy of Adalimumab in Adult Patients

Clinical trial data focusing on the use of adalimumab in pediatric IBD are somewhat limited, especially for patients with UC; however, there is extensive research in the adult IBD population. These data are often used as an adjunct to the limited pediatric data, although whether the efficacy and safety data can be extrapolated to patients under the age of 18 remains unclear. Adalimumab was first approved for the treatment of moderate to severe adult CD in 2007 and subsequently for UC in 2012. Unlike in the pediatric population, dosing of adalimumab in adults is not weight based; induc-

tion dosing is 160 mg at week 0, 80 mg at week 2 and 40 mg every other week thereafter. Escalation to weekly dosing has been demonstrated to be both safe and effective [19].

The first randomized placebo-controlled trial evaluating the use of adalimumab as an induction treatment for moderate to severe ileocolonic CD naïve to anti-TNFα therapy was the CLASSIC I trial [20]. This study included 299 patients and investigated the efficacy of 3 dosing regimens to induce clinical remission at week 4. In this study, clinical remission at week 4 was seen in 12% of the placebo group and 18%, 24% and 36% respectively for adalimumab dosed 40 mg/20 mg, 80 mg/40 mg and 160/80 mg (week zero/week two doses). The CLASSIC II trial sought to evaluate the long-term efficacy of adalimumab maintenance therapy utilizing patients from the CLASSIC I trial [21]. 276 patients from CLASSIC I were enrolled in CLASSIC II and these patients received open-label adalimumab 40 mg at week 0 (week 4 of CLASSIC I) then at week 4 were randomized to maintenance with adalimumab based on response. 55 patients in remission at week 4 of CLASSIC II were then randomized to either placebo, adalimumab 40 mg every other week or adalimumab 40 mg weekly for a total follow-up of 56 weeks. Those not in remission after 4 weeks of CLASSIC II were enrolled in a separate, open-label arm of the study and received adalimumab 40 mg every other week. The primary endpoint of CLASSIC II was maintenance of remission, which was defined as a CDAI score <150 at week 56. In this study, among the 55 patients who entered the randomization arm at week 4, 79% of patients who received adalimumab 40 mg every other week, 83% of patients who received adalimumab 40 mg weekly and 44% of those who received the placebo were in remission at week 56. In the open-label group (those not in remission at week 4), which included 93 patients, 46% were in clinical remission at week 56.

The CHARM trial was a randomized, double-blind, multicenter placebo-controlled trial that enrolled 854 patients with moderate to severe CD to study maintenance of remission using adalimumab [22]. Patients received induction therapy with 80 mg of adalimumab at week 0 and 40 mg at week 2 then were randomized at week 4 to receive placebo, adalimumab 40 mg every other week or adalimumab 40 mg weekly. Primary endpoints were clinical remission at week 26 and 52. Remission rates were significantly greater at 26 weeks in both adalimumab treatment groups compared to placebo (40% every other week adalimumab, 47% weekly adalimumab and 17% placebo, $p < 0.001$). At week 56, there was again a significant difference in clinical remission rates for patients taking adalimumab every other week or every week compared to placebo (36%, 41%, and 12%, $p < 0.001$). Patients in both treatment groups had a significant clinical response as early as 6 weeks into therapy. A secondary endpoint analysis for quality of life using the IBDQ also was significantly improved in patients receiving adalimumab. In this trial the most durable maintenance of remission was observed in patients with a shorter duration of disease prior to initiation of therapy (<3 years) [23].

The EXTEND trial was the first randomized, double-blind, multicenter placebo-controlled trial that evaluated the use of adalimumab in the induction and maintenance of mucosal healing in patients with moderate to severe CD [24]. A total of 135 patients were enrolled in this study with a baseline endoscopic evaluation followed by induction with adalimumab 160 mg/80 mg at weeks 0/2. The patients were then randomized to adalimumab 40 mg every other week or placebo and monitored for 52 weeks. Mucosal healing was assessed at weeks 12 and 52. In this study, 27% of patients treated with adalimumab had mucosal healing at week 12 compared to 13% in the placebo group. At week 52, 24% of patients treated with adalimumab had mucosal healing compared to 0 who received placebo ($p < 0.001$). At week 12 the rate of clinical remission was higher in patients treated with adalimumab compared to placebo but this difference was not significant (47% vs. 28%, $p = 0.21$). At week 52 there was a significant difference between treatment and placebo groups for maintenance of clinical remission (33% vs. 9%, $p = 0.001$).

The GAIN trial was a randomized, double-blind placebo-controlled trial of maintenance adalimumab in patients with CD who had previously been intolerant to infliximab or had a secondary loss of response [25]. In this study, 301 patients were assigned to adalimumab (160 mg/80 mg at weeks 0/2) or placebo and evaluated for clinical response at week 4. 21% of patients in the adalimumab group compared to 7% in the placebo group achieved clinical remission at week 4 ($p < 0.001$). A subgroup analysis of the GAIN trial demonstrated that adalimumab had improved efficacy compared with placebo regardless of concomitant immunosuppressive therapy, previous intolerance or loss of response to infliximab, or presence of antibodies against infliximab.

The efficacy of adalimumab in inducing and maintaining clinical remission in adult patients with UC was initially demonstrated in the ULTRA trials. In ULTRA-1390 patients with moderate to severe UC were randomized to adalimumab with standard dosing (160 mg/80 mg then 40 mg q2 weeks) or placebo [26]. The primary endpoint of the study was clinical remission (Mayo score ≤2) after 8 weeks of therapy. 16.5% of patients treated with adalimumab were in remission compared to 9.2% of placebo ($p = 0.019$). The study was later amended to include a third treatment arm with an adalimumab dose regimen of 80 mg/40 mg induction and 40 mg q2week maintenance. This low-dose adalimumab group had a remission rate of 10.0% after 8 weeks of therapy. In follow-up, ULTRA-2 studied the long-term maintenance of remission with adalimumab in patients with moderate to

severe UC [27]. 494 patients were randomized to adalimumab therapy (160 mg/80 mg at weeks 0/2 and then 40 mg q2 weeks) or placebo and followed through week 52. At week 8, 16.5% in the adalimumab group and 9.3% in the placebo group were in clinical remission ($p = 0.19$). At week 52, 17.3% of patients in the treatment group and 8.4% of patients in the placebo group were in clinical remission ($p = 0.004$). A second study was subsequently published as a post hoc analysis of the ULTRA I and 2 data, assessing the efficacy of adalimumab at week 52 in patients with UC who failed prior TNFα therapy and achieved clinical response at week 8 of ULTRA 2. Of the 248 patients evaluated in this study, 49.6% achieved clinical response at week 8. Of these patients, 30.9%, 49.6% and 43.1% achieved clinical remission, clinical response and mucosal healing respectively by week 52. Of those who entered ULTRA 2 on corticosteroids, ($n = 90$), 21.1% achieved steroid-free remission and 37.8% were steroid free by week 52 [28]. To evaluate longer-term remission rates in patients with moderate to severe UC, an open-label extension trial was performed (ULTRA-3) [29]. Roughly 60% of the 199 patients who entered ULTRA-3 and had achieved remission as well as mucosal healing by year 1 were able to maintain these endpoints at year 4. While patients who had previous TNFα exposure had lower rates of remission and mucosal healing throughout ULTRA-1 and -2, some of these differences diminished at the later time points in ULTRA-3 [29].

Certolizumab

Certolizumab is a monoclonal antibody against TNFα where the Fc portion of the antibody has been replaced with a polyethylene glycol moiety (Fig. 32.1). The lack of Fc portion and subsequent pegylation makes certolizumab unique among other TNFα inhibitors including infliximab, adalimumab and golimumab. The pegylation with a 40 kDa polyethylene glycol (PEG) moiety attached to the monoclonal antibody increases the effective half-life of the Fab molecule and thereby reduces the dosing frequency [30]. While certolizumab binds and neutralizes both soluble and transmembrane TNFα, exchanging the Fc region for a PEG moiety limits its ability to induce complement dependent cytotoxicity and antibody dependent cell mediated cytotoxicity, both of which are induced by the other anti- TNFα agents. The PEG moiety however does make certolizumab unique among anti-TNFα agents in that it does not cross the placenta during pregnancy [30]. Certolizumab was approved for the treatment of adults with moderate to severe CD in 2008 and is under investigation in adults with UC. Certolizumab is not approved for the treatment of pediatric IBD or any other condition in patients under the age of 18. The dosing regimens for children are extrapolated from the adult literature. In adults, certolizumab pegol is given subcutaneously; standard induction dosing is 400 mg at weeks 0, 2, and 4 and then 400 mg every 4 weeks thereafter.

Efficacy of Certolizumab in Pediatric Patients

To date, there are no randomized controlled trials evaluating the use of certolizumab in the treatment of pediatric IBD; in fact, there are no peer-reviewed articles evaluating this drug in the treatment of pediatric CD or UC at the current time. Despite the lack of studies on certolizumab, pediatric IBD specialists have extrapolated data from the adult IBD publications as well as pediatric rheumatologic studies (Table 32.2). Interestingly, there was a preliminary phase II

Table 32.2 Pivotal trials on the efficacy of certolizumab pegol in pediatric and adult patients with inflammatory bowel disease

Study	Year	Study Type	Patients	Disease	Pediatric	Findings
Winter et al. [32]	2004	RCT	92	CD	No	At week 2, 47.1% in the 10 mg/kg treatment group achieved clinical remission compared to 16% in the placebo group
Schreiber et al. [33]	2005	RCT	292	CD	No	At week 2,- 52.8% of patients receiving 400 mg CZP had a clinical response compared to 35.6% placebo
PRECiSE 1 [34]	2007	RCT	662	CD	No	At week 6, 35% in treatment group had clinical response compared to 27% placebo. At week 26, 23% had a clinical response compared to 16% placebo
PRECiSE 2 [35]	2007	RCT	688	CD	No	At week 26, 62% of responders maintained their clinical response in the treatment group compared to 34% in the placebo group
PRECiSE 3 [36]	2010	Open-label extension	595	CD	No	At week 80, 66% of patients in the treatment group maintained their clinical response
MUSIC [38]	2010	Open label	89	CD	No	At week 10, 62% had an endoscopic response and 42% were in endoscopic remission. At week 54 week, 62% had an endoscopic response and 28% endoscopic remission
WELCOME [39]	2010	RCT	539	CD	No	All patients infliximab exposed. At week 6, 62% of patients had a clinical response and 39.3% of patients were in clinical remission

CZP Certolizumab pegol, *CD* Crohn disease, *UC* Ulcerative colitis, *RCT* randomized controlled trial.

open-label prospective study entitled "The Use of Certolizumab Pegol for Treatment of Active Crohn Disease in Children and Adolescence (NURTURE)" that enrolled roughly 160 patients in 2013. As per the clinical trial information, this study was designed to evaluate the safety, pharmacokinetics, efficacy, and immunogenicity of certolizumab and planned to evaluate inflammatory markers, clinical disease activity, and growth scores at the end of 62 weeks of therapy. Unfortunately, this study was terminated prior to completion due to "higher than projected discontinuation rate during the maintenance phase." However, prior to the study termination, preliminary data were presented at the Digestive Disease Week Meeting in 2011, simply suggesting that after induction with 400 mg of certolizumab pegol at weeks 0,2, and 4, (if patients were ≥40 kg) or 200 mg at the same intervals (in patients 20–40 kg), patients had similar serum levels compared with adults [31].

Efficacy of Certolizumab in Adult Patients

In 2004, the first randomized, placebo-controlled trial with certolizumab was performed to evaluate the safety and efficacy of a single dose of intravenous certolizumab over 12 weeks [32]. In this study, 92 adult patients with CD were included and randomized to placebo or 10–20 mg/kg of certolizumab. The primary endpoint of this study was clinical response (decrease in CDAI ≥100 points) or remission (CDAI ≤150) after 4 weeks. A statistically significant improvement in clinical remission was seen at week 2 in 47.1% of those in the 10 mg/kg treatment group compared to 16% remission in the placebo group ($p = 0.041$). A subsequent randomized placebo-controlled trial was published in 2005 evaluating the use of certolizumab administered subcutaneously to induce remission in adult patients with CD [33]. 292 patients were randomized to 100 mg, 200 mg or 400 mg of certolizumab pegol or placebo given at weeks 0, 4, and 8. All of the certolizumab pegol doses produced significant clinical improvement compared to the placebo at 2 weeks, ($p = 0.033$, $p = 0.026$, $p = 0.010$, respectively). The improvement in clinical disease activity was greatest in patients who received 400 mg of certolizumab pegol (52.8% response) compared to placebo (35.6%), although this difference did not reach significance.

The PRECiSE 1 trial evaluated the efficacy of certolizumab in the induction of remission in adult patients with moderate to severe CD [34]. This trial enrolled 662 patients with moderate to severe CD and randomly assigned them to receive 400 mg of certolizumab or placebo at weeks 0,2, and 4 and then 400 mg every 4 weeks after that. The primary endpoints were the induction of clinical response at week 6 and maintenance of this response at week 26. Significantly more patients treated with certolizumab pegol compared to those treated with placebo had a clinical response at week 6 (35% vs. 27%, $p = 0.02$) and 26 (23% vs. 16%, $p = 0.02$). A comparison of clinical remission rates in both groups at weeks 6 and 26 did not differ significantly ($p = 0.17$) [34].

Following this study, PRECiSE 2 was a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy of certolizumab pegol for maintenance therapy in adults with CD [35]. In this study, 668 patients were enrolled and given induction dosing of 400 mg of certolizumab pegol subcutaneously at weeks 0, 2, and 4. Patients who had a clinical response at week 6 were then randomized to 400 mg of certolizumab every 4 weeks or placebo and followed for 24 weeks. 62% of patients in the treatment group maintained their clinical response at week 26 compared to 34% in the placebo group ($p < 0.001$). In the treatment group, clinical remission was achieved independent of corticosteroid use, concurrent immunosuppressants, or prior infliximab exposure.

As a follow-up, the PRECiSE 3 trial was an open-label extension to PRECiSE 2 to understand the efficacy of certolizumab for long-term maintenance in 595 patients who previously responded to certolizumab [36, 37]. At week 80, 66.1% of patients maintained a clinical response and 62.1% of patients were in clinical remission. Patients who received a placebo during weeks 6–26 as part of the PRECiSE 2 trial and started back on certolizumab as part of the open-label extension (drug interruption group) had higher levels of antibodies against certolizumab compared to the group who received continuous treatment. This study was extended further to look at the long-term safety and efficacy data of certolizumab in 117 patients over 7 years. Clinical remission rates by last observation carried forward and non-responder imputation were 58% and 45% at year 1, 56% and 26% at year 3, and 55% and 13% at year 7, respectively.

The MUSIC trial was the first study to evaluate the efficacy of certolizumab in patients with CD using mucosal healing as a primary endpoint [38]. In this prospective, open-label single arm study performed over 54 weeks, 89 patients with moderate to severe CD were treated with certolizumab pegol 400 mg subcutaneously at weeks 0, 2, 4, and then every 4 weeks thereafter. Endoscopic response was evaluated with the Crohn Disease Endoscopic Index of Severity (CDEIS). After 10 weeks, 62% had an endoscopic response and 42% were in endoscopic remission. After 54 weeks of therapy, endoscopic response and remission rates were 62% and 28% respectively.

To date there are no studies published on the efficacy of certolizumab for the treatment of adult UC.

Efficacy of Certolizumab in Adult Patients with Previous Infliximab Exposure

Similar to the studies on adalimumab, many of the randomized trials and smaller case series included patients who were previously exposed to infliximab; however, these studies did not focus on this population as their primary endpoint. The

WELCOME study was a prospective, randomized, double-blinded trial looking at the efficacy of certolizumab pegol in adults with moderate to severe CD who were secondary non-responders to infliximab [39]. This study included an open-label induction phase of treatment with certolizumab pegol 400 mg at weeks 0, 2, and 4; patients who responded were then randomized to receive placebo or certolizumab pegol 400 mg every 2 weeks or every 4 weeks. At week 6, 62% of patients in the treatment group had a clinical response to certolizumab and 39.3% of patients were in clinical remission. After 26 weeks of therapy, there was no significant difference in the rates of clinical remission or response between those who received certolizumab pegol 400 mg every 2 weeks and those who received 400 mg every 4 weeks.

Golimumab

Golimumab is a fully humanized monoclonal antibody against TNFα and is FDA approved for the treatment of adults with UC. Similar to adalimumab and certolizumab, golimumab is administered subcutaneously with an induction dose of 200 mg at week 0, 100 mg at week 2, and then 100 mg every 4 weeks. Golimumab's structure and mechanism of action are more similar to adalimumab and infliximab binding both soluble and membrane bound TNFα [40]. Golimumab is not currently approved for the treatment of pediatric IBD or any other inflammatory conditions in patients under 18 years of age.

Efficacy of Golimumab in Pediatric Patients

There are no randomized controlled studies of golimumab in pediatric patients with IBD. In 2017 a multicenter open-label study of golimumab in 35 pediatric patients with moderate to severe UC was published [41]. Patients received golimumab induction at weeks 0 and 2 based on weight (90/45 mg/m^2 if <45 kg and 200/100 mg if ≥45 kg). At week 6, 60% of patients had a clinical response, 34% where in clinical remission and 54% had mucosal healing (Mayo Score, PUCAI). In addition, serum levels of golimumab were lower in those <45 kg compared to those >45 kg. In a subsequent study looking at the pharmacokinetics of golimumab in adult and pediatric patients with UC, golimumab clearance increased with increased body weight, lower serum albumin, lack of concurrent methotrexate use, and positive antibodies to golimumab [42]. After controlling for weight, age did not influence golimumab clearance suggesting that the pharmacokinetics of the drug are likely similar in pediatric and adult patients. The PURSUIT PEDS PK Long-Term study published data on the use of golimumab for maintenance therapy in moderate to severe pediatric UC [43]. In this multicenter open-label study, patients who were responders (at week 6) to induction therapy were allowed to continue receiving open-label golimumab maintenance therapy (subcutaneous injection, 100 mg every 4 weeks) with a follow-up of 2 years. Thirty-five children entered the trial and 60% had a clinical response at week 6, resulting in a total of 20 children entering the open-label extension. Of these patients, 50% were in clinical remission (Pediatric Ulcerative Colitis Activity Index <10) at week 110. (Table 32.3).

Although golimumab is not approved for the treatment of CD, a small case series of 6 patients from Finland was published to understand the efficacy of golimumab in pediatric CD patients refractory to infliximab and adalimumab [44]. 83% of patients exposed to infliximab were secondary non-responders. Among these 6 patients, inflammatory markers and fecal calprotectin all decreased initially with golimumab induction; however, the improvement was not maintained and all needed dose escalation to 50 mg every 2 weeks (from 50 mg every 4 weeks) to maintain the improvement. Only two patients in this study continued past 1 year on golimumab both which received higher dosages of golimumab

Table 32.3 Pivotal trials on the efficacy of golimumab in pediatric and adult patients with inflammatory bowel disease

Study	Year	Study Type	Patients	Disease	Pediatric	Findings
Hyams et al. [41]	2017	Open label	35	UC	Yes	At week 6, 60% of patients had a clinical response, 34% where in clinical remission, and 54% had mucosal healing
PURSUIT -PK [43]	2020	Open-label extension	35	UC	Yes	At week 6, 60% of patients had a clinical response at week 6 and 50% were in clinical remission
PURSUIT -SC [46]	2014	RCT	1030	UC	No	At week 6, clinical response was seen in 51% and 54.9% of patients receiving 200 mg/100 mg and 400 mg/200 mg, respectively, compared to the 30.3% who were treated with the placebo
PURSUIT M [47]	2014	RCT	464	UC	No	Clinical response was maintained in 47% (50 mg dose) and 49.7% (100 mg dose) of patients receiving golimumab compared to 31.2% of those on placebo
GO OBSERVE [49]	2019	Observational	102	UC	No	Clinical response was achieved in 36.4%, 39.1%, and 26.3% of patients at weeks 6, 10, and 14, respectively

CZP Certolizumab pegol, *CD* Crohn disease, *UC* Ulcerative colitis, *RCT* randomized controlled trial

(100 mg every 3 weeks and 50 mg every 2 weeks). In another small case series of 7 patients with refractory CD treated with golimumab a clinical response was seen in 71% of patients with 28% achieving clinical remission based on PCDAI [45].

Efficacy of Golimumab in Adult Patients

The PURSUIT trial was the initial study supporting the approval of golimumab for the treatment of adults with moderate to severe UC [46–48]. This study was divided into two phases: the induction phase (PURSUIT-SC) and the maintenance phase (PURSUIT-M). PURSUIT-SC, a multicenter randomized placebo-controlled trial, evaluated the efficacy of golimumab in inducing remission in anti-TNFα-naïve patients with moderate to severe UC [46]. The PURSUIT-SC study had two parts: a phase 2 dose escalation study for induction and a phase 3 dose confirmation study to look at efficacy and safety of the selected induction regimen. In this second section, the primary endpoint was clinical response at week 6. In total, 1030 patients were included in this study; in the phase 2 portion of this study, the largest improvement in Mayo score was seen with 400/200 mg golimumab given at weeks 0 and 2. In the phase 3 part of the study, clinical response at week 6 was seen in 51% and 54.9% of patients receiving 200 mg/100 mg and 400 mg/200 mg respectively compared to the 30.3% who were treated with the placebo. Rates of clinical remission were significantly higher when comparing golimumab 400 mg/200 mg (17.9%) and golimumab 200 mg/100 mg (17.8%) to the placebo (6.4%), ($p < 0.001$ for both comparisons). Likewise, mucosal healing was seen in 42.3% and 45.1% of those receiving golimumab 200 mg/100 mg and 400 mg/200 mg, respectively, which were significantly higher than the rate in those who received the placebo (28.7%), ($p < 0.0014$ for both comparisons.) Finally, looking at change from baseline in IBDQ scores, those who received 400/200 mg and 200/100 mg had improved IBDQ scores compared to those who received the placebo ($p < 0.001$ for both comparisons) [46, 48]. Of note, a separate study evaluating the use of intravenous golimumab for induction of remission was conducted (PURSUIT-IV); however, the clinical response and remission rates were low and the study was abandoned [48].

The maintenance phase of the PURSUIT studies (PURSUIT-M) was a multicenter randomized, placebo-controlled study in which patients who had a positive response to induction with golimumab were randomized to receive golimumab (50 mg or 100 mg) subcutaneously or placebo every 4 weeks through 52 weeks [47]. In this study, a clinical response was maintained in 47% (50 mg dose) and 49.7% (100 mg dose) of patients receiving golimumab compared to 31.2% of those on placebo, $p = 0.010$ and $p < 0.001$ (golimumab vs. placebo respectively). At week 54, clinical response was maintained in more patients treated with 100 mg golimumab (49.7%) and 50 mg golimumab (47%) compared to placebo (31.2%, $p < 0.001$ and $p = 0.01$ respectively). Among those who responded to golimumab induction, clinical remission rates were significantly higher at both 30 weeks and 54 weeks in those who received golimumab 100 mg (27.8%) compared to placebo (15.6%, $p = 0.004$).

A post hoc analysis of the PURSUIT data was performed to better understand the longer-term outcomes of those who had a delayed response to golimumab (patients who had a clinical response at week 14 but had not previously responded at week 6) [48]. In these patients, 35.7% and 30.4% achieved clinical remission at weeks 30 and 54, respectively, which is similar to the rates of clinical response among those who were initial responders by week 6 (39.7% and 33.8% at weeks 30 and 54). Similar results were seen with mucosal healing suggesting that perhaps some patients have a delayed response with equal long-term outcomes at 1 year. A long-term three-year follow-up study of 195 patients in PURSUIT-M demonstrated that 86% of patients continued to have inactive or mild disease at week 104 and 69% remained on golimumab through week 216. Of note, this study only evaluated disease activity using the PGA.

Currently, an international multicenter trial evaluating the use of golimumab in patients with moderate to severe UC is underway [49]. The GO OBSERVE trial included patients naïve to and previously exposed to biologic therapy and treated them with standard-dose subcutaneous golimumab induction, followed by maintenance therapy with either 50 mg or 100 mg of golimumab every 4 weeks. Preliminary data from this study showed that among 102 patients, clinical response was achieved in 36.4%, 39.1%, and 26.3% of patients at weeks 6, 10, and 14 respectively [49].

Numerous case series and retrospective studies have evaluated the use of golimumab in patients with UC [50]. These studies range in size from 21 patients to 205 patients, and follow patients anywhere from 6 weeks to 54 weeks. Clinical response rates in these studies are quite variable, ranging from 14% to 69% [51, 52]. Four of these studies looked at endoscopic healing as well as clinical response and remission [50]. The largest of these studies that evaluated mucosal healing was a case series of 93 patients [53]. The primary endpoint in this study was induction and maintenance of clinical remission, defined as a Mayo score ≤ 2 after 6 months of therapy. In this study, remission was obtained in 36.5% of patients and clinical response was seen in 64.5% of the cohort. Mucosal healing was only seen in 19.3% of patients.

Additional Clinical Endpoints

Growth and Bone Health

The presence of systemic inflammation in IBD appears to play a significant role in growth failure, pubertal delay and poor bone health. Given this, researchers have focused on the restoration of growth and bone health as outcomes of interest for treatments, such as TNFα inhibitors. To date there are only studies of infliximab or adalimumab on growth velocity or bone health in children. Future studies will hopefully report on whether this effect can be extended to other TNFα inhibitors, including golimumab and certolizumab.

A retrospective study of 49 children used growth failure as a primary outcome in patients who received infliximab or adalimumab [54]. The study concluded that use of TNFα inhibitors to improve linear growth and pubertal delay is most effective when used early in childhood and when patients are treated to clinical remission. A smaller retrospective case series in Europe studied the effect of adalimumab on growth, bone mineral density, and bone metabolism among 18 pediatric patients with IBD [55]. In this study 61% of patients had improved growth velocity after the initiation of adalimumab. There was, however, no significant improvement in weight, height, and BMI after adalimumab ($p > 0.05$ for all) or an influence on markers of bone metabolism or bone mineral density.

In the IMAGINE 1 trial linear growth was measured as a secondary endpoint [56]. Adalimumab resulted in significantly improved and normalized growth rates at week 26 ($p < 0.001$) and 52 ($p < 0.001$). Interestingly, improvement in Z-scores was significantly greater in those who received low-dose (80 mg/40 mg) adalimumab (vs. placebo) compared to high-dose (160 mg/80 mg) adalimumab (vs. placebo).

In a retrospective case series focused on changes in growth velocity with adalimumab use, 36 pediatric patients were included and growth data were collected at three time points: 6 months prior to adalimumab, at the initiation of adalimumab therapy, and 6 months after drug initiation [57]. In this study 42% of children had "catch up growth" which was associated with clinical remission ($p = 0.007$), concomitant immunosuppression ($p = 0.03$), and use of adalimumab in a secondary non-responder to infliximab ($p = 0.02$). Controlling for steroid use, the improvement in growth velocity was still present suggesting the effect of adalimumab is independent of a steroid sparing effect.

Finally, a prospective single-center open-label study in patients with moderate to severe CD who failed prior immunomodulator therapy was published evaluating the effect of adalimumab on bone metabolism utilizing in vivo and in vitro systems [58]. This study analyzed healthy patients and patients with CD on adalimumab. A variety of markers of bone health were measured, including parathyroid hormone, vitamin d, bone formation serum markers, inflammatory and anti-inflammatory cytokines, as well as osteoprotegerin and sRANKL. In the in vitro studies, patient serum was plated onto osteoblast cells obtained from human fetal tissue and monitored for viability as well as hormone production. Bone mineral density was measured with DEXA scans. This study demonstrated that adalimumab use was associated with a significant increase in osteocalcin ($p < 0.05$) and procollagen type 1 N terminal propeptide ($p < 0.01$) after 1 and 3 months of therapy. Adalimumab also resulted in a numeric although not statistically significant drop in a bone resorption marker (C-telopeptide of type 1 collagen). Serum from patients who had been treated with adalimumab showed increased osteoblast differentiation compared to controls ($p = 0.001$) which the authors suggest is a sign of new bone growth.

Quality of Life

Quality of life in pediatric IBD has been evaluated as a secondary endpoint in certain randomized controlled trials for anti-TNFα therapy. In the IMAGINE 2 trial evaluating the use of adalimumab in pediatric CD health-related quality of life was assessed using the IMPACT III questionnaire [9]. At enrollment in the trial, the mean IMPACT III score was 116.9 indicating substantial impairment in quality of life. At week 52 IMPACT III scores were significantly improved with sustained improvements through week 240 ($p = 0.001$).

While there are somewhat limited data on quality-of-life metrics in the setting of anti-TNFα therapy (other than infliximab) among pediatric patients, there are additional studies published in this field in adults with IBD [59]. The InspirADA study was a multicenter prospective study evaluating the effect of adalimumab on quality-of-life measures in patients with moderate to severe UC. Quality of life was assessed using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and European Quality of Life 5 Dimensions 5 Level (EQ5D5L) questionnaire. In this study, treatment with adalimumab resulted in improvement in work productivity (11% absolute decrease in absenteeism, 25% absolute decrease in impairment while working) and improvement in ability to perform daily activities (27% decrease in impairment of ability to perform daily activities). In addition, this study looked at medical costs (all cause and IBD specific) and found that both general medical costs and UC-specific medical costs were significantly reduced by 59% ($p < 0.001$) and 77% ($p < 0.001$), respectively, when comparing costs 6 months prior to initiation of adalimumab to costs 6 months after initiation of adalimumab.

In addition, utilizing data from the CHARM study, a phase III randomized, double-blind trial of patients with moderate to severe CD treated with adalimumab, health-related quality-of-life outcomes were compared between the treatment groups (adalimumab maintenance weekly, adalimumab maintenance every other week, and adalimumab induction only) [60]. This study utilized the Zung Self-Rating Depression Scale, the Function Assessment of Chronic Illness Therapy (FACIT) Fatigue Score, visual analog pain scales, the IBDQ, and the SF-36. Compared to patients who received the placebo after induction (no maintenance adalimumab), patients treated with maintenance adalimumab reported less depression ($p < 0.01$), less fatigue ($p < 0.001$), improved IBDQ scores (<0.05), and greater SF-36 scores ($p < 0.05$) at week 12 and through week 56.

In a sub-analysis of the PRECiSE 2 cohort, patients receiving continuous certolizumab therapy compared with those in the placebo group had improved Inflammatory Bowel Disease Questionnaire (IBDQ) scores (60% vs. 43%, $p < 0.001$), significantly higher Short Form 36 (SF-36) scores (60% vs. 43%, $p < 0.001$) and improved mental health (44% vs. 32%, $p = 0.016$) responses [61]. In this same analysis, treatment with certolizumab was associated with a greater gain in quality adjusted life years than placebo ($p = 0.001$). Moreover, after 26 weeks of therapy with certolizumab 21% of patients compared to 13% of those in the placebo group reported living a normal life ($p = 0.019$) [61, 62]. Improvements in work productivity, success in school and employment status were seen after induction and maintenance with certolizumab pegol [62]. These improvements in productivity, ability to perform daily activities, and increased health related quality of life were also demonstrated in patients who were treated with certolizumab pegol who previously lost response or could not tolerate infliximab [62, 63].

Postoperative Prophylaxis

In patients with CD who undergo a "curative" surgical resection of inflamed or strictured bowel a decision must be made as to whether to start a biologic in the postoperative period to prevent recurrence of disease. In 2017, NASPHGHAN released a clinical report on postoperative recurrence of CD, suggesting that a decision to initiate postoperative prophylactic treatment should be made individually, weighing the risk of disease recurrence with the overall goal of avoiding any unnecessary immunosuppression. This report noted that of all medication classes, TNFα inhibitors have the best efficacy in preventing disease recurrence, concluding that based on adult studies, postoperative prophylaxis should be considered in pediatric patients with moderate to high risk of recurrence.

There are few studies evaluating the effectiveness of postoperative prophylactic treatment in children with CD. One is a retrospective cohort study of 122 children looking at postoperative prophylaxis (mesalamine, thiopurines, methotrexate, or TNFα inhibitors) within 30 days [64]. The study unfortunately did not break down the results by class of drug or specific agent; however, it concluded that immediate postoperative therapy with any of the above agents reduced the risk of both clinical (HR 0.3, 95%CI 0.1–0.6, $p = 0.001$) and surgical (HR 0.5, 95%CI 0.1–0.9, p = 0.035) recurrence.

Data from the adult IBD literature can again be used to extrapolate in the pediatric population given the limited literature available. In a randomized controlled trial of 51 adult patients, postoperative prophylaxis with adalimumab was compared to azathioprine or mesalamine [65]. In this study, the rate of endoscopic recurrence was significantly lower in the adalimumab treated group (6.3%) compared with the azathioprine (64.7%, OR 0.036, 95%CI 0.004–0.347) and mesalamine (83.3%, OR 0.013, 95%CI 0.001–0.143) groups. In addition, significantly fewer patients had clinical recurrence in the adalimumab group (12.5%) compared with the azathioprine group (64.7%, OR 0.078, 95%CI 0.013–0.464) and mesalamine group (50%, OR 0.143, 95%CI 0.025–0.819). Finally, a multicenter prospective observational study evaluated the effectiveness of adalimumab in preventing postoperative recurrence in 29 adult CD patients [66]. All of the patients in this study had undergone an ileal or ileocolonic resection and were defined as high risk for recurrence based on having 2 or more of the following characteristics: smoking, penetrating disease, or a prior resection. Subcutaneous adalimumab (160 mg/80 mg and then 40 mg thereafter) was administered 2 weeks after surgery. In this study, despite adalimumab therapy, 13.7% developed clinical recurrence and 20.7% had endoscopic recurrence.

There are no studies specifically focused on the use of certolizumab pegol or golimumab as an agent for postoperative prophylaxis; however, future studies may elucidate their role in preventing CD recurrence.

Optimizing the Use of Adalimumab, Certolizumab Pegol, and Golimumab

Treat to Target

The conventional approach to treatment of IBD has focused on improving symptoms and escalating therapeutic interventions based on progression of clinical disease. However, it has become increasingly clear that treatment strategies aimed purely at controlling symptoms are failing to improve the overall trajectory of the disease and prevent long-term com-

plications. More recently a treat-to-target approach has been widely adopted by the IBD community, in which the focus has shifted to understanding additional goals of therapy, including endoscopic remission and using biomarkers to guide therapies. Interestingly, this treat-to-target approach is not unique to IBD and has been described in numerous chronic conditions including rheumatoid arthritis and diabetes.

The "Selecting Therapeutic Targets in Inflammatory Bowel Disease" (STRIDE) group released an expert consensus on the best strategies for a treat–to-target approach in patients with UC and CD [67]. Within these recommendations, the primary goal was to achieve both clinical/patient reported remission and endoscopic remission. Clinical or patient reported remission was defined as a resolution of symptoms and endoscopic remission was defined as a Mayo score of 0–1 in patients with UC and resolution of ulceration on ileoscopy/colonoscopy or resolution of inflammatory findings on cross-sectional imaging in CD. This committee recommended that clinical remission should be assessed every 3 months in patients with active UC and every 6 months in those with active CD. Other targets, including histologic remission on pathology and biomarker remission, such as calprotectin or C-reactive protein, were not recommended due to lack of evidence. The STRIDE recommendations were supported by evidence suggesting that patients who used a treat-to-target approach had improved clinical disease activity scores, fewer surgeries, fewer hospitalizations, and faster steroid tapering [67, 68].

The majority of the data supporting the use of a treat-to-target approach come from retrospective studies, few of which include pediatric patients. In a study of 67 adults with active CD, mucosal healing was associated with early endoscopic evaluation after initiation of therapy (defined in this study as within 26 weeks of initiation of treatment) (HR 2.35, 95%CI 1.15–4.97, $p = 0.019$) and adjustment of medical therapy (adding a medication or switching to a different medication) if mucosal healing was not observed on the endoscopy (HR: 4.28, 95%CI 1.9–11.5, $p = 0.003$) [69]. In this study of the 72 adjustments made in therapy, 12.5% were done in the absence of clinical symptoms. A similar retrospective study was performed in adults with UC where 60 patients were evaluated for endoscopic and histologic healing as a means to guide therapy [70]. Only patients who had a minimum of two endoscopic evaluations performed during the study period were included. At the time of each endoscopy, the chart was reviewed for endoscopic and histologic findings as well as any adjustments in medical therapy as a result of the endoscopy (within 3–6 months of the procedure). In patients with active disease on endoscopy regardless of symptoms, subsequent mucosal healing on the next endoscopy was associated with an adjustment in the medical therapy (HR 9.8, 95%CI 3.6–34.5, $p < 0.0001$) as was histologic healing (HR 9.2, 95%CI 3.4–31.9, $p < 0.001$). In this study 51 adjustments to the medical regimen were made, 15.6% of which were done in the absence of symptoms.

While these data certainly support a clinical benefit with repeated endoscopic evaluation, this practice is costly and not always practical. Therefore, researchers have looked to serum and stool biomarkers as a way to frequently and non-invasively evaluate the degree of inflammation and subsequently use this information to guide management decisions. In the CALM study, an open-label randomized controlled phase 3 trial, adults with active CD (Crohn Disease Endoscopic Score >6) and no prior biologic use were randomized into two groups: tight clinical control using biomarkers or standard clinical management [71]. In both groups, treatment was escalated in a stepwise manner, from no biologic to adalimumab induction with maintenance injections every other week, then further escalated to weekly if necessary, with or without the addition of azathioprine. In the tight control group, treatment escalation occurred for a C-reactive protein ≥5, fecal calprotectin ≥250, CDAI ≥150, or any prednisone use in the prior week. In the standard management group, treatment escalation occurred based on symptoms (using changes in CDAI score as a marker) as well as any prednisone use in the prior week. The primary endpoint in this study was mucosal healing (CDEIS <4) at endoscopy at 48 weeks. Of the 244 patients enrolled in this study, a significantly higher number achieved mucosal healing at week 48 in the tight control group (46%) compared to the standard management group (30%), $p = 0.01$. This study demonstrated that timely dose escalation with adalimumab on the basis of biomarkers and not just clinical symptoms results in improved clinical and endoscopic outcomes.

Combination Therapy

The landmark SONIC trial was the first major publication to demonstrate that combination therapy with infliximab and azathioprine was superior to infliximab alone [72]. After this paper, subsequent studies designed to understand what the mechanism of this effect was and whether it can be extended to other anti-TNFα therapies were published. While some of these data have been published in the pediatric literature, much of it focuses on adults with IBD.

To date, only one randomized controlled trial has been published evaluating the use of combination therapy vs. monotherapy in pediatric patients with IBD; however, this study was in patients treated with infliximab. A post hoc analysis of IMAGINE 1 was presented at Digestive Disease Week (DDW) in 2014 and demonstrated that remission and response rates were similar among those treated with adali-

mumab plus an immunomodulator and adalimumab alone over 26 weeks [73]. A few retrospective studies have been published evaluating the use of combination therapy with adalimumab in pediatric patients; however, the results are quite variable. In one case series from Britain, including 72 children with IBD from 19 different pediatric centers, clinical remission (defined with the PCDAI) was seen in 61% of patients [74]. Remission rates in this study were higher in those on concomitant immunomodulators (74% vs. 37%, $p = 0.003$). Conversely, a retrospective observational study of 78 CD patients treated with either infliximab or adalimumab concluded that there was no change in outcomes when comparing use of concomitant immunomodulators and anti-TNFα therapy vs. anti-TNFα monotherapy [75].

In adults with IBD, the literature on the efficacy of combination vs. monotherapy with adalimumab has also demonstrated significant variability. One study evaluated the effect of concomitant immunomodulators on the pharmacokinetics, efficacy, and safety of adalimumab in patients included in the major randomized, placebo-controlled trials (CLASSIC-1, GAIN, CHARM, EXTEND, ULTRA 1, and ULTRA 2) [76]. A total of 1382 patients with CD and 754 patients with UC were included. None of the trials had a significant difference comparing those on adalimumab monotherapy and those on combination therapy for induction of clinical remission (CLASSIC-1: p = 0.700, GAIN: $p = 0.862$, CHARM weekly $p = 0.233$, CHARM every other week $p = 0.670$, EXTEND: $p = 0.228$). Similarly, an open-label prospective study was performed evaluating the efficacy of adalimumab with azathioprine compared to adalimumab alone among adults with CD who were biologic naïve. In this study, the clinical efficacy of combination therapy (adalimumab plus azathioprine) was not significantly different at week 26 compared to monotherapy [77]. In a retrospective observational study, including 123 adult patients, a greater rate of clinical remission was seen at week 12 in those who were treated with a concomitant immunomodulator (81%) compared to those on monotherapy (60%), $p = 0.0001$ [78]. Multivariate analysis suggested that therapeutic 6TGN levels were a strong predictor of induction response (OR 4.3, $p = 0.01$). Another retrospective study evaluating thiopurine use in adalimumab induction and maintenance demonstrated that thiopurines dosed to therapeutic 6TGN levels were significantly more likely to be associated with CD remission than subtherapeutic doses ($p = 0.004$) when used in combination therapy [79]. Given concerns of increased side effects with combination therapy compared to monotherapy (specifically concern for increased lymphoma risk), if combination therapy is used, the goal should be to taper off the immunomodulator once clinical remission is induced and the patient is stable on the TNF inhibitor to reduce the risk of complications [80].

Therapeutic Drug Monitoring

Proactive monitoring of serum drug and antibody levels in order to optimize drug dosing is an area of great interest given the relatively high rates of loss of response to anti-TNFα agents in patients with IBD. To date, the use of therapeutic drug monitoring and the impact of anti-drug antibodies have been most extensively studied in patients on infliximab and adalimumab; however, a few studies have been published looking at these relationships in patients on certolizumab and golimumab. Therapeutic drug monitoring is covered extensively in a separate chapter in this book.

Comparative Effectiveness

Once a decision is made start a biologic it remains unclear how to choose among the anti-TNFα agents. There are certain considerations that may lead to choosing one medication over the other in terms of ease of administration, need for concurrent immunomodulator, or potential pregnancy. There are no head-to-head trials comparing anti-TNFα agents at this time. While the TNFα inhibitors have the most data available, newer biologics have emerged, including vedolizumab and ustekinumab, adding to the difficulty of selecting a first line agent. Certainly, the clinical context in which the biologic is being prescribed may impact the choice of agent, as infliximab is the only biologic studied in hospitalized patients.

Given the very limited head-to-head comparisons of biologic therapy, the majority of the comparative effectiveness data come from large, retrospective analyses and meta-analyses. In a meta-analysis from 2016, 3205 biologic naïve patients with CD were identified and included for analysis [81]. The primary outcomes were all cause and CD-related hospitalization, abdominal surgery, steroid use, and serious infections. This study suggested that infliximab was superior to adalimumab and certolizumab pegol for all outcomes studied. In 2018, the same research group published a network meta-analysis evaluating the comparative effectiveness of various biologics in adults with CD [82]. Ranking was assessed using surface under the cumulative ranking (SUCRA) probabilities. In this study infliximab (SUCRA 0.93) and adalimumab (SUCRA 0.75) were ranked highest for induction of clinical remission among patients who were biologic naïve. In patients with prior anti-TNF exposure, adalimumab (SUCRA 0.91) and ustekinumab (SUCRA 0.71) were ranked highest for induction of clinical response, although with a low quality of evidence. Finally, among patients who had a response to induction, infliximab (SUCRA 0.68) and adalimumab (SUCRA 0.97) were the highest ranked for maintenance of remission. Interestingly, in a sepa-

rate systematic review with network meta-analysis evaluating the effectiveness of various biologics for the treatment of adults with UC, infliximab (SUCRA 0.85) and vedolizumab (SUCRA 0.82) were the highest ranking for induction of clinical remission and mucosal healing in biologic naïve patients [83]. Looking at mucosal healing as an endpoint of various biologics, a subsequent systematic review with meta-analysis compared data from 12 randomized controlled trials [84]. This study demonstrated that anti-TNFα therapy (infliximab or adalimumab) was superior to placebo for maintenance of mucosal healing (28% vs. 1%, OR 19.71, 95%CI 3.51–110.84) in patients with CD. Similar results were found in patients with UC; anti-integrins and anti-TNFs (adalimumab and infliximab) were more effective than placebo at inducing (45% vs. 30% and maintaining mucosal healing (33% vs. 18%) compared to placebo. In the network analysis, adalimumab therapy was found to be inferior to infliximab use (OR 0.45, 95%CI 0.25–0.82) for inducing mucosal healing in adults with UC. This study concluded that infliximab and adalimumab had similar efficacy in CD for induction of mucosal healing while both infliximab and anti-integrin agents are similarly effective in UC and superior to adalimumab.

Finally, in the first head-to-head trial comparing two biologics, the VARISTY trial evaluated the use of adalimumab and vedolizumab for the treatment of moderate to severe UC [85]. In this double-blind, double-dummy, randomized study conducted at 245 centers in 34 countries, 769 patients were randomized to vedolizumab or adalimumab. At 52 weeks clinical remission (31.3% vs. 22.5%, $P = 0.006$) and endoscopic improvement (39.7% vs. 27.7%, $P < 0.001$) were significantly higher in patients treated with vedolizumab.

Safety Data

When infliximab was approved it was on the leading edge of a new class of medications, biologics, and as such there was significant concern from patients and providers over the safety of this unknown class of drugs and specifically the risk with blocking tumor necrosis factor α signaling. With time it has become clear that anti-TNFα therapy is safe and tumor necrosis factor α is not critical to tumor surveillance. Studies, however, continue to show persistent concerns from patients when adopting this therapy [86].

General adverse events will be reviewed here and certain serious adverse events will be reviewed more in detail in specific sections. In the IMAGINE I trial of adalimumab induction in pediatric patients, the most common adverse events reported included non-serious infectious events and injection site reactions [7]. In the open-label induction period, 101 (52.6%) patients reported treatment-related adverse events, including two serious infections (one Yersinia infection and one viral infection, both of which resolved without significant morbidity or mortality). Adverse events reported during the double-blind maintenance period were very similar in terms of number and type comparing the low-dose to high-dose adalimumab groups. More rare events included opportunistic infections (such as tuberculosis), allergic reactions, hepatic- and hematologic-related adverse events, as well as malignancy. No deaths were reported. The IMAGINE 2 trial had a similar rate of adverse events with the most common being headache and nasopharyngitis [9]. A systematic review of 664 patients exposed to adalimumab reported adverse events in 49% of patients, including headache, abdominal pain, and rash [10].

While there are no data on the safety of certolizumab in pediatric patients the PRECiSE studies included follow-up to 7 years for reporting of adverse events [37]. Over 7 years of treatment with certolizumab 88.2% of patients experienced one or more adverse events, including worsening of the patient's underlying CD and infectious complications, such as nasopharyngitis and urinary tract infections. In this trial the majority of adverse events (71.8%) were considered "unrelated" to the study drug.

In a multicenter open-label study of 33 pediatric patients exposed to golimumab, 94.3% reported one or more adverse events through 14 weeks of follow-up [41]. The most common adverse events with golimumab were worsening UC symptoms (37%), abdominal pain (26%), and headache (26%). In the PURSUIT PEDS PK Long-Term Results study, pediatric patients with IBD treated with golimumab were observed for the development of any adverse events over 126 weeks [43]. Among patients in this study, 95% reported one or more adverse events, including worsening of underlying disease, headache, abdominal pain, and upper respiratory tract infections.

Malignancy

TNFα was originally discovered in 1975 by a tumor immunologist who was seeking a serum factor which led to tumor necrosis in response to an antigen challenge with endotoxin [87]. Despite its origin of discovery, its role in the immune surveillance of tumors is believed to be less significant and studies have demonstrated little risk for the development or recurrence of malignancy. A large population-based study demonstrated that children with IBD (regardless of treatment regimen) had a three-fold increase in mortality risk secondary to a malignancy (HR of 6.6 95%CI 5.3–8.2) [1]. These cancers included colorectal carcinoma, cholangiocarcinoma as well as lymphoma. To understand if the increase in malignancy was secondary to therapy, especially anti-TNFα, there

have been a number of prospective and retrospective studies. Here we will focus on the relationship between anti-TNFα therapies (other than infliximab) and malignancy risk.

The majority of the data on risk of malignancy with TNFα inhibitor use are related to adalimumab exposure. A Swedish group evaluated outcomes in 9405 pediatric IBD patients and did not find an association between cancer risk and drug exposure, including anti-TNFα [1, 88]. A systematic review to understand the risk of malignancy in IBD patients included 65 publications with a total of 5528 patients and 9516 patient-years of follow-up in the final analysis [89]. Among the patients included in this study, the majority had CD (84%) and were treated with infliximab while 10% of the patients included were treated with adalimumab. Two patients developed lymphoma both of whom were previously treated with infliximab. This study concluded that the risk of lymphoma was similar to that in children with IBD treated with non-anti-TNFα therapies and similar to the rate seen in the adult IBD population. A second systematic review looking specifically at patients exposed to adalimumab included 14 studies and a total of 664 patients [10]. In this study there was a single case of medulloblastoma identified; however, no cases of lymphoma were reported. In the IMAGINE I trial and the IMAGINE II trial there were no reported malignancies (including solid tumors and lymphomas) in follow-up [7, 9].

While there are no data on the development of malignancy in pediatric patients on certolizumab, the PRECiSE studies included seven-year follow-up to monitor for malignancy [37]. The rate of malignancy in the PRECISE studies was 0.84 cases/100 patient-years. A total of 20 malignancies were reported the most common of which was basal cell carcinoma. No cases of lymphoma were reported. The studies of golimumab exposure in children are short term, though the PURSUIT PEDS PK study observed patients through 126 weeks with no reported malignancies [43].

The development of hepatosplenic T cell lymphoma which is a devastating and often fatal outcome in pediatric IBD was initially found to be associated with infliximab and led to a large level of concern [1, 90, 91]. It was subsequently determined though that this fatal lymphoma was associated with combination use of infliximab and an immunomodulator (azathioprine or 6 mercaptopurine) and not anti-TNFα use alone [1, 90, 91].

Infection

Studies on the risk of infection using adalimumab are the most common. Two large systematic reviews have been published evaluating the risk of infection in pediatric IBD treated with TNFα inhibitors. One systematic review previously discussed included 65 publications with a total of 5528 patients and 9516 patient-years of follow-up in the final analysis [89]. Among patients treated with adalimumab 5.4% developed a serious infection requiring termination of the drug which was similar to the rate seen in patients treated with infliximab. Seven deaths were reported in this study two of which were while on adalimumab therapy. Both of these deaths resulted from a central line infection while on total parenteral nutrition. The rate of serious infection was lower in children treated with anti-TNFα therapy compared to pediatric patients on corticosteroids as well as adults on TNFα inhibitors. In the IMAGINE I trial, eight serious infections were observed including two opportunistic infections (one non-serious aeromonas infection and disseminated histoplasmosis infection) [7]. In the IMAGINE 2 trial non-serious opportunistic infections, including oral candidiasis ($n = 7$), aeromonas infection ($n = 1$), fungal esophagitis ($n = 1$), and esophageal candidiasis ($n = 1$), were seen. One case of disseminated histoplasmosis was seen and no active tuberculosis cases were reported [9].

While there are no data on the safety of certolizumab in pediatric patients, the PRECISE studies again provide insight into potential infectious complications [37]. In the PRECISE studies nasopharyngitis was the most reported infectious complication in 15.3% of patients. Patients treated with concomitant corticosteroids were more likely to have a serious infection compared to those on TNFα therapy without steroids. Three cases of disseminated tuberculosis were reported (0.5%).

In a multicenter open-label study of 33 pediatric patients with UC treated with golimumab, 94.3% reported one or more adverse events through there were no serious infections [41]. Similarly, in a small case series evaluating the use of golimumab in 6 children with CD, no serious infections were reported [44]. In the PURSUIT PEDS PK Long-Term Results study of golimumab, upper respiratory tract infections were among the most common adverse event reported (25% of patients) and only 1 patient experienced a serious infection [43].

Postoperative Infections

With the introduction of biologics and their use in hospitalized patients with severe IBD came concerns over the safety of these agents in the perioperative period. To date, the majority of the literature in this field comes from adult patients treated with infliximab, though a few studies did include adalimumab or other biologics in their data. In a meta-analysis of 22 observational studies evaluating postoperative complications, including infections, were evaluated in 4251 patients who received perioperative biologics [92].

The pooled prevalence of infectious postoperative complications was 16% and 17% in CD and UC, respectively. In this study, the prevalence of infectious complications was slightly increased in patients who received perioperative TNFα inhibitor use (OR 1.45, 95%CI 1.03–2.05). Conversely, numerous studies have suggested that perioperative infliximab, adalimumab, and certolizumab pegol do not increase postoperative infectious complications. In an analysis of a national database of 2068 IBD patients, the incidence of postoperative complications after perioperative exposure to anti-TNFα (infliximab, adalimumab, and certolizumab) was no different from patients who were not exposed (33.3% vs. 37.1%, $p = 0.7969$) [93]. In a case matched retrospective observational study of 123 adult patients with CD, the effect of adalimumab on postoperative complications was again analyzed and did not demonstrate a difference in overall surgical complications (36% vs. 12%, $p = 0.095$) [94].

Novel Viral Infections

Today, in the setting of the recent Coronavirus (COVID-19) pandemic, new concerns have surfaced regarding the safety of TNF inhibitors and specifically the impact that systemic immunosuppression may have on susceptibility to COVID-19 and severity of disease course. Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) is the largest cohort to date evaluating outcomes of patients with IBD and confirmed COVID-19 [95]. 294 pediatric patients were included in this dataset (ages 19 and under) which suggests that patients on TNFα inhibitor monotherapy are at no increased risk of becoming infected with COVID-19 or having a worse outcome if infected (hospitalization, intubation, or death).

Immune Reactions (TNFα-Induced Psoriasis, Drug-Induced Lupus, Auto-Immune Hepatitis)

Biologics targeting TNFα, including infliximab, adalimumab, certolizumab, and golimumab, have been associated with paradoxical inflammatory reactions, including psoriasis, drug-induced lupus, and auto-immune hepatitis (AIH). The histopathology of TNFα-induced psoriasis is not well understood; however, it is thought to involve a spectrum of cutaneous pathology, including psoriasis, like inflammatory patterns, eosinophilic hypersensitivity reactions, or sterile pustular folliculitis [96]. TNFα-induced psoriasis is thought to affect roughly 1.6%–2.7% of IBD patients. Currently, infliximab is thought to be the most common TNFα inhibitor to cause psoriasis; however, this paradoxical reaction has been documented in patients on adalimumab, certolizumab, and golimumab. In a prospective Spanish cohort of IBD patients treated with infliximab and adalimumab patients were monitored and the development of psoriasis [97]. In this study of 7415 patients, 1.7% of patients developed TNFα-induced psoriasis with an incidence rate of 0.5% per patient-year. In a multivariate analysis, female sex (HR 1.9, 95%CI 1.3–2.9) and being an active or former smoker (HR 2.1, 95%CI 1.4–3.3) were associated with increased risk of psoriasis. In this study, topical steroids were effective in the majority of patients (78%) for treatment. Interestingly, among patients who switched to another TNFα inhibitor, 60% had recurrence of psoriasis with a different agent, and 37% required switching to a different biologic class. For psoriasis refractory to topical steroids, switching to ustekinumab can help treat the skin disease as well as the underlying IBD [98].

Anti-TNFα-induced lupus is poorly understood and continues to be a diagnostic and therapeutic challenge for physicians. The majority of cases of TNFα inhibitor-induced lupus have been reported secondary to infliximab use; however, adalimumab and other TNFα inhibitors, including etanercept have been associated with this rare paradoxical side effect. Symptoms of drug-induced lupus can range from mild cutaneous lesions to more serious coagulopathies, including deep venous thrombosis as well as pleural or pericardial effusions. Differentiating between primary systemic lupus erythematosus and TNFα inhibitor-induced lupus is usually based on timing of symptoms in relation to TNFα initiation and the development of serum markers, such as anti-histone antibodies (although this can be seen in de novo cases of lupus as well as in drug-induced lupus) [99]. The pathogenesis of anti-TNFα-induced lupus is not well understood, however several mechanisms have been proposed, including a possible "cytokine shift," from Th1 cytokine to Th2 cytokines, leading to the production of autoantibodies. Other suggested mechanisms include a reduction in apoptosis from decreased CD44 expression, impairing the ability of the body to clear nuclear debris and promoting autoantibody production against nuclear antigens and possible inhibition of cytotoxic T cells which regulate auto-antibody producing B cells [99]. While there are little data on the incidence of adalimumab-induced lupus in patients with IBD, a post-marketing surveillance study in patients with rheumatoid arthritis demonstrated that this adverse event is very rare, with four cases reported after 4870 patient-years of adalimumab exposure [100]. In this study, the majority of cases reported cutaneous lesions, photosensitivity, and serositis; however, no significant internal organ involvement was documented.

Auto-immune hepatitis has been reported as a complication of biologic use, specifically with TNFα inhibitors. AIH is a chronic inflammatory condition that can unfortunately progress into end stage liver disease. Numerous medications have been associated with the development of AIH, most recently biologics, including infliximab and adalimumab.

Adalimumab-induced AIH was first described in 2010 in a patient being treated for psoriatic arthritis [101]. The majority of the literature on adalimumab-induced AIH stems from case reports in adults with various inflammatory conditions. The first two reports of adalimumab-induced AIH were in women in their 40s who did not have any underlying liver pathology prior to initiating adalimumab [102]. In both of these women, symptoms of AIH started within months of initiation of the adalimumab and both had liver biopsies consistent with a diagnosis of AIH. In a retrospective cohort study of 659 pediatric patients with IBD, an index case of AIH secondary to infliximab use was identified [103]. This patient developed abnormal liver enzymes and features of AIH 23 weeks after initiating infliximab. There are no data on the incidence of adalimumab-induced AIH in pediatric patients with IBD.

Biosimilars

Biosimilars are biologic therapies that are very similar to the previously approved reference or originator biologic drug in terms of efficacy, makeup, and safety. As drugs, such as adalimumab, come off of patent, biosimilars are increasingly being used worldwide as alternative therapies to reduce treatment cost [104]. To date, six biosimilars have been approved in the US for the treatment of adult IBD. Three of these approved medications are biosimilars to the originator adalimumab. Of note, there are very limited data on the use of these drugs in pediatric patients with IBD although utilization rates are increasing. While these agents are rather new in the United States, biosimilars have been approved for use in Europe and Canada for over a decade. Biosimilars undergo different testing and have different regulatory requirements as compared to their originator drug [105]. All biosimilars undergo extensive structural and functional analyses to confirm that the biosimilar has a high degree of similarity to the originator drug. Animal studies are also conducted to demonstrate pharmacokinetics, immunogenicity and toxicity. Finally, the biosimilar must be evaluated in at least one clinical study to demonstrate similar efficacy and safety as compared to the originator drug. Of note, some regulatory agencies, including the U.S Food and Drug Association (FDA), reserve the right to waive the requirement of a clinical study [105]. Once a biosimilar is approved for a single indication, it is subsequently approved for the other indications of the originator drug without further studies [106, 107]. One of the first position papers on the use of biosimilars in patients with pediatric IBD is from the Porto IBD working group of ESPGHAN in 2015 [106, 108]. With very limited data on the use of these novel agents in pediatric IBD, the group concluded that extrapolation to children with IBD should be done with caution. This group pointed to the fact that all of the studies were done in adults and that the dosing can be different from the originator drugs to argue against the generalized acceptance of biosimilars for pediatric patients [106].

Two major areas for research in biosimilars is the efficacy, safety and comparability of these drugs to their originators and the interchangeability of these drugs with the originators. The early studies on biosimilars in pediatric patients all focus on infliximab and its biosimilars; no similar studies have been published with adalimumab. However, these early studies suggested that the biosimilars did in fact have similar efficacy compared to infliximab and patients were able to maintain clinical remission despite changing from infliximab to the biosimilar [106, 109–111]. Perhaps similar data will be published in the near future evaluating adalimumab biosimilars in pediatric IBD patients. In adults a phase I randomized trial of safety, pharmacokinetics and immunogenicity were conducted comparing the adalimumab biosimilar BI 695501 to the originator (VOLTAIRE-PK) [112]. In this trial there were no differences in any outcomes between BI 695501 and adalimumab in healthy adults. ABP-501 and SB5, two other adalimumab biosimilars, showed no immunogenicity concerns in healthy adults and were comparative to adalimumab in efficacy in patients with plaque psoriasis in double-blind placebo-controlled trials [106, 113, 114].

Looking forward, there are over ten new adalimumab biosimilars awaiting approval from the FDA. Moreover, the patent on certolizumab is set to expire in Europe in 2021 and in the US in 2024. Biosimilars to certolizumab are already being investigated and likely will be approved in the future. Likewise, the patent on golimumab is set to expire globally in 2024 and numerous biosimilars have been described in the literature that are awaiting future use.

Future Directions

While novel biologic targets and new small molecule therapies have been studied and brought to the market, the cornerstone of IBD therapy in the past decade has certainly focused on biologics targeting TNFα. Although infliximab is the most commonly used drug in this category, adalimumab, certolizumab, and golimumab have been used in the treatment of moderate to severe CD and UC. To date, adalimumab is the only one of these agents approved specifically for the treatment of pediatric IBD; looking forward, randomized controlled trials evaluating the efficacy and safety of these agents in children with CD and UC will help elucidate their role in the treatment algorithm.

Novel biologics targeting TNFα are also in the pipeline including oral antibody formulations, which could certainly change the landscape of IBD therapy going forward. AVX-470 is an orally administered bovine polyclonal antibody against TNFα that is being studied in adults with UC. V565

is an engineered Vorabody which is resistant to proteases and facilitates delivery to the intestine with the hope of reducing systemic absorption. There is currently an ongoing an international phase II trial looking at the efficacy of this agent in the treatment of CD. In addition to traditional methods for delivering anti-TNFα therapy a Belgium-based biopharmaceutical company has reported positive results from a Phase I trial of AG014, a strain of genetically modified Lactococcus lactis bacteria that is being studied for oral administration of certolizumab directly to the gastrointestinal tract.

It is likely that anti-TNFα therapy will continue to be a mainstay in the treatment of IBD for years to come. As more is understood about the specific mechanisms that underlie this therapy and innovations are made to deliver these therapies in a safe and cost-effective manner, it is likely we will continue to see new products pushing the limits of what this class of therapies can do for patients with IBD.

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Therapeutic Drug Monitoring in Pediatric Inflammatory Bowel Disease

33

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Introduction

A key management strategy in the care of IBD patients includes maximizing the efficacy of IBD medications while minimizing their toxicity. The recognition of factors leading to a therapeutic response and remission allows for individualized dosing regimens to meet these goals. Standard dosing of immunomodulator and anti-TNF therapy is often insufficient giving inter-patient variability with regard to response and tolerability. Therapeutic drug monitoring (TDM) is a concept worth understanding in order to optimize drug efficacy with the goal of achieving a sustained and durable remission. The concept of dose optimization initially started over a decade ago with the use of thiopurines and is now utilized in anti-TNF therapies. With the additional classes of biologics introduced in the past several years, including antibodies to alpha4beta7 integrin and IL12/IL23, the use of TDM may broaden to these classes of medications, although sparse supporting data exist currently. Given the limited approved medications available for young patients with IBD and the need for durable treatment strategies, TDM can be an invaluable tool to guide treatment decisions. This chapter will review the historical and current utilization of TDM, as well as the accompanying challenges, in treating pediatric patients with IBD.

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Thiopurine Monitoring

TPMT and thiopurine metabolite levels are used in current clinical practice to manage IBD patients receiving thiopurines, including 6-mercaptopurine (6-MP) and azathioprine (AZA). 6-MP and its prodrug, AZA, undergo intestinal and hepatic metabolism by numerous enzymes, including hypoxanthine phosphoribosyltransferase (HPRT), TPMT, xanthine oxidase (XO), and inosine monophosphate dehydrogenase (IMPDH), to produce the active metabolites, 6-thioguanine nucleotides (6-TGNs), and 6-methylmercaptopurine ribonucleotides (6-MMPs) [1] (Fig. 33.1). Through the study of these enzymes and metabolites, the mechanisms of drug efficacy and toxicity have been well described [2].

Prior to initiating a thiopurine, obtaining a TPMT level is considered standard practice, as this determines the starting dose for an individual patient. For the majority (89%) of patients with a normal TPMT level, standard initial dosing is 2.5 mg/kg/day of AZA or 1.5 mg/kg/day of 6-MP. For the 10% of patients who are heterozygote for the TPMT gene, known as intermediate metabolizers, the clinician should prescribe half the standard dose to minimize high 6-TGN levels and the associated risks, including leukopenia. In patients who are homozygote for the TPMT gene (1 in 300), thiopurines are contraindicated given the risk of life-threatening leukopenia [3]. TPMT guided dosing avoids sub-therapeutic use, as knowledge of TPMT activity identifies the variability in metabolism, improving clinician confidence in dosing selection.

TPMT levels drive initial dosing, yet 6-TGN and 6-MMP metabolites influence the subsequent efficacy and safety. Cuffari et al. showed in 1996 that higher 6-TGN metabolite concentrations correlate with clinical remission in pediatric Crohn disease (CD) patients [4]. Subsequent pediatric studies demonstrated that the therapeutic response doubled in patients whose 6-TGN levels were >235 pmol/8 × 10(8) RBC (78% vs. 41%, $p < 0.001$) [5]. The odds of responding to thiopurines was 5 times higher in patients with 6-TGN

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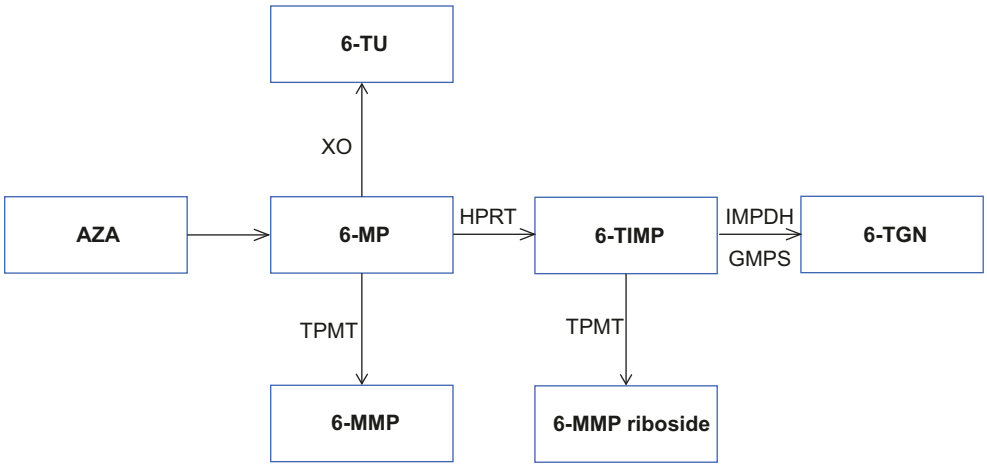

Fig. 33.1 Azathioprine/6-mercaptopurine metabolism pathways. *AZA* Azathioprine, *GMPS* Guanosine monophosphate synthetase, *HPRT* Hypoxanthine phosphoribosyltransferase, *IMPDH* Inosine monophosphate dehydrogenase, *6-MMP* 6-Methylmercaptopurine, *6-MP* 6-Mercaptopurine, *6-TG* 6-Thioguanine, *6-TIMP* 6-Thioinosine monophosphate, *TPMT* Thiopurine *S*-methyltransferase, *6-TU* 6-Thiouric acid, *XO* Xanthine oxidase

levels >235 pmol/8 × 10(8) RBC, as compared to those below this therapeutic threshold [5]. A 6-TGN level of 235 pmol/8 × 10(8) RBC has been supported as a cut point in other pediatric and adult studies, and a meta-analysis also reported that patients with 6-TGN concentrations above this threshold had a three-fold increased odds of being in remission than those below this threshold (62% vs. 36%; pooled odds ratio 3.3, 95% confidence interval, 1.7–6.3; $p < 0.001$) [6–9]. In a patient not responding clinically to standard thiopurine dosing, obtaining a 6-TGN and 6-MMP level would be clinically useful to ensure therapeutic dosing. If 6-TGN levels are <235 pmol/8 × 10(8) RBC, dose escalation is warranted; yet if therapeutic (235–400 pmol/8 × 10(8) RBC), switching to a non-thiopurine therapy would be reasonable.

Leukopenia is the most concerning toxicity associated with the use of thiopurines. This is most commonly attributable to high 6-TGN metabolite levels. Patients that are homozygous deficient for TPMT polymorphisms are most at risk of thiopurine-related myelosuppression. Colombel et al., however, reported that only one-third of myelosuppression cases were secondary to a low TPMT activity, indicating other factors contributing to leukopenia, such as effects of concomitant medications and secondary viral infections (EBV, CMV, parvovirus) [10]. It is unclear what 6-TGN level is considered "too high"; however, a level >400 pmol/8 × 10(8) RBC has been suggested as the cut point which clinicians should avoid [11].

Hepatotoxicity is another risk with thiopurine use, with some studies associating it with 6-MMP concentrations above 5700 pmol/8 × 10(8) RBC ($p < 0.05$) [5, 11]. If a patient has a therapeutic 6-TGN level with a 6-MMP level >5700 pmol/8 × 10(8) RBC and normal liver enzymes, more frequent clinical monitoring of liver enzymes is indicated, rather than a reflexive thiopurine dose decrease. If a patient, however, has both a high 6-TGN level (>400 pmol/8 × 10(8) RBC) *and* 6-MMP level (>5700 pmol/8 × 10(8) RBC), then dose de-escalation is warranted in order to minimize the risk of leukopenia and hepatotoxicity. Perhaps the most important application of high 6-MMP levels is in the patient who also has a low 6-TGN level, with subsequent dose-escalation resulting in decreasing 6-TGN and increasing 6-MMP [12]. This group has been defined as being "thiopurine-resistant," or "6-MMP preferential metabolizers," and such patients would benefit from changing to another class of medications, such as methotrexate (MTX) or biologic therapy. The proposed use of allopurinol in these patients to reverse the metabolism to favor more 6-TGN and less 6-MMP may carry additional toxicity risks with relation to leukopenia but has been shown to be an effective strategy [13]. The understanding of the importance of thiopurine drug monitoring paved the way for applying the TDM concept to other IBD therapies and more specifically, anti-TNF therapies.

Anti-TNF Drug Concentrations

Only recently studies have examined the durability of anti-TNF agents and their pharmacokinetic profiles, despite being approved since 1998 in adults and 2006 in pediatric patients. Most studies have examined infliximab (IFX), with evolving literature for the other anti-TNF agents, including adalimumab, certolizumab pegol (CZP), and a paucity of data with golimumab.

Although the response to IFX induction is highly successful in 75–90% of pediatric IBD patients, more challenging is the maintenance of a sustained and durable remission [14, 15]. In the REACH trial, only 60% of pediatric CD patients who responded to induction were in remission at 1 year, and half of these patients required dose modification after losing response [14]. In a meta-analysis of adult IBD patients on

IFX, 23–46% required dose escalation and 5–13% discontinued the drug at 1 year [16]. Using TDM, one can better understand the etiology of primary non-response and secondary loss of response, and TDM may be used in clinical management with the goals of a sustained response to therapy.

In 2003, initial studies found higher serum IFX concentrations to be correlated with longer duration of response [17]. It was reported in 2006 that detectable serum IFX concentrations were associated with a higher rate of clinical remission, endoscopic improvement, and lower CRP values in CD patients [18]. Other studies also support the findings that detectable IFX concentrations were predictive of a sustained response in CD patients [19]. In UC, the data are just as strong, with detectable IFX concentrations associated with higher remission rates, endoscopic improvement, and a significant decrease in colectomy risk (55% vs. 7%, OR 9.3; 95% CI 2.9–29.9; $p < 0.001$) [20]. In the post hoc analysis of the ACT trials, higher IFX concentrations in UC patients were associated with an increased likelihood of achieving clinical remission and mucosal healing with increasing quartiles of IFX levels [21]. Patients with drug levels in the third or fourth quartile had remission rates at week 30 closer to 60% as compared to those in the second quartile whose remission rates were 25%. In the recent UK PANTS study consisting of 955 CD patients, low drug concentration at week 14 for both infliximab and adalimumab was the only factor independently associated with primary non-response in a multivariable analysis [22]. Other studies have found that higher adalimumab concentrations correspond to mucosal healing and clinical remission; higher CZP concentrations in CD patients are associated with endoscopic remission and response; and higher golimumab concentrations were associated with clinical remission [23–25].

The minimum anti-TNF trough concentration associated with improved outcomes remains debatable and may vary depending on the outcome measured (clinical/biochemical/endoscopic/histologic remission). Murthy et al. demonstrated that an IFX concentration of >2 μg/mL in UC patients was associated with a higher rate of corticosteroid-free remission, compared to a trough concentration of <2 μg/mL (69% vs. 16%; $p < 0.001$) [26]. A trough concentration >3 μg/mL during IFX maintenance therapy has been shown by Vande Casteele et al. to be independently associated with a lower CRP and has been proposed as a cut-off to improve outcomes [27]. Recent studies suggest that yet even higher IFX trough drug concentrations at week 14, the time of the first maintenance dose, are associated with better one-year efficacy outcomes [28, 29]. In one study, a ≥3.5 μg/mL post-induction serum infliximab concentration level and a ≥60% CRP decrease from baseline to week 14 significantly predicted durable sustained response to infliximab in patients with raised baseline CRP [29]. In the PANTS study, week 14 infliximab drug concentration of 7 μg/mL was associated with remission at both week 14 and week 54 [22]. Fistula healing with IFX in CD has been associated with even higher concentrations (>15 μg/mL) [30].

In a pediatric IBD study, median IFX trough levels were significantly higher when children achieved clinical remission (5.4 μg/mL vs. 4.2 μg/mL), biological remission (5.2 μg/mL vs. 4.2 μg/mL), combined clinical and biological remission (5.7 μg/mL vs. 4.4 μg/mL), and endoscopic remission (6.5 μg/mL vs. 3.2 μg/mL) compared with not meeting these criteria [all $p \leq 0.001$] [31]. In an Israeli study, pediatric IBD patients in clinical remission were found to have higher IFX concentrations than those with active disease (4 vs. 2.25 μg/mL, $P < 0.0001$). In this study, a week 2 IFX level >9.2 μg/mL predicted clinical remission by week 14 (AUC 0.72, $p = 0.02$); at week 6 IFX level >2.2 μg/mL predicted IFX durability beyond 1 year of treatment (AUC 0.974, $p < 0.0001$) [32]. Another pediatric study reported that the median IFX pre-fourth dose level in responders was significantly higher at 12.7 μg/mL, compared with 5.4 μg/mL in the active perianal disease group [33]. In further examining earlier IFX trough levels, Buhl et al. found that the optimal IFX thresholds early in treatment associated with response to IFX was 22.9 μg/mL at week 2 (sensitivity 51%, specificity 80%, AUCROC 0.67, $p < 0.05$) [34]. Another study revealed IFX concentration below 6.8 μg/mL at week 2 are associated with primary non-response in Crohn disease patients. Clarkson et al. found that infusion 2 (≥29 μg/mL) and infusion 3 (≥18 μg/mL) infliximab concentrations were strongly associated with improved early outcomes and higher first maintenance dose levels [35].

Differing cut-offs have also been suggested for adalimumab concentrations. Velayos et al. found that an adalimumab concentration of >5 μg/mL was associated with decreased CRP level; Yarur et al. confirmed this association [36, 37]. Karmaris et al. suggested a higher therapeutic threshold of >8 mg/mL [38]. In the PANTS study examining adult CD patients, an adalimumab trough concentration of 12 μg/mL was associated with remission at 1 year [22].

For CZP, in the post hoc analysis of the WELCOME trial, evaluating induction therapy of CZP in 203 patients, remission rates were higher among patients whose CZP concentration fell within the two highest quartiles during induction at weeks 0, 2, 4, and 6 (27.5–33.8 μg/mL and ≥33.8 μg/mL, respectively); thus, a CZP concentration of >27.5 μg/mL has been proposed for clinical use [39]. For golimumab, patients with drug concentrations in the highest quartile with a concentration of >3.1 μg/mL had higher rates of clinical remission at 30 and 54 weeks when compared to lower quartiles [25].

The importance of optimized anti-TNF levels is exemplified by recent expert consensus that reactive TDM should be used for all biologics for both primary non-response and sec-

ondary loss of response. It was recommended that treatment discontinuation should not be considered for infliximab or adalimumab until a drug concentration of at least 10–15 μg/mL was achieved [40].

Anti-TNF Drug Antibodies and Outcomes

Despite a high primary response rate to the anti-TNF agents, two-thirds of patients losing response do so within the first year [16]. The loss of response to anti-TNF agents is most often due to an individual's unique physiologic profile driven by drug clearance, with factors that influence drug clearance, including low serum albumin concentration, high baseline CRP levels, large body size, male sex, and a high degree of systemic inflammation [41]. In children younger than 10 years, the clearance of IFX has been estimated to be more rapid, with higher likelihood of developing anti-drug antibodies (ADAs) and these young children often require higher and more frequent doses of IFX [42]. The development of ADAs in all patients, referred to as immunogenicity, remains a significant driver of loss of response. It should be noted that non-chimeric anti-TNF therapies have the same issues with ADA formation as chimeric anti-TNF agents [43]. The presence of ADA increases the clearance of the drug, resulting in lower drug concentrations. This, in turn, results in shorter duration of response, which has been demonstrated in multiple studies [17, 18, 22, 23, 41, 44–47]. Other factors may be responsible for ADA development, including the presence of specific genetic alleles. Recent data reveal that the HLA-DQA1*05 gene allele is associated with development of antibodies to anti-TNF agents (hazard ratio [HR], 1.90; 95% confidence interval [CI], 1.60–2.25; $P = 5.88 \times 10^{-1}$) [48].

In a prospective study of patients receiving IFX therapy, ADA development preceded clinical loss of response in over half of patients [49]. Similar results have been reported with adalimumab, with 20% of patients developing anti-adalimumab antibodies which predicted biochemical and clinical loss of response [50]. Another study also confirmed the association of anti-adalimumab antibodies with increased markers of inflammation and with clinical indices, indicating increased disease activity [51]. Antibodies to certolizumab were also found to be associated with reduced remission rates through week 26 in the PRECISE 2 trial (71 vs. 62%), and similarly found in the WELCOME trial [52, 53]. In addition to the negative effect ADAs have on efficacy, they also increase toxicity, with the example of anti-infliximab antibodies (ATIs) being associated with infusion reactions [45]. Additionally, a 2015 pediatric study found that the presence of ATIs was a predictor of lower IFX concentrations, and a higher risk of surgery [54].

Additionally, ATIs may be transient. Vande Casteele et al. retrospectively found that in 28% of patients' ATIs disappeared over time, whereas they were sustained in 72% of patients [47]. They also suggested that ATI concentrations of >9.1 U/mL were less likely to be overcome with a likelihood ratio of 3.6 of failure [47], and thus, such patients should be changed to another anti-TNF therapy.

The knowledge of the presence of ADA is also important in the setting of reintroduction of anti-TNF therapies after a prolonged interruption, or "drug holiday". Baert et al. reported that the presence of ATI 2 weeks after the first re-induction dose of IFX was associated with lower response rates and higher rates of infusion reactions [55]. The data suggest that if a patient has discontinued IFX for at least 6 months, it is important to check for the presence of ATIs prior to administering the second induction dose. It remains unclear whether, following a drug holiday, a patient should be re-induced with the standard initial induction regimen (0, 2, 6 weeks) or forego re-induction and resume with every eight-week interval.

The reported rates of ADA are entirely dependent on the specific assay used to measure ADA. Several techniques are available for measuring anti-TNF concentrations and ADA. Thus, comparison of results from different assays should be performed with caution, as there remains no standardization between different assays. Drug concentrations are generally detected sensitively between assay types, yet the detection and accurate quantification of ADAs have been more challenging. First-generation assays, such as the enzyme-linked immunosorbent assay (ELISA), have less clinical utility, given the lower sensitivity for measuring ADAs. Using the ELISA assay, serum anti-TNF drug competes with the ADA detection moiety so when drug is detected in the sample, ADA is unable to be accurately measured. Radioimmunoassay (RIA) is sensitive and specific for drug and ADA detection, yet disadvantages include the complexity of the test, prolonged incubation time, expense, and the handling of radioactive materials [56, 57]. The homogeneous mobility shift assay (HMSA), using high-performance liquid chromatography, has the advantage of separating and quantifying the drug and antibody concentrations independently, making it feasible to detect ADAs in the presence of anti-TNF drug. ELISA and ELISA-like assays (LabCorp, Esoterix Inc) as well as HMSA assays (Prometheus labs) are currently commercially available for IFX and adalimumab.

Immunomodulator Use with Anti-TNF Agents

Given the negative effects of ADA on therapeutic efficacy, durability, and association with infusion reactions, attempts should be made to reduce the likelihood of ADA formation. Various strategies have been recommended in order to do so,

such as the addition of an immunomodulator and even proactive optimization of drug concentrations.

In the ACCENT 1 trial, concomitant immunomodulator use with IFX was associated with lower rates of ATI formation [58]. In another prospective CD cohort, patients who received concomitant immunomodulator therapy had higher IFX concentrations and less likelihood of ATI formation than those not receiving a concomitant immunomodulator (43% vs. 75%; $p < 0.01$) [17]. A logistic regression analysis further demonstrated that the only significant variable predictive of IFX concentrations was the use of a concomitant immunosuppressive agent ($p < 0.001$) [17]. The SONIC trial demonstrated that combination therapy of IFX with AZA is superior to IFX monotherapy in achieving clinical remission and mucosal healing [46]. This is potentially due to less formation of antibodies and higher trough levels associated with combination therapy. A study of Danish registries found that combination therapy, without use of TDM, improved two-year clinical outcomes in pediatric CD patients treated with IFX [59]. In the UC SUCCESS trial, combination therapy with IFX was also superior to monotherapy after 16 weeks [60]. In a recent study, Lega et al. proposed utilizing IFX monotherapy with a proactive TDM approach, after finding that IFX durability in young IBD patients did not differ between those receiving IFX monotherapy with proactive TDM and those receiving combination therapy [61]. Additionally, with golimumab therapy, patients receiving a concomitant immunomodulator had a lower incidence of antibody formation (1.1% vs. 3.8% $p = 0.01$) [25].

Data regarding the utility of combination therapy with adalimumab are mixed. Patients receiving an immunomodulator in combination with adalimumab have been noted to have higher drug concentrations than those on monotherapy [37]. In the DIAMOND trial, Crohn's patients treated with adalimumab and immunomodulator therapy had increased adalimumab trough levels, which in turn were associated with endoscopic response and mucosal healing at 6 and 12 months [62]. Recent data further reveal that combination therapy with an immunomodulator and adalimumab decreases the risk of developing ADAs (hazard ratio; 0·44 [0·31–0·64] $p < 0·0001$) [22]. However, the post hoc analysis of the randomized control PAILOT trial revealed no significant difference in outcomes between pediatric CD patients on adalimumab and immunomodulator therapy and those on adalimumab monotherapy with regard to clinical and biochemical remission. Furthermore, adalimumab trough concentrations and immunogenicity were not significantly different between groups [63]. In a recent post hoc analysis of the IMAgINE 1 study, immunomodulator therapy with adalimumab in pediatric CD did not lead to improvement of response, remission or increased serum adalimumab trough levels, when compared to those on adalimumab monotherapy [64]. An observational study revealed that concomitant immunomodulators decreased immunogenicity in patients receiving infliximab but not adalimumab, further confounding the role of combination therapy on immunogenicity [65].

Studies suggest that concomitant immunomodulator use may be used to recapture response in patience with low drug concentrations. Ben Horin et al. reported in a small case series that the addition of an immunomodulator to maintenance infliximab monotherapy increased IFX concentrations and lowered antibody concentrations, improving patient outcomes by restoring clinical response [66]. Other small studies have shown that the addition of a thiopurine in patients losing response to anti-TNF monotherapy was an effective strategy to recapture response [67]. Overall, these studies suggest that not only does concomitant immunomodulator use decrease immunogenicity preemptively as suggested by SONIC, but its use may also recapture response in patients with low drug concentrations.

In pediatric patients, particularly in males, the substitution of MTX for thiopurines may provide a safety advantage, given the rare yet positive association between combination therapy of IFX with thiopurines and malignancy, including hepatosplenic T-cell lymphoma in this age group. The efficacy of combining an anti-TNF agent with MTX has been examined as well. In the rheumatoid arthritis literature, a low dose of 7.5 mg weekly was associated with lower rates of ATI development in IFX treated patients [68]. However, no clinical benefit in IFX durability or efficacy was found when using very low-dose oral MTX (<10 mg/week) as concomitant therapy in pediatric IBD patients [69]. It has been proposed that a dose of at least 12.5 mg of oral MTX is needed to avoid immunogenicity [70]. The COMMIT trial found that patients on IFX combination therapy with 25 mg of weekly subcutaneous MTX were significantly less likely to develop ATIs and had higher IFX concentrations, yet no clear benefit was found in inducing and maintaining clinical remission [71]. A German group found that concomitant use of MTX with infliximab had a positive effect in the treatment of refractory CD adult patients, using a MTX dose of 20 mg weekly, both parenterally and orally administered [72].

Proactive Dose Optimization

Perhaps most the most important utilization of TDM is proactively preventing the loss of response, rather than awaiting a treatment failure. This can be accomplished by dose adjusting early in the treatment course. Researchers have attempted to determine whether a drug concentration obtained early in maintenance is a predictor of a more durable response. Bortlik et al. found that, on retrospective evaluation, an IFX threshold of greater than 3 μg/mL at either the week 14 or week 22 dose was predictive of a sustained response [19]. Vande Casteele et al. described that low IFX concentrations

at 14 weeks (<2.2 μg/mL) predicted IFX discontinuation due to persistent loss of response and was associated with increased incidence of ATIs [47]. In a recent post hoc analysis of ACCENT1, patients with post-induction week 14 IFX concentrations of ≥3.5 μg/mL and a ≥ 60% CRP decrease were significantly associated with durable sustained response at week 54 [29]. Using a cohort of pediatric IBD patients, Singh et al. was the first to prospectively determine the optimal cut point for a week 14 IFX trough concentration in predicting one-year durable remission. In this study a concentration of at least 5.5 μg/mL was described as optimal ($p = 0.01$) [28]. Using a cohort of pediatric IBD patients on IFX therapy, Stein et al. found that IFX concentrations of ≥9.1 μg/mL at week 10 was found to be predictive of continuing on IFX at 12 months, with a sensitivity of 80% and specificity of 60% [73].

Given the growing body of literature supporting the role of TDM, prospective trials using TDM-based dose adjustment have been performed. The TAXIT trial showed that proactive dose adjustments, maintaining an IFX concentration between 3 and 7 μg/mL, resulted in improved disease activity in CD patients, even though the primary outcome at 1 year was not achieved. Additionally, up to 30% of the TAXIT patients may be able to have their IFX dose de-escalated, again suggesting a cost-saving potential of proactive, individualized TDM [74]. In TAILORIX, IFX dosing intensification beyond week 14 based on symptoms, biomarkers and IFX drug concentrations did not lead to improved outcome of steroid-free remission. It is possible that the target IFX goal of >3 μg/mL in both TAXIT and TAILORIX was too low to achieve primary endpoints. Another study demonstrated that proactive dose adjustment using TDM, keeping IFX drug concentrations between 5 and 10 μg/mL, was associated with sustained remission as compared to those with concentrations lower than 5 μg/mL or without TDM monitoring [75].

Pediatric-specific studies also demonstrate the utility of proactive drug monitoring for anti-TNF therapy. In the PAILOT trial utilizing a pediatric CD cohort, adjusting adalimumab dosing to achieve a trough concentration of 5 μg/mL was associated with sustained corticosteroid-free clinical and biochemical remission through week 72 compared to a reactive monitoring (82% vs. 48%, $p = 0.002$) [76]. Lyles et al. demonstrated higher rates of achieving a sustained clinical steroid-free remission by utilizing proactive drug monitoring, with goal IFX or adalimumab concentration of >5 μg/mL in pediatric IBD patients treated with anti-TNF therapy [77].

Although societal guidelines have not yet adopted recommendations to use TDM proactively, expert IBD consensus is to utilize proactive TDM. This has been associated with decreased cost up to 34% when using TDM algorithm as opposed to routine IFX dose intensification, without affecting rates of clinical response [78]. Proactive TDM of IFX has been associated with higher rates of mucosal healing, as well as decreased rates of unfavorable outcomes (surgery, hospitalization, treatment failure, lack of mucosal healing) compared with non-TDM-based treatment [79]. Another multi-center study also revealed fewer treatment failures, hospitalizations, surgeries, infusion reactions, and antibodies to IFX compared to reactive TDM [80]. The long-awaited Norwegian randomized trial of standard of care dosing versus proactive TDM revealed that among patients with immune-mediated inflammatory diseases undergoing maintenance therapy with infliximab, proactive TDM was more effective than treatment without TDM in sustaining disease control without disease worsening [81]. A recent expert consensus panel recommends to perform proactive TDM, after induction, at least once during maintenance while on anti-TNF therapies [40]. More advanced methods may be used, such as the application of a pharmacokinetic dashboard, which takes into account factors that influence anti-TNF clearance; using such a dashboard early during induction may render proactive TDM even more effective, as it has been shown to improve IFX durability and immunogenicity [82].

Practical Use of TDM with Anti-TNF Agents

TDM is integral to treating IBD patients on anti-TNF therapy. It may more readily establish the mechanism for loss of response or lack of response and allow the clinician to appropriately tailor therapy for the individual patient. It is important that anti-TNF drug concentration and ADA be evaluated in the context of each other and thus that a drug-tolerant assay is used. Our suggested guideline for TDM in a patient on IFX therapy is outlined in Fig. 33.2.

In a patient with a therapeutic drug concentration and no ADA present, ongoing therapy should continue if in remission; if not in clinical and mucosal remission despite therapeutic drug concentrations and lack of ADA, that patient is likely a non-responder to the anti-TNF class of medications and should be changed to another class of medications. If a patient is in deep remission and therapeutic drug concentrations with low ADA is present (i.e., IFX ATI <9.1 μg/mL [47]), attempt should be made to overcome the low ADA and stay on drug. Options include adding an immunomodulator as previously mentioned or escalating the dose and or shorten the interval.

In a patient with low or undetectable drug concentrations without ADA, optimizing drug dose by escalating therapy is warranted and may prevent development of ADA. In a patient with low/undetectable drug concentrations and high ADA, if that patient has responded prior to anti-TNF mechanism then switching to another anti-TNF agent is indicated. However,

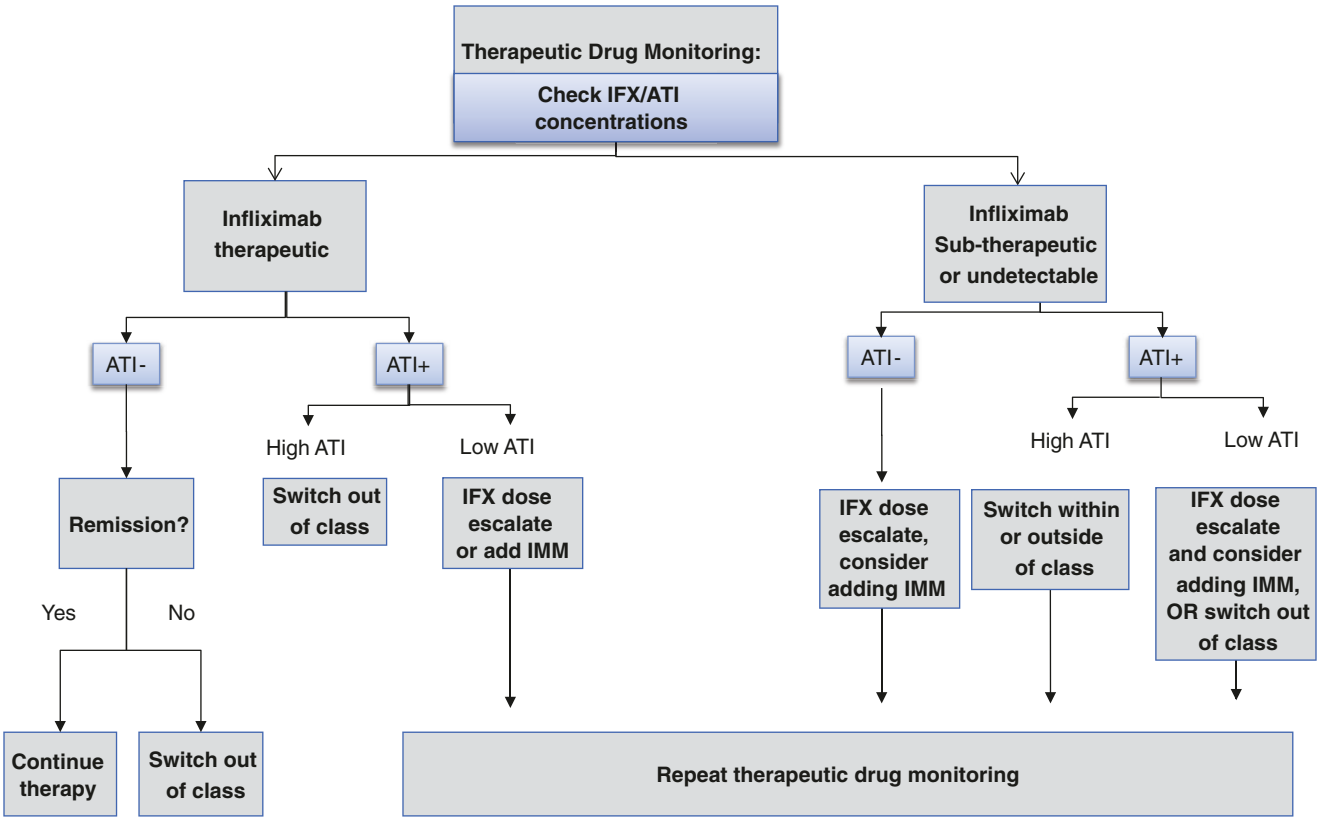

Fig. 33.2 Utilizing therapeutic drug monitoring (IFX). *ATI* Anti-infliximab antibody, *IFX* Infliximab, *IMM* Immunomodulator

if no response to anti-TNF therapy had been evidenced, switching out of class would best serve the patient. With low/undetectable drug concentration and low ADA, options would be to dose escalate and add an immunomodulator to overcome low ADA, or to entirely switch out of class. With each change, if staying within class, TDM should be repeated in next 2–3 infusions, once reaching a drug steady state.

TDM with Vedolizumab and Ustekinumab

Vedolizumab

Since its approval in 2016 for adult patients with CD and ulcerative colitis, vedolizumab has been used in this population as well as in the pediatric populations, albeit off-label. The safety profile of vedolizumab and its gut specificity has made it an appealing agent to use in some pediatric IBD patients. Although not yet FDA approved in pediatrics, several studies have found it to be safe and efficacious in this population [83–86]. Clear consensus on goal trough concentrations is not yet present, yet there are data associating higher trough levels with improved clinical responses. Post hoc analysis of the registration studies of vedolizumab (GEMINI) revealed that higher vedolizumab concentrations at week 6 were associated with higher rates of clinical remission at week 14. Increases in trough concentrations resulted in increased remission rates [87]. Using data from GEMINI 1, vedolizumab serum concentrations of 37.1 at week 6, 18.4 at week 14, and 12.7 μg/mL in maintenance were associated with improved 1 year clinical outcomes [88]. In a pooled analysis of five cohort studies, proposed cut-off vedolizumab concentrations of >20 μg/mL at week 6 and >12 μg/mL during maintenance was associated with improved outcomes [89]. Similarly, in a study encompassing pediatric IBD patients, Ungaro et al. demonstrated that IBD patients were 2.4 times more likely to be in a corticosteroid-free clinical and biochemical remission with a vedolizumab trough concentration >11.5 μg/mL [90].

Dose escalation of vedolizumab may help to restore or gain response. A French study found that patients with lower week 2 and 6 vedolizumab trough levels necessitated dose escalation within 6 months. In a systemic review of adult cohorts, dose intensification restored response to vedolizumab in 53.8% of patients who were found to be secondary non-responders [91].

Registration studies have found low incidence of persistent antibodies (<1%), and the use of a concomitant immu-

nomodulator has not been found to be beneficial [92–94]. In fact, real-world studies have reported a wide range of ADAs to vedolizumab of 0–17%, without notable effects on efficacy. Immunogenicity has not been found to be the cause of vedolizumab treatment failure, with only 8% of patients with transient ADAs at time of discontinuation of vedolizumab [95]. A pediatric study examining trough and antibody concentrations similarly found no association between anti-drug antibodies and efficacy [96]. Thus, in using TDM, one may consider optimizing dose of vedolizumab regardless of presence of antibodies. In secondary loss of response, clinicians may consider measuring vedolizumab drug serum concentrations and dose escalating. However, prospective trials are further required before recommending a widespread approach to proactive TDM with vedolizumab.

Ustekinumab

Ustekinumab (UST) is a fully human IgG1 monoclonal antibody targeting the IL-12p40 subunit of IL-23 and IL-12 and was approved for adult IBD patients in 2016, with an evolving body of literature demonstrating efficacy in pediatric IBD, although not yet FDA approved in this population [97–99]. In patients with CD, ustekinumab clearance is affected by body weight, serum albumin concentration, C-reactive protein (CRP), TNF antagonist failure status, sex, race, and antibody to UST status [100].

In examining the phase 3 registration Crohn disease UNITI studies (UNITI-1,2, IM-UNITI), serum UST concentrations were positively associated with clinical remission at 8 weeks [101, 102]. There was a significant association between clinical remission, endoscopic response, and CRP normalization [102]. Overall, receiver operating characteristic (ROC) analysis demonstrated an area under curve (AUC) of 0.64 ($P < 0.003$) for clinical remission and UST concentrations, with an optimal cut-off being approximately 1 μg/mL. In addition, UST concentrations greater than 1.1 μg/mL were associated with CRP normalization at week 24 (52% vs. 25%, $P < 0.0001$). In a smaller subset of patients, UST concentrations greater than 0.5 μg/mL were associated with increased endoscopic response at week 44 (40% vs. 8%, $P < 0.003$). Serum UST concentrations during maintenance treatment (q4/8week dosing) above 4.5 μg/mL were associated with endoscopic response and biomarker reduction and also associated with a composite outcome of steroid-free clinical remission and endoscopic response (75.9% for >4.5 μg/mL vs. 40.7% if below; $P = 0.008$) [102]. In UNIFI, a UST concentration of 3.7 μg/mL at week 8 was identified by ROC analysis to be associated with clinical response, and 1.3 μg/mL at week 44, in UC patients [103]. In the only pediatric study to date, Dayan et al. revealed no significant difference in UST drug concentrations in pediatric IBD patients in remission compared to those not [98].

In IM-UNITI, patients with a clinical loss of response during maintenance period were successful in recapturing response by UST dose escalation [104]. In clinical experience, several studies have demonstrated the ability to recapture response with dose escalation in patients who have not responded or lost response, with varying degrees of success (61%,73%) [105, 106]. One pediatric study also revealed that 62% of patients required dose escalation [98]. Unlike anti-TNF therapies, concomitant immunomodulator therapy does not seem to have a significant impact on ustekinumab concentrations in adult and small pediatric studies [98, 102, 107]. Immunogenicity also appears to be low, with rates up to 2.3% at 1 year, and 4.6% through the three-year UM-UNITI extension study [101–103]. At this time, further studies are required before recommending utilizing a TDM approach with ustekinumab in pediatric IBD patients.

Conclusion

The body of evidence correlating serum anti-TNF drug and ADA concentrations to clinical outcomes is growing, and the value of TDM is well recognized. The use of TDM allows clinicians to gain insight into the etiology of loss of response and enables the optimization of therapy for an individual patient. With increasing prospective studies on TDM of anti-TNF therapies, new algorithms are being developed with the goal of achieving a sustained, durable remission on these therapies. Future TDM may evolve with point-of-care anti-TNF drug concentration assays, identification, and testing of other genetic alleles impacting response to anti-TNF therapy and use of dashboards. Already, data modeling and use of dashboards to individualize IFX dosing have been shown to be improve outcomes in IBD patients of all ages [108–112]. Issues related to TDM, including clearance and immunogenicity, are not unique to anti-TNF therapies and these concepts will be applicable to other biologics used in IBD patients. As more data are obtained, there may be an evolving role of TDM in vedolizumab and ustekinumab. In this era of personalized medicine, TDM allows for optimized, individualized dosing, and improved care for IBD patients of all ages.

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New Non-anti-TNF-α Biological Therapies for the Treatment of Inflammatory Bowel Disease

34

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Introduction

Blockade of the tumor necrosis factor-alpha (TNF-α) pathway has been a major advancement for the treatment of inflammatory bowel disease (IBD). However, 20–40% of patients with moderate to severe disease do not have a response to treatment with TNFα antagonists (primary nonresponse), and 23–46% lose response within the first 12 months of treatment (secondary nonresponders) [1]. As a result, there is an ongoing need to develop new medidations with different mechanisms of action. This chapter will discuss the major non-anti-TNF-α agents in the pipeline that are currently undergoing evaluation to effectively and safely treat patients with IBD. This chapter discusses the major non-anti-TNF-α agents in the pipeline that are currently undergoing evaluation in order to effectively and safely treat patients with IBD. Figure 34.1 illustrates the drugs currently in the pipeline, and Table 34.1 is a summary of the treatments that is discussed in this chapter.

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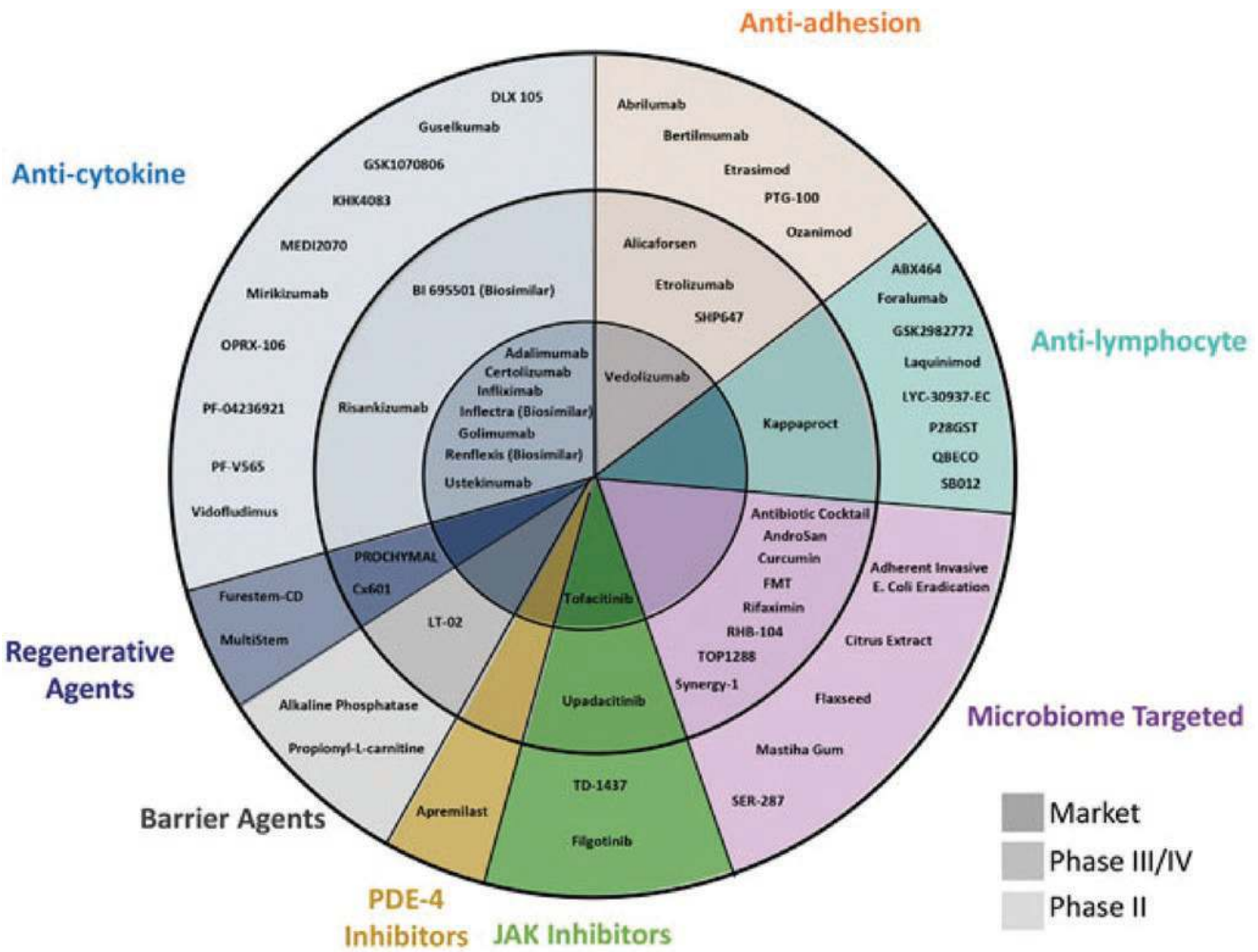

Fig. 34.1 Drugs in pipeline for IBD [2]

Table 34.1 Treatments discussed in this chapter

Target	Name	Development in IBD	Mechanism of action
Cytokines			
IL-12/IL-23	Ustekinumab Briakinumab	Approved (CD,UC) Phase II (CD)	Inhibits p40 subunit of IL12/23 Inhibits p40 subunit of IL12/23
IL-23 selective	Brazikumab	Phase II (CD)	Inhibits p19 subunit of IL23
	Risankizumab	Phase II (CD)	Inhibits p19 subunit of IL23
	Mirikizumab	Phase II (CD,UC)	Inhibits p19 subunit of IL23
	Guselkumab	Phase II (CD,UC)	
IL-6	PF-04236921	Phase II (CD)	IL-6 inhibitor
IL-13	Tralokinumab QAX576 Bertilimumab	Phase II (UC) Phase II (CD) Phase II (CD, UC)	IL-13 receptor antagonist Inhibits of IL-13 Blocks the activity of eotaxin-1
IL-17	Vidofludimus	Phase II (CD,UC)	Inhibits IL-17 secretion
IL-21	ATR107 NNC0114-0006	Phase I Phase II (CD)	Anti-IL-21 receptor antibody IL-21 inhibitor
Signaling pathways mediated by cytokines			
JAK/STAT	Tofacitinib	Approved (UC)	Inhibits JAK1 and JAK3, and mildly JAK 2
	Filgotinib	Phase II (CD,UC)	JAK1 inhibitor
	Upadicitinib	Phase II (CD,UC)	JAK1 inhibitor

Table 34.1 (continued)

Target	Name	Development in IBD	Mechanism of action
	Peficitinib	Phase II (UC)	Non-selective JAK inibitor
	TD-1473	Phase I (UC)	Non-selective JAK inibitor
TGF-b	GED0301 (Mongersen)	Phase III/II (CD/UC)	SMAD7 antisense oligonucleotide
Chemokines			
Anti CXCR2/CXCL10	BMS936557 (Eldelumab)	Phase II (CD, UC) Phase I/III	CXCL-10 inhibitor
Anti CCR9/CCL25	CCX282-B (Vercirnon)	(UC/CD)	CCR9 antagonist
Antiadhesion molecules	Natalizumab	Approved (CD), phase I (UC)	α4 integrin antaogmist
	Vedolizumab	Approved (CD, UC)	α4β7 integrin antagonist
	Etrolizumab (rhuMAb β7)	Phase III (CD, UC)	Blocks β7 subunit of α4β7 and αEβ7 integrins
	Ontamalimab (PF-00547659, SHP647)	Phase II (CD, UC)	MAdCAM-1 protein inhibitor
	AJM300	Phase III (UC)	α4 integrin antagonist
	Alicaforsen (ISIS 2302)	Phase II/III (CD/UC)	Targets intercellular adhesion molecule 1 (ICAM-1)
	AMG181 (abrilumab)	Phase II (CD/UC)	α4β7 integrin antagonist
	Firategrast (SB 683699)	Phase II (CD)	α4 integrin antagonist
	GLPG0974	Phase II (UC)	Against FFA2
	TRK-170	Phase II (CD)	α4β1/α4β7 integrin antagonist
Anti-inflammatory cytokine	IL-10 (rhu-IL-10)	Phase III (CD)	IL-10 replacement
T-cell stimulation and induction of apoptosis blockades	Laquinimod	Phase II (CD)	Modulation of immune cells
	Cobitolimod (DIMS0150)	Phase III (UC)	Activates TLR9
	Monarsen (BL 7040)	Phase II (UC)	TLR9 modulator
Spingosine-1-phosphate receptor modulators	Etrasimod (APD334)	Phase II (CD/UC)	S1P receptor 1 modulator
	Ozanimod (RPC1063)	Approved	Agonist for S1P receptors 1 and 5
Antisense oligonucleotides	GATA3 DNAzyme	Phase II (UC)	Modulate production of Th2, Th9 related cytokines
	STNM01	Phase I/II (CD/UC)	Blocks carbohydrate sulfotransferase 15 mRNA
Miscellaneous	Apremilast (CC-10004)	Phase II (UC)	Inhibitor of phosphodiesterase 4 enzyme
	RDP58 (delmitide acetate)		
	LT02	Phase II (UC)	Mitogen-activated protein kinase inhibitor
	LYC-30937-EC	Phase III (UC)	Modified release phosphatidylcholine
	TOP-1288	Phase II (UC) Phase II (UC)	Gut-directed ATPase modulator Narrow spectrum protein kinase inhibitor
	GSK2982772	Phase II (UC)	Receptor Interacting Protein 1 Kinase inhibitor
	Rosiglitazone	Phase II (UC)	Peroxisome proliferator-activated receptor agonist
	VB-201	Phase II (UC)	Oxidised phospholipid molecule

Cytokine Targets

IL-12/IL-23

Interleukin (IL)-12 and IL-23 have been shown to have a central role in the inflammatory pathway in Crohn disease, psoriasis and multiple sclerosis [3]. The risk for a patient to develop CD and UC has been demonstrated through genome-wide association studies studying variants of the gene encoding the IL-23 receptor and the locus for the gene encoding the p40 chain [4].

IL-23 is a heterodimer of the same p40 subunit and a p19 subunit which induces naïve CD4+ T cells into T helper 17 cells, which then induce the production of proinflammatory cytokines such as IL-17, IL-6, and TNF-α [5].

Ustekinumab

Ustekinumab is a human monoclonal antibody (IgG1) that targets the IL-12/23 shared p40 subunit. The result is the inhibition of IL-12 and IL-23 binding to their receptor on the surface of T cells, natural killer cells, and antigen-presenting cells (see Fig. 34.2).

Ustekinumab (UST) has been shown to be clinically effective in the treatment of moderate to severe CD and UC in phase III studies. Both UNITI 1, UNITI 2 and IM-UNITI, proved the efficacy for UST in the treatment of CD over placebo [7]. In UNITI 1 trial included 741 patients who were primary or secondary non responders to TNFα antagonists or had unaccepatable side effects, whereas UNITI 2 included 628 patients who had failed conventional therapies or experienced unacceptable side effects. These two were induction trials where patients in the test arm received 130 mg or 6 mg/kg UST intravenously, as opposed to placebo. Patients who responded in the induction arms were randomly assigned to the IM-UNITI or maintenance arm of the trial. In the maintenance study, 397 patients were randomly assigned to receive either 90 mg of UST every 8 weeks or 12 weeks versus placebo. The primary end point for the induction trial was clinical response at 6 weeks as defined by reduction in Crohns Disease Activity Index (CDAI) score of ≥100 points

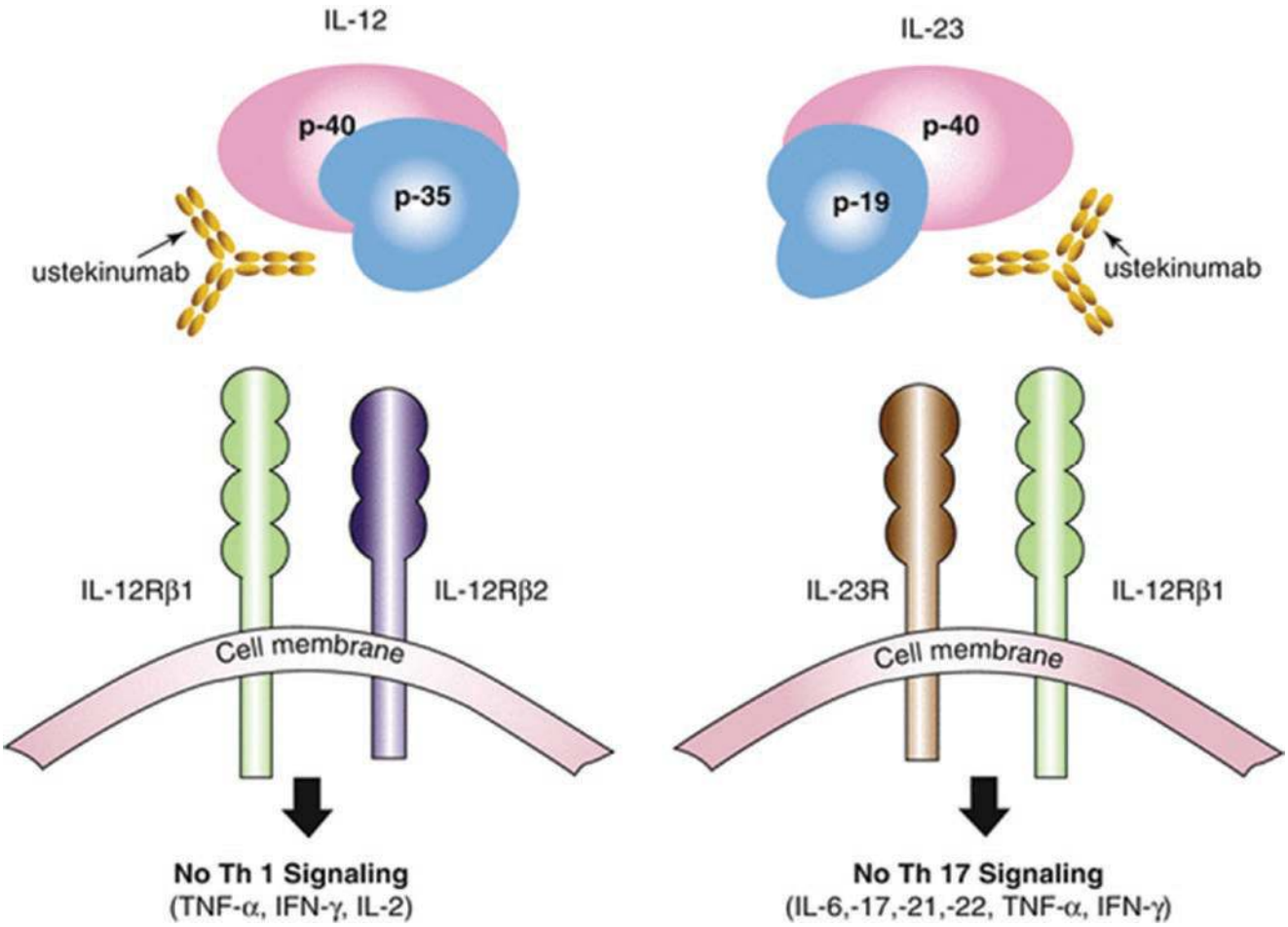

Fig. 34.2 Ustekinumab mechanism of action (Onuora [6])

or CDAI score <150, whereas primary end point for the maintenance arm was remission at week 44 defined as CDAI score <150. In the induction arms, remission rates were significantly higher in the UST receiving patients, either at 130 mg or 6 mg/kg intravenously as compared to placebo (UNITI I: 34.3%, 33.7%, versus 21.5%, $P \leq 0.003$ for both comparisons with placebo; UNITI-2, 51.7%, 55.5%, and 28.7%, $P < 0.001$ for both doses). Similarly in the in the IM-UNITI arm, patients receiving UST 90 mg every 8 weeks or 12 weeks had significantly higher remission rates as compared to placebo (53.1%, 48.8%, respectively, versus 35.9%, $P = 0.005$ and $P = 0.04$, respectively).

The UNIFI study proved the efficacy of UST for use in UC [8]. It had an 8-week induction and 44-week maintenance arm. In the induction arm, 961 patients were assigned to receive either UST 130 mg or 6 mg/kg intravenously as compared to placebo, and those who had response to treatment were included in the maintenance arm to receive UST 90 mg either every 8 or 12 weeks versus placebo. The primary end point was clinical remission defined as total Mayo Score ≤2 and no sub-score >1 on any of the four Mayo scale components. At the end of 8 weeks, significantly higher number of patients receiving UST as 130 mg or 6 mg/kg intravenously were in remission compared to placebo (15.6%, 15.5% vs 5.3%, $P < 0.001$ for both comparisons). At the end of maintenance at 44 weeks, significantly higher number of patients receiving UST as 90 mg at 8 weks or 12 weeks were in remission compared to placebo (43.8%, 38.4% versus 24%, $P < 0.001$ and $P = 0.002$, respectively).

Another study looking at 334 patients with moderate to severe CD from three-phase three randomized controlled trials showed significantly higher endoscopic response as defined by reduction in change in the Simplified Endoscopic Activity Score for Crohn Disease (SES-CD), from baseline, at week 8 for patients given ustekinumab when compared to placebo (reduction of 2.8 versus a reduction of 0.7 points, $P = 0.012$) [9].

Pediatric Data

Data regarding the efficacy of ustekinumab in pediatric CD are not as robust as that in adults. The best data comes from a multicenter retrospective analysis of 44 pediatric patients who failed at least one biologic treatment and received open-labelled subcutaneous UST. Primary outcome was changes in mean abbreviated Pediatric Crohn Disease Activity Index (aPCDAI) and rate of clinical remission at 3 and 12 months. UST was shown to significantly lower aPCDAI at 3 months and 12 months (16 and 19.6 at 3 and 12 months respectively), and also shown to achieve 47.8% clinical response and 38.6% clinical remission [10]. However additional larger studies are awaited.

Safety

In a 3-year extension study of IM-UNITI evaluating the safety of UST in patients who were selected for a 5 year long term extension trial, 69.5% of patients who responded to Q8 week treatment and 61.9% of patients who responded to Q12 week treatment at the end of 44 weeks continued to be in remission at 3 years. The overall safety was similar for patients receiving UST versus placebo (389.7 versus 444.17 adverse events per 100 patient-years, P = NS) [11].

In both UNITI 1 and 2, the rates of adverse events for patients receiving 130 mg and 6 mg/kg intravenously were similar to placebo (UNITI 1: 64.6%, 65.9%, and 64.9%, respectively; in UNITI 2: 50.0%, 55.6%, and 54.3%, respectively). At the end of 1 year there were no deaths, three opportunistic infections in those receiving UST and no cases of reversible posterior leukoencephalopathy syndrome [9].

Similarly in the UNIFI study for UC, rates of adverse events for patients receiving 130 mg and 6 mg/kg intravenously were similar to placebo (41.4%, 50.6%, and 48.0%, respectively) in the induction phase. Even in the maintenance phase rates of adverse events for patients receiving 90 mg every 8 weeks or 12 weeks subcutaneously were similar to placebo (77.3%, 69.2% and 78.9%, respectively). Overall there were 3 deaths, 7/825 cancers and four opportunistic infections in those receiving UST [8].

Briakinumab

In a phase 2b multicenter, double-blind, parallel group study, 246 patients with CD who had failed prior TNFα antagonists were randomised to induction treatment with briakinumab vs. placebo, with responders entering the maintenance arm [12]. The study did not meet primary outcome, but patients in the treatment arm had numerically higher response and remission rates at 6, 12 and 24 weeks.No additional studies are currently in progress.

Selective IL23 Inhibition

In contrast to IL-12/23 inhibition, selective IL-23 inhibition has been previously shown to be associated with a decreased incidence of tumor formation and incidence of serious infections and major adverse cardiovascular events [13]. Therefore, IL-23-specific antagonism may provide similar or greater efficacy than blocking IL-12/23p40 and without the potential risks associated with blocking IL-12.

Brazikumab

This is a monoclonal antibody that targets the p19 sub-unit of IL-23. In a phase 2a double-blind, placebo-controlled study of adults with moderate to severe CD, with prior anti-TNF

therapy failure, 119 patients were randomly assigned 1:1 to Brazikumab (700 mg) or placebo intravenously at weeks 0 and 4. Patients received open-label 210 mg subcutaneously every 4 weeks from weeks 12 to 112. Clinical response was defined as 100-point decrease in CDAI score from baseline and clinical remission defined as CDAI score <150 at week 8. Patients receiving Brazikumab compared with placebo had significantly higher rates of clinical response (49.2% versus 26.7%, $P = 0.01$). There was a tendency to higher likelihood of response in patients with higher baseline serum concentrations of IL22, a cytokine whose expression is induced by IL23 [14].

There are current phase 2 studies to assess the efficacy and safety of brazikumab in patients with moderate to severe UC and long term data via open label extension (OLE) studies in CD patients is being collected [15]. Additionally, Phase 2b/3 assessment is ongoing. (https://clinicaltrials.gov/ct2/show/NCT03759288).

Pediatric Data

At the time of writing this chapter, there are no published data on the use of Brazikumab in children or adolescents with IBD.

Safety

Data from phase 2a trial referred to earlier showed that the most common adverse events were headache and nasopharyngitis. A similar proportion of treatment-related adverse events and serious adverse events of > Grade 3 severity occurred in both induction and maintenance study arms. Placebo patients had higher rates of treatment-related adverse events compared to treatment arms (21.7% versus 10.2%) [14].

Risankizumab

Risankizumab (BI 655066) is another monoclonal antibody that targets the p19 sub-unit of IL-23. In a randomised, double-blind, placebo-controlled phase 2 study conducted across 36 referral sites in North America, Europe, and southeast Asia, 121 adult patients (79% of whom had failed prior anti-TNF therapy) with moderate-severe CD, Risankizumab induced clinical remission in 31% patients versus 15% with placebo ($P = 0.048$) [16].

Additional larger studies to further assess the efficacy and safety of risankizumab in subjects with moderately to severely active CD and UC who failed prior biologic therapy are currently ongoing [17–19].

Recently, the results of ADVANCE (NCT03105128), a double-blind randomized phase 3 study evaluating efficacy and safety of Risankizumab as induction therapy in patients with moderate to severe CD was reported (**Reference:** D'Haens GD et al. DDW 2021, Abstract 775a). Eligible patients had a demonstrated inadequate response (IR) or intolerance to biologic therapy (bio-IR) and/or to conventional therapy (non-bio-IR), CD Activity Index (CDAI) 220-450, average (avg) daily(liquid/very soft) stool frequency (SF) ≥4 and/or avg. daily abdominal pain (AP) score ≥2, and Simple Endoscopic Score for CD (SES-CD) ≥6 (≥4 for isolated ileal disease) excluding the narrowing component. Patients were randomized 2:2:1 to receive IV Risankizumab 600 mg, 1200 mg, or placebo (PBO) at Weeks 0, 4, and 8. Randomization was stratified by number of prior biologics failed, baseline (BL) corticosteroid use, and BL SES-CD. Co-primary endpoints were clinical remission (per US protocol, CDAI <150; per ex-US protocol, avg. daily SF ≤2.8 and avg. daily AP score ≤1, not worse than BL for both) and endoscopic response (decrease in SES-CD >50% from BL [or for patients with isolated ileal disease and a BL SES-CD of 4, ≥2-point reduction from BL])at Week 12. Safety was assessed in patients receiving ≥1 dose of study drug. Risankizumab 600 mg and 1200 mg was found to be more effective than placebo at inducing clinical remission and endoscopic response at Week 12 in patients with moderate-to-severe CD. Both Risankizumab doses were generally well-tolerated and AEs were consistent with the known safety profile of Risankizumab.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of BI 655066 in children or adolescents with IBD.

Safety

Safety data from phase 2 trial showed that the most common adverse event was nausea and most common serious adverse event was worsening of underlying Crohn disease. No deaths were reported, and serious infections occurred in 3 patients in placebo and one patient in the treatment arm [16].

Mirikizumab

A phase 2 trial to study the efficacy and safety of Mirikizumab for patients with moderate to severely active UC from 14 countries with primary outcome of clinical remission (defined as Mayo subscores of 0 for rectal bleeding, with 1-point decrease from baseline for stool frequency, and 0 or 1 for endoscopy) at 12 weeks was conducted [20]. Patients ($n = 188$) were randomized to receive intravenous placebo versus 50 mg, 200 mg or 600 mg of Mirikizumb at induction, with responders (decrease in 9-point Mayo score, including ≥2 points and ≥35% from baseline with either a decrease of rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1) being randomized to receive 200 mg subcutaneously at Q4 weeks or Q12 weeks. At week 12, only the 200 mg group showed significantly higher remission and when compared to placebo

(22.6% versus 4.8%, $P = 0.004$). At week 52, 46.8% of patients given subcutaneous mirikizumab 200 mg every 4 weeks and 37.0% given subcutaneous mirikizumab 200 mg every 12 weeks were in clinical remission.

At DDW 2019, phase 2 study of Mirikizimab for moderate to severely active CD was presented. Primary outcome was assessing for endoscopic response defined as a 50% reduction from baseline in SES-CD score, at Week 12 [21]. Patients were randomized to receive either intravenous placebo versus 200 mg, 600 mg or 1000 mg of Mirikizumab. Significantly higher endoscopic response was seen compared to placebo for all Mirikizumab groups (25.8%, $P = 0.079$, 37.5%, $P = 0.003$, 43.8%, $P < 0.001$ for 200 mg,600 mg and 100 mg respectively, versus 10.9% for placebo).

At DDW 2021 phase 2 maintenance of the SERENITY trial was presented (Reference: Sands BE et al. DDW 2021, Abstract 132) (NCT02891226). Patients with moderate-to-severe CD were randomized 2:1:1:2 across 4 treatment arms (PBO, 200, 600, 1000 mg Mirikizumab, administered intravenously (IV) every 4 weeks (Q4W) at Weeks 0, 4, and 8. Patients who received miri and achieved ≥1 point improvement at Week 12 in Simple Endoscopic Score for Crohn Disease (SES-CD) were re-randomized 1:1 into double-blind maintenance to continue IV treatment assignment Q4W (IV-C; $N = 41$) or to 300 mg miri SC Q4W (SC; $N = 46$). Due to small sample sizes and lack of an apparent trend across doses at Week 52, all IV and all SC arms were pooled. Clinical and endoscopic endpoints at Week 52 were evaluated. Missing data were imputed as nonresponse.

Endoscopic (SES-CD) response rates at Week 52 were 58.5% (24/41) and 58.7% (27/46) in the IV-C and SC groups, respectively. PRO remission rates were 46.3% (19/41) and 45.7% (21/46) in the IV-C and SC groups, respectively. Among those with endoscopic response (50% reduction from baseline in SES-CD) at Week 12, 69.6% (16/23) and 66.7% (16/24) in the IV-C and SC groups, respectively, also had endoscopic response at Week 52. Among those with endoscopic remission at Week 12, 50.0% (3/6) and 64.3% (9/14) in the IV-C and SC groups, respectively, also had endoscopic remission at Week 52. One patient in each group discontinued due to an adverse event (AE), and similar frequencies of treatment-emergent AEs and serious AEs were reported in IV-C and SC groups.

The findings of this study demonstrated that Mirikizumab demonstrated sustained efficacy to 52 weeks by multiple measures, with few discontinuations due to AEs during the maintenance period. These Phase 2 data supported continued characterization of Mirikizumab efficacy and safety in Crohn disease in the ongoing VIVID Phase 3 program. Tne safety findings were consistent with the anti-IL-23 p19 class with few discontinuations in the re-randomized maintenance group due to AEs.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of Mirikizumab in children or adolescents with IBD. But there is a multicenter open labelled clinical trial ongoing for pediatric patients with UC [22].

Safety

In the phase 2 study for UC the most frequent treatment-emergent adverse events were nasopharyngitis, worsening of UC, anemia, headache, nausea, cough, and worsening of gastroenteritis during induction and worsening of UC, nasopharyngitis, headache, upper respiratory tract infection, arthralgia, hypertension, and influenza during maintenance. No deaths or hypersensitivity reactions were reported at the end of 1 year [20].

Similarly in the phase 2 study for CD the frequencies of serious adverse events and treatment-emergent adverse events across treatment groups were similar to placebo [21].

Guselkumab

This is another anti p19 sub-unit antibody specific to IL23. Guselkumab is currently undergoing phase 2/3 clinical trials for both CD (estimated completion in 2028) [23]and UC (estimated completion in 2025) [24].

Recent data was presented at DDW 2021 (reference: Sands BE et al. DDW 2021, Abstract Fr532 and D'Haens GD et al. DDW 2021, Abstract 455) The GALAXI 1 study was presented. GALAXI 1 is a phase 2, double-blind, placebo-controlled, multicenter study of guselkumab (GUS) in patients (pts) with moderately to severely active Crohn disease (CD) who had inadequate response or intolerance to conventional therapies (corticosteroid, immunosuppressant) and/or biologics (TNF antagonist, vedolizumab). Endoscopic improvement at Week (Wk) 12 following induction treatment was presented and the influence on biomarkers was also presented.

The GALAXI 1 study is a 5-arm Phase 2 double-blind placebo-controlled multicenter study of Guselkumab with Ustekinumab and Placebo. This represented a report on the interim pooled analysis of 3 Guselkumab arms versus placebo. Patients were randomized 1:1:1:1:1 into 5 arms: Guselkumab 200 mg, 600 mg, or 1200 mg IV at Wks 0, 4, 8; ustekinumab (UST) ~6 mg/kg IV at Wk 0 and 90 mg SC at Wk 8; or placebo (PBO) IV. Video ileocolonoscopies performed during screening and at Wk 12 were assessed by blinded central read. Interim analyses at Wk 12 evaluated SES-CD change from baseline and endoscopic response, healing, and remission (as defined in Table 34.1) in pts. treated with GUS vs PBO. Endoscopic outcomes were assessed by serum Guselkumab concentration quartiles. UST was a reference arm.

250 pts were evaluated; approximately 50% had failed biologic therapy. Baseline demographics and disease characteristics were generally similar among treatment groups (mean CD duration, 8.8 year; mean CDAI, 306.2; median SES-CD, 11.0). Per central endoscopy read, 29.6% of pts. had isolated ileal disease, 42.8% had colonic disease, and 27.6% had ileocolonic disease. At Wk 12, the mean reduction in SES-CD from baseline was greater in the Guselkumab combined group than in the PBO group (LS mean −4.6 vs −0.5, respectively) and was greater across all 3 Guselkumab induction dose groups vs PBO (Table 34.1). Across all Guselkumab induction doses, in the overall population, as well as biologic- and conventional-failure subgroups, a greater proportion of Guselkumab-treated pts. achieved endoscopic response vs PBO-treated pts. In the Guselkumab combined group, a greater proportion of pts. achieved endoscopic healing and remission vs PBO (17.3% and 14.0% vs 3.9% and 3.9%, respectively). Among conventional therapy failures, in the Guselkumab combined group vs the PBO group, 44.6% vs 10.7% achieved endoscopic response, 23.0% vs 0% achieved endoscopic healing, and 17.6% vs 0% achieved endoscopic remission, respectively. Neither a dose-response nor a consistent exposure-response relationship was observed with respect to endoscopic outcomes with GUS.

Thus, in pts. with moderate to severely active CD, the mean reduction in SES-CD from baseline was greater with GUS than with PBO. Endoscopic response, healing, and remission were seen in a greater proportion of Guselkumab-treated pts. vs PBO. Higher rates of endoscopic response, healing and remission occurred with Guselkumab in the conventional therapy failure sub-population compared with PBO, but small sample sizes limit conclusions. A dose-response relationship with GUS was not demonstrated for endoscopic outcomes within the induction dose-range evaluated. This data looks promising, but final results are awaited.

IL-6

Interleukin-6 (IL-6) is a cytokine with central roles in immune regulation, inflammation, hematopoiesis, and oncogenesis. It is a contributor of Th-17 differentiation [25]. Increased levels of IL-6 and soluble IL-6 receptor have been demonstrated in both serum and intestinal tissues of the patients with active Crohn disease, especially in those with more severe disease phenotypes [26].

PF-04236921 is a monoclonal antibody against IL-6. A phase II placebo-controlled study has been completed to evaluate the safety and efficacy of this subcutaneously administrated antibody in patients with active CD (the ANDANTE study) [27]. There were limitations of the study including early termination which led to small numbers of participants and technical problems with measurement resulting in unreliable or uninterpretable data.

A parallel-group, dose-ranging, double-blind trial with 4-week screening and 12-week treatment periods (ADVANTE I) was conducted in adults with CD who had prior inadequate response to anti-TNF therapy. They randomized 247 patients (1:1:1:1) to placebo, PF-04236921 10, 50 or 200 mg by subcutaneous injection on days 1 and 28 and 191 subjects were enrolled in the OLE and received PF-04236921 50 mg every 8 weeks up to six doses followed by 28-week follow-up (ADVANTE II). During the study the 200 mg dose was discontinued due to safety findings in another trial. Response rates as gauged by Crohn Disease Activity Index (CDAI)-70 with PF-04236921 50 mg were significantly greater than placebo at weeks 8 (49.3% vs 30.6%, $P < 0.05$) and 12 (47.4% vs 28.6%, $P < 0.05$). Week 12 CDAI remission rates were also higher with PF-04236921 50 mg than placebo (27.4% vs. 10.9%, $P < 0.05$) [28].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of PF-04236921 in children or adolescents with IBD.

Safety

Adverse effects noted in both studies included a worsening of disease activity, abdominal pain (including events of gastrointestinal perforation and abscess) and nasopharyngitis [28].

IL-13

Interleukin-13 (IL-13) is a central cytokine in the T helper 2 immune response [29–31]. IL-13 has effects on many cell types including B cells, monocytes, macrophages, epithelial cells, smooth muscle cells and neurons and has been indicated in the pathogenesis of many diseases including asthma and scleroderma in addition to IBD [32]. Its upregulation has been proposed to be a key driver of mucosal inflammation—specifically in UC.

Tralokinumab

Tralokinumab (CAT-354, Adtralza®) is an IL-13-specific human immunoglobulin G4 monoclonal antibody that binds to and neutralizes IL-13 [33, 34].

In a phase IIa, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial, 111 patients with UC (total Mayo score ≥6) were randomized to

tralokinumab 300 mg subcutaneous or placebo [35]. The primary endpoint of clinical response at week 8 was 38% (21/56) for tralokinumab vs. 33% (18/55) for placebo (P = 0.406). Clinical remission rate at week 8 was 18% (10/56) vs. 6% (3/55) (P = 0.033) and mucosal healing rate was 32% (18/56) vs. 20% (11/55) (P = 0.104) for tralokinumab vs. placebo.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of tralokinumab in children or adolescents with IBD.

Safety

Tralokinumab had an acceptable safety profile in the only phase IIa study to date [35]. The median duration of exposure was 84 days. The number of patients who experienced adverse events was similar in the tralokinumab and placebo groups. The most frequently reported adverse events were symptoms of UC and headache. The number of patients discontinuing treatment because of adverse events was similar in both groups and the most common adverse event leading to discontinuation was symptoms of UC.

Dectrekumab

Dectrekumab (QAX576) is a highly potent and specific inhibitor of human IL-13 activity in cell-based in vitro assays. A phase II study to assess the safety and efficacy of intravenously administered QAX576 in patients with fistulizing Crohn disease has been completed [36]. Another phase II study to test the safety and efficacy of the drug in the treatment of perianal fistulas has also been completed. Results are not available in either of the studies [37]. The study sponsor noted: " In this study, QAX576 was well tolerated. As expected IFX was a powerful agent to induce fistula closure. Blockade of IL-13 may be effective, too, as compared to historical placebo rates, although the very low patient number does not allow a formal assessment." (https://oak.novartis.com/21363/).

Pediatric Data

At the time of writing this chapter, there are no published data on the use of QAX576 in children or adolescents with IBD.

Bertilimumab

Bertilimumab is a fully human, IgG_4-type monoclonal antibody that blocks the activity of a protein called eotaxin-1. Eotaxin-1 plays an important role in inflammation and causes eosinophils to migrate towards sites of inflammation where they become activated and release substances that result in tissue damage and enhance inflammation.

A randomized, double-blind, placebo-controlled, parallel-group, multicenter study in adult patients with active moderate to severe UC is ongoing. Patients are currently being enrolled and eligible patients will be randomly assigned in a 2:1 ratio to one of two treatment groups, bertilimumab 10 mg/kg intravenously or matching placebo, respectively [38].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of Bertilimumab in children or adolescents with IBD.

IL-17

Vidofludimus

Vidofludimus (4SC-101, IMU-838) is a novel oral immunomodulatory drug that inhibits dihydro-orotate dehydrogenase and lymphocyte proliferation in vitro and inhibits interleukin (IL)-17 secretion in vitro, independently of effects on lymphocyte proliferation [39].

A phase IIa open-label, single-arm trial with vidofludimus (ENTRANCE trial) in IBD was performed [40]. The primary outcome was to assess remission-maintenance potential in steroid-dependent IBD patients upon steroid weaning (ECCO 2011). There were 26 CD and UC patients. Complete, partial and non response was seen in 53.9% (14/26), 34.6% (9/26) and 11.5% (3/26) of patients. There was no difference in response rates between CD (85.7%) and UC (91.7%). In addition, the average prednisolone consumption dramatically dropped during treatment with the drug.

Currently, a phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-finding study is actively recruiting patients with moderate-to-severe UC (CALDOSE-1) to evaluate the efficacy and safety of vidofludimus calcium for induction and maintenance therapy [41].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of vidofludimus in children or adolescents with IBD.

Safety

Vidofludimus was safe and well tolerated by all patients in the ENTRANCE trial [40]. A total of 75 adverse events were reported (53 mild, 18 moderate, and 4 severe) of which 19 adverse events were judged as possibly or probably drug-related and included nasopharyngitis, abdominal pain, fatigue, insomnia, glucosuria, leucocyturia, microhematuria, musculoskeletal pain, myalgia, tachycardia, and dyspepsia. No drug-related serious adverse events were reported.

IL-21

ATR-107

ATR-107 is a fully human anti-IL-21 receptor (IL-21R) monoclonal antibody designed to block IL-21 from binding and activating the receptor, as a novel approach to the treatment of systemic lupus erythematosus and other autoimmune diseases [42–44].

The first human ascending single-dose study was terminated in 2011, due to the development of anti-drug antibodies in 70% of the subjects and other factors. No other trials are currently planned for this agent.

NNC0114-0006

NNC0114-0006 is an anti-IL-21-antibody. A randomized, double-blind, placebo-controlled, parallel-group trial phase II study to assess the clinical efficacy and safety of NNC0114-0006 in subjects with active Crohn disease has been completed. Results are not yet known [45].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of NNC0114-0006 in children or adolescents with IBD.

Blockade of the Downstream Signaling Pathways Mediated by Cytokines

JAK/STAT Pathway

Janus kinases (JAK) 1, 2 and 3 and Tyk2 are extremely important in cytokine signaling that is involved in lymphocyte survival, proliferation, differentiation and apoptosis [45]. JAK3 is found only in hematopoietic cells and is part of the signaling pathway activated by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 which is crucial in the activation, function and proliferation of lymphocytes [46] (see Fig. 34.3). As an important component of the JAK-STAT signaling pathway, Tyk2 regulates IL12, INFα and IL23. Selective Tyk2 inhibition has the potential to achieve benefit in the treatment of several disease states including psoriasis, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), rheumatoid arthritis (RA), cancer, and diabetes mellitus.

Tofacitinib

Tofacitinib (CP-690,550) is an oral small molecule inhibitor of JAK 1 and 3. In vitro studies have shown that it interferes with Th2 and Th17 cell differentiation and blocks the production of IL-17 and IL-22 [48].

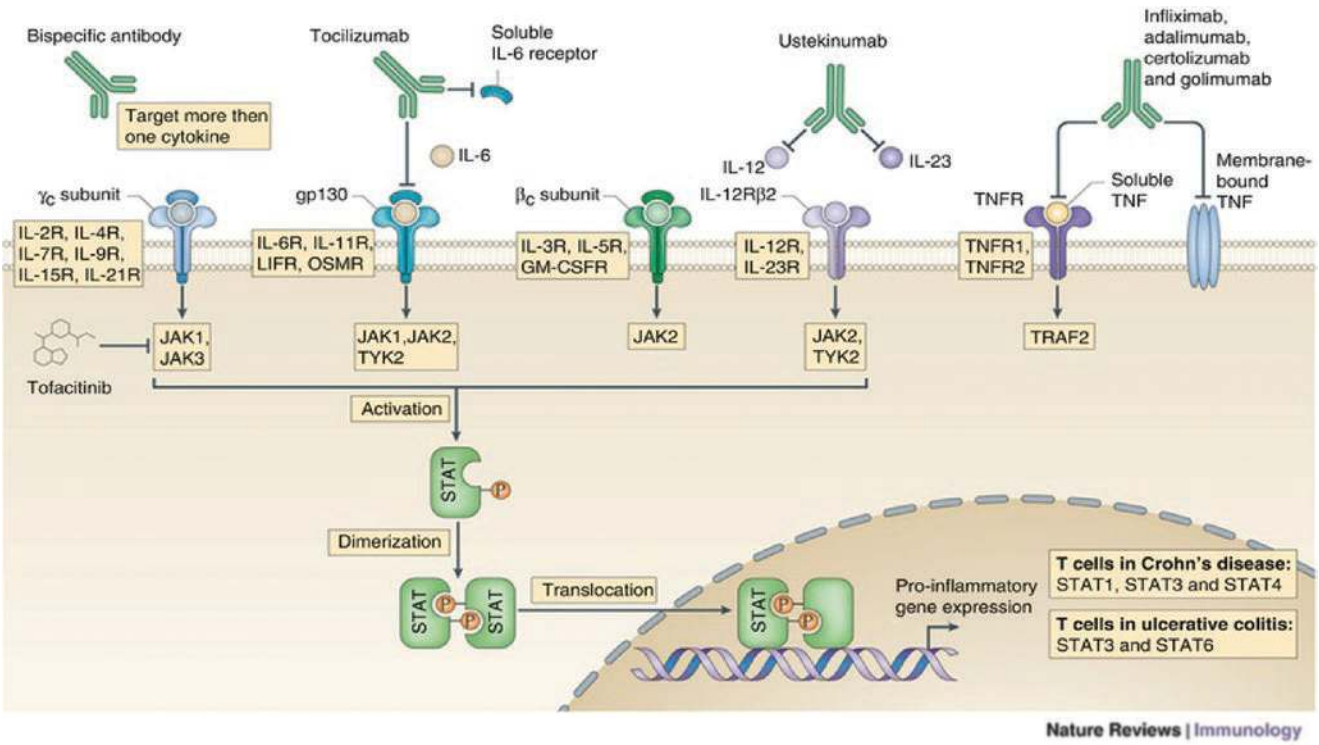

Fig. 34.3 JAK pathway inhibitors (Neurath [47])

Three phase 3, randomized, double-blind, placebo-controlled trials of tofacitinib therapy in adults with UC were conducted [49]. The OCTAVE Induction 1 and 2 trials included 598 and 541 patients with moderate to severely active UC and randomly assigned them to receive induction therapy with tofacitinib (10 mg twice daily) or placebo for 8 weeks. The OCTAVE Sustain trial re-randomised [1:1:1] clinical responders [$N = 593$] from induction studies to placebo, tofacitinib 5 mg BID, or 10 mg BID, for 52 weeks. Remission with tofacitinib vs. placebo at 8 weeks was 18.5% vs. 8.2% ($p = 0.007$) in OCTAVE 1 and 16.6 vs. 3.6% ($p < 0.001$) in OCTAVE 2. Remission at 52 weeks in the OCTAVE Sustain trial was achieved in 34.3% of the patients in the 5-mg tofacitinib group and 40.6% in the 10-mg tofacitinib group versus 11.1% in the placebo group ($P < 0.001$ for both comparisons with placebo).

Tofacitinib was also evaluated in patients with moderate to severely active CD. Patients were randomized to receive tofacitinib twice daily for 4 weeks at doses of 1 mg, 5 mg, 15 mg, or placebo [50]. The primary endpoint was not met in this phase II trial in CD patients receiving tofacitinib, but the placebo response rate was high. The primary endpoint was clinical response at week 4 and the rates were as follows: 36% ($P = 0.467$), 58% ($P = 0.466$), and 46% ($P \geq 0.999$) in those patients given 1, 5, or 15 mg tofacitinib twice daily versus 47% given placebo. As the clinical response was not significant, the trial was negative. However, the placebo response and remission rates were unexpectedly high and in addition, the reduction in fecal calprotectin and C-reactive protein levels among patients receiving 15 mg tofacitinib twice daily suggested biological activity of the drug.

Two additional randomised, double-blind, placebo-controlled, multicentre phase IIb studies were pursued. Adult patients ($n = 280$) with moderate-to-severe CD were randomised to tofacitinib 5 or 10 mg twice daily or placebo for 8 weeks [51]. Clinical responders ($n = 180$) were re-randomised to maintenance treatment with placebo, tofacitinib 5 or 10 mg twice daily for 26 weeks. Rate of clinical remission at 8 weeks was 43% vs. 43.5% vs, 36.7% with tofacitinib 10 mg twice daily, 5 mg twice daily and placebo respectively, which failed to meet statistical significance. At week 26, rates of clinical response or remission were 55.8% vs. 39.5% vs, 38.1% with tofacitinib 10 mg twice daily, 5 mg twice daily and placebo respectively, which again failed to meet statistical significance.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of tofacitinib in children or adolescents with IBD. There is an ongoing study evaluating Oral Tofacitinib in Children Aged 2–17 Years Old Suffering From Moderate to Severe Ulcerative Colitis (NCT04624230). This study is "designed to evaluate the efficacy, safety and pharmacokinetics (PK) of tofacitinib in pediatric participants with moderately to severely active UC. In the US patients with prior TNFi failure or intolerance will be enrolled. Outside of the US, TNFi naïve and TNFi experienced patients will be enrolled. All eligible participants will initially receive open label tofacitinib at a dose expected to produce equivalent systemic exposure to that observed in adults receiving 5 mg BID with the option for an individual dose increase to 10 mg BID adult dose equivalent if dose escalation criteria are met. The primary objective of this study is to evaluate the efficacy of tofacitinib based on remission in pediatric participants with moderately to severely active UC. The primary endpoint is remission by central read Mayo score following 44 weeks in the maintenance phase. Remission is defined by a Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0. The study Design is an open-label Phase 3 study that includes a screening period of up to 4-weeks duration, an 8-week or 16-week induction phase, a 44-week maintenance phase, and a 24-month extension phase for pediatric participants with moderately to severely active UC. Participants will have a follow-up visit 4 weeks after the last dose of study intervention and telephone contact 8 weeks later to assess for any adverse events (AEs)/serious adverse events (SAEs). The total maximum duration of this study will be up to 180 weeks." (reference: https://clinicaltrials.gov/ct2/show/NCT04624230).

Safety

In OCTAVE 1 adverse events occurred in 56.5% patients in 10 mg group and 59.8% in placebo. OCATVE-2 had adverse event rates of 54.1% in 10 mg and 52.7% in placebo [49]. In OCTAVE sustain, adverse events occurred in 72.2% in 5 mg group, 79.6% in the 10 mg group and 75.3% in placebo. In OCTAVE 1 and 2 rates of infections were higher for 10 mg group versus placebo 23.3% and 18.2% versus 15.6% and 15.2%, respectively for OCTAVE 1 and 2). In the SUSTAIN trial infections occurred at rates of 35.9% in 5 mg group, 39.8% in 10 mg group and 24.2% in the placebo arm. Most infections were mild to mkoderate in severity. In OCTAVE 1 and 2 herpes zoster infection occurred in 3 patients (0.6%) and 2 patients (0.5%), respectively, in tofacitinib groups and in 1 (0.8%) patient and no patients in the placebo groups. In the sustain trial, herpes zoster infection occurred in 3 patients (1.5%) in the 5 mg group, 10 (5.1%) in the 10 mg group, and 1 (0.5%) in the placebo group. Two non-melanoma skin cancers occurred in the induction trials and four occurred in the sustain trial. Of note, patients in induction and maintenance trials had high lipids (total cholesterol, high density lipoproteins and low-density lipoproteins) which plateaued at 4 weeks. This effect is of unknown significance. Three patients treated with tofacitinib (one at dose of 10 mg twice daily and two at dose of 15 mg twice daily) had an absolute neutrophil count of less than 1500 (with none being <1000).

In a composite assessment of all tofacitinib-treated UC, patients enrolled in phases 2,3, open label, long-term extension trials, the rates of herpes zoster were found to be increased compared to placebo at 5.6% [52]. These rates are higher in older and Asian patients and those with prior anti-TNF failure [53]. The overall risks of infections and mortality with tofacitinib seem to be similar to those observed with other biologic agents [54].

Based on interim analysis results from a post-marketing trial in rheumatoid arthritis, the tofacitinib package insert now contains a boxed warning describing the increased risk of thrombosis and mortality with a dosage of 10 mg twice daily [55].

However, in UC, Sandborn et al. performed a post hoc analysis of data from induction, maintenance and overall patients receiving ≥1 dose of tofacitinib 5 or 10 mg b.d. in any phase 2, 3 or open label extension study cohorts [56]. Of the 1157 patients (2404 patient-years exposure; ≤6.1 years' tofacitinib treatment); one patient had deep vein thrombosis and four had pulmonary embolism, all during the OLE study, on a predominant dose 10 mg b.d. (83% of overall cohort patients received predominant dose 10 mg b.d.), and in the presence of venous thromboembolism risk factors.

Filgotinib

Filgotinib (GLPG0634) [brand name: Jyseleca] selectively inhibits JAK1 receptors. The FITZROY study was a randomized, double-blind, placebo-controlled phase 2 trial that studied the efficacy and safety of filgotinib for the treatment of moderate-to-severe Crohn disease [57]. From 52 European centers, 175 patients were randomly assigned (3:1) to receive filgotinib 200 mg once a day or placebo for 10 weeks. The primary endpoint was clinical remission, defined as CDAI less than 150 at week 10. After week 10, patients were assigned based on responder status to filgotinib 100 mg once a day, filgotinib 200 mg once a day, or placebo for additional 10 weeks., At week 10, 47% patients in the filgotinib group achieved clinical remission versus 23% patients in the placebo group ($p = 0.007$). In TNF naïve patients this effect was even larger at 60% clinical remission for Filgotinib group versus 13% for placebo.

Phase-III studies, which include CD patients with the perianal fistulizing disease and isolated small bowel disease are still ongoing and will help decide whether Filgotinib will be a worthwhile drug in the treatment of CD [58]. A combined phase 2b/3 study for the efficacy and safety of filgotinib in the induction and maintenance of remission in subjects with moderately to severely active UC was completed in May 2020 and the results have been presented recently [59]. Data from the SELECTION trial were presented at DDW 2021.

The SELECTION induction studies aimed to evaluate the efficacy and safety of FIL as a therapy for patients with moderate to severely active UC. This phase 2b/3, double-blind, randomized, placebo-controlled trial included two induction studies and one maintenance study. Eligible patients were aged 18–75 years with moderately to severely active ulcerative colitis for at least 6 months before enrollment (induction study A: inadequate clinical response, loss of response to or intolerance to corticosteroids or immunosuppressants, naive to tumour necrosis factor [TNF] antagonists and vedolizumab [biologic-naive]; induction study B: inadequate clinical response, loss of response to or intolerance to any TNF antagonist or vedolizumab, no TNF antagonist or vedolizumab use within 8 weeks before screening [biologic-experienced]). Patients were randomly assigned 2:2:1 to receive oral filgotinib 200 mg, filgotinib 100 mg, or placebo once per day for 11 weeks. Patients who had either clinical remission or a Mayo Clinic Score response at week 10 in either induction study entered the maintenance study. Patients who received induction filgotinib were rerandomized 2:1 to continue their induction filgotinib regimen or to placebo. Patients who received induction placebo continued receiving placebo. The primary endpoint was clinical remission by Mayo endoscopic, rectal bleeding, and stool frequency subscores at weeks 10 and 58.

The results of this study demonstrated Filgotinib 200 mg was well tolerated, and efficacious in inducing and maintaining clinical remission compared with placebo in patients with moderately to severely active ulcerative colitis [60].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of filgotinib (GLPG0634) in children or adolescents with IBD.

Safety

Adverse events in the FITZROY trial were combined, and the pooled analysis of adverse events was similar between Filgotinib and placebo groups (75% versus 67%) [57]. Serious adverse events were encountered in 9% of patients in Filgotinib group versus 4% in the placebo group. Serious infections were reported in 3% of patients in the Filgotinib group versus none in the placebo group. There was a 11% increase in HDL and 12% increase in LDL seen in patients treated with Filgotinib for 20 weeks.

Upadicitinib

Upatacitinib (ABT-494) is an oral JAK 1 selective inhibitor. Sanborn et al. evaluated the safety and efficacy of a JAK 1 inhibitor upadacitinib in CD patients who had inadequate

response or intolerance of immunomodulators or anti-TNF therapy in phase II, multicenter, randomized, double-blind placebo-controlled trial [61]. This trial included 220 patients with moderate-to-severe CD (CDAI 220-450), where patients were randomised to upadacitinib 3, 6, 12, 24 mg twice a day, 24 mg once a day or placebo for 16 weeks. The primary endpoints were clinical remission at week 16 (stool frequency [SF] ≤1.5 or abdominal pain [AP] ≤1, and both no worst from baseline) and endoscopic remission at week 12/16 SES-CD score ≤4 and ≥2 point reduction from baseline, no subscore >1). Significantly more patients achieved clinical remission with 6 mg twice-a-day dose when compared with placebo (27% vs 11% $P \leq 0.05$). There was a significant dose relationship for endoscopic remission when doses of 12 mg, 24 mg twice a day and 24 mg once a day compared to placebo (8% $P \leq 0.05$, 22% $P \leq 0.001$, 14% $P \leq 0.01$ and 0% respectively). This study demonstrated both clinical and endoscopic benefits with 6 mg doses and above. Upadacitinib use also results in a significant and sustainable reduction in markers of inflammation.

Another double-blind, phase 2 trial in adults with moderate to severe UC was conducted by Sandborn et al. [62]. Patient were randomly assigned to receive placebo versus or 7.5 mg, 15 mg, 30 mg, or 45 mg, extended release once daily for 8 weeks. Primary end points were clinical remission as per adapted Mayo score at week 8. At week 8 there was higher rates of clinical remission in Upadicitnib groups versus placebo (8.5% $P = 0.052$, 7.5 mg; 14.3% $P = 0.013$, 15 mg; 13.5% $P = 0.011$, 30 mg; and 19.6% $P = 0.002$, 45 mg versus 0%, placebo). Similarly significantly higher endoscopic improvement was achieved in 14.9%, 30.6%, 26.9% and 35.7% of Upadicitnib 7.5 mg, 15 mg, 30 mg, or 45 mg, respectively, when compared to 2.2% receiving placebo ($P = 0.033$, $P < 0.001$, $P < 0.001$, and $P < 0.001$ compared with placebo, respectively).

Pediatric Data

At the time of writing this chapter, there are no published data on the use of Upadicitinib in children or adolescents with IBD.

Safety

In the phase-2 CD trial higher rates of adverse events were observed during induction with a higher Updaicitinib dose (>12 mg twice daily) [61]. Similarly, the highest serious adverse event rates were also seen in >12 mg twice daily group (28%). The most frequently observed adverse events were headache, worsening of CD, fatigue, upper respiratory tract infection, urinary tract infection, nausea, vomiting, and acne. During induction and maintenance periods 9 patients and 5 patients, respectively developed serious infections in the Upadicitnib group. Herpes zoster was encountered in 1 and 2 patients receiving upadicitnib in the induction and maintenance arm, respectively. There was 1 acute myocardial infarction, 1 non melanoma skin cancer, 1 Hodgkins lymphoma and 1 thymus cancer reported. Elevations in total cholesterol, LDL, HDL and CPK levels and decreases in triglyceride levels were observed in the upadacitinib 24-mg twice-daily arm compared with the placebo at week 16; total cholesterol and LDL levels were also significantly elevated in the 12-mg twice-daily group vs placebo.

In the phase-2 UC trial, a higher incidence of adverse events was seen in the treatment group as compared to placebo (0%, 4.1%, 5.8%, and 5.4%, 10.9%, for upadacitinib 7.5 mg, 15 mg, 30 mg, and 45 mg once daily and placebo, respectively) [62]. One herpes zoster event was noted in the Upadicitinib group at 45 mg once daily. One participant on 45 mg once daily had an acute pulmonary embolism and mild acute deep venous thrombosis, but this was seen 26 days after discontinuing drug and with worsening of underlying UC. Similar to CD study, elevations of cholesterol, LDL, HDL and CPK levels were noted in all groups on Upadicitinib.

Peficitinib

Peficitinib [Smyraf® (Astellas Pharma)] is a Janus kinase (JAK)1, JAK2, JAK3 and tyrosine kinase (Tyk)2 (pan-JAK) inhibitor recently approved in Japan for the treatment of rheumatoid arthritis. A Phase IIb multi-center randomized, double-blind, placebo-controlled, parallel group, dose-response trial evaluating the safety and efficacy of peficitinib (ASP015) a nonselective JAK inhibitor was done in patients with moderate-to-severe active UC [63]. Patients received either placebo versus 25 mg once daily, 75 mg once daily, 150 mg once daily., and 75 mg twice daily of study drug. The primary outcome was Mayo score change from baseline at week 8, which did not meet statistical significance, but was met by numerically higher proportion of patients receiving 75 mg twice daily peficitnib.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of Peficitinib in children or adolescents with IBD.

Safety

Adverse, serious adverse events, and serious infection rates in the patients receiving Peficitinib were similar to placebo (45.5% versus 34.9%; 4.7% versus 3.4%; 12.5% versus 14% for Peficitinib versus placebo,respectively) [63]. Elevations in total cholesterol, LDL, HDL and CPK levels were also observed with Peficitinib, especially at higher doses.

TD-1473

TD-1473-an oral gut-selective pan-JAK inhibitor-TD-1473 is an orally administered nonselective JAK inhibitor that has been evaluated in a phase I trial in patients with

moderate-to-severe UC showing significant endoscopic improvement in patients receiving 20 mg, 80 mg or 270 mg daily versus placebo (20%, 30%, 18% versus 0% for TD-1473 versus placebo) [64]. TD-1473 is a gut-selective treatment specifically designed to distribute adequately and predominantly to the tissues of the intestinal tract, treating inflammation in those tissues while minimizing its systemic exposure.

TGF-β

One mechanism by which Crohn disease develops involves transforming growth factor (TGF)-b which is a suppressive cytokine [65, 66]. SMAD7 is an endogenous inhibitor of the immunosuppressive cytokine transforming growth factor-β1. In CD, TGF-b1 activity is inhibited by high Smad7, an intracellular protein that binds to the TGF-b1 receptor and prevents TGF-b1-driven signaling [67, 68].Studies in mice have consistently shown that the induction of experimental CD-like colitis is associated with enhanced expression of Smad7 and reduced TGF-b1 activity [67]. The inhibition of Smad7 in CD mucosal cells with a specific antisense oligonucleotide has been demonstrated to restore TGF-b1 activity which therefore down-regulates the production of inflammatory cytokines [69].

Mongersen

GED0301 is an antisense oligonucleotide targeting SMAD7 and is an oral gastro-resistant compound with a pH-dependent, delayed-release of the oligonucleotide in the terminal ileum and right colon.

A phase I clinical trial was performed which showed that GED0301 in active, steroid-dependent/resistant CD patients resulted in a clinical benefit in all patients [70, 71]. In a placebo-controlled phase II study (IGONI) in patients with active CD, patients were randomized to receive induction treatment with different doses of Mongersen or placebo for 2 weeks [72]. The primary endpoint was clinical remission and this was seen in 55, 65, and 9.5% of patients receiving Mongersen 40 mg/day, 160 mg/day, or placebo ($p < 0.0001$, for both comparisons) at 15 days and maintained for ≥2 weeks. A post hoc analysis of the IGONI study noted that CD patients with higher CDAI scores achieved clinical remission most frequently with the highest mongersen dose, without any significant impact of disease duration and baseline CRP level [73].

A subsequent trial randomly assigned 63 CD patients to 4-, 8-, or 12-week course of mongersen 160 mg/day and found that at week 12, 32% (4 weeks), 35% (8 weeks), and 48% (12 weeks) of patients receiving mongersen were in clinical remission (CDAI < 150) and endoscopic improvement occurred in 37% of all participants [74].

Based on the above promising results, a phase 3, blinded study was pursued where patients were randomized (1:1:1:1) to placebo, mongerson 160 mg for 12 weeks followed by 40 mg continuously, or alternating placebo with 40 or 160 mg every 4 weeks through week [75]. This study was prematurely terminated based on its concerning results where rates of 52 week clinical remission were similar among individuals in mongersen groups and placebo. At week 12 more patients who received placebo had achieved endoscopic response and at week 12 and 52 endoscopic endpoints were similar across groups. Several study design flaws have been suggested to be responsible for the negative results and the premature termination of the study [76]. However, since then subsequent studies exploring the role of mongersen in CD therapy have been terminated or withdrawn based on the sponsor's decision.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of GED0301 in children or adolescents with IBD.

Safety

A phase I clinical trial using GED0301 in active, steroid-dependent/resistant CD patients was safe and well tolerated [70]. Adverse events were similar across the treatment groups in two phase II clinical trials [72, 74].

However in the phase 3 trial similar rates of treatment-associated adverse events were reported for the treatment group versus placebo (70.2% versus 71.3%, GED-0301 versus placebo) [75]. Most frequently reported events were arthralgia, exacerbation of CD, abdominal pain, upper respiratory tract infection, pyrexia, headache, nausea, and diarrhea. Adverse events were predominantly secondary to poorly controlled CD from poor treatment response, and also two deaths in the mongersen group (due to small intestinal obstruction and pneumonia) occurred.

Targeting Chemokines

Chemokines are cytokine proteins expressed in lymphoid and nonlymphoid tissue, thought to be involved in leukocyte trafficking. Persistent, aberrant leukocyte chemotaxis to inflamed mucosa is thought to play a role in the pathogenesis of IBD. Increased expression of several chemokines has been reported in patients with UC and Crohn disease.

Anti CXCR3/CXCL10

Interferon-γ-inducible protein-10 (IP-10 or CXCL10) is a chemokine that plays an important role in the migration of cells into sites of inflammation by influencing the activation and migration of activated T-cells, monocytes, eosinophils, natural killer, epithelial and endothelial cells [77, 78].

CXCL10 has been found to be expressed in higher levels in the colonic tissue and plasma of patients with UC [79, 80].

BMS936557 (MDX-1100, Eldelumab)

Mayer and colleagues in 2014 published data from an 8-week phase II, double-blind, multicenter, randomized study in patients with active UC [77]. Patients with moderately to severely active UC were given either BMS-936557 (10 mg/kg) or placebo intravenously every other week. The primary endpoint was the rate of clinical response at day 57. Primary and secondary endpoints were not met. However, what was found was that with higher steady-state trough levels of BMS-936557 (108–235 μg/mL), there was an increased clinical response (87.5% vs. 37% $p < 0.001$) and histological improvement (73% vs. 41% $P = 0.004$) compared to placebo.

In a phase IIb study of patients with CD patients ($n = 121$) with CDAI ≥220 and ≤450 were randomly assigned 1:1:1 to placebo or intravenous eldelumab 10 or 20 mg/kg given on days 1 and 8 and then every other week [81]. Patients with a score of 2–3 on the ulcerated surface subscore of SES-CD in at least 1 of 5 segments had a follow up endoscopy at 11 weeks. Primary outcome was defined as a reduction in CDAI 100 points from baseline or an absolute CDAI score <150 (clinical remission) and endoscopic improvement. There was a trend towards efficacy as remission and response rates at week 11 for the 10 mg/kg dose, 20 mg/kg and placebo groups were 22.5 and 47.5%, 29.3 and 41.5%, vs. 20 and 35% and were higher in anti-TNF-naive patients versus those patients who experienced anti-TNF failures. Both drug groups achieved a greater reduction from baseline in mean endoscopy scores compared to placebo and were similar in the eldelumab-treated groups across the anti-TNF-naive and anti-TNF failure subgroups.

In a 11-week Phase IIb study, 252 adult patients with active UC were randomised 1:1:1 to placebo or eldelumab 15 or 25 mg/kg intravenously on Days 1 and 8, and alternate weeks thereafter [82].Primary outcome was clincal remission defined as Mayo score ≤2; no individual subscale score >1. Results showed numerically higher remission and response rates with eldelumab 25 mg/kg [17.6% and 47.1%, respectively] and 15 mg/kg [13.1% and 44%] versus placebo [9.6% and 31.3%].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of BMS936557 in children or adolescents with IBD.

Safety

In the UC phase II study infusion reactions occurred in 19%, 14%, and 5% in the 25 mg/kg, 15 mg/kg, and placebo groups, respectively, without any detectable anti-drug antibodies [77]. The CD phase 2 study also noted higher infusion reactions in the study drug group (10% and 27% of patients receiving 10 mg/kg and 20 mg/kg arms), with 3 cases being considered serious [81]. Rates of infections in the UC phase 2 trial were 26% (25 mg/kg), 17.9% (15 mg/kg) and 18% (placebo) with the most common type of infection being nasopharyngitis [82].

Anti CCR9/CCL25

The chemokine CCL25 and its receptor CCR9 are essential for optimal mucosal immune development and function, with the latter being expressed by 58–97% of lymphocytes imprinted with guttropism [83]. Elevated serum levels of CCL25 are found to be present in patients with UC [84] and, most significantly, a strong positive correlation between CCL25 gene expression in the colonic mucosa and both the Mayo endoscopic sub-score and mucosal TNFα levels in UC patients has been noted [85].

Vercirnon (CCX282-B)

This is an orally bioavailable CCR9 antagonist, which is a potent inhibitor of CCR9+ T cell-mediated chemotaxis in vitro, and shows near complete protection against ileitis and attenuation of colitis in animal models [86].

The PROTECT-1 phase IIb trial randomly allocated patients with CD to placebo or one of three treatment dosages, organized into: an induction phase (induction of clinical response at Weeks 8 and 12); an active, open-label study phase (4 weeks) in which all eligible participants received CCX282-B at 250 mg twice daily; and a maintenance period in which patients who showed clinical response during the active phase were re-randomised to receive placebo or CCX282-B at a dose of 250 mg twice daily [87]. The induction phase of PROTECT-1 failed to attain its primary endpoint of a significant reduction in the CDAI of 70 points at Week 8. During the maintenance phase, remission was

achieved in 47% of patients on CCX282-B treatment compared with 31% of those on placebo ($P = 0.012$).

In a phase III double-blind randomised placebo-controlled trial (SHIELD-1) conducted over 162 centres in 23 countries, CD patients with active disease, who had failed corticosteroid or immunosuppressive therapy were enrolled [88]. In the 608 participants, the placebo, 500 mg od and 500 mg twice daily vercirnon arms showed no significant difference in remission rates. Clinical trial design flaws and higher rate of anti-TNF exposed patients in the SHIELD-1 study have been hypothesized as possible explanations to address the discrepancy in results between PROTECT-1 and SHIELD-1.

In the SHIELD-4 study, patients with moderate-to-severe Crohn disease were randomized for a double blind 12 week induction study with 500 mg once daily or twice daily vercirnon or placebo, followed by a phase 3 maintenance trial (SHIELD-2) [89]. An incremental increase in response and remission rates with the higher dose of vercirnon, similar to PROTECT-1 was noted, however primary endpoints of CDAI ≥100-point response at week 12 were not met.

In UC a first-in-human, double-blind, randomized, placebo-controlled trial was performed to evaluate safety, tolerability, and immunological response of selective removal of circulating CCR9-expressing monocytes by leukapheresis in patients with moderate to severe disease [90]. Patients received five sessions of leukapheresis every other day, with a C-C chemokine ligand 25 [CCL25; CCR9 ligand] column or a placebo column. Pro-inflammatory HLA-DRhi cells ($p = 0.039$) and Mayo score ($p = 0.016$) decreased significantly in the active treatment group whereas no statistically significant change was seen in the placebo group ($p = 0.469$ and $p = 0.125$ respectively). A dose-response correlation was observed between the blood volume processed and clinical outcome. No major safety concerns were raised and the procedure was well tolerated.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of CCX282-B in children or adolescents with IBD.

Safety Data

While the phase 2 study noted no specific safety concerns [87], in the phase 3 trial, patients in the vercirnon group, especially with higher treatment doses, showed greater incidence of gastrointestinal adverse events (30%, 37%, and 48% for placebo, Vercirnon once daily, and Vercirnon twice daily respectively [$P < 0.001$, 500 mg twice daily vs placebo] [88].The most common adverse effects were abdominal pain, nausea, dyspepsia and CD worsening.

Antiadhesion Molecules

Natalizumab

Natalizumab is a humanized IgG_4 monoclonal antibody against the adhesion molecule α4 integrin, which is involved in migration of leukocytes across the endothelium, and is upregulated in sites of inflamed endothelium. Six randomized, double-blind, placebo-controlled trials assessed the efficacy in patients with Crohn disease, whereas only one uncontrolled pilot study has been conducted in patients with UC.

Three Phase III trials have been conducted in CD. In Efficacy of Natalizumab as Active Crohn Therapy (ENACT-1), 905 patients with moderate to severe Crohn disease were randomly assigned to receive induction therapy at weeks 0, 4, and 8 with either natalizumab 300 mg or placebo [91]. The primary endpoint in the induction trial was clinical response defined as at least 70-point decrease in baseline CDAI score at week 10 and it was achieved in 56% and 49% of natalizumab and placebo recipients, respectively ($P = 0.05$) [80]. In ENACT-2, 339 patients who had a response to natalizumab in induction ENACT-1 trial at both week 10 and 12 were randomly reassigned to receive 300 mg of natalizumab or placebo every 4 weeks from week 12 through week 56 [91]. The primary endpoint in ENACT-2 trial was a sustained response through week 36. Patients with at least 70-point increase in CDAI score after week 12 with an absolute CDAI score of at least 220 or needed therapeutic intervention after week 12 were considered to lose response. Rates of sustained response at week 36 were 61% in patients receiving maintenance treatment with natalizumab and 28% in those receiving placebo maintenance ($P < 0.001$). Patients who maintained remission on natalizumab over 12 months in the ENACT-2 trial were enrolled into a subsequent phase III, open-label, 2-year open-label extension trial designed to assess long-term efficacy and safety of natalizumab [92]. This open-label trial comprised of 146 patients who received 12 natalizumab infusions over 12 months. The proportion of patients who maintained remission after 6 (week 24) and 12 (week 48) additional infusions of natalizumab was 89% and 84%, respectively. This open-label extension trial supported data from ENACT-2 trial that natalizumab maintains remission over additional 12 months in patients with sustained remission on natalizumab in the preceding 12 months.

In the ENCORE trial, 509 patients with moderate to severe Crohn disease were randomized to receive natalizumab 300 mg or placebo at weeks 0, 4, and 8 [93]. Natalizumab was significantly superior over placebo in

inducing remission at week 8 that was sustained through week 12 (primary endpoint defined as at least 70-point decrease in CDAI score) with respective proportions of patients of 48% vs. 32% ($P < 0.001$).

Finally, Sands et al. performed a placebo-controlled trial in which 79 patients with active Crohn disease during ongoing treatment with infliximab 5 mg/kg every 8 weeks for at least 10 weeks before initiation of randomization were randomly assigned to receive three intravenous infusions of either natalizumab 300 mg or placebo every 4 weeks while continuing their initial infliximab regimen during the duration of the trial [94]. At week 6 patients treated with natalizumab plus infliximab experienced mean decrease in their CDAI score of 37.7 points, while those treated with placebo plus infliximab experienced small increase in CDAI score of a mean of 3.5 points ($P = 0.084$). A trend towards greater efficacy of combined treatment with natalizumab and infliximab over infliximab alone was shown in patients with active Crohn disease not responding to infliximab therapy.

Gordon et al. published results of one small open-label study of 10 patients with active UC who were treated with a single infusion of natalizumab 3 mg/kg [95]. All patients had their disease activity evaluated using Powell-Tuck score 2 weeks after infusion. Treatment with natalizumab resulted in significant decrease in median disease activity score from 10 at baseline to 6 at 2 weeks postinfusion ($P = 0.004$). It was suggested that future randomized, placebo-controlled trials are warranted to further assess the efficacy of natalizumab in UC.

Overall, natalizumab, was the first non-anti-TNF biological drug to be approved for treatment of CD patients and is an effective option for patients with refractory CD. However, the association with the serious adverse event, PML and the current availability of more specific anti-integrin drugs with a more favorable safety profile, has limited further studies of natalizumab. However, its use in select patients, may be considered after a risk-benefit consideration.

Pediatric Data

There was only one open-label study conducted on 38 pediatric patients (ages 12–17 years) with active Crohn disease that assessed the efficacy of natalizumab in a pediatric population [96]. Among 38 enrolled patients 31 of them received three intravenous infusions of natalizumab 3 mg/kg at weeks 0, 4, and 8. Disease activity was measured using Pediatric Crohn disease Activity Index (PCDAI) at baseline and then every 2 weeks through week 12. There was a significant decrease observed in PCDAI score from baseline at every time point ($P < 0.001$) with the greatest decrease observed at week 10 with 55% of patients achieving clinical response (>15-point decrease from baseline) and 29% of patients achieving clinical remission (PCDAI <10). These promising findings however need to be validated in large randomized controlled trials.

Safety

In one study in patients with Crohn disease, 7% of patients given one or two induction doses of natalizumab (at weeks 0 and 4) had formed anti-natalizumab antibodies at 12 weeks [91]. Patients in the ENACT-2 trial who received concomitant immunosuppressants did not develop persistent anti-natalizumab antibodies, compared to 7.5% of patients who received natalizumab alone [97].

The largest ENACT-1 ($n = 905$) and ENACT-2 ($n = 339$) trials of natalizumab observed that serious adverse events occurred in similar proportion of patients in both trials (7% in natalizumab and placebo arms in induction ENACT-1 trial and 8% in natalizumab arm and 10% in placebo arm in maintenance trial) [97, 98]. However, one patient died (three doses of natalizumab combined with azathioprine during ENACT-1, placebo with azathioprine during ENACT-2 and -5 doses of natalizumab alone after completion of ENACT-2 trial) from progressive multifocal leukoencephalopathy, associated with the JC virus was observed [99]. In the other large induction trial ENCORE (n=509) a similar proportion of adverse events was observed between natalizumab (85%) and placebo (82%) without any deaths [93]. The most common adverse events that were observed in at least 10% among either treatment arms were headache, nausea, abdominal pain, nasopharyngitis, dizziness, fatigue, and exacerbation of Crohn disease. There was a significant greater proportion of patients in natalizumab group versus placebo that experienced nasopharyngitis (11% vs. 6%, $p < 0.05$), headache (29% vs. 21%, $p < 0.05$) and hypersensitivity reaction (4% vs. 0.8%, $p < 0.05$). On the other hand, exacerbation of Crohn disease was observed in greater proportion of placebo treated patients when compared to natalizumab (13% vs. 7%, $P < 0.05$).

A placebo-controlled trial by Sands et al. assessed primarily safety of concurrent therapy with natalizumab in 79 patients with Crohn disease already receiving infliximab [94]. The observed incidence of adverse events was similar in the treatment groups (natalizumab plus infliximab vs. infliximab plus placebo). The most frequent adverse events in both groups were headache, Crohn disease exacerbation, nausea, and nasopharyngitis. No one experienced a hypersensitivity-like reaction to natalizumab, whilst 4 patients (5%) experienced such reactions to infliximab. The development of antibodies to natalizumab was reported in 4% of patients whereas antibodies to infliximab were detected in 14% of patients.

Data from pediatric open-label study showed that the most common adverse events were headache (26%), pyrexia

(21%) and exacerbation of Crohn disease (24%) [96]. Anti-natalizumab antibodies were detected in 8% of patients.

Clinical trials and marketing of natalizumab were suspended in February 2005 after two patients with multiple sclerosis treated with natalizumab and interferon beta-1A developed progressive multifocal leukoencephalopathy (PML) from reactivation of the latent human Jacob Creutzfeldt polyoma virus [100, 101]. A third patient treated with natalizumab and prior exposure to azathioprine was reclassified from malignant astrocytoma to PML [102]. An independent adjudication committee performed a safety evaluation in all patients who had recently been treated with natalizumab in clinical trials. Evaluation consisted of a referral to a neurologist, brain magnetic resonance imaging, and polymerase chain reaction analysis of cerebral spinal fluid and serum for JC virus. Of 3826 initial patients enrolled in clinical trials of natalizumab, safety evaluation included 87% (1275), 91% (2248), and 92% (296) of patients with Crohn disease, multiple sclerosis, and rheumatoid arthritis patients. No additional cases of PML were identified. The median duration of treatment for all patients was 17.9 months, while that of patients with Crohn disease was 7 months. The absolute risk of developing PML during treatment with natalizumab was 1:1000 (0.1%) with 95% confidence intervals of 1:200–1:2800 [103]. The FDA reapproved natalizumab for multiple sclerosis in September 2006, with the requirement of mandatory participation in a risk management and registry program called the TOUCH program [99].

In the meta-analysis encompassing 1771 participants they noted rates of adverse effects after 1, 2 and 3 infusions of natalizumab as 74%, 86% and 86% (compared to 81%, 81% and 83% among the placebo participants) [104]. The corresponding rates of serious adverse effects after 1, 2 and 3 infusions were 10%, 9% and 7% with natalizumab (versus 11%, 11% and 8% with the placebo). Withdrawal due to an adverse effect at these time points occurred in 1%, 3% and 8% of those treated with natalizumab (versus 3%, 3% and 10% of those treated with placebo). Hence overall the rates of AEs (moderate quality evidence), withdrawals due to AEs (low-quality evidence) and serious AEs (low-quality evidence) were similar across the groups at 10 weeks. The adverse events included headache, exacerbation of CD, nausea, and nasopharyngitis. Although natalizumab is asoosicated with the development of PML, the studies included in the meta-analysis were not powered to detect it.

Vedolizumab (MLN-002, MLN-02, Entyvio®)

Vedolizumab (also known as MLN-002 and MLN-02) is a recombinant IgG1 humanized monoclonal antibody against the adhesion molecule α4β7 integrin and is the first gut-selective humanized monoclonal antibody. In contrast to natalizumab, vedolizumab specifically targets α4β7 integrins that are exclusively present on gut homing T cells and as a result the interaction between α4β7 and antimucosal vascular addressin cell adhesion molecule (MAdCAM)-1 is blocked.

GEMINI I was a double-blind, phase III trial in patients with moderate to severe UC [105]. Patients were randomized to receive vedolizumab (300 mg intravenously) or placebo on day 1 and day 15. The primary endpoint of the induction trial was clinical response at week 6 and this was achieved in 47% vs. 26% of patients receiving vedolizumab and placebo, respectively ($P < 0.0001$). Clinical remission at week 6 was seen in 17% versus 5% on vedolizumab vs. placebo ($P = 0.0009$) and mucosal healing was seen in 41 and 25% in the vedolizumab versus placebo groups ($P = 0.0012$). Patients who achieved a clinical response after induction therapy were randomized to receive placebo or further intravenous vedolizumab at 300 mg at 4- or 8-week dosing intervals up to 46 weeks. Clinical remission rates at week 52 were 42 and 45% in the vedolizumab 8- and 4-weekly groups, respectively, versus 16% in the placebo arm; $P < 0.0001$. Mucosal healing rates were also significantly higher in the vedolizumab group—52 and 56% in the vedolizumab 8- and 4-weekly group versus 20% in the placebo group; $P < 0.0001$. The overall clinical efficacy was higher with vedolizumab in those patients naive to anti-TNF-naïve compared to those who had a prior failure or intolerance to anti-TNF therapy.

GEMINI II was a clinical trial evaluating vedolizumab in patients with moderate to severe CD [106]. Week 6 clinical remission rates were 13.3 vs. 9.7% ($P = 0.157$) and 22.7 vs. 10.6% ($P = 0.005$) in patients who had failed anti-TNF therapy vs. those who were naive to anti-TNF therapy compared to placebo. Week 10 clinical remission rates were 21.7 versus 11% ($P = 0.0008$) and 24.7 versus 15.4% ($P = 0.044$) in patients who had failed anti-TNF therapy and anti-TNF naive patients compared to placebo, respectively. Week 52 clinical remission rates were 52 and 27% in vedolizumab vs. placebo groups naive to anti-TNF but in those patients who had failed anti-TNF therapy, the clinical response rate was lower (28 versus 13% in the vedolizumab and placebo groups, respectively).

GEMINI III is a placebo-controlled phase III induction trial evaluating the efficacy and safety of vedolizumab in CD patients who had failed anti-TNF therapy [107]. At week 6, clinical remission rates were not found to be superior in vedolizumab vs. placebo groups (15.2 and 12.1% ($P = 0.433$)). However, at week 10 the therapeutic efficacy of vedolizumab was detected and vedolizumab was statistically superior to placebo for inducing clinical remission at week 10 (26.6% versus 12.1% in the vedolizumab vs. placebo groups, respectively ($P = 0.001$).

Overall, the results with vedolizumab seem to be somewhat better in UC compared to CD and the 6-week time

point in CD was thought to have been set too early to appreciate optimal efficacy given the mode of action of this agent. In the open-label long-term extension study (GEMINI LTS) there was a suggestion that certain patients with both UC and CD benefited from an increase in vedolizumab dosing frequency from every 8 weeks to every 4 weeks [108].

This drug was approved in 2014 by the FDA and EMA for both UC and CD, refractory to standard therapy and/or anti-TNF agents. In one of the only head-to-head trials of therapies done to date, a phase 3b, double-blind, double-dummy, randomized trial conducted at 245 centers in 34 countries, compared vedolizumab ($n = 383$) with adalimumab ($n = 386$) in adults with moderately to severely active UC [109]. The patients were assigned to receive infusions of 300 mg of vedolizumab on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (plus injections of placebo) or subcutaneous injections of 40 mg of adalimumab, with a total dose of 160 mg at week 1, 80 mg at week 2, and 40 mg every 2 weeks thereafter until week 50 (plus infusions of placebo). Dose escalation was not permitted in either group. At week 52, the vedolizumab group showed higher rates of clinical remission (defined as total score of ≤2 on the Mayo scale, and no subscore >1) (31.3% vs. 22.5%; $P = 0.006$) and endoscopic improvement (subscore of 0 to 1 on the Mayo endoscopic component) (39.7% vs. 27.7%; $P < 0.001$) than the adalimumab group. Interestingly, rates of corticosteroid-free clinical remission were higher with adalimumab compared to vedolizumab (21.8% vs. 12.6%). Safety data was favorable to vedolizumab with exposure-adjusted incidence rates of infection being 23.4 with vedolizumab and 34.6 events per 100 patient-years with adalimumab. The corresponding rates for serious infection were 1.6 and 2.2 events per 100 patient-years. These above results will likely influence the positioning of vedolizumab in the treatment armamentarium for UC patients, and possibly make it the first choice biologic for those with moderate to severe disease.

Pediatric Data

A small observational prospective cohort study of 21 pediatric patients with refractory IBD (16 with CD and 5 with UC) and prior anti-TNF therapy failure suggested notable response rates with vedolizumab therapy within the first 6 weeks, which increased further by week 22 [110]. In an Australian case series, 12 IBD patients (CD = 7 and UC = 5), aged 8–17 years, with prior anti-TNF exposure were then administered vedolizumab [111].While CD activity scores did not significantly change from baseline to week 38 (median 47.5 vs. 40 points, $p = 1.0$), the median UC activity scores changed from 70 to 5 points ($p < 0{,}001$), thus suggesting the utility of vedolizumab, especially in pediatric UC patients.

In a 3 center restrospective review of 52 pediatric IBD patients (58% CD and 42% UC) with median age, 14.9 years and 90% having prior failure to ≥1 anti-TNF agent, week 14 remission rates for UC and CD were 76% and 42%, respectively ($P < 0.05$) [112]. Eighty percent of anti-TNF-naive patients experienced week 14 remission and at week 22, anti-TNF-naive patients had higher remission rates than TNF-exposed patients (100% versus 45%, $P = 0.04$). No infusion reactions or serious adverse events/infections were noted.

Another retrospective study pooled 54 children [aged 2-18 years] treated with vedolizumab after prior anti-TNF exposure, from 19 centres affiliated with the Paediatric IBD Porto group of ESPGHAN (UC/IBD-unclassified = 41, CD = 23) and assessed corticosteroid-free remission [CFR] at 14 weeks [113]. Week 14 CFR was 37% in UC, and 14% in CD [$P = 0.06$] and mucosal healing rate among the 16 endoscopically evaluated was 19%. Concomitant immunomodulatory drugs did not affect remission rate [42% vs 35%; $p = 0.35$]. Only minor drug related events ($n = 3$) were noted. Thus this study further corroborated the safety and efficacy of vedolizumab in pediatric IBD patients, particularly pediatric UC.

Safety

Patients with UC (GEMINI I) and CD (GEMINI II) who completed 52 weeks of vedolizumab treatment were enrolled in GEMINI LTS for an additional 52 weeks [105, 106]. The 2-year efficacy data of vedolizumab in CD and in UC showed the safety of vedolizumab in the GEMINI program [108, 114].To date, there have been no cases of PML. Furthermore, Milch and colleagues conducted a study to determine whether vedolizumab alters T cell subpopulations in cerebrospinal fluid and no significant changes in T cell populations were observed [115]. Also, the incidence of systemic and gastrointestinal infections was similar among patients on vedolizumab or placebo [115].

Furthermore, safety data (May 2009–June 2013) from six trials of vedolizumab were integrated and treatment with vedolizumab for up to 5 years demonstrated a favorable safety profile. In total, 2830 patients had 4811 person-years of vedolizumab. No increased risk of any infection or serious infection was associated with vedolizumab exposure. No cases of progressive multifocal leucoencephalopathy were observed. Infusion-related reactions as defined by the investigator were reported for ≤5% of patients in each study. Eighteen vedolizumab-exposed patients (<1%) were diagnosed with a malignancy [116]. Thus vedolizumab has emerged as a safe alternative in IBD, especially for patients for whom systemic immunosuppression is preferred to be avoided, such as the elderly, or those at increased risk for infection or malignancy.

Etrolizumab (rhuMAb β7)

Etrolizumab is a humanized monoclonal antibody that selectively targets the β7 subunit of α4β7 and αEβ7 integrins and as a result blocks leucocyte migration.

In a placebo-controlled, randomized phase II trial, patients with moderate to severe UC received subcutaneous etrolizumab (100 mg at weeks 0, 4, and 8, with placebo at week 2 or 420 mg at week 0 and 300 mg etrolizumab at weeks 2, 4, and 8) or placebo [117]. At week 10, etrolizumab was found to be more effective in achieving clinical remission (primary endpoint) as compared to placebo - 21% and 10% of patients in the 100 mg or 300 mg etrolizumab group, respectively, and in 0% of patients receiving placebo; the low placebo rate was thought to be a result of very careful patient selection. Subsequently, higher levels of granzyme A and Integrin αE ITGAE mRNAs in the colonic tissue have been highlighted as potential biomarkers to identify UC patients that are most likely to benefit from etrolizumab treatment [118].

A meta-analysis of 7 trials to pool data for etrolizumab and infliximab in moderate to severe UC to perform an indirect comparison found no significant differences in clinical remission between etrolizumab and infliximab, however larger studies to assess clinical response and mucosal healing of etrolizumab vs. infliximab, especially in anti-TNF alpha naïve patients would be necessary to understand the utility of each drug better [119].

The etrolizumab phase 3 clinical program is the largest and most comprehensive in IBD, enrolling more than 3000 patients for six randomized controlled trials (RCTs; UC: HIBISCUS I and II, GARDENIA, LAUREL, HICKORY; Crohn disease: BERGAMOT) and two open-label extension trials (OLEs; UC: COTTONWOOD; Crohn disease: JUNIPER) evaluating patients with moderately to severely active UC or Crohn disease [120]. In the UC RCTs, patients are randomly assigned according to each protocol to receive etrolizumab, adalimumab, infliximab, or placebo. In BERGAMOT, patients are randomly assigned to receive etrolizumab 105 mg, etrolizumab 210 mg, or placebo. This program with the various trials are underway or have been completed to explore both induction and maintenance regimens and the OLEs will primarily provide long-term efficacy and safety data.

Pediatric Data

A phase I, open-label, randomized, pharmacokinetic, pharmacodynamic, and safety study of etrolizumab followed by open-label extension and safety monitoring in pediatric patients from 4 years to less than 18 years of age with moderate to severe UC or moderate to severe CD is currently recruiting patients.

Safety

In the UC phase 2 trial adverse events occurred in 25/41 patients (61%) in the etrolizumab 100 mg group (12% regarded as serious), 19/40 patients (48%) in the etrolizumab 300 mg plus loading dose group (5% serious), and 31/43 patients (72%) in the placebo group (12% serious) [117]. The indirect comparison of infliximab and etrolizumab in the meta-analysis showed higher odds for adverse events with the former (OR: 3.04, p = 0.003), however serious adverse events were comparable [119].

Ontamalimab

Ontamalimab (SHP647, PF-00547659) is a fully human monoclonal antibody that binds specifically to human MAdCAM-1 which is involved in leukocyte recruitment to the site of inflammation has been explored as a therapeutic target in IBD due to its overexpression in the inflamed mucosa and successful intervention based on this ligand in preclinical animal models [121].

In a randomized, placebo-controlled trial evaluating the safety and efficacy of PF-00547659 in patients with active UC, 80 patients received a single or three doses of PF-00547659 (0.03–10 mg/kg, intravenously or subcutaneously administered) or placebo at 4-week dosing intervals [122]. No statistical differences were found between patients given the drug compared to placebo although some benefits were seen in the actively treated group in terms of clinical and endoscopic improvements. Clinical response at week 4 was seen in 32 and 52% of patients on placebo or PF-0054659 (all doses) ($P = 0.102$) and clinical response at week 12 was 21 versus 42% in the placebo and PF-00547659 groups, respectively ($P = 0.156$).

Larger clinical trials evaluating efficacy of PF-00547659 in UC and CD were completed in 2015. The TURANDOT study was a phase II trial evaluating the safety and efficacy of PF-00547659 in patients with UC [123]. Three hundred and fifty-seven adults with UC (with disease extending more than 15 cm beyond the rectum and with a total Mayo Score at least 6 and endoscopic subscore of at least 2) who had failed at least one prior therapy were randomized to receive 7.5, 22.5, 75, or 225 mg of PF-00547659 or placebo every 4 weeks for three doses. Clinical remission at week 12 was the primary endpoint defined as total Mayo score 2 or less with no subscore more than 1. Clinical remission at week 12 was significantly greater in the 7.5, 22.5, and 75 mg dose groups compared with placebo.

OPERA was a randomized, multicenter double-blind, placebo-controlled study that evaluated the safety and efficacy of PF-00547659 in patients with Crohn disease [124]. Two hundred and sixty-seven adults with moderate to severe

Crohn disease (CDAI 220–450), who had failed or did not tolerate other therapy (anti-TNF and/or immunosuppressant drugs), had C-reactive protein (CRP) more than 3.0 mg/L and ulcers on colonoscopy were randomized to placebo or PF-00547659 at the dose of 22.5 mg, 75 mg, or 225 mg. The primary endpoint was CDAI-70 response at week 8 or 12. The CDAI-70 response was not significantly different between any of PF-00547659 doses and placebo but in patients who had a baseline CRP level more than 18 remission at week 12 was higher in the drug groups compared to placebo (37%, 24 and 39% with increasing doses vs. 14% placebo). At week 2, soluble MAdCAM-1 decreased significantly in a dose-dependent manner and remained low during the study in patients who received drug.

However, in a subpopulation analyses of the OPERA study for Asian subjects (n = 21), efficacy of PF-00547659 could not be demonstrated using any clinical endpoints compared with placebo and larger analysis were called for [125].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of PF-00547659 in children or adolescents with IBD.

Safety

While the concern for PML arises with the use of anti-integrin drugs that inhibit lymphocyte translocation from bloodstream to tissue, an analysis of cerebrospinal fluid in 39 patients with active CD and previous immunosuppression over 12 weeks of PF-00547659-induction therapy showed no reduction of cerebrospinal fluid lymphocytes, T-lymphocyte subsets, or CD4:CD8 ratio, thus suggesting that the compound does not affect immune surveillance in the central nervous system [126]. Treatment-related adverse events, none serious, were reported in 23/49 [47%] patients and even in the TURANDOT and OPERA studies, adverse events were mild, comparable to the placebo group and most often related to the underlying disease [123, 124].

AJM300

AJM300 is an orally active small molecule with antagonistic properties to α4-integrin (both $\alpha_4\beta_7$ and $\alpha_4\beta_1$) . A randomized trial involving 71 patients with active Crohn disease compared oral treatment with either AJM300 (40 mg tid, 120 mg tid, or 240 mg tid) to placebo for 8 weeks [127]. The primary endpoint was the decrease of CDAI score from baseline to final evaluation at week 4 or later, while the secondary efficacy endpoint was clinical response (≥70 point decrease in CDAI). There was no significant difference in clinical response was observed between active treatment and placebo arms. Among patients with high CDAI at baseline a significant decrease from baseline CDAI score (mean decrease 41.5 points, P = 0.0485) was observed in those treated with AJM300 at the dose of 120 mg tid and mean 41.6 point decrease from baseline CDAI in those treated with AJM300 at the dose of 240 mg tid (p-value not reported). In addition, patients treated with AJM at the dose of 240 mg tid had significant twofold decrease in C-reactive protein from baseline over 8 weeks (P = 0.0220). The investigators suggested that AJM300 at dose 120 mg tid and 240 mg tid showed clinical efficacy in treating patients with active Crohn disease.

A double-blind, placebo-controlled, phase 2a study, recruited 102 patients with moderately active UC with inadequate response or intolerance to mesalamine or corticosteroids, and randomly assigned them to receive AJM300 (960 mg) or placebo 3 times daily for 8 weeks [128]. Clinical response (decrease in Mayo Clinic score of at least 3 points and a decrease of at least 30% from baseline, with a decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1) rates were 62.7% and 25.5% at week 8 in the AJM300 group vs. placebo group (p = 0.0002), clinical remission rates (Mayo Clinic score ≤2 and no subscore >1) were 23.5% and 3.9% in the AJM300 group vs. placebo groups (p = 0.0099), and rates of mucosal healing (endoscopic subscores of 0 or 1) were 58.8% and 29.4% (p = 0.0014) respectively. No serious adverse events, including PML were observed.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of AJM300 in children or adolescents with IBD.

Safety

AJM300 was tolerated well with incidence of adverse events that was not dose-dependent (0.0%, 23.5%, and 22.2% for AJM300 40 mg, 120 mg and 240 mg treated patients, respectively, vs. 16.7% for placebo-treated patients, p-value not reported) [127]. In the UC trial, the incidence of drug-related adverse events was 21.6% (11 of 51 patients) in the active treatment group and 7.8% (4 of 51 patients) in the placebo group, all of which were mild. The most common adverse events were nasopharyngitis and related to the underlying UC. Adverse events leading to discontinuation of the study drug included exacerbation of UC (1 patient in the active treatment group and 8 in the placebo group) and abnormality

of liver function (1 patient in the placebo group). Overall, infection, neurologic symptoms, or onset of PML was not observed in the study.

Alicaforsen

Alicaforsen (ISIS 2302) is a oligodeoxy-nucleotide that can downregulate intercellular adhesion molecule 1 (ICAM-1) expression in an RNAse H-dependent manner and thus hinder leukocyte migration and trafficking to the site of inflammation [129].

There have been three randomized, placebo-controlled trials that assessed the efficacy of alicaforsen administered intravenously [130–132] and one randomized, placebo-controlled trial that evaluated the efficacy of this agent administered subcutaneously [133] in patients with active CD.

A phase IIA, double-blind, randomized, placebo-controlled trial of 20 patients with active Crohn disease suggested the efficacy of intravenously administered alicaforsen [132]. Patients were randomly assigned to be treated with 13 infusions of either alicaforsen (0.5, 1, or 2 mg/kg, $n = 15$) or placebo ($n = 5$) over the period of 26 days with subsequent 6-month follow-up. The rates of clinical remission (CDAI <150) at the end of treatment were 47% and 20% in active drug and placebo arms, respectively (p-value not reported). ISIS 2302 showed corticosteroid sparing effect with significantly lower dose of corticosteroids over time when compared to placebo ($p = 0.0001$). Data from subsequent dose ranging pharmacokinetic trial of high-dose alicaforsen administered intravenously at the dose of 300 or 350 mg three times a week for 4 weeks in 22 patients with active Crohn disease demonstrated that 41% of patients achieved clinical remission indicating that this agent might be efficacious in treating Crohn disease. Unfortunately, large randomized, placebo-controlled trials with intravenous alicaforsen did not support these preliminary findings.

In the subsequent large clinical trial that comprised of 299 patients with active steroid dependent (prednisone 10–40 mg) Crohn disease patients were randomly assigned to intravenous treatment three times a week with either ISIS 2302 (2 mg/kg) or placebo for 2 or 4 weeks and the regimen was then repeated after 1 month without treatment [130]. The corticosteroid-free remission (CDAI <150) at week 14 (primary endpoint) was comparable between combined ISIS 2302 and placebo arms (20.2% vs. 18.8%, p-value not reported). On the other hand, a significantly greater proportion of patients receiving ISIS 2302 than placebo had successful corticosteroids withdrawal at week 14 (78% vs. 64%; $P = 0.032$). According to pharmacodynamic analysis, statistically significant results for clinical remission, improvement in CDAI and quality of life based on IBD questionnaire were observed in the highest area under the curve subgroup of ISIS 2302 arm when compared to placebo. Finally, data from two double-masked, placebo-controlled trials of patients with Crohn disease who received intravenous treatment with either alicaforsen ($n = 221$) or placebo ($n = 110$) three times a week for 4 weeks did not show any benefit of alicaforsen over placebo in achieving clinical remission at week 12 with respective remission rates of 33.9% and 34.5% ($P = 0.89$) [131]. Subcutaneous administration of alicaforsen also did not demonstrate any superiority over placebo in achieving clinical remission in patients with Crohn disease. Schreiber et al. randomized 75 patients with corticosteroid-refractory Crohn disease to subcutaneous treatment with either ISIS 2302 or placebo [133]. The primary endpoint, corticosteroid-free remission at week 14 (CDAI <150) was observed in 3.3% of ISIS-2302-treated and 0% of placebo treated patients. On the other hand, there was a trend towards efficacy of ISIS 2302 in achieving one of the secondary endpoints, namely corticosteroid-free remission at week 26 (13.3% vs. 6.7%, p-value not reported). Similarly, a greater proportion of patients receiving active drug when compared to placebo achieved a corticosteroid dose <10 mg/day at week 14 (48.3% vs. 33.3%) and week 26 (55.0% vs. 40.0%) and a prednisone equivalent dose of 0 mg at week 26 [23.3% vs. 6.7%, respectively].

There have been three randomized, placebo-controlled trials assessing the efficacy of alicaforsen enemas in patients with active left-side UC [134–136].Van Deventer et al. performed a randomized, placebo-controlled trial of alicaforsen enema in 40 patients with mild to moderately active distal UC who received 60 mL of alicaforsen enema (0.1, 0.5, 2, or 4 mg/mL) or placebo once daily for 28 consecutive days [136]. There was observed a significant dose-dependent reduction in disease activity index in patients treated with active drug than placebo at day 29 that was observed for alicaforsen given at the highest dose 4 mg/mL (70% vs. 28%, $P = 0.004$). After 3 months alicaforsen 2 mg/mL and 4 mg/mL caused significant reduction in disease activity index when compared to placebo by 72% and 68%, respectively (vs. 11.5% for placebo, $P = 0.016$ and 0.021, respectively). In the subsequent phase II dose ranging, double-blind, placebo-controlled study of alicaforsen enema (120 mg daily for 10 days, then every other day; 240 mg every other day; 240 mg daily for 10 days, then every other day; 240 mg daily) given daily for 6 weeks in 112 patients presenting with acute exacerbation of mild to moderate left-sided UC there was no significant difference observed between active drug and placebo in reduction of disease activity index at week 6 [134]. However, a greater proportion of patients receiving alicaforsen 240 mg daily had prolonged clinical improvement at week 18 (51% vs. 18%) and week 30 (50% vs. 11%) when compared to placebo. Finally, Miner et al. compared two dose formulations of alicaforsen enema (120 mg or

240 mg) with 4 g mesalamine enema given for 6 weeks in 159 patients with mild to moderate left-sided UC [135]. There was no difference observed between treatment arms in reduction of disease activity index at week 6 with reduction in mean disease activity index when compared to baseline of 50% for the mesalamine arm and 40% and 41% for the 120 and 240 mg alicaforsen groups (P = 0.27 and 0.32, respectively). However, higher dose of alicaforsen enema was significantly more efficacious than mesalamine in achieving clinical remission at week 18 (20% vs. 6%, P = 0.03).

An open-label study of alicaforsen enema given at daily dose of 240 mg for 6 weeks to 15 patients with active UC showed a 46% reduction in mean disease activity index and 33% rate of complete mucosal healing at the end of treatment [137]. In addition, alicaforsen concentrations were greater in mucosal colonic tissue biopsies than those observed in plasma suggesting that alicaforsen enemas allow for achieving high local concentrations with little systemic exposure. Another open-label study of 12 patients with chronic pouchitis following an ileal pouch-anal anastomosis for UC showed that alicaforsen enemas given at dose of 240 mg daily for 6 weeks resulted in significant reduction in the mean pouchitis disease activity index from baseline value of 11.42 points to 6.83 points at 6 weeks (P = 0.001) [138].

In summary, clinical trials of an intravenous formulation in Crohn disease showed no significant treatment effect with alicaforsen compared to placebo. After 6 weeks of treatment, topical alicaforsen has significantly more effective than placebo in inducing remission in patients with moderate-severe distal UC, with treatment effects lasting up to 30 weeks. No difference has been seen in head-head comparison with mesalamine topical enema, although alicaforsen appears to have more durable treatment effect. An open-label trial in alicaforsen for pouchitis demonstrated encouraging results, and it is now being assessed in a multi-national phase 3 trial. No major safety signals have been observed in UC patients treated with alicaforsen enemas. Its promising signals as a novel therapy, have led to a Fast-Track and orphan designation for this indication by the Food and Drug Administration and European Medicines Agency [139].

Pediatric Data

At the time of writing this chapter there are no published data on the use of alicaforsen in children or adolescents with IBD.

Safety

Data from a large trial of 331 patients treated with intravenous alicaforsen or placebo showed that the only adverse events that occurred in greater proportion of patients treated with alicaforsen were symptoms related to infusion reactions such as fever (22.6% vs. 14.7%, p-not significant), chills (14% vs. 1.8%, P = 0.0005), and myalgia (5.4% vs. 0.92%) [131]. Data from the second largest trial of 299 patients with Crohn disease receiving alicaforsen or placebo intravenously showed that the only adverse events that occurred in significantly greater proportion of patients treated with active drug than placebo were infusion reactions described as transient facial flushing or a feeling of warmth during infusion (11.6% vs. 4%, P = 0.03) [130]. There was a significantly greater average transient aPTT increase without bleeding sequelae (8.66 s vs. 0.8 s, P + 0.0001) after alicaforsen than placebo infusion. Safety analysis of alicaforsen administered subcutaneously in the largest trial of 75 patients determined that injection site reactions, headache, pain, fever, rash, arthritis, asthenia, and flu-like symptoms injection site reactions occurred in greater proportion of patients treated with active drug than placebo with injection site reactions demonstrating the largest difference (23.3% vs. 0%, p-value not reported) [133].

Gastrointestinal complaints were associated with the alicaforsen enemas in a dose-dependent fashion. Community-acquired pneumonia and sinusitis were also reported and were associated with the study drug [134, 136–138].

Abrilumab

Abrilumab (AMG181) is a human monoclonal IgG2 antibody that specifically binds to α4β7 heterodimers.

In a phase 2b, placebo-controlled, double-blind study that evaluated the efficacy and safety of the anti-$\alpha_4\beta_7$ antibody abrilumab in patients with moderate-to-severe UC despite treatment with conventional therapies, 354 patients were randomized to receive subcutaneous abrilumab (7, 21, or 70 mg) on day 1, weeks 2 and 4, and every 4 weeks; abrilumab 210 mg on day 1; or placebo [140]. Those who received ≥1 dose of investigational product (placebo, n = 116; 7 mg, n = 21; 21 mg, n = 40; 70 mg, n = 98; 210 mg, n = 79), non-adjusted rates of remission (total Mayo Score ≤2 points, no individual sub-score >1 point) at week 8 were 4.3%, 13.3%, and 12.7% for the placebo and abrilumab 70-mg and 210-mg groups, respectively (P < 0.05 for 70 and 210 mg vs placebo). Response and mucosal healing rates with these dosages also were significantly greater than with placebo and while higher baseline $\alpha_4\beta_7$ levels on naïve $CD4^+$ T cells were a prognostic indicator for overall outcome, it was not a predictive biomarker of abrilumab response.

In a Japanese study, 45 UC patients were randomized to abrilumab 21 mg (n = 11), 70 mg (n = 12), 210 mg (n = 9), or placebo (n = 13) via subcutaneous (SC) injection for 12 weeks. The double-blind period was followed by a 36-week open-label period, in which all patients received

abrilumab 210 mg SC every 12 weeks, and a 28-week safety follow-up period [141]. Week 8 clinical remission rates were 10%, 16.7% and 11.1% for abrilumab 21 mg, 70 mg and 210 mg groups vs. 0 in the placebo arm.

A phase 2b, randomised, multi-centre, double-blind, placebo controlled study enrolled 249 patients with moderate to severe CD and biochemical/endoscopic evidence of active inflammation, with prior failure with anti-TNF therapy or corticosteroids and data was presented at the ECCO meeting [140]. Patients were randomised to receive placebo or abrilumab (21 or 70 mg) SC on day 1, weeks 2 and 4, and every 4 weeks (Q4W) for up to 24 weeks, or one dose of abrilumab 210 mg SC on day 1. The results were impacted by a systematic misalignment in investigational product, however the study blind and randomisation remained intact. Statistically significant improvement was not achieved between the abrilumab 70 mg Q4W and placebo arms for the primary endpoint of CDAI remission (score <150) at week 8 ($p = 0.76$). However, higher rates of remission and response were observed in the active treatment arms at week 12, particularly in patients with prior failure of TNF antagonists assigned to the 210 mg abrilumab group. Abrilumab induced a significant post-dose increase in α4β7-high central memory CD4+ T cell counts between baseline and week 8. Adverse events were similar among treatment groups through week 24, with no cases of PML or deaths. No No neutralizing antibodies to abrilumab were detected.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of Abrilumab in children or adolescents with IBD.

Firategrast

Firategrast (SB 683699) is an orally bioavailable small molecule α4β1 and α4β7 integrin antagonist [142]. A phase II study evaluating the effectiveness and safety of Firategrast in treating subjects with moderately to severely active CD has been completed. Results are not available [143].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of Firategrast in children or adolescents with IBD.

TRK-170

TRK-170 is a novel orally active α4β1 and α4β7 integrin antagonist [144]. A study evaluated the effect of TRK-170, as compared to an anti-alpha4 antibody and prednisolone, on 2, 4, 6-trinitrobenzene sulfonic acid (TNBS)-induced colitis. Oral administration of TRK-170 significantly inhibited the increase of macroscopic damage scores. TRK-170 also reduced the elevation of myeloperoxidase activity in colons, and the increase in colon weight. Efficacy of TRK-170 is almost comparable to the anti-alpha4 antibody and prednisolone at this dosage and dose regimen. Detailed mechanisms of action of TRK-170, such as potential effects on immune cells, are being characterized. These results indicate that TRK-170 is expected to provide an attractive approach for the future therapy of IBD. Because TRK-170 is orally active unlike anti-alpha4 antibody, TRK-170 may be more beneficial than the antibody.

A 2 part, multi-centre, randomized, placebo-controlled, double-blind study to evaluate the efficiacy, safety and pharmacokinetics of TRK-170 in CD has been completed and the results are awaited.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of TRK-170 in children or adolescents with IBD.

GLPG0974

Free fatty acids (FFA) act as inflammatory signaling molecules through receptors such as FFA2, which is activated by short chain fatty acids (SCFA). Through FFA2, SCFAs induce neutrophil activation and migration. In IBD patients, FFA2 expression is up-regulated in the colon. GLPG0974 is a potent and selective antagonist of FFA2, inhibiting SCFA-induced neutrophil migration and activation in vitro.

In a 4-week, first-in-UC study with GLPG0974 in patients with mild to moderate UC, GLPG0974 was well tolerated and safe. Biomarkers (MPO and FC) indicate that GLPG0974 reduces neutrophil activation and influx, suggesting a role for FFA2 in neutrophil migration in UC. The reduction in neutrophil influx is not sufficient to induce a measurable clinical difference between GLPG0974 treated patients and placebo within 4 weeks [145]. An exploratory, phase II, randomized, double-blind, placebo-controlled, proof-of-concept study to evaluate the safety, tolerability, efficacy, pharmaco-

kinetics and pharmacodynamics of GLPG0974 in subjects with mild to moderate UC has been completed, but the results are yet to be released [146].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of GLPG0974 in children or adolescents with IBD.

Administration of Anti-Inflammatory Cytokine

Interleukin-10 (IL-10)

Interleukin-10 is secreted by T helper cells, B cells, monocytes, macrophages, dendritic cells and keratinocytes. It suppresses inflammation by reducing HLA class I expression decreasing secretion of IL-2 and diminishing production of IL-1α, Il-1β, IL-6, IL-8, and TNF-α. The recombinant human rHuIL-10 may be administered subcutaneously, intravenously, or orally via a genetically modified *Lactococcus lactis* (LL-Thy12).

A randomized, double-blind, placebo-controlled phase IIa trial by Van Deventer et al. suggested that intravenous bolus of recombinant human IL-10 once daily for 7 consecutive days (rhu-IL-10) might be efficacious for the treatment of active Crohn disease [147]. Among 46 patients with active steroid-resistant Crohn disease who were treated with rhu-IL-10 (0.5, 1, 5, 10, or 25 μg/kg) or placebo 50% treated with active drug and 23 who received placebo achieved a complete remission (decrease in baseline CDAI <150 and >100-point decrease in CDAI when compared to baseline) at any time during 3-week follow-up (*p*-value not reported). The second randomized, placebo-controlled trial of subcutaneous rhuIL-10 (1, 5, 10, or 20 μ/kg) given for 28 consecutive days with subsequent 20-week follow-up in 95 patients with active Crohn disease observed that only rhu-IL-10 administered at dose 5 μg/kg showed benefit over placebo with 23.5% (CI, 6.8–49.9%) and 0% (CI, 0–14.8%) rates of complete remission (CDAI <150 and at ≥100 point decrease in CDAI from baseline with improvement or resolution in on endoscopy) measured on day 29 [147].

A double-blind, placebo-controlled phase III trial of 329 patients with chronic, active and refractory to corticosteroids Crohn disease randomly allocated patients to receive subcutaneous injections with either rhu_IL-10 (1, 4, 8, or 20 μ/kg) or placebo daily for 28 days [148]. There was no significant difference between any of rhu-IL-10 dose and placebo in inducing primary endpoint, clinical remission (CDAI ≤150 with concomitant decrease in CDAI ≥100 points from baseline) with rates of 18% for dose 1 μg/kg ($P = 0.79$ vs. placebo), 20% for dose 4 μg/kg ($P = 0.76$), 20% for dose 8 μg/kg ($P = 0.76$), 28% for dose 20 μg/kg ($P = 0.17$) when compared to 18% for placebo-treated patients. There was a significant superiority in achieving clinical improvement (decrease in CDAI ≥100 points when compared to baseline) in patients who received rhu-IL-10 at the dose 8 μg/kg when compared to placebo (46% vs. 27%, $P = 0.034$).

A subsequent randomized, double-blind, placebo-controlled phase III trial (published only in an abstract form) assessed the efficacy of rhu-IL-10 in 373 patients with corticosteroid-dependent Crohn disease who received once daily subcutaneously for 2 weeks then 3 times per week for 26 weeks either rhu-IL-10 (4 μg/kg or 8 μg/kg) or placebo [149]. Rhu-IL-10 4 μg/kg or 8 μg/kg was not statistically significant more efficacious than placebo in achieving the ability to discontinue corticosteroids by 16 weeks and to maintain clinical remission (CDAI<150) by week 28 with respective rates of 25%, 32%, and 29% (*p*-value not reported).

Colombel et al. analyzed 65 patients with Crohn disease after curative ileal or ileocolonic resection and primary anastomosis who were randomized within 2 weeks after surgery to subcutaneous injections of either rhu-IL-10 4 μg/kg once daily, rhu-IL-10 8 μg/kg twice weekly or placebo and were followed-up for 12 weeks [150]. Of 65 patients 58 underwent endoscopy at the end of follow-up that showed that 46% of patients treated with active drug and 52% of placebo recipients had recurrent lesions (*p* not significant).

Successful treatment of a murine model of colitis with *L. lactis* secreting interleukin-10 has been reported [131]. A pilot Phase Ia study has demonstrated the potential of a genetically modified *L. lactis* (LL-Thy12) given orally at the dose of 10 capsules with 1 × 10 [10] colony-forming units (CFU) of LLThy12 twice daily for 7 days to 10 patients with active Crohn disease [151]. Clinical benefit was observed in 8 of 10 patients with 5 patients achieving complete remission (CDAI <150) and 3 patients experiencing clinical response (decrease in CDAI >70). Future clinical trials are needed to validate these preliminary findings.

Pediatric Data

At the time of writing this chapter, there is no published data on the use of rhu-IL-10 in children or adolescents with IBD.

Safety

The only clinical trial that assessed safety of intravenously administered rhu-IL-10 observed similar proportion of

adverse events between active drug and placebo arms [147]. The only exception was the abdominal pain that was reported in 9% of patients receiving rhu-IL-10 and 31% of placebo recipients. Data from 329 patients with Crohn disease who were treated with either rhu-IL-10 (n = 262) or placebo (n = 66) provided the largest population of patients that was assessed for safety of rhu-IL-10 and showed that both active drug and placebo arms had comparable proportion of adverse events (95% vs. 94%) [148]. The only events that occurred in greater proportion of patients treated with rhu-IL-10 than placebo were headache (P = 0.02), fever (P = 0.02), back pain (P = 0.01), decrease in hemoglobin concentration (P = 0.0007), dizziness (P = 0.005), and thrombocytopenia (P = 0.0006) [127]. Severe adverse events were observed in 28% 17% of patients treated with rhu-IL-10 and placebo, respectively (P = 0.057). A dose-dependent decrease in hemoglobin of unknown mechanism occurred in 33% of patients treated with rhuIL-10 at the dose of 20 μg/kg when compared to 8% of placebo patients (P = 0.0003). Thrombocytopenia of unknown mechanism was also observed in greater proportion of patients receiving rhuIL-10 at the dose 8 μg/kg (6, P = 0.04) and rhuIL-10 at the dose 20 μg/kg (27%, P < 0.0001) when compared to 0% among placebo recipients. All hematologic abnormalities were reversible upon cessation of study medication. Reversible anemia and thrombocytopenia are common, as are mild to moderate headaches, fever, back pain, diarrhea, arthralgias, and dizziness. Antibodies to IL-10 have not been detected [147, 150].

Blockade of T Cell Stimulation and Induction of Apoptosis

Laquinimod

Laquinimod is an oral agent that produces anti-inflammatory effects by modulating immune cells with result of reduced synthesis of several cytokines.

A phase IIa trial was performed using different doses of laquinimod (0.5, 1, 1.5, or 2 mg/day) for 8 weeks in patients with active Crohn disease [152]. Clinical remission rates at week 8 were as follows: 48.3, 26.7, 13.8, and 17.2% of patients receiving 0.5, 1, 1.5, and 2 mg laquinimod versus 15.9% placebo. This may be an effective treatment of Crohn disease and further studies are needed.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of laquinimod in children or adolescents with IBD.

Safety

Overall, induction treatment with laquinimod was tolerated and the most common adverse effects were headache, abdominal pain, nausea, vomiting, and musculoskeletal pain [152].

Cobitolimod (DIMS0150)

DNA-based immunomodulatory sequence (DIMS0150) is a single-stranded partially modified synthetic oligonucleotide of 19 bases in length and activates the Toll-Like Receptor 9 (TLR9) present in immune cells such as T and B cells, macrophages and plasmacytoid dendritic cells (pDCs) that are found in abundance on mucosal surfaces such as the colonic mucosa. In experimental colitis models, administration of DIMS0150 has resulted in marked suppression of colitis, with microarray analysis showing mucosal IL10 upregulation and suppression of IL17 pathways via activation of TLR9 [153]. The drug has also interestingly been shown to increase steroid sensitivity in steroid resistant UC patients and human monocytes [154]. Administration of DIMS0150 in the form of an enema in steroid-refractory subjects with UC allows the drug to come into direct contact with a large number of target cells harboring the TLR9 receptor and has been shown to be beneficial in steroid refractory patients with UC.

In a study where a single dose of DIMS0150 was given to steroid unresponsive IBD patients on concomitant steroid therapies, single doses of 3 and 30 mg were effective in inducing a clinical response [155]. Five of seven patients (70%) that received active treatment had a clinical response 1 week after therapy and after more than 8 years, two remained in glucocorticoid free remission.

In a phase II study, 151 patients with mild or moderately active UC were given DIMS0150 as a single rectal dose at one of four dose levels (0.3, 3, 30, and 100 mg) with the hopes of inducing clinical remission. No significant benefit was demonstrated at any dose level.

In a randomized, double-blind, placebo-controlled trial (COLLECT study) conducted in 131 patients with moderate to severe UC, patients were randomized to receive two topical endoscopic administrations of cobitolimod at a dosage of 30 mg at baseline and week 4, or placebo [156]. There was no statistical difference in clinical remission, (44.4% of cobitolimod treated patients vs. 46.5% of those treated with placebo). More patients treated with cobitolimod compared to placebo had mucosal healing [34.6% vs. 18.6%; p = 0.09] and histological improvement (defined by the Geboes score of 0–2) [30.9% vs. 9.3%; p = 0.0073] at Week 4. Overall the drug showed no safety signals compared with placebo and was well tolerated.

Currently, a phase 2 study (CONDUCT) comparing different doses and different administration intervals of cobito-

limod in an enema formulation over 12 weeks is being conducted in moderate to severe UC patients [157].

Safety Data

Altogether, agonists of the Toll-like receptor-9 appeared safe and well-tolerated in moderate to severe UC patients and could represent a novel promising therapeutic option for the management of UC patients.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of DIMS0150 in children or adolescents with IBD.

Monarsen

Monarsen (BL 7040) is a TLR9 modulator that is orally administered and in a prospective multicenter phase 2a study in patients with moderately active UC it was investigated at doses of 12 mg once daily for 3 weeks followed by 40 mg once daily for 2 weeks [158]. Clinical remission was seen in 12.5% patients (2/16). Clinical response as well as mucosal healing were achieved in 50% of the patients.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of BL7040 in children or adolescents with IBD.

Safety

Total of 29 adverse events were reported in 16 patients (72.7%) in the phase 2a study discussed above, of which 10 were considered drug related [158]. Most common AEs were exacerbation of UC and influenzalike illness.

Sphingosine-1-Phosphate Receptor Modulators

S1P (sphingosine-1-phosphate) is a bioactive sphingolipid and its concentration gradient (between tissues and blood) regulates lymphocyte recirculation [159]. In order for lymphocytes to leave lymph nodes, the S1P receptors on the surface of the lymphocyte must bind to S1P and S1P modulators cause the S1P receptors on the surface of lymphocytes to be internalized and degraded, blocking lymphocyte egress from lymph nodes. As a result lymphocytes are trapped in lymph nodes resulting in a reduction of the peripheral lymphocyte count and circulating effector T cells making fewer immune cells available in the circulating blood to effect tissue damage. S1P receptor agonism is a novel strategy for the treatment of inflammatory conditions and success in clinical trials led to the approval of the non-selective S1P modulator, fingolimod, for relapsing forms of multiple sclerosis. However, given the association of this non-selective S1P modulator with serious adverse events, the development of more selective S1P receptor modulators has since gained focus, including etrasimod (APD334), ozanimod (RPC1063) and amiselimod (MT-1303). The development of amiselimod has since been discontinued by the developer to focus on other drugs in their portfolio. The S1P receptor agonists offer the advantage of being orally administered and might avoid triggering the formation of anti-drug antibodies [160].

Etrasimod

Etrasimod (APD334), an orally available $S1P_1$ receptor modulator, discovered by Arena Paramaceuticals, has therapeutic potential in autoimmune diseases such as UC.

In a phase 2, proof-of-concept, double-blind, parallel-group study, conducted across 87 centers in 17 countries, adult outpatients with moderately to severely active UC were randomly assigned to groups given once-daily etrasimod 1 mg (n = 52), etrasimod 2 mg (n = 50), or placebo (n = 54) for 12 weeks [161]. The primary endpoint was an increase in the mean improvement in modified Mayo clinical score (MCS) from baseline to week 12. Secondary endpoints included the proportion of patients with endoscopic improvement (subscores of 1 or less) from baseline to week 12. At week 12, the etrasimod 2 mg group met the primary and all secondary endpoints. Etrasimod 2 mg led to a significantly greater increase in mean improvement in modified MCS from baseline than placebo, while the 1 mg dose showed no significant difference. Endoscopic improvement occurred in 41.8% of patients receiving etrasimod 2 mg vs 17.8% receiving placebo (P = 0.003). Currently, 3 phase 3 trials ranging from 12 to 52 weeks for evaluating the efficacy of etrasimod for moderate to severely active UC [162–164] and a phase 2b trial to assess the efficacy and safety of etrasimod as induction therapy for moderate to severely active CD are actively ongoing [165].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of etrasimid in children or adolescents with IBD.

Safety

In the phase 2 UC study, among the 102 patients who received etrasimod, three patients experienced asymptom-

atic, low-grade atrioventricular block which was tranisent and resolved spontaneously [165]. These patients also had evidence of atrioventricular block prior to etrasimod exposure. All other reported adverse events were mild to moderate.

Ozanimod

Ozanimod (RPC1063) is an oral selective agonist for S1P receptors 1 and 5 and has been shown in phase II studies to be effective for the treatment of both multiple sclerosis and UC [166]. The US Food and Drug Administration (FDA) has approved ozanimod (Zeposia) for adults with moderately to severely active ulcerative colitis (UC). (Reference: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209899s001lbl.pdf).

The UC TOUCHSTONE phase II study evaluated the safety and efficacy of 0.5 and 1 mg RPC1063 compared to placebo and after the 8-week induction period, there was a continuing maintenance period for responders [167]. One hundred and ninety-seven patients with moderate to severe UC (Mayo score of 6–12 with an endoscopic subscore 2). The primary endpoint of clinical remission (Mayo score 2, no subscore >1) at week 8 was 16.4% for high dose ($P = 0.048$ versus placebo), 13.8% for low dose ($P = 0.14$), and 6.2% for placebo. Ninety-five percent of patients completed the induction portion of the study. Clinical response (reduction in Mayo score of 3 and 30% with a decrease in the rectal bleeding score of 1 or a rectal bleeding score 1) was 56.7% for high dose ($P = 0.01$), 53.8% for low dose ($P = 0.06$), and 36.9% for placebo. Mucosal improvement (endoscopy score 1) was 34.3% for high dose ($P = 0.002$), 27.7% for low dose ($P = 0.03$), and 12.3% for placebo. The improvement in Mayo score from baseline was 3.3 points for high dose ($P = 0.003$), 2.6 points for low dose ($P = 0.098$), and 1.9 for placebo. The trial was thought to be not large enough or of sufficiently long duration to establish clinical efficacy or assess safety.

In the STEPSTONE phase 2 uncontrolled, multicenter clinical trial in adults with moderate to severely active CD recruited from 28 hospitals across North America and Europe, where 69 patients began treatment with a 7-day dose escalation (4 days on ozanimod 0·25 mg daily followed by 3 days at 0·5 mg daily), followed by 1 mg oral capsule daily for a further 11 weeks, for a 12-week induction period, and finally a 100-week extension. The primary endpoint was a change in Simple SES-CD from baseline to week 12 [168]. At week 12, the mean change from baseline in SES-CD was -2·2 and 16 (23·2%) patients experienced endoscopic response.

Currently, there is a Phase 2/3 trial to evaluate the efficacy and long-term safety of ozanimod in Japanese subjects with moderate to severe UC [169] and multiple ongoing phase 3 studies in patients with moderate to severe CD [170–172].

Recently, data was presented on the TRUE NORTH data. [173].

There were two components of the trial reported, the induction phase and the maintenance phase of the trial. The 10-week induction period findings from this phase 3, randomized, double-blind study in patients with moderate-to-severely active ulcerative colitis (True North; NCT02435992) were enrolled. Results from the maintenance period were remarkable and are reviewed separately below.

In the TRUE NORTH study adult patients with moderate-to-severely active ulcerative colitis (total Mayo score 6-12 with a Mayo endscopy score ≥2 on oral aminosalicylates or corticosteroids) were randomized 2:1 to receive ozanimod HCl 1 mg (equivalent to ozanimod 0.92 mg) or placebo once daily (stratified by prior tumor necrosis factor inhibitor [TNFi] and corticosteroid use at screening) during a 10-week induction period. The primary endpoint was the proportion of patients in clinical remission per the 3-component Mayo score at week 10. Ranked secondary endpoints were the proportions of patients with a clinical response, endoscopic improvement, and mucosal healing.

This trial enrolled a total of 645 patients to receive ozanimod ($n = 429$) or placebo ($n = 216$), of whom 94% and 89%, respectively, completed the induction period. All primary and key secondary efficacy endpoints showed statistically significant improvements with ozanimod vs placebo at week 10. For the primary endpoint, 18.4% and 6.0% of patients in the ozanimod and placebo groups, respectively, achieved clinical remission at week 10 (absolute difference 12.4% [95% CI, 7.5-17.2]; $P < 0.0001$). Key secondary endpoints of clinical response ($P < 0.0001$), endoscopic improvement ($P < 0.0001$), and mucosal healing ($P < 0.001$) were also statistically significant for ozanimod vs placebo. In patients with prior TNF-inhibitor exposure, clinical remission results favored ozanimod over placebo but this was not statistically significant, while a nominally statistically significant difference was observed for clinical response. The most common treatment-emergent adverse events (TEAEs) for patients who received ozanimod vs placebo, respectively, were anemia (4.2% vs 5.6%), nasopharyngitis (3.5% vs 1.4%) and headache (3.3% vs 1.9%). Cardiovascular events were infrequent and included bradycardia (0.5% vs 0%) and hypertension (1.4% vs 0%). The frequency of serious TEAEs were 4.0% vs 3.2%, respectively, and serious infections occurred in <1% in each group. No cases of progressive multifocal leukoencephalopathy were reported in the trials. Thus the overall conclusion from the induction phase of the trial was that Ozanimod treatment for 10 weeks in patients with

moderate-to-severe UC led to statistically significant improvements in clinical remission, clinical response, endoscopic improvement, and mucosal healing. Safety findings were consistent with ozanimod's known profile and in a moderate-to-severe UC study population; no new safety signals were observed with ozanimod in this study.

In this trial, patients who had demonstrated the presence of a clinical response after 10 weeks to treatment with ozanimod induction therapy were enrolled in a maintenance arm. These patients were offered and followed as double-blind and open-label cohorts to be re-randomized 1:1 to double-blind maintenance treatment with ozanimod HCl 1 mg/day (equal to ozanimod 0.92 mg) or matching placebo. The efficacy and safety of ozanimod vs placebo at week 52 in the maintenance period of a randomized, double-blind, phase 3 study in patients with moderate-to-severe UC (True North; NCT02435992) will now be reviewed [174].

Patients were stratified by clinical remission status and corticosteroid use at week 10. Endpoints were assessed at week 52 and tested sequentially via closed hierarchical procedure. The primary endpoint was the proportion of patients in clinical remission per 3-component Mayo score. Ranked key secondary endpoints were assessment of the proportions of patients with clinical response, endoscopic improvement, maintenance of clinical remission, corticosteroid-free remission, mucosal healing (both endoscopy and histology), and durable clinical remission. Data were also analyzed by prior tumor necrosis factor inhibitor (TNFi) use.

Overall, a total of 457 patients were re-randomized to maintenance treatment with either ozanimod ($n = 230$) or placebo ($n = 227$). Of these, 80% and 54.6% of patients who received ozanimod and placebo, respectively, completed the study. In this study disease relapse (13.5% ozanimod, 33.9% placebo) was the most common reason for discontinuation of ozanimod. All primary and key secondary efficacy endpoints showed statistically significant improvements with ozanimod vs placebo at week 52 . Ozanimod resulted in a significantly higher clinical remission rate vs placebo (37.0% vs 18.5%; difference: 18.6% [95% CI, 10.8-26.4]; $P < 0.0001$). Significant results were also observed in all key secondary endpoints; clinical response ($P < 0.0001$), endoscopic improvement ($P < 0.001$), maintenance of remission ($P < 0.0047$), corticosteroid-free remission ($P < 0.001$), mucosal healing ($P < 0.001$), and durable remission ($P = 0.003$). Clinical remission and response also improved with ozanimod regardless of previous TNF inhibitor use. The most common treatment-emergent adverse events (TEAEs) for ozanimod vs placebo, respectively, were alanine aminotransferase increase (4.8% vs 0.4%; no serious events), and headache (3.5% vs 0.4%). Frequency of possible, probable, or related serious TEAEs was low (≤1% in both groups). The autors of this study thus concluded that patients with moderate-to-severe UC treated with ozanimod for up to 52 weeks in this study demonstrated clinically relevant and statistically significant benefits on clinical, endoscopic, and mucosal healing endpoints. No new safety signals were observed for ozanimod.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of ozanimod in children or adolescents with IBD.

Safety

In the UC Touchstone study no differences in adverse events were observed between the treatment and placebo groups [167]. Four patients in ozanimod group had an elevated alanine aminotransferase >3 times upper limit of normal. In the STEPSTONE trial, the most commonly reported serious treatment-related adverse events were Crohn disease (9%) and abdominal abscess (3%) [168].

Oligonucloetides

Antisense oligonucleotides (ASOs) or synthetic oligonucleotides comprise novel drugs which could act as therapies against precise pro-inflammatory molecular targets to avoid unwanted systemic side effects [175, 176]. Their molecular action spans a range and includes inhibition of the translational process of mRNA transcripts of pro-inflammatory molecules, to mimicking bacterial DNA which can activate cellular targets for immunomodulation. A few of these agents have been discussed already (Alicaforsen: selectively targets ICAM-1 mRNA, Mongersen: against SMAD7 mRNA, cobitolimod: mimics bacterial DNA by activiating Toll-like receptor 9 on different immune cells). Two additional agents under investigation are discussed below.

GATA3 DNAzyme

Th17 cells are a subset of lymphocytes which play a major role in intestinal inflammation in both CD and UC [177]. The GATA3 specific DNAzyme (SB010) is an oligonucleotide which can mediate the cleavage of the mRNA of the transcription factor GATA3 and a study conducted with intestinal biopsies of UC patients as well as murine models of colitis showed a correlation between the expression of the transcription factor GATA3 and the production of inflammatory Th2 and Th9 related cytokines. Conditional GATA3 deficiency in T cells prevented experimental colitis in mice [178]. Intrarectal administration of a GATA3 specific DNAzyme (hgd40) significantly ameliorated colitis in murine colitis models.

A phase 2a study of this novel drug as an enema formulation (SECURE study) in patients with moderate to severe UC has recently been completed and the results are awaited [179].

STNM01

Nearly one-third of patients with CD and 5% of UC patients are diagnosed with fibrotic stenosis during their clinical course [180]. Carbohydrate sulfotransferase 15 (CHST15) is an intracellular enzyme that mediates the biosynthesis of sulfated matrix glycosaminoglycans which can induce fibrotic reactions in IBD patients. STNM01 is a novel double-strand RNA oligonucleotide that selectively blocks the expression of CHST15 mRNA and can inhibit the excessive production of glycosaminoglycans in the colon by fibroblasts [181].

A subsequent phase 1 placebo-controlled trial recruited 18 CD patients, with mucosal ulcerative lesions refractory to conventional therapy and randomized them to receive a single endoscopic submucosal injection of STNM01 (2.5, 25, or 250 nM) or placebo, administered at 8 sites directly surrounding the bigger ulcer [182].STNM01 was able to reduce day 30 segmental SES-CD score and induce a reduced extension of fibrosis per histologic analysis, compared to placebo, along with a good safety profile.

Miscellaneous Agents

Apremilast (CC-10004)

Phosphodiesterase 4 (PDE4) enzyme is responsible for lysis of cyclic adenosine monophosphate (cAMP) in inflammatory cells and thereby regulates the inflammatory response by increasing production of proinflammatory mediators (eg TNF-α and IL-23) and decreasing production of anti-inflammatory mediators (eg IL-10) in IBD patients [183]. Apremilast is an oral small-molecule inhibitor of PDE4 and dose of 30 mg twice daily is approved for treatment of patients with active psoriatic arthritis, moderate to severe plaque psoriasis, or oral ulcers associated with Behçet's disease.

A double-blind, phase 2 trial recruited UC patients from 14 countries and randomized them to apremilast 30 mg ($n = 57$), apremilast 40 mg ($n = 55$), or placebo ($n = 58$) twice daily for 12 weeks, followed by random assignment to groups that received apremilast, 30 or 40 mg twice daily, for an additional 40 weeks [184]. Clinical remission at 12 weeks was achieved in 31.6%, 21.8% and 12.6% of patients in the apremilast 30 mg, 40 mg and placebo arms (p = 0.01 for placebo vs. 30 mg and $p = 0.27$ for placebo vs. 40 mg). At week 52, clinical remission was achieved by 40.4% of patients initially assigned to the apremilast 30 mg group and 32.7% of patients initially assigned to the apremilast 40 mg group. The most frequent apremilast-associated adverse events were headache and nausea.

No additional pediatric or adult studies of apremilast for IBD patients are currently in progress.

RDP58 (Delmitide Acetate)

RDP58 also known as delmitide acetate, is a drug that disrupts cell signaling responsible for production of pro-inflammatory cytokines via the mitogen-activated protein kinase superfamily, which have been shown to be significantly activated in the inflamed colonic mucosa of IBD patients [185]. In two phase 2 studies that enrolled patients with mild to moderate UC and compared varied doses of RDP58 100 mg, 200 mg, 300 mg vs. placebo; while primary and secondary endpoints were not met with the 100 mg dose, treatment success was noted with increasing doses 71% and 72% for the 200 mg and the 300 mg dose respectively when compared to 43% for placebo ($P = 0.016$) and the study drug was well tolerated [186].No further clinical trials evaluating RDP58 in IBD are currently planned.

LT02

One hypothesis for explain the increased susceptibility to inflammation and ulcers in UC patients has been the low intrinsic phosphatidylcholine content that reduces intestinal mucus barrier function [187]. LT02 is a modified release phosphatidylcholine, administered as an oral agent to stabilize the gut barrier. In a phase 2 trial of 156 UC patients with prior inadequate response to mesalazine, randomization to placebo, 0.8, 1.6 or 3.2 g of phosphatidylcholine was done [188]. Simple clinical colitis activity index score change for placebo, 0.8, 1.6 and 3.2 g was 33.3%, 44.3% and 51.7% respectively and The 3.2 g dose was statistically superior when compared to placebo at 51.7% compared to 33.3% ($P = 0.03$). Histological remission for placebo and all phosphatidylcholine doses was 20% compared to 40.5% ($P = 0.016$). LT02 was also found to be well tolerated. However, since then two phase III trials have been terminated; one due to failure to induce remission and the second for reasons unknown. Another phase III trial comparing phosphatidylcholine to placebo and mesalamine for maintenance of remission in UC has been completed and results are awaited [189].

LYC-30937-EC

This is a first-in-class, oral, gut-directed ATPase modulator, that selectively targets and induces apoptosis in pro-inflammatory T-lymphocytes. A randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of induction therapy with LYC-30937-EC was undertaken in subjects with active UC. Patients were randomized to receive LYC-30937-EC 25 mg od or placebo for 8 weeks [190]. Clinical remission at 8 weeks was the primary endpoint and since it was not met, the OLE trial has been discontinued and no additional trials are currently planned.

TOP-1288

This is a first in narrow spectrum protein kinase inhibitor, which when given rectally, has shown local anti-inflammatory action in experimental models of UC. A Phase I placebo-controlled, single and multiple ascending dose study of TOP1288 conducted in 61 healthy volunteers demonstrated that rectal administration of TOP1288 at doses up to 200 mg BID for 4 days was safe and well tolerated, with minimal systemic absorption [191]. A Phase 2a proof-of-concept study evaluated the efficacy and safety of daily administration of 200 mg of TOP1288 rectal solution, compared with placebo solution, for 4 consecutive weeks and the results are still awaited [192].

GSK2982772

Receptor Interacting Protein 1 (RIP1) Kinase is a critical driver of inflammation via various pathways [193]. GSK2982772 is a RIP1 kinase inhibitor that has shown excellent activity in blocking many TNF-dependent cellular responses and in reducing the spontaneous production of cytokines from human UC explants. A multicentre, randomised, double-blind, placebo-controlled study with OLE to investigate the safety and tolerability, pharmacokinetics, pharmacodynamics, and efficacy of GSK2982772 in subjects with active UC has been completed and the results are awaited [194].

Rosiglitazone

Thiazolidinedione ligands for the gamma subtype of peroxisome proliferator-activated receptors (PPARgamma), widely used to treat type 2 diabetes mellitus, have also been found to attenuate inflammatory cell proliferation, expression of selected adhesion molecules, inflammatory cytokine production (e.g. interleukin-1β and TNF-α), and reduce colonic inflammation in murine colitis models [195]. A multicenter, randomized, double-blind, placebo-controlled clinical trial compared the efficacy of rosiglitazone 4 mg orally twice daily vs placebo twice daily for 12 weeks in 105 patients with mild to moderately active UC vs. placebo [196]. At week 12, rates of clinical response (44% vs. 23%, $p = 0.04$ and clinical remission (17% vs. 2%, $p = 0.01$) were higher with rosiglitazone vs. placebo. Endoscopic remission was uncommon in both groups (8% rosiglitazone vs 2% placebo; $P = 0.34$).

New concerns related to increased risk of heart disease in patients taking rosiglitazone for diabetes has since emerged and currently no further studies for rosiglitazone for IBD are in process.

VB-201

This is a small oxidised phospholipid molecule that was explored in UC at a dose of 160 mg daily for 24 weeks, via a randomised, cross over placebo-controlled phase II trial [197]. However no statistically significant effect of VB-201 was observed compared to placebo on the primary or secondary endpoints (disease remission at 12 and 24 weeks) and hence further drug development is not planned.

Summary

Blockade of the TNF-a pathway has provided significant strides in the treatment of IBD. However, still a substantial proportion of patients with IBD, specifically those with moderate to severe Crohn disease, do not have a response to treatment with TNF antagonists and are primary or secondary nonresponders or they develop side effects or intolerances leading to discontinuation of medical therapy. As discussed in this chapter, several new biologic treatments utilizing different mechanisms of action are currently in the pipeline and are promising new treatments for IBD.

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Medical Treatment of Perianal Crohn Disease

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Jan-Michael A. Klapproth and Gary R. Lichtenstein

Background

Case

The patient is an 18-year-old female with a recent diagnosis of mild to moderate ileo-colonic Crohn disease, confirmed by endoscopy, histology, and radiography. Her initial fecal calprotectin concertation was determined at 59 micrograms per gram of stool and treatment with a combination of mesalamine and Budesonide 9 mg by mouth per day was initiated. Six months after her initial visit, she is seen in follow up, now complaining of recurrent malaise, fever, and dull right lower quadrant abdominal discomfort. Repeat fecal calprotectin was found to be 450 micrograms per gram stool and a pelvic magnetic resonance imaging scan revealed a complex inter-sphincteric fistula with a 3 cm pelvic abscess.

The patient underwent percutaneous drainage of the pelvic abscess in interventional radiology, and placement of a central venous access port for intravenous antibiotics and parenteral nutrition. Antibiotics were stopped after 2 weeks and a follow up magnetic resonance imaging study 4 weeks later revealed complete resolution of the pelvic abscess. Induction and maintenance of remission were achieved with Infliximab at 5 mg per kg body weight, currently given every 6 weeks. Her test for trough and antibody levels were negative antibodies and 12.45 microgram per ml. She continues to be asymptomatic.

Classification

In a position statement and technical review, the American Gastroenterological Association has stratified perianal fistulae into two groups, simple and complex [1, 2]. Anatomically, simple fistulae develop below the dentate line, and are of either superficial, low inter-sphincteric, or low trans-sphincteric origin. Simple fistulae usually have a single opening, without evidence of abscess formation, anorectal stricture, or genitourinary involvement. In contrast, complex fistulae are classified as high in origin (high inter-sphincteric, high trans-sphincteric, or supra-sphincteric), with possibly multiple external openings, pain or evidence of abscess formation. Complex fistulae are likely to extend into vagina, rectum, or contributing to the development of a rectal stricture. Precise classification of fistulas is mandatory for successful treatment, as well as prognosis, as simple fistulae have a high degree of healing, whereas complex fistulae have a lower rate of achieving remission i.e., cessation of discharge [3–6].

Pathogenesis

As opposed to ulcerative colitis, the transmural nature of the inflammation that typifies CD predisposes patients to fistula formation. This process is initiated by epithelial to mesenchymal transition, characterized by increased epithelial mobility and cells spreading. During this transformation, epithelium-specific barrier proteins, such as E-cadherin and claudin-4, are down-regulated, whereas mesenchymal proteins, such as vimentin, are up-regulated [7]. This process is driven by increased expression of tumor necrosis factor α and transforming growth factor β [8], leading to activation of transcription factors, namely SNAIL1 and SLUG. SNAIL1 and SLUG have also been found to be induced by interleukin-13, a molecule that favors fibrosis, itself up-regulated by transforming growth factor β. Interestingly, cell wall component muramyl dipeptide, found in Gram-positive and Gram-negative bacteria, stimulates expression of SNAIL1, SLUG, interleukin-13, tumor necrosis factor α and transforming growth factor β. The inability to neutralize muramyl dipeptide due to a C-terminal mutation in nucleotide oligomerization domain, has been described in up to 50% of patients with ileo-colonic CD [9]. Eventually, immune acti-

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vation as described above, leads to the expression of β6-integrin, a molecule associated with cell invasion and matrix remodeling.

Natural History

The reported incidence of fistulae in patients with CD ranges from 17% to 43% in referral-center-based case series [10–19]. Early studies examined 176 patients diagnosed with CD in Olmsted County, Minnesota, from 1970 to 1993 and found a cumulative incidence of at least one fistula (at any site) of 21% at 1 year, 26% at 5 years, 33% at 10 years, and 50% at 20 years [20]. The corresponding cumulative incidences of at least one perianal fistula were 12% at 1 year, 15% at 5 years, 21% at 10 years, and 26% at 20 years. An updated and more recent population-based cohort study from this cohort found out of 414 participants 20.5% had at least one rectovaginal or perianal fistula with a 1:1 female-to-male ratio [9]. The cumulative incidence of rectovaginal fistulae increased over time: 18% at 10 years, 23% at 20 years, and 24% at 30–40 years following the diagnosis of Crohn disease. Interestingly, the incidence of fistulae was significantly lower in the patient population diagnosed after 1998 in comparison to before 1998 (14.5% vs. 25.8%, respectively; $p = 0.03$) with a 10-year risk reduction of 12%. This time frame appears to coincide with the introduction of biologic therapy for fistulizing CD [21]

Population-based studies have also examined the natural history of CD fistulae [17–19]. A study from Stockholm County with 826 patients, diagnosed between 1955 and 1974, observed a 23% cumulative incidence of perianal fistulae [19]. Interestingly, while the frequency of perianal fistulae formation increased, the incidence of inflammation increased from proximal to distal: 12% ileum, 15% ileocolonic, 41% colonic without rectal involvement, and 92% rectum. As opposed to inflammation, this study identified fistulae in the following locations: 54% perianal, 24% enteroenteric, 9% rectovaginal, 6% enterocutaneous, 3% enterovesical, and 3% entero-intraabdominal. Remarkably, 45% of patients developed a perianal fistula before or at the time of diagnosis of CD, first described by Gray et al in 1965 [22] and followed up by Hellers et al [17–19]. This observation highlights the frequent difficulties encountered in attempting to diagnose CD in patients with isolated perianal disease.

At this point it is worthwhile discussing the characteristics and long-term outcomes of pediatric patients. In a recent study, out of 234 included patients (mean age 14.2 ± 2.4 years; 8), 56% were male participants, and 24% had evidence of perianal disease, but only 9% had fistulae. Interestingly, children with perianal disease had significantly lower body weight, z scores for height, serum albumin concentrations, but a higher pediatric CD activity index, Magnet Resonance Enterography Global Inflammatory Score, rectal and jejunal involvement, and a high prevalence of granulomas in biopsy material. These data were interpreted that children with fistulizing disease display a distinctly different phenotype with a predisposition to greater inflammatory burden. In a related study [23] it was found that male pediatric patients with inflammation from CD are at increased risk for the development of fistulizing disease over time, similar to adults. In contrast, female sex was associated with a higher incidence of perianal involvement. In a more recent study, involving 2406 children, perianal disease was present at time of diagnosis in 5.5% of participants, with 80.9% being male. During the follow-up period of 2 years, an additional 4.3% of patients developed perianal disease, steroids being potential risk factors for the development of perianal disease.

The clinical course of perianal fistulae depends on their complexity. Simple fistulae may heal spontaneously in up to 50% of cases [24] whereas complex fistulae rarely heal spontaneously [25]. A number of studies have demonstrated that simple perianal fistulae tend to heal more completely and recur less frequently than complex fistulae [4, 6, 26–28].

Diagnosis

Since healing rates seem to decrease when fistulae transform from simple to complex, it is tantamount to recognize and treat perianal CD fistulae as soon as symptoms or abnormal imaging raise suspicion for penetrating CD. Thus, fistula location and extent must be accurately ascertained prior to commencing therapy. Unfortunately, digital rectal examination alone is not sufficient in this capacity, with accuracy as low as 62% [29] Similarly, fistulography and CT are of limited use, given their low diagnostic accuracy of 16–50% and 24–60%, respectively [30–41]

Magnetic resonance imaging is currently the gold standard for the assessment of perianal fistulae. MRI scanning is free of ionizing radiation, but is more costly than convention CT radiography. Cross-sectional imaging by MRI is superior to barium studies for detecting fistulizing disease, and equally accurate as CT in assessing luminal disease activity and bowel damage in Crohn disease. Diagnostic accuracy has been reported at a range of 76–100% [42–50]. A related study, investigating 219 MRI studies comparing images from an adult and pediatric population, identified an increased prevalence of perianal disease in children (34.% vs. 16.1%. (OR = 2.8, $p = 0.0017$;12. The pediatric population had a high incidence of rectal involvement (29.7% vs, 13.5%, OR = 2.7, $p = 0.0045$).

Equally accurate in characterizing perianal fistulae is endoscopic ultrasound (EUS) with a diagnostic accuracy ranging from 56–100% [41, 46, 51–57]. Ultrasound can be

further enhanced with hydrogen peroxide fistulography, originally described in 1993 [58]. With this method the external opening of the fistula is located, cannulated and injected with hydrogen peroxide, allowing for exact delineation of the fistulous tract. Although initially described, this is not performed in clinical practice. An additional enhanced technique is three dimensional endo-anal sonography, in which multiple parallel two dimensional ultrasound images are synthesized into a three dimensional data set [57]. Diagnostic accuracy consistently exceeds 96%, defined as an agreement among operators with a consensus of equal to or more than 85% of patient findings. Combining two investigations of either EUS, MRI, or examination under anesthesia provides the most accurate tests for determining fistula anatomy patients with perianal Crohn disease, reaching 100% [59].

When assessed in a prospective trial evaluating patients with perianal Crohn disease use of both pelvic MRI or anorectal EUS has been found to change surgical management in 10–15% of cases [44–50, 56].

EUA performed by an experienced colorectal surgeon has long been considered the gold standard for diagnosis of perianal fistulae in CD. However, this view has recently been challenged by Schwartz et al who compared EUA, MRI, and EUS in a prospective blinded study of 34 patients with suspected CD perianal fistulae [49]. In this study, a consensus gold standard was determined for each patient. The authors observed a diagnostic accuracy exceeding 85% for all three modalities, specifically 91% for EUA and EUS and 87% for MRI. Of note, when any two of the tests were combined, diagnostic accuracy increased to 100%.

Medical Therapy of Fistulas

5-Aminosalicylic Acid Derivatives

5-Aminosalicylic acid and derivatives have not been shown to be efficacious in inducing remission in luminal CD and also have never been studied for the treatment of CD fistulae in controlled trials. Thus, they cannot be recommended for the treatment of fistulizing CD.

Corticosteroids

There have been no controlled studies evaluating the use of steroids in the management of CD fistulae. Unfortunately, neither the National Cooperative Crohn Disease trial, nor the European Cooperative Crohn Disease trial provided data on response in the subgroup of patients with fistulae. However, two large uncontrolled studies have shown that corticosteroid use may actually be detrimental to patients with fistulizing CD, as it was associated with higher rates of surgical intervention [60, 61]. A retrospective case-control study of 432 patients with CD studied the risk of intra-abdominal or pelvic abscess with systemic corticosteroid use during the previous 3 months [62]. The authors found a significant nine-fold increased risk of intra-abdominal or pelvic abscess in patients with perforating CD who had received systemic corticosteroids during the prior 3 months (adjusted OR = 9.03, 95% CI = 2.40–33.98). In patients with relapsed active disease, they also reported a significant nine-fold increased risk of abscess in patients receiving systemic steroids in the 3 months prior to presentation (unadjusted OR = 9.31, 95% CI = 1.03–83.91). For these reasons, corticosteroids should be avoided in patients with fistulizing CD.

Antibiotics

There is increased evidence to suggest that the intestinal microbiome actively contributes to the pathogenesis of CD. Although antibiotics are the most commonly used medication for the treatment of fistulae in CD, there are limited controlled data indicating that these agents are effective in this regard. The use of antibiotics in fistulizing CD is largely based upon a number of uncontrolled case series, each with a small number of patients [63–72]

A randomized and controlled study investigating ciprofloxacin, metronidazole, or placebo involving 25 patients was recently completed [73]. In this study, remission was defined as closure of all fistulae and response was defined as closure of at least 50% of all fistulae that were draining at baseline. Among the 25 patients who completed the study, remission and response rates for the ciprofloxacin (n = 10), metronidazole (n = 7), and placebo (n = 8) groups were 30% and 40%, 0% and 14%, and 13% and 13%, respectively. It is worth noting, that in a separate study 21 therapy refractory patients with perianal Crohn disease were treated with 6.5 months of metronidazole. In this uncontrolled trial, fistula drainage, erythema, and induration decreased in all patients, with complete healing of fistulous tracts observed in 10/18 patients, chronically treated with this antibiotic. Of concern is the fact that half the patient population experienced neuropathy, requiring reduction or even discontinuation of this medication. Discontinuation of maintenance therapy with metronidazole was associated with relapse in all patients [66] However, rapid healing was noted in all patients upon re-administration of metronidazole. Thus, while efficacious in the induction of improvement, metronidazole is limited in that maintenance therapy is often required. Three other small, uncontrolled studies have also observed efficacy with metronidazole in fistulizing CD with fistula closure rates of 40–50%, but a high rate of relapse after cessation of therapy was seen in one of these studies

[65, 67, 68] The typical dose of metronidazole in the treatment of fistulizing CD ranges from 750–1500 mg/day. Adverse events caused by metronidazole are quite common, often leading to intolerance and discontinuation of the drug, and include a distal sensory neuropathy with paresthesias, nausea, dyspepsia, fatigue, glossitis, metallic taste, and a disulfiram-like reaction to alcohol ingestion [74].

Given that adverse events are commonly encountered with the use of with metronidazole, ciprofloxacin began to be used in the late 1980s to treat CD fistulae [69–72]. A meta-analysis, originally published in 2015, discussing three trials with ciprofloxacin to treat perianal fistulas, revealed a significant increase in clinical response and remission in the treatment group, versus placebo (18C; RR = 1.54, 95%CI: 1.16–2.32, p = 0.0005). Other, significantly smaller trials with ciprofloxacin have been performed. This includes an investigation with eight metronidazole-refractory CD patients who were subjected to 1000–1500 mg/day ciprofloxacin for 3–12 months [69]. The initial response was favorable, but almost all patients developed recurrent and persistent fistula drainage, requiring surgical intervention. And even a small study with 5 patients noted clinical improvement in 4/5 participants, following 5 weeks of therapy [70].

Ciprofloxacin and metronidazole have been used in combination therapy in a retrospective study with 14 patients [71] Their group observed improvement in 9 patients and fistula closure in 3 patients within 12 weeks, but like previous antibiotic studies, they also reported that relapse was the norm following discontinuation of therapy. The typical dose of ciprofloxacin in the treatment of fistulizing CD ranges from 1000 to 1500 mg/day. Adverse events with ciprofloxacin are uncommon and include headache, nausea, diarrhea, rash, and spontaneous tendon rupture [74, 75]. Recently, neuropathy [76] and aortic aneurysm or aortic dissection [77] have been described to occur in patients using fluoroquinolones.

Azathioprine/6-Mercaptopurine/Methotrexate

Early investigations into the effect of azathioprine and 6-MP on active perianal CD showed that after 3 years, cumulative probabilities of remaining free of perianal complications and achieving a clear anatomic improvement were 0.47 (95% CI 0.36–0.58) and 0.4 (95% CI 0.29–0.53) [78]. In this study, a total of 29% responded azathioprine or 6-mercaptopurine. The absence of fistulae, perianal disease duration shorter than 22 months, and age 40 years and older, were independent factors associated with a response to immunomodulatory therapy. Interestingly, there was no correlation between the resolution of perianal disease and intestinal remission.

The study by Present et al observed a 31% rate of complete closure of the fistulae in the group receiving 6MP versus 6% for the placebo group [79]. A meta-analysis of these five trials reported an overall response rate (defined as improvement or complete healing) in 54% of patients treated with azathioprine or 6MP compared to 21% in patients treated with placebo [80]. The corresponding pooled odds ratio for fistula healing with azathioprine or 6MP was 4.44 (95% CI = 1.50–13.20). In the pediatric population, represented by 15 CD subjects and treated for 6 months (25), 67% had an improvement in drainage, 73% in tenderness, 60% in induration, and 40% in fistula closure. The authors also concluded, that immunomodulators are warranted for healing perianal CD.

Given the favorable response on perianal disease, a total of 16 patients, mean age 37 years, 13 subjects with perianal fistulas, were treated with a combination of infliximab and 6-mercaptopurine or azathioprine [81]. Interestingly, 75% of patients develop complete closure of fistulae, persisting for more than 6 months, with the median time to closure of about 14 days (range 2–36 days). The authors speculated that immunomodulator therapy could prolong the effect of initial infliximab therapy, leading to fistula closure in patients with CD.

In a prospective, open label study with 31 patients, the effect of ciprofloxacin 500–1000 mg/day and/or metronidazole 1000–1500 mg/day in combination with azathioprine were tested [77]. Endpoint was reduction in fistula drainage assessment and the perianal disease activity index at week 8 and 20. Approximately 50% of participants responded to antibiotic therapy and 25% achieved complete healing by week 8. The perianal disease activity index decreased from 8.4 to 6.0 (p = 0.0001). By week 20, the response was achieved in 35% of patients, and complete healing was achieved in 18% of patients. Interestingly, participants receiving combination therapy with azathioprine and antibiotics were more likely to achieve a response, leading the authors to conclude that antibiotics play a role in bridging the time until immunomodulators become active.

Over the past few years, Methotrexate has secured a role in the management of inflammatory CD. Its role in fistulizing disease was investigated by recruiting 33 adult patients with luminal and or fistulizing Crohn disease. In 16 patients with fistulae, 25% experienced complete closure, 31% had partial closure and an overall response to methotrexate therapy of 62% was observed. It is worth noting that 6% of patients had significant adverse events.

In a follow-up study, 12 patients with fistulizing Crohn disease, having failed azathioprine, were subjected to combination therapy with infliximab at 5 mg/kg and long-term methotrexate, 20 mg per week [82]. The primary endpoint in this trial was sustained closure of fistulas for greater or equal

to 6 months after fistula closure. In 4/12 patients the primary endpoint was reached, with additional partial closure in 3 patients. Unfortunately, 5 patients did not achieve closure, or experienced side effects from the medication.

Finally, 34 CD patients with complex perianal fistulae were subjected to infliximab infusions [83] as well as maintenance therapy with methotrexate in combination with at least removal of one seton between the second and third infliximab infusion. At week 14, the overall response rate was 85%, with 74% of patient's showing a complete response. At 12 months, 50% of patients still responded with recurrent luminal inflammation as the major cause of relapse.

Thus, methotrexate may represent a reasonable alternative to patients who fail or cannot tolerate azathioprine or 6MP, and long-term maintenance therapy is likely necessary; however, prospective randomized placebo-controlled trials are still needed to evaluate formally the efficacy of methotrexate for fistulizing CD. The initial dose of methotrexate suggested is 25 mg intramuscularly every week. Interestingly, concurrent and mandatory administration of folate is advocated to lessen nausea. Adverse events are common and include hepatic fibrosis, bone marrow suppression, pneumonitis and pulmonary fibrosis, nausea, and teratogenicity [84, 85].

In addition, two uncontrolled case series, one in adults and one in children, have been published [86, 87]. The adult series, by Korelitz et al, treated 34 patients with 6MP at a dose of 1.5 mg/kg/day with various types of fistulae, including perianal (18 patients), abdominal wall (8 patients), enteroenteric (7 patients), rectovaginal (6 patients), and vulvar (2 patients) [86]. Complete fistula closure was achieved in 39% of patients, with an additional 26% showing improvement. This study also underscored the importance of maintenance therapy. Fistulae remained closed for 1–5 years in 46% of patients (6 out of 13) who remained on 6MP, and relapses tended to occur within 2 weeks to 9 months after discontinuation of the drug. Healing was once again achieved upon re-administration of 6MP. Furthermore, the authors noted that although all types of fistulae responded to 6MP, abdominal wall and entero-enteric fistulae responded particularly well.

Typical doses of immunomodulators azathioprine and 6MP are 1–1.5 mg/kg/day and 2–3 mg/kg/day, respectively. A meta-analysis has demonstrated that higher 6-thioguanine nucleotide levels (especially ≥230–260 pmol/10^8 red blood cells) were associated with a higher likelihood of clinical remission [88]. Adverse events are common with azathioprine and 6MP, occurring in 9–15% of patients, and include allergic reactions, bone marrow suppression (especially leukopenia), pancreatitis, infection, hepatotoxicity, non-Hodgkin's lymphoma, and other gastrointestinal side effects (nausea, vomiting, and abdominal pain) [80, 89, 90].

Tacrolimus

Few studies have been performed with tacrolimus for fistulizing CD. Previously, a randomized, double-blind, placebo-controlled, multi-center clinical trial involved 48 patients with Crohn disease and actively draining perianal and enterocutaneous fistulas [91]. The subject received oral tacrolimus at 0.2 mg/kg and day, or placebo, for a total of 10 weeks. The primary outcome in this study was the closure of more than 50% of particular fistulas that were actively draining at baseline and maintained closure for at least 4 weeks. The secondary outcome was remission as defined by closure of all fistulas and maintenance of that closure for at least 4 weeks. At 4 weeks, 43% of tacrolimus-treated subjects displayed fistula improvement, compared to 8% of placebo-treated patients ($p = 0.004$). Unfortunately, only 10% of tacrolimus treated patient's experienced remission of fistulae, compared with 8% of placebo-treated patients, leading the authors to speculate that oral tacrolimus is effective for fistula improvement, but not remission.

A pilot study, investigating oral tacrolimus for infliximab-refractory fistulizing CD, enrolled 10 patients [92]. The subjects were resistant to azathioprine, antibiotics, 6 mercaptopurine and infliximab. The patient has received tacrolimus at 0.05 mg/kg every 12 h. Clinical response was determined by the perianal Crohn Disease Activity Index and MRI. Follow-ups at 6 and 24 months revealed 4 patients who achieved a complete and 5 patients a partial response. It is worth noting, that all steroid-dependent patient's stopped therapy with prednisone and concomitant immunomodulatory therapy being tapered. However, despite the interpretation that tacrolimus appears to be effective and safe for therapy refractory CD patient's, results were obtained from a rather heterogeneous cohort with a broad variety of fistulizing disease and no controls. Tacrolimus is not widely used for patients and is not a maintenance medication for treating fistulizing Crohn disease.

Cyclosporin A

Results for clinical trials investigating the efficacy of cyclosporin A in fistulizing CD are limited have been published as case series [93–101]. In an older series, a total of 16 patients were investigated with symptomatic perianal, rectovaginal, and enterocutaneous fistulae receiving cyclosporine A intravenously. Cyclosporin A at 4 mg/kg/day resulted in clinical improvement an 88% of subjects with complete fistula closure in 44% [97]. However, within a week's time 36% of patients experienced recurrent symptoms when converted to oral cyclosporine A. Unfortunately, fistula recurrence after discontinuation of cyclosporin A was 62%.

Therefore, cyclosporin A functions as a temporizing measure for immunomodulatory therapy (azathioprine, 6-MP or a biologic). The recommended initiation intravenous dose of cyclosporine is 4 mg/kg/day for 1 week, followed by oral formulation, typically 6–8 mg/kg/day, all dosed by levels. Adverse events are common and include paresthesias, hirsutism, hypertension, tremor, renal insufficiency, headache, opportunistic infections, gingival hyperplasia, seizures, and hepatotoxicity [84, 102].

Infliximab

In the management of perianal fistulizing CD, neutralizing Tumor Necrosis Factor α plays a key role in controlling penetrating disease. Infliximab, a chimeric (75% human, 25% murine) IgG1 monoclonal antibody directed against Tumor Necrosis Factor α, is the prototype anti-tumor necrosis factor α agent and has now become the cornerstone in medical therapy of fistulizing CD. The efficacy of infliximab in controlling fistulae was first established in a randomized, double blind, placebo controlled trial, involving 94 patients with fistulizing disease [103, 104]. This cohort consisted of 10% of patients with draining abdominal (10% of patients) or perianal (90% of patients) fistulae. Infliximab was given at 5 mg/kg, or 10 mg/kg intravenously at week 0, 2, and 6 [103]. The primary endpoint was a reduction in the number of draining fistulae by ≥50%, maintained for at least 4 weeks, with a secondary end point being closure of all fistulae. The primary goal was achieved in 68% of patients receiving infliximab at 5 mg/kg and 56% of patients who received infliximab at 10 mg/kg, compared to 26% of patients who received placebo ($p = 0.002$ and $p = 0.02$, respectively). Closure of all fistulae was achieved in 55% of patients who received infliximab at 5 mg/kg and 38% of patients who received infliximab at 10 mg/kg, compared to only 13% of patients who received placebo ($p = 0.001$ and $p = 0.04$, respectively). The median time to response was 14 days for infliximab-treated patients vs. 42 days for patients assigned to placebo. The majority of infliximab-treated patients achieved fistula closure prior to the third infusion and 6 weeks. Eleven patients experienced at least 1 fistula closure in infliximab-treated subjects developed a perianal abscess, possibly resulting from premature closure of the cutaneous end before closure of the rest of the fistula tract. However, the overall rates of infection did not differ between the infliximab and placebo groups. The median duration of response was 3 months, suggesting that maintenance therapy may be required.

Subsequently, the long-term efficacy of infliximab in the treatment of fistulizing Crohn disease was investigated in the ACCENT II trial (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn Disease). This study recruited 282 patients with draining perianal, abdominal, and rectovaginal fistulae [104]. All patients received infliximab at 5 mg/kg at weeks 0, 2, and 6, followed by assessment of reduction in the number of draining fistulae by ≥50% for at least 4 weeks. This primary endpoint was achieved in 195 patients (69%). At week 14, the 195 responders were then randomly assigned to receive infusions of either infliximab 5 mg/kg or placebo every 8 weeks until week 54. The primary endpoint was time to loss of response. The authors observed a median time to loss of response of 40 weeks in infliximab-maintained patients vs. 14 weeks in placebo-assigned patients ($p = 0.001$). Overall, 42% of patients in the infliximab group had a loss of response, compared to 62% in the placebo group. At week 54, 46% of patients treated with infliximab still had a response, versus 23% of patients treated with placebo ($p = 0.001$). In addition, at week 54, 36% of patients in the infliximab group had a complete absence of draining fistulae, compared to 19% in the placebo group ($p = 0.009$). A post-hoc analysis of the ACCENT II data looked at efficacy of infliximab induction and maintenance in a subset of women with rectovaginal fistulae [104]. Twenty-five of the original 138 women had a total of 27 draining rectovaginal fistulae at baseline. At week 14, 64% of these 25 women had responded and were then randomized to receive infliximab or placebo maintenance therapy. The authors reported a median time to loss of response of 46 weeks for the infliximab group vs. 33 weeks in the placebo group.

The social impact of infliximab in patients with active fistulizing CD has also been investigated in two recent studies. Cadahia et al were interested in the effect of infliximab induction treatment on health-related quality of life, and thus, they conducted a prospective observational study of 25 patients who received three-dose induction infliximab therapy for single or multiple draining abdominal or perianal fistulae [105]. The authors found that health-related quality of life, as measured by the SF-36, demonstrated significant improvement in the physical domain after 4 and 10 weeks. In addition, a significant increase in IBDQ score was seen after 4 weeks. Lichtenstein et al evaluated the impact of infliximab maintenance therapy on the number of hospitalizations, surgeries, and procedures in patients with fistulizing CD [106]. Using data from the ACCENT II trial, they revealed that compared to patients who received placebo, patients who received maintenance infliximab had significantly fewer number of mean hospitalization days (0.5 vs. 2.5 days), hospitalizations (0.11 vs. 0.31), total surgeries and procedures (65 vs. 126), inpatient surgeries and procedures (7 vs. 41), and major surgeries (2 vs. 11).

A retrospective survey performed with 66 patient's suffering perianal disease [107], determined that trough concentrations were significantly higher in patients with closed fistulae as opposed to patients with actively draining fistulae (6 μg/

mL [5.4–6.9] vs. 2.3 μg/mL [1.1–4.0], respectively). From this study, it was concluded that serum concentrations of equal to or greater 5.0 μg/mL were associated with fistula closure.

Similar findings have been reported for the pediatric population suffering from fistulizing Crohn disease. An analysis of 50 children with perianal fistulizing Crohn disease, age range 9–18 years, received induction therapy with infliximab at 5 mg/kg at week 0, 2, and 6 [108]. Maintenance therapy was given at 5 milligrams/kilogram every 8 weeks. The results revealed that 76% of children after induction therapy with infliximab and 71.8% after maintenance therapy achieved and maintained closure of fistulae, respectively. A multi-center inception cohort study investigated 667 consecutive children younger than age 17 years with fistulizing perianal Crohn disease to further characterize the serum infliximab concentration required fistula closure. The authors determined that the median infliximab concentration in responders was 12.7 μg/mL vs. 5.4 μg/mL in those with active fistulizing disease, which is significantly higher than in the adult population.

The effectiveness of infliximab in combination with other medical therapies for fistulizing CD has also been investigated in several studies [81, 109, 110]. West et al conducted a double-blind, placebo-controlled trial of ciprofloxacin overlapping with infliximab in patients with perianal CD fistulae [109]. In this study, 24 patients were randomized to receive either ciprofloxacin at 1000 mg/day or placebo for 12 weeks in addition to infliximab at 5 mg/kg at weeks 6, 8, and 12. Patients were followed for 18 weeks, and the primary endpoint was reduction in the number of draining fistulae by ≥50%. The authors reported that 73% of the ciprofloxacin-treated patients responded, compared to 39% in the placebo group. One caveat is that the response rate to infliximab alone was much less than in other infliximab studies, in which at least 60% of patients responded.

Infliximab has also been evaluated in combination with immunomodulator therapy. Ochsenkühn et al performed an uncontrolled pilot study of long-term azathioprine (at 2–2.5 mg/kg/day) or 6MP (at 1 mg/kg/day) in combination with induction infliximab in 16 patients [81]. They found that 75% of patients achieved complete fistula closure, which persisted for more than 6 months (median time of 10 months). As seen previously, the median time to fistula closure was 14 days. A similar uncontrolled pilot study by Schröder et al followed 12 consecutive patients with CD fistulae intolerant or resistant to azathioprine [110]. Patients were treated with induction infliximab and long-term methotrexate at 20 mg/week (intravenously for 6 weeks, followed by oral thereafter). The authors observed that 33% of patients experienced complete fistula closure for at least 6 months (median 13 months), and 25% had a partial response. While providing a suggestion of efficacy of combination therapy for the treatment of fistulizing CD, controlled trials have yet to be performed.

In order to increase the rate of fistula closure a recent study evaluated if there was added benefit for concurrent seton placement. In this study, 156 patients were treated with infliximab and 62% received additional therapy with placement of a seton [111]. Follow-up at 250 weeks revealed 69% of patients had at least one fistula closure. Among patients who experienced fistula closure, the probabilities of fistulae recurrence where 16.6% and 40.1% at 1 and 5 years, respectively. Interestingly, 28.9% developed abscesses during follow-up, with the number of infliximab infusions greater than 19 to be associated with less abscess recurrence. In conclusion, two-thirds of patients experienced fistula closure, and one third of patients had recurrence after infliximab initiation. It appears that combination therapy, duration of seton drainage less than 34 weeks and long-term treatment with infliximab were associated with better outcomes including combination with an examination under anesthesia [112].

Despite all of its reported success, the use of infliximab may not obviate the need for surgical management of CD fistulae in many cases. Poritz et al retrospectively examined surgical rates in patients treated with infliximab for fistulizing CD at a single institution [113]. Among the 26 patients with various types of fistulae, 46% experienced a partial response to infliximab, and an additional 23% had fistula closure. However, 54% of patients overall still required surgery after infliximab therapy and another 23% continued to open fistulous drainage but refused surgery. Of note, none of the patients with either enterocutaneous or peristomal fistulae were healed with infliximab treatment.

The combination of infliximab with surgical intervention (i.e. seton placement) in the treatment of CD perianal fistulae has been assessed in a several studies [4, 5, 114–116]. Three single-center retrospective case series, from Calgary, Leeds, and Oxford, each of which included 21 patients, have documented favorable rates of fistula healing with seton placement followed by induction and maintenance therapy with infliximab, with complete and partial healing rates of 67% and 19%, 47% and 53%, and 21% and 42%, respectively [5, 114, 115]. Two studies were able to compare the outcomes of patients treated with infliximab and seton placement to those treated with infliximab and/or seton placement alone [6, 120]. The first, by Regueiro and Mardini, retrospectively analyzed 32 consecutive patients with perianal CD fistulae, all of whom had received at least 3 induction doses of infliximab and some of whom had additionally undergone an EUA with seton placement prior to infliximab treatment [4]. Response was defined as complete closure and cessation of drainage from the fistula. They found that compared to patients treated with infliximab alone ($n = 23$), patients who had a pre-infusional EUA with seton placement ($n = 9$) had a significantly higher rate of initial response (100% vs. 83%,

$p = 0.014$), lower rate of recurrence (44% vs. 79%, $p = 0.001$), and longer time to recurrence (13.5 months vs. 3.6 months, $p = 0.0001$). The second study, by Scaudione et al, prospectively subdivided 35 consecutive patients with complex perianal fistulae into 3 different interventional groups: infliximab with seton placement ($n = 14$), infliximab alone ($n = 11$), and seton placement alone ($n = 10$) [116]. The authors reported that patients in the combination group had a non-significantly higher rate of complete response, defined as closure of all draining fistulae and cessation of drainage for 3 months, of 79% vs. 64% and 70%, respectively, and a significantly longer time to recurrence of 10.1 months vs. 2.6 and 3.6 months, respectively ($p < 0.02$).

The combination of infliximab with immunomodulators and seton placement has also been investigated more recently. A prospective open-label study of 34 patients from three hospitals in France, by Roumeguere et al., had patients undergo seton placement 3 months prior to start of medical therapy, followed by initiation of methotrexate 25 mg per week, followed by induction infliximab, after which patients were maintained on methotrexate alone [117]. At 14 weeks, 74% of patients had a complete response and another 11% had a partial response. Of patients with the initial response, 90% had maintained at least a partial response after 56 weeks. A prospective study of 41 patients from St. Mark's Hospital in London, by Tozer et al., assessed long-term fistula response and remission rates after treatment with infliximab (or adalimumab in 9 patients who lost response to infliximab) combined with thiopurines in which 73% of patients had seton placement which was removed after 2–6 weeks [118]. They reported rates of fistula response and remission at 2 years of 35% and 29%, respectively, and at 3 years of 37% and 21%, respectively. A large retrospective study from two referral centers in France, by Bouguen et al., assessed long-term rates of initial and sustained fistula closure in 156 patients treated with infliximab and immunomodulators (in 58%) and seton placement (in 62%) [111]. They observed rates of initial fistula closure of 59%, 73%, and 88% at 3, 5, and 10 years, respectively, and rates of sustained fistula closure of 22%, 43%, and 57% at 3, 5, and 10 years, respectively. Interestingly, the use of infliximab for more than 118 weeks and the use of combination therapy were associated with significantly higher rates of initial fistula closure. [Discontinuation of infliximab for any reason can result in severe relapses of fistulizing disease] [119]. Median follow-up of 62 months revealed 24/45 patient is experiencing recurrent perianal disease, with 79% of patients requiring surgical drainage. The cumulative probabilities perianal relapse at 1 and 5 years was determined at 24 in 55%, respectively associated with perianal relapse were external fistula opening, second line anti TNF alpha use, or lack of dose optimization. Reintroduction of infliximab resulted in remission in 96% of patients.

Adverse events with infliximab treatment are common and include infusion reactions, delayed-type hypersensitivity reactions, formation of human anti-chimeric antibodies, formation of antinuclear and anti-double-stranded DNA antibodies, and drug-induced lupus-like reactions [120]. In addition, infectious complications seem to be increased, but serious infections, such as pneumonia, sepsis, tuberculosis, and opportunistic infections, including listeriosis, aspergillosis, histoplasmosis, coccidiomycosis, and *Pneumocystis carinii* pneumonia, occur only rarely [121–127]. Finally, there have been isolated case reports of hepatic necrosis and non-Hodgkin's lymphoma in patients treated with infliximab, although it has not been determined whether these events were the direct consequence of infliximab therapy.

Adalimumab and Certolizumab Pegol

Similar to infliximab, the other commonly used anti-TNF-α medications for CD treatment, adalimumab and certolizumab pegol, have shown efficacy in the treatment of fistulizing disease. Although data focusing on patients with fistulae for both adalimumab and certolizumab pegol were obtained from randomized placebo-controlled studies, the data assessed on fistula healing was not a primary endpoint in these studies. Adalimumab, a fully human IgG1 monoclonal antibody, was found to be efficacious for maintenance of remission in The Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM), in which 854 patients received open-label induction treatment with subcutaneous adalimumab 80 mg at week 0 and 40 mg at week 2, followed by randomized maintenance treatment with adalimumab 40 mg every week or every other week or placebo up to week 56, with a co-primary endpoint of clinical remission at weeks 26 and 56 [128]. In this study, 117 patients had draining fistulae and 113 of these had perianal fistulae. A subgroup analysis of these patients, in which complete fistula healing was defined as the absence of draining fistulae at the last two consecutive post-baseline evaluations, reported complete fistula healing rates of 30% for the combined adalimumab groups versus 13% for the placebo group at week 26 ($p < 0.05$), and 33% for the combined adalimumab groups versus 13% for the placebo group at week 56 ($p < 0.05$) [129]. The authors also observed that these rates of fistula healing were largely maintained for up to 2 years of follow-up in a long-term extension study of CHARM called ADHERE [130]. Similar findings have been described for the pediatric population where 36 children/adolescent with moderately to severely active Crohn disease were treated with Adalimumab induction therapy, resulting in fistula closure and improvement at 44.4% and 52.8%, comparing week 0–52 and week 240, respectively [131].

Analogous to infliximab, combination therapy with Adalimumab and Ciprofloxacin is more effective than monotherapy to achieve fistula closure in Crohn disease. In a randomized, double blind, placebo-controlled trial, conducted at multiple sites, 76 patients received Adalimumab induction therapy in combination with ciprofloxacin 500 mg twice a day versus placebo, for a total of 12 weeks. Ciprofloxacin was discontinued after 3 months. The primary endpoint was defined at a 50% reduction of fistulae from baseline to week 12. Secondary end points include remission, defined by the perianal Crohn disease activity index, Crohn disease activity index, and inflammatory bowel disease questionnaire. A clinical response was achieved in 71% of patients receiving adalimumab plus ciprofloxacin, and 47% in patients treated with adalimumab plus placebo. Rate of remission at 12 weeks was significantly higher for the combination group vs. monotherapy with Adalimumab (65% vs. 33%, $p = 0.0005$). Mean improvement in IBDQ and CDAI scores were significantly higher in the combination group at 12 weeks, but not at 24 weeks. Therefore, combination therapy with Adalimumab plus Cipro is more efficacious in fistula closure than Adalimumab alone.

Certolizumab pegol, a pegylated humanized Fab fragment of an anti-TNF-α monoclonal antibody, was shown to have efficacy in the maintenance of remission in active Crohn disease in the Pegylated Antibody Fragment Evaluation in Crohn Disease: Safety and Efficacy 2 (PRECISE 2) randomized placebo-controlled trial, in which 668 patients received open-label induction treatment with subcutaneous certolizumab pegol 400 mg at weeks 0, 2, and 4, followed by randomized maintenance treatment with certolizumab pegol 400 mg or placebo every 4 weeks through week 24 and followed to week 26 [132]. In this study, 58 patients had draining fistulae and 55 of these had perianal fistulae. A subgroup analysis of these patients, in which complete and partial fistula closure was defined as closure of 100% and at least 50%, respectively, of all draining fistulae at two consecutive post-baseline evaluations at least 3 weeks apart, reported complete fistula healing rates of 36% for the certolizumab pegol group versus 17% for the placebo group ($p = 0.038$) and partial fistula healing rates of 54% for the certolizumab pegol group versus 43% for the placebo group (p = NS) at week 26 [133]. Rates of adverse events associated with the use of adalimumab and certolizumab pegol were similar to those seen with infliximab.

Other Anti-TNF-α Agents

Other anti-TNF-α medications, including CDP571 and thalidomide, have also been preliminarily investigated for the treatment of fistulizing CD. Of note, golimumab has not been studied for the treatment of CD fistulae. CDP571, a humanized (95% human, 5% murine) IgG4 monoclonal antibody, has been assessed for efficacy in the treatment of CD fistulae in two multicenter, randomized, double-blind, placebo-controlled trials [134, 135]. The first study, by Feagan et al, published only in abstract form, treated 71 patients with steroid-dependent CD with intravenous CDP571 at 20 mg/kg or placebo at week 0, followed by a second infusion of CDP571 at 10 mg/kg or placebo at week 8 [134]. At week 16, among the subgroup of patients with draining perianal fistulae, fistula closure was achieved in 25% of patients who received CDP571, compared to none in the placebo group. The other study, by Sandborn et al, followed 169 patients for 24 weeks, during which patients received an initial infusion of CDP571 at either 10 mg/kg or 20 mg/kg or placebo, followed by CDP571 at 10 mg/kg or placebo every 8–12 weeks [135]. This study included 37 patients with open perianal or enterocutaneous fistulae and reported that 50% of patients treated with CDP571 achieved fistula closure vs. 15% of patients who received placebo. Adverse events due to CDP571 include infusion reactions, formation of anti-idiotype antibodies, development of new antinuclear or anti-double-stranded DNA antibodies, insomnia, pruritus, and rash [134, 135].

Thalidomide has also been preliminarily evaluated in the treatment of fistulizing CD in two open-label pilot studies [136, 137]. The first study, by Ehrenpreis et al, enrolled 22 patients with refractory CD to receive oral thalidomide at 200 or 300 mg/day for 12 weeks [136]. At week 4, of the 13 patients with fistulae, 9 patients (69%) responded, 3 patients (23%) achieved remission, and 2 patients (15%) had closure of all fistulae. Nine patients with fistulizing disease completed the 12 weeks of treatment. Of these 9 patients, all (69%) were responders, 6 patients (46%) achieved remission, and 5 patients (38%) had complete closure of all fistulae. The other pilot study, by Vasiliauskas et al, treated 12 patients with steroid-dependent CD with 50 or 100 mg/day of thalidomide for 12 weeks [140]. Of the 6 patients with active perianal fistulae at the time of entry into the study, five (83%) had improvement in symptoms after 4 weeks. Four of these 6 patients with fistulizing disease completed 12 weeks of treatment. Fistula closure was achieved in 1 patient (17%) at week 12, with improvement in another 2 patients (33%). Adverse events are common with thalidomide therapy and include severe somnolence, peripheral neuropathy, teratogenicity, peripheral edema, constipation, seborrheic dermatitis, hypertension, muscle spasm, and diffuse rash [136, 137].

Vedolizumab

Anti-integrin therapy has been used more recently in the treatment of CD as a means to target reduction of lymphocyte trafficking to the gut. The α4β7 integrin, a cell surface glycoprotein

expressed on lymphocytes, helps to regulate lymphocyte migration into inflamed intestinal tissue via interaction with mucosal addressin-cell adhesion molecule 1 (MAdCAM-1) on intestinal blood vessels [138]. Natalizumab, which is not gut-specific as it binds both α4β7 and α4β1 integrins (the latter which are located in the central nervous system), was shown to be effective for the treatment of CD in a large randomized controlled trial but patients with draining fistulae were excluded [139]. However, the use of Natalizumab is associated with an increased risk of progressive multifocal leukoencephalopathy [140], and thus Vedolizumab was developed as a purely gut-selective blocker of α4β7. Vedolizumab was shown to be efficacious for the treatment of moderate-to-severe active Crohn disease in the GEMINI 2 double-blind randomized placebo-controlled trial [141]. Although fistula treatment was not the primary endpoint in this trial, 57 patients had actively draining fistulae at baseline. Treatment with Vedolizumab 300 mg every 8 weeks was associated with a significantly higher rate of fistula closure than treatment with placebo after 52 weeks (41% vs. 18%, $p = 0.03$).

Recently, a nationwide multi-center cohort study was conducted in a population of 151 patients, investigating the role of Vedolizumab in perianal Crohn disease [65]. Demographics include mean disease duration of 14.6 years, mean age 39.8 years, and 32.4% male patients, with the majority of having received at least one anti TNF alpha medication prior to receiving Vedolizumab. Primary endpoint was defined by absence of draining fistula at clinical examination and no anal ulcers at 6 months without medical or surgical treatment. Unfortunately, 68% of patients discontinued therapy after median time of 33 weeks, only 22.5% of patients who finished this study achieved the primary endpoint, and almost 1/3 of patients with inactive disease had perianal recurrence.

Other Therapies

A variety of other therapies for fistulizing CD have been suggested to be of possible benefit in uncontrolled case series or anecdotally. These include elemental diets, bowel rest with total parental nutrition, mycophenolate mofetil, granulocyte-colony stimulating factor, hyperbaric oxygen, local mesenchymal cell injection, and coagulation factor XIII [142–162]. However, controlled trials are required before any of these modalities can be recommended for routine use. Other novel therapies are also currently under investigation (refer to www.clinicaltrials.gov).

Conclusions

The treatment of perianal fistulizing CD has evolved greatly in the last two decades, due largely to improvements in medical therapy. Tables 35.1 and 35.2 summarize all published controlled and uncontrolled trials of immunomodulator and anti-TNF-α therapy for the treatment of CD. The advent of immunomodulators and biologic agents has transformed the treatment of CD from almost exclusively surgical to placing a much larger emphasis on medical therapy, either as initial therapy alone, with surgery reserved for refractory cases, or in combination with surgery from the start. For this reason, gastroenterologists and surgeons must work in concert in order to provide the best care for each patient. Proper fistula management also relies heavily on accurate diagnosis, especially defining the anatomy of the fistula, ascertaining whether abscess formation is present, and determining the location and extent of intestinal inflammation.

Table 35.1 Randomized controlled trials for treatment of fistulizing Crohn disease with azathioprine or 6-mercaptopurine[a]

Author (year)	*N*	Drug, dose	Rx time	Response drug	Response placebo	*P*-value
Willoughby et al. (1971) [71]	3	AZA, 2 mg/kg/d	24 wk	0/2 (0%)	0/1 (0%)	NR
Rhodes et al. (1971) [72]	6	AZA, 2 mg/kg/d	2 mo	2/4 (50%)	0/2 (0%)	NR
Klein et al. (1974) [73]	10	AZA, 3 mg/kg/d	4 mo	4/5 (80%)	2/5 (40%)	NR
Rosenberg et al. (1975) [74]	5	AZA, 2 mg/kg/d	26 wk	0/4 (0%)	1/1 (100%)	NR
Present et al. (1980) [75]	46	6MP, 1.5 mg/kg/d	1 yr	16/29 (55%)	4/17 (24%)	NR

Abbreviations: *N* Number of patients, *Rx* Treatment, *AZA* Azathioprine, *NR* Not reported, *6MP* 6-Mercaptopurine
[a]Fistula outcome not a primary endpoint

Table 35.2 Controlled Trials for Treatment of Fistulizing Crohn Disease with Immunomodulators or Anti-TNF-α Agents

Author (year)	*N*	(Drug), dose	Rx time	Response drug	Response placebo	*P*-value
Immunomodulators						
Azathioprine/6MP[a]						
Willoughby et al. (1971) [71]	3	AZA, 2 mg/kg/d	24 wk	0/2 (0%)	0/1 (0%)	NR
Rhodes et al. (1971) [72]	6	AZA, 2 mg/kg/d	2 mo	2/4 (50%)	0/2 (0%)	NR
Klein et al. (1974) [73]	10	AZA, 3 mg/kg/d	4 mo	4/5 (80%)	2/5 (40%)	NR
Rosenberg et al. (1975) [74]	5	AZA, 2 mg/kg/d	26 wk	0/4 (0%)	1/1 (100%)	NR
Present et al. (1980) [75]	46	6MP, 1.5 mg/kg/d	1 yr	16/29 (55%)	4/17 (24%)	NR
Total	70			22/44 (50%)	7/26 (27%)	
Tacrolimus						
Sandborn et al. (2003) [104]	48	0.2 mg/kg/d	10 wk	9/21 (43%)	2/25 (8%)	0.004
Anti-TNF-α agents						
Infliximab						
Present et al. (1999) [109]	94	5 mg/kg 10 mg/kg	14 wk	21/31 (68%) 18/32 (56%)	8/31 (26%)	0.002 0.02
Sands et al. (2004) [81]	195	5 mg/kg	54 wk	42/91 (46%)	23/98 (23%)	0.001
Total	289			81/154 (53%)	31/129 (24%)	
Adalimumab[a]						
Colombel et al. (2009) [130]	117	40 mg EOW or Qwk	56 wk	6/47 (13%)	23/70 (33%)	<0.05
Certolizumab Pegol[a]						
Schreiber et al. (2011) [132]	58	400 mg Q4 wk	26 wk	10/28 (36%)	5/30 (17%)	0.038
CDP571[a]						
Sandborn et al. (2001) [134]	37	CDP571, 10 or 20 mg/kg	24 wk	12/24 (50%)	2/13 (15%)	0.074
Vedolizumab	57	300 mg Q8 wk	52 wk	7/17 (41%)	2/18 (11%)	0.03
Sandborn et al. (2013) [1]		300 mg Q4 wk		5/22 (23%)		0.32

Abbreviations: N Number of patients, *Rx* Treatment, *AZA* Azathioprine, *d* Day, *wk.* Week(s), *NR* Not reported, *mo* Months(s), *6MP* 6-Mercaptopurine, *yr.* Year(s), *EOW* Every other week, *Q* Every

[a] Fistula outcome not a primary endpoint

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Treatment of Acute Severe Ulcerative Colitis

36

Jess L. Kaplan and Harland S. Winter

Case

A 13-year-old boy was previously well until he acutely developed non-bloody diarrhea while on a skiing vacation. The following day he continued to have nausea, vomiting, and diarrhea, and started a clear liquid diet. On day 3 of this acute illness, he continued to pass 6–8 liquid stools daily and began to notice red blood in the stool. He was treated in the local emergency room with intravenous fluids and discharged. Stool cultures for enteric pathogens, including *Escherichia coli* 0157, ova, parasites, and *Clostridium difficile* were all negative. His white blood cell count (WBC) was 15,900, hemoglobin 13 g/dL, and hematocrit 37%. Liver function tests, amylase, and lipase were all normal. C-reactive protein (CRP) was elevated at 25 mg/dL.

On day 6 of the illness, he noted increased bloody diarrhea and was admitted to the local hospital. Despite being kept nil per os (NPO), he continued to pass 3–4 loose, grossly bloody stools daily. On the seventh day of the illness, he became febrile to 39 °C and continued to pass 5–6 bloody stools daily. His albumin was decreased at 2.2 g/dL. He was transferred to a tertiary care facility.

On transfer, his vital signs were stable and he was afebrile. His weight was 46 kg. He appeared pale but was resting comfortably. He had no oral ulcers. His chest and cardiac examinations were normal. His abdomen was soft with diffuse but mild tenderness without guarding or rebound tenderness. He had no organomegaly. Upon admission, an upper endoscopy was normal, but the ileocolonoscopy revealed pancolitis (Fig. 36.1) with normal-appearing terminal ileum, consistent with ulcerative colitis. His Pediatric Ulcerative Colitis Activity Index (PUCAI) score was 65. He was made NPO, given intravenous fluids at 1.5 times maintenance, and started on intravenous methylprednisolone sodium succinate 20 mg every 12 h. Repeat stool analysis was negative for enteric pathogens. Biopsies of the colon showed moderate-to-severe chronic pancolitis without evidence of granulomas, and biopsies of the terminal ileum were normal. Electrolytes were monitored daily and corrected as necessary; hematocrit was maintained over 30% with packed red blood cell transfusions; albumin was replaced with salt-poor albumin (1 g/kg) when below 3.0 g/dL. After 3 days of intravenous corticosteroids, his PUCAI was 55. Because of ongoing diarrhea and bleeding, a peripherally inserted central catheter (PICC) was placed for nutritional support and total parenteral nutrition was started. His PUCAI score on day 5 of intravenous corticosteroids was 60. Options for rescue therapy were discussed with the patient and family, and the pediatric surgery team was consulted. On hospital day 6, he was given 10 mg/kg of infliximab intravenously. Over the next 2 days, stool output decreased; he was restarted on oral feedings and was dis-

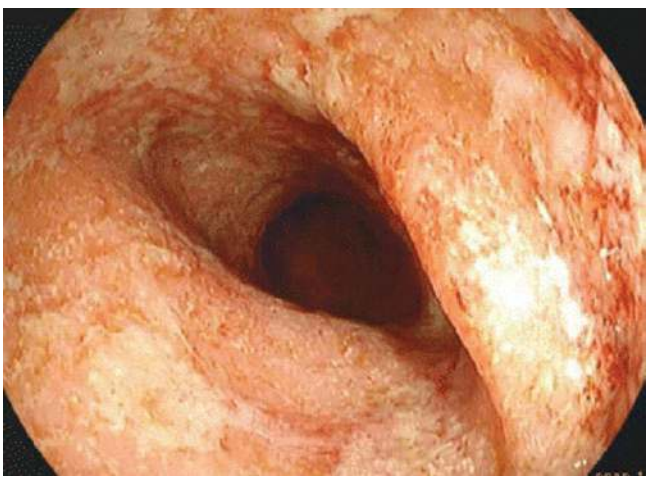

Fig. 36.1 Sigmoid colon: Diffuse inflammation with loss of vascular pattern and ulceration, typical of the pattern seen in ulcerative colitis

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charged on day 10. He returned in 2 weeks for his second infliximab infusion, passing formed stools without visible blood, and a prednisone taper was started.

He continued to do well, and maintenance infliximab therapy was continued after induction therapy was complete. Approximately 7 months later, hematochezia and abdominal cramping returned 6 weeks following an infliximab dose. The infliximab trough concentration was 9 μg/mL, and the presence of anti-infliximab antibodies could not be determined. Stool cultures were negative for enteric pathogens, and *Clostridium difficile* testing was also negative. Oral prednisone was started, but symptoms did not improve. He was passing 10–12 grossly bloody liquid stools daily, with three nocturnal stools with peridefecatory cramping and fecal urgency. He was admitted to the hospital, made NPO, and started on intravenous methylprednisolone sodium succinate 20 mg every 12 h. On day 3, his PUCAI score was 60. A sigmoidoscopy was performed that revealed severe proctitis. Rectal biopsy showed severely active chronic colitis without evidence of granulomas, and immunohistochemistry for cytomegalovirus (CMV) was negative. A 10 mg/kg dose of infliximab was given (6.5 weeks following the previous dose) without clinical improvement. He developed a fever of 38.5 °C, and intravenous ampicillin, gentamicin, and metronidazole were started. Total parenteral nutrition was started on day 4. On day 6 of intravenous steroids, his stool output was >2 L, and he required a blood transfusion for symptomatic anemia. His C-reactive protein was 10 times the upper limit of normal. On day 9 of the hospitalization, he underwent a total abdominal colectomy and ileostomy. He was discharged 6 days later and subsequently returned for completion of the colectomy, creation of a J-pouch with ileostomy reversal, and ileal pouch-anal anastomosis (IPAA).

Introduction

The clinical course of ulcerative colitis (UC) in children is unpredictable. Compared to patients with adult-onset disease, children with UC have more extensive disease and often a more severe course, characterized by higher rates of corticosteroid use and shorter time to surgery [1, 2].

Severe exacerbations of UC are common in both children and adults and cause significant morbidity. These exacerbations can occur both at disease onset and as relapse in patients with established disease.

In 2008, the European Crohn's and Colitis Organization (ECCO) defined acute severe colitis (ASC) in adults as an exacerbation with more than six bloody stools per day with at least one of the following: tachycardia (>90 b/min), temperature >37.8 °C, anemia (hemoglobin <10.5 g/dL), or an erythrocyte sedimentation rate (ESR) >30 mm/h [3]. In children, ASC is generally defined by a Pediatric Ulcerative Colitis Activity Index (PUCAI) score ≥ 65 [4], a cutoff that has been validated in independent cohorts and has predictive value with regard to response to intravenous corticosteroid (IVCS) therapy [5, 6] (see Chap. 46, Appendix 3.2 for more details regarding PUCAI scoring). In adults, fulminant colitis has been defined by >10 stools per day with continuous bleeding, abdominal tenderness and distension, systemic toxic symptoms such as fever and anorexia, and blood transfusion requirement; this can progress to toxic megacolon with severe colonic distension (>6 cm), hypotension, altered mental status, and high mortality [7]. While colonic dilation is a hallmark of current or impending toxic megacolon (TMC), precise criteria for TMC in children have not been established. One study showed that in children ≥10 years of age, a transverse colon diameter ≥ 5.6 cm was suggestive of TMC [8], while in children younger than 10 years of age, a diameter > 4 cm is concerning for toxic megacolon [9].

The frequency of ASC in children with UC is not fully known, but it is suggested that rates are as or even higher than the rates in adults. For example, over a 3-year period, in the greater Toronto area, it was estimated that 28% of all children with UC developed a severe exacerbation requiring hospitalization for intravenous corticosteroids before the age of 15 [10]. Colectomy rates have decreased significantly since the introduction of biological agents to treat ulcerative colitis [11]. A retrospective European and North American study of 5-year outcomes in children with ASC demonstrated that about one-third of patients had colectomy. Children with new-onset disease who had oral corticosteroids within 3 months of admission, elevated ESR and hypoalbuminemia were more likely to have a colectomy. These data were obtained prior to therapeutic drug monitoring which could change outcomes [12].

The remainder of this chapter addresses the management and ASC in children.

Initial Management

ASC is a serious and potentially life-threatening exacerbation of pediatric UC. As such, care for patients with ASC should be in the hospital setting so that frequent monitoring of clinical status, disease progression, and potential complications can take place. The goals of management are medical stabilization, treating exacerbating factors such as certain infections and implementing a stepwise active treatment approach typically beginning with intravenous corticosteroids (IVCS) in order to control gastrointestinal hemorrhage while avoiding/limiting complications from the disease and/or therapy. Response to therapy should be frequently reassessed by a multidisciplinary team of providers, including, in many cases surgeons with experience in IBD, in order to help guide plans for subsequent treatment.

The initial management of ASC includes a complete history and physical examination, beginning with the assessment of vital signs and general appearance which may reveal signs of systemic toxicity such as hypotension, fever, significant tachycardia, or altered mental status. Abdominal tenderness should be assessed, keeping in mind that tenderness and even colonic perforation and peritoneal signs may be masked in patients on high-dose corticosteroids. The absence of bowel sounds is an ominous prognostic indicator. Frequent reassessment is necessary as progression to fulminant disease may be rapid. A PUCAI score should be calculated at the onset of symptoms and then daily during the exacerbation until improvement and disposition. A PUCAI score over 65 correlates with severe disease. This validated scoring system not only gives the provider an idea of the general well-being of the child but also predicts response to IVCS and helps guide the timing of subsequent "rescue" therapy [6].

Hospitalized patients with ASC should have intravenous access and be fluid-resuscitated to assure adequate hydration. Laboratory studies including a complete blood count, serum electrolytes, albumin, ESR, and CRP should be obtained and repeated frequently. Despite the lack of randomized controlled clinical trials to provide evidence-based guidance for optimal therapy, expert opinion suggests that mucosal healing is best achieved by keeping the hematocrit over 30%, the albumin over 3 g/dL, and the electrolytes in the normal range. Although not evidence-based, in theory, avoiding anemia and hypoalbuminemia may enhance the delivery of oxygen to the intestinal tissues and improve mucosal blood flow. Hypoalbuminemia was identified as a predictor of long-term colectomy [12]. Normal electrolytes decrease the likelihood of stasis related to poor motility. Measurement of fecal calprotectin or lactoferrin may be a useful baseline as repeated assessment can help define response to medical therapy.

Patients with IBD are at higher risk of being diagnosed with *Clostridium difficile* infection (CDI). In one single-center study, 18.4% of children with UC had a positive polymerase chain reaction (PCR) for the toxin B gene of *C. difficile* [13]. The percentages may be even higher in hospitalized children with IBD [14]. CDI is implicated in disease exacerbation and increases the risk for complications such as colectomy in adults with UC [15, 16]. Although there is not yet direct evidence that treating CDI in children with ASC improves outcomes, testing for and treatment of CDI is current standard practice and was recommended in the joint ECCO/European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) ASC guidelines [9]. Stools should be screened for both toxins A and B. Stools should also be cultured for other potentially treatable bacterial pathogens.

Plain films of the abdomen are recommended as part of the initial evaluation of severe colitis if there are any signs of systemic toxicity that may suggest fulminant disease or TMC [9]. However, since examination findings can be masked by corticosteroid therapy, our practice is to obtain a baseline KUB on every hospitalized patient with ASC. As previously mentioned, transverse colon dilation ≥56 mm and ≥40 mm is suggestive of TMC in children ≥10 and <10 years of age, respectively. Colonic dilation has also been shown to predict response to IVCS therapy in this setting [17].

Although children with ASC may not wish to eat or drink due to their physical symptoms, unless surgery is imminent, they should be allowed to do so, since available evidence from the adult literature shows that while bowel rest may decrease stool frequency and volume, it does not improve outcomes and may worsen nutritional status [18]. If a regular diet cannot be tolerated by the third or fourth day, then enteral or parenteral nutrition should be considered, as malnutrition may impair healing and delay clinical improvement. The risks of parenteral nutrition, including complications from central venous catheters (e.g., infection, thrombus) and electrolyte abnormalities, need to be balanced with potential benefits. There is no evidence to support any particular oral diet or dietary restrictions in ASC.

Unlike in Crohn disease, antibiotics are generally not indicated in ulcerative colitis, unless there is evidence of toxicity or infection. Since bowel perforations may be silent in patients on high doses of corticosteroids, any clinical signs of infection should be investigated and treated. In well-controlled trials in adults with ASC, intravenous (IV) antibiotics including ciprofloxacin [19] and metronidazole [20] have not been shown to improve ASC outcomes when used as adjunctive therapy to corticosteroids. No large or controlled pediatric studies directly address the efficacy of antibiotics in ASC; however, the recommendations are to treat with IV antibiotics if the infection is suspected or while awaiting confirmatory testing [9]. ASC patients with fulminant disease or suspicion or diagnosis of TMC should be treated with IV antibiotics. The antibiotic agent(s) used should target enteric bacteria, including anaerobes.

In a small series of 28 children with ASC who were randomized to receive quadruple antibiotics (amoxicillin, vancomycin, metronidazole, doxycycline/ciprofloxacin) plus corticosteroids or corticosteroids alone for 14 days, the PUCAI on day 5 was lower in the antibiotic group, but five children underwent colectomy by 1 year—3 who received antibiotics and 2 who received only corticosteroids [21]. A group of adults with ASC were randomized to intravenous placebo or ceftriaxone and metronidazole along with standard care. Patients in the antibiotic group had similar CRP, partial Mayo score and fecal calprotectin and were as likely to have complete remission on day three as the placebo group. There were no differences in the likelihood of requiring a colectomy [22]. These studies, albeit with a small num-

ber of subjects raise doubts about the short-term and long-term benefit of antibiotic therapy in ASC.

Adults who are hospitalized with ASC are routinely treated with anticoagulants for venous thromboembolism (VTE) prophylaxis. Hospitalized children with IBD are also at increased risk for VTE [23]. The prothrombotic tendency in IBD is thought to be attributable to many different factors including an increase in procoagulants, a decrease in anticoagulants, thrombocytosis, as well as endothelial and immunologic factors [24]. VTE is more common in children with active IBD than in those who have the quiescent disease [25]. This risk may be augmented by the relative immobility of sick, hospitalized IBD patients. In one study, risk factors for VTE in hospitalized children with IBD included older age, central venous catheters, parenteral nutrition, and the presence of a hypercoagulable condition [23]. Children with colonic IBD appear to be at higher risk for VTE [26]. Despite this, the overall incidence of VTE in hospitalized children remains low (11.8/1000 hospitalizations) [23], and there have been no pediatric studies assessing the benefits and risks of prophylactic anticoagulation in ASC or in IBD in general. As such, the routine use of anticoagulation in children with ASC is not currently recommended [9]. However, non-invasive methods of VTE prophylaxis like frequent mobilization, adequate hydration, and pneumatic/mechanical devices are advised, as they are of low risk, even if not well supported by current evidence. It is reasonable to consider anticoagulation in patients with other risk factors for VTE, including known hereditary causes of thrombophilia, smoking, and the use of oral contraceptives. When used, anticoagulation does not seem to worsen bleeding during IBD flares.

Intravenous corticosteroids (IVCS) are the recommended first-line treatment for ASC in children. IVCS have been used for acute exacerbations of UC for more than 60 years and have been shown to reduce mortality in adults [27]. There are no randomized trials evaluating the comparative efficacy of various CS doses in children. The current recommendations for CS dosing are for 1–1.5 mg/kg/day of methylprednisolone up to 40–60 mg/day [9]. The daily dose is often divided over two daily doses. Doses above 60 mg/day have not been found to be more effective in adults with ASC [28]. More recently, a prospective pediatric cohort study which followed 283 children with ASC for 1 year concluded that an IVCS dose of 2 mg/kg/day was not more effective than doses of 1–1.25 mg/kg/day in preventing the need for salvage therapy during the hospitalization or by 1 year, although day 5 PUCAI scores were improved in the high-dose CS group before sensitivity analysis [29]. In this study, IVCS dosing was at the discretion of the provider (not randomized), but propensity matching was performed to limit bias. Interestingly, glucocorticoid bioactivity in serum did not predict response to IVCS in a study of children with ASC [30].

Not all children with ASC improve with IVCS. A systematic review found a 34% (range 9–47%) IVCS failure rate in a pooled analysis of five studies of children with ASC [31]. In the one prospective study included in the analysis, 37 of 128 children (29%) failed to respond to IVCS and required second-line treatment [6]. Multiple predictors for poor response to IVCS in children have been identified. A multicenter prospective study that followed 128 children with ASC found a response to IVCS less likely in older patients and in patients with the established disease [6]. The same study showed that after multivariate analysis, additional day 3 and day 5 predictors of IVCS failure included high stool frequency and a large amount of blood in the stool. A high CRP on day 5 also predicted CS failure. The PUCAI score outperformed other clinical indices in predicting IVCS failure on both days 3 and 5. A PUCAI score >45 on day 3 predicted CS failure with a sensitivity of 92% and a negative predictive value (NPV) of 94%, indicating a high likelihood of response if the PUCAI score is ≤45. On day 5, a PUCAI score of >70 had a specificity and positive predictive value (PPV) of 100% for CS failure, while a score of >65 has specificity and PPV of 96% and 82%, respectively. The addition of fecal calprotectin or CRP to the model did not improve the accuracy of the PUCAI score. The findings from this study and others have formed the basis of recommendations for disease monitoring and for the timing of second-line/rescue therapy in children with ASC. Additional predictors of poor response to IVCS have also been identified. A prior single-center study found that a high number of nocturnal stools and high CRP were predictive of CS failure on days 3 and 5 [10]. The presence of a megacolon, defined as a transverse colon diameter >40 mm and >60 mm in children <12 and >12 years of age, respectively, and ulceration on abdominal x-ray may also predict IVCS failure [17]. A separate study showed that day 3 interleukin (IL)-6 levels predicted IVCS failure, although this did not hold true after multivariate analysis [32]. Finally, there is limited evidence that IVCS nonresponders have decreased fecal microbial richness/diversity compared to responders, though this is not yet clinically applicable [33].

Monitoring Response to Corticosteroids

In general, monitoring for response to initial therapy begins with a careful and frequent reassessment of vital signs, stool frequency, volume, blood loss, and abdominal pain as well as changes in the abdominal examination. The validation of the PUCAI score in predicting IVCS failure has led to a suggested algorithm and the following recommendations for disease monitoring and for the timing of second-line, also referred to as "rescue" or "salvage", therapy [9]. A PUCAI score > 45 on day 3 of IVCS should initiate preparation for

second-line therapy, including discussion of potential risks and benefits with patients and families and inclusion of a surgeon with experience in IBD. A PUCAI score > 65 on day 5 should prompt initiation of second-line therapy. Patients with PUCAI scores between 35 and 65 on day 5 can continue IVCS for an additional 2–5 days, at which point further recommendations are based on the PUCAI score at that time. Patients who improve on IVCS and have a PUCAI score <35 on day 5 are unlikely to require rescue therapy before discharge [9]. Thiopurines can be considered in IVCS responders, particularly in those who were previously naive, but the therapeutic benefit is often delayed for 2–3 months; so, they have little role in the acute setting.

There is no current evidence to support the value of repeat colonoscopic evaluation in ASC patients who are improving on IVCS in the clinical setting. However, repeat sigmoidoscopy is suggested if the day 3 PUCAI score is >45 in order to search for evidence of Crohn disease such as granulomas and to exclude cytomegalovirus (CMV) colitis, which can complicate ASC and may alter therapy. While the prevalence of CMV colitis in children with ASC is not known, it is relatively common in adults with UC, particularly in those with steroid-refractory disease [34]. Mucosal biopsies should be obtained and evaluated for signs of CMV disease (deep ulcerations and viral inclusions) as well as immunohistochemistry [9]. CMV colitis should prompt an infectious disease consultation, and antiviral treatment should be considered [35]. In a small study pediatric patients who were found to be CMV-positive during hospitalization for ASC did not have an increased incidence of colectomy during admission when compared to children with ASC who were CMV-negative [36].

Medical Rescue Therapy

Patients with ASC with poor response to IVCS require rescue therapy. About one-third of children with ASC require rescue therapy before discharge from the hospital. In adults, the earlier use of rescue therapy appears to decrease mortality [37], and extending IVCS without rescue treatment beyond 14 days is unlikely to provide benefit and may increase the risk for complications, including, but not limited to, opportunistic infections, metabolic and electrolyte abnormalities, osteopenia/porosis, and psychiatric disturbance. The goals of rescue therapy are to improve symptoms and allow for the eventual discontinuation of CS. Current rescue therapy options for children with ASC include infliximab, calcineurin inhibitors (cyclosporine and tacrolimus), and colectomy. Although the data supporting these rescue therapies are primarily in CS refractory patients, these treatments are also used without IVCS in patients with contraindications or prior lack of response to CS.

Infliximab (IFX) is a monoclonal antibody against TNF-α that can induce and maintain remission in pediatric UC [37]. Pooled data from six pediatric case series (n = 126) of ASC patients treated with IFX showed a 75% (67–83%, 95% CI) response rate by the time of hospital discharge and a 64% colectomy-free rate during follow-up which ranged from a few months to a few years [31]. In one prospective study, 76% (25/33) of children with ASC refractory to IVCS had short-term responses to IFX [6]. The remaining 24% underwent colectomy. At 1 year, 55% had sustained response to IFX and 45% had CS-free sustained response, while an additional 28% required colectomy by 1 year. In a more recent retrospective study from a single center in Italy, 80% of ASC patients had short-term responses to IFX, but 50% of these patients went on to colectomy by 24 months [38]. Predictors of IFX failure may include shorter disease duration and more active disease at the time of admission and day 3 of IVCS [6]. IFX is typically dosed at 5 mg/kg at baseline and then repeated at 2 and 6 weeks following the initial dose. The pharmacokinetics of IFX in children with moderate-to-severe UC appears to be similar to that in adults [39]. However, many pediatric centers use higher doses (10 mg/kg) and/or shorter dosing intervals of IFX in ASC. The introduction of therapeutic drug monitoring has resulted in the clinical practice of adding additional doses if the IFX level is below 10. Since IFX is bound to albumin, patients who have serum protein loss in the stool are more likely to also lose IFX. While there is currently a lack of direct evidence to support this practice, some have suggested that IFX clearance may be higher in patients with acute severe disease leading to a requirement for higher dosing [40]. A recent retrospective study of children with IBD (CD and UC) showed that patients with a larger colonic inflammatory burden were more likely to require IFX dose escalation by 12 months than patients with limited or moderate disease and that 43% of patients who started at 5 mg/kg dosing did not improve with dose escalation [41]. Although this study was not limited to ASC patients, it does provide some indirect evidence that children with more extensive disease may benefit from higher IFX doses at the start of treatment. ECCO/ESPGHAN guidelines recommend IFX as the preferred rescue therapy in patients with previous thiopurine failure as IFX can also be effective as a maintenance agent in UC [9]. Prior to starting IFX, tuberculosis and Hepatitis B status should be documented.

Cyclosporine (CsA) is a calcineurin inhibitor that has been shown to be effective at inducing remission in adults with ASC [42, 43]. Support for the use of CsA in children with ASC comes from eight retrospective case series (n = 94) [31]. Pooled short-term response rates were 81% (76–86%, 95% CI), but long-term colectomy-free rates dropped to 39% (29–49%, 95% CI) in patients treated with CsA. There is heterogeneity in the eight studies with regard to CsA dose, route of administration, and duration of follow-up, which makes

interpretation difficult. CsA is generally used for 3–6 months as a bridge to maintenance therapy, often thiopurine treatment, which can take 2–3 months to become effective. CsA has not been studied as a long-term maintenance agent at UC. More prolonged use of CsA is limited by serious potential side effects such as hypertension, gingival hyperplasia, electrolyte disturbance, and renal and neurologic toxicity. Dosing is generally started intravenously and then transitioned to oral dosing (4–8 mg/kg/day) once the response is achieved [9]. Trough levels should be monitored frequently with preferred levels starting in the range of 150–300 ng/mL. Clinical response is generally seen in 5–7 days. Adult guidelines suggest that *Pneumocystis jiroveci* prophylaxis should be routinely given to patients treated with CsA, who are also treated with other immunosuppressive agents [44].

Tacrolimus, another calcineurin inhibitor, also appears effective as short-term rescue therapy for children with CS-resistant ASC. Retrospective studies report short-term response rates between 50 and 89% with long-term colectomy-free rates ranging from 0 to 40% [45–47]. The largest of these studies reported a 40% colectomy-free rate at 26 months, with most patients having been bridged to either thiopurines or IFX [45]. Hypertension (52%), tremor (46%), and hyperglycemia (35%) were common side effects of tacrolimus treatment. Initial dosing is typically 0.1 mg/kg/dose twice daily (0.2 mg/kg/day), and the dose is adjusted to reach levels of 10–15 ng/mL during induction and 5–10 ng/mL during maintenance therapy [45]. Tacrolimus may have more reliable oral absorption and may be better tolerated than CsA. Otherwise, time to response and side effects are similar to those of CsA, as is the need for *P. jiroveci* prophylaxis when used with other immunosuppressive agents.

There are no pediatric studies that directly compare the efficacy of medical rescue options in ASC. A prospective, multicenter, randomized open-label trial in adults with ASC refractory to IVCS found no difference in the efficacy of CsA and IFX [48]. A recent meta-analysis confirmed that these two treatments were equally successful in randomized trials but concluded that IFX appeared slightly more effective than CsA in nonrandomized trials [49]. Adverse events, postoperative complications, and mortality were similar with both treatments. Two small retrospective studies have compared tacrolimus and IFX rescue in adults with ACS [50, 51]. Neither study showed a difference in short-term efficacy, but the larger of the two studies showed that IFX was more effective than a tacrolimus bridge to thiopurine strategy in the longer term [51].

There is limited evidence from retrospective adult studies that a second medical rescue therapy (IFX following calcineurin inhibitor or vice versa) can prevent colectomy in ~30–70% of ASC patients following failure of a first rescue agent [52–54]. However, due to the high risk for serious toxicity with this approach, the use of a second rescue agent is not currently recommended for children with ASC until additional data on efficacy and safety can be obtained [9].

Surgery

The indications for surgical treatment in ASC are perforation, toxic megacolon, massive hemorrhage, or failure to respond to maximal medical management. However, in rare circumstances in which there are contraindications to medical rescue therapy, surgery may be considered first. The details of surgical options for UC are detailed in Chap. 41. The current surgical standard of care for UC is a restorative proctocolectomy consisting of a total colectomy, and rectal mucosectomy with ileal pouch-anal anastomosis (IPAA). This procedure can be done in one, two, or three steps. The first step in a three-step procedure includes a subtotal colectomy with ileostomy and Hartmann's pouch creation. This is followed by completion of the colectomy, rectal mucosectomy, and restorative IPAA with diverting ileostomy (step 2), and finally by ileostomy takedown reversal (step 3). In a typical two-step procedure, bowel continuity is immediately restored when the ileal pouch is formed (step 2), without a diverting ileostomy. Alternatively, the abdominal colectomy and mucosectomy may be performed with IPAA and diverting ileostomy in step 1 followed by ileostomy takedown (step 2). At some centers, abdominal colectomy and mucosectomy with IPAA may be done as a single operation [55]. The decision on which operation(s) to select is highly dependent on the experience and expertise of the surgical team.

High-dose corticosteroids have been shown to increase short-term complications such as postoperative infection [56]. Additionally, adult studies show a lower risk of IPAA leak in patients with a temporary protective ileostomy [57]. For these reasons, it is recommended that a two- or three-step procedure be considered in more complicated patients including those requiring emergent surgery, those treated with high-dose corticosteroids, or for those with significant malnutrition [9]. In a retrospective pediatric study, preoperative exposure to calcineurin inhibitors or thiopurines within 30 days of surgery or to IFX within 90 days of surgery was not associated with an increase in postoperative complications [58]. Whenever possible, efforts should be made to maximize nutritional status before surgery. Postoperative risks as well as typical outcomes should be discussed with patients and families to help form realistic goals. Additional issues that need to be discussed prior to surgery include the risk for pouchitis and potential issues with future fertility in female patients [59]. Patients also need to be aware that the risk for an eventual diagnosis of Crohn disease following restorative proctocolectomy for UC is 5–10% [60]. In addition to medical and surgical management, stress management and support for the patient and family are essential

components of the multidisciplinary approach needed to optimally care for children with ASC. Speaking with other patients/parents and a mental health evaluation should be part of the care of patients with ASC in whom surgical treatment is being considered.

Future Directions/Conclusions

Recommendations for the management of ASC in children are somewhat limited by the lack of pediatric data. Important questions remain unanswered and the rarity of ASC in children makes prospective interventional trials challenging to complete. Large, multicenter collaborative studies may be best positioned to answer some of these questions. Specific gaps in knowledge include longer-term outcomes of children with ASC, the most effective dosing regimens for rescue medications like IFX and calcineurin inhibitors, and the role of CMV in pediatric ASC. There needs to be an improved understanding of predictors of response to first-line rescue therapy which can help personalize care going forward. The role of established UC treatments like adalimumab, which has recently been approved by the FDA for ASC, and vedolizumab need to be elucidated. Despite recent improvements in medical treatment, many patients continue to require surgical intervention before discharge, and still more within the following 12 months.

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Dietary Therapies for Inflammatory Bowel Disease

37

Natalie Stoner and Ronen Stein

Abbreviations

AIP	Autoimmune protocol
CD	Crohn disease
CDED	Crohn disease exclusion diet
CD-TREAT	Crohn disease treatment with eating diet
DHA	Docosahexaenoic acid
EDIP	Empirical dietary inflammation pattern
EEN	Exclusive enteral nutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
FODMAP	Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
GAPS	Gut and Psychology Syndrome
HBI	Harvey Bradshaw Index
IBD	Inflammatory bowel disease
IBD-AID	Inflammatory Bowel Disease Anti-Inflammatory Diet
IL-10	Interleukin 10
n-3	Omega-3
n-6	Omega-6
PEN	Partial enteral nutrition
PUFA	Polyunsaturated fatty acids
SCD	Specific carbohydrate diet
TNFα	Tumor necrosis factor-alpha
UC	Ulcerative colitis

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Introduction

Inflammatory bowel diseases (IBD) Crohn disease (CD) and ulcerative colitis (UC), are chronic, relapsing, and remitting inflammatory conditions of the gastrointestinal tract. They are complex disorders with genetics, environmental influences, and the immune system all involved in disease development and progression [1]. To date, over 200 genetic polymorphisms have been associated with the development of IBD [2]. However, data from twin studies have demonstrated that genetics alone cannot entirely explain the etiology of IBD as the concordance rates for CD and UC among monozygotic twins are only 45% and 15%, respectively [3]. This indicates that environmental factors play a large role in the development of IBD. The current understanding of the etiology of IBD is that in a genetically susceptible host, environmental factors may trigger dysregulation of the innate and adaptive immune response and lead to chronic inflammation in the gastrointestinal tract [4].

The two largest environmental exposures for the gastrointestinal tract are the microbiota and dietary intake, although cigarette smoking, antibiotics, nonsteroidal anti-inflammatory drugs, and infectious agents are among the other environmental exposures associated with IBD [5]. As mentioned in Chap. 4, there is strong evidence from multiple studies that the gut microbiota is involved in the pathogenesis of IBD, as many of the genetic polymorphisms associated with IBD regulate the body's interactions with microbes [6]. As we will describe later in the chapter, there have been multiple studies showing that dietary intake itself plays an important role in the composition and function of the gut microbiota. Therefore, diet is likely involved in the pathogenesis of IBD and may be a potential therapeutic target.

In this chapter, we will summarize epidemiological data supporting the role of diet in IBD, show that the composition of the gut microbiota is heavily influenced by diet, and describe the relationship between macronutrients, food

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additives, oral supplements, and IBD. We will also review the literature on a number of structured diets proposed to treat IBD.

Diet and Worldwide Trends in IBD

The incidence and prevalence of IBD vary by region, with the highest rates in developed nations, particularly in North America and Northern Europe. The overall global incidence of IBD is rapidly increasing worldwide, not only in westernized societies but also in developing countries with historically low rates [7, 8]. The influences of globalization and industrialization in countries such as China, India, Japan, and South Korea have resulted in increased urbanization, improved sanitation, increased antibiotic use, sedentary lifestyles, and refrigeration [9, 10]. However, this has also resulted in the adaptation of a westernized diet, which is associated with the development of CD in a newly industrialized population [11].

Population migration studies also suggest that westernization may be a risk factor for the development of IBD. Children who immigrate to western countries from developing nations have a higher risk of IBD than their counterparts from their country of origin, but lower risk than children in their new country [12, 13]. The younger the child is at the time of immigration, the higher the risk of IBD [12]. However, second-generation immigrants have an even higher risk of developing IBD and, in fact, assume the same incidence of IBD as their peers in their new country [9, 12]. This may indicate that environmental exposures, such as a westernized diet, particularly early in life, impact the development of IBD.

Diet and the Gut Microbiota

Multiple studies have shown that the composition of the gut microbiota differs between healthy controls and individuals with IBD [14–17]. There is decreased microbial diversity in IBD with an increased proportion of bacteria in the phyla *Actinobacteria* and *Proteobacteria*, including *Escherichia coli*, and a decrease in *Firmicutes*, specifically in the group *Clostridia* [18, 19]. This dysbiosis, or alteration in the balance between commensal and pathogenic microorganisms, has been hypothesized to be involved in the pathogenesis of IBD. *Clostridia*, including *Faecalibacterium prausnitzii*, produce butyrate, a short-chain fatty acid that is an important energy source associated with colonic epithelial health. Conversely, adherent invasive *E. coli*, which are able to cross across ileal epithelium and can be found within granulomas in CD patients, may be linked to the development of IBD [20].

Dietary patterns can alter the composition of the gut microbiota starting in infancy. The composition of the gut microbiota differs between breastfed and formula-fed infants. The intestinal tract of formula-fed infants is colonized with increased numbers of *E. coli*, whereas in breastfed infants, *Bifidobacterium* species predominate and account for approximately 75% of microorganisms in the intestinal tract [21]. The human milk oligosaccharides contained in breast milk are felt to selectively promote the growth of *Bifidobacterium* species [22], which may have anti-inflammatory properties [23]. A decrease in *Bifidobacterium* species has been found among CD patients [15]. The effect of breastfeeding on *Bifidobacterium* species may help explain why breastfeeding has been shown to have a protective effect against the development of pediatric CD [24].

Long-term dietary patterns also affect the microbiome. Individuals on a westernized diet, high in animal fat and low in fiber, have high levels of *Bacteroides* species, whereas, in those on a high-carbohydrate, low-fat diet, *Prevotella* species predominate [25]. Likewise, another study compared the microbiome of healthy children from a village in rural Africa on a low-fat, high-fiber diet to counterparts in Europe on a westernized diet. The African children had a high proportion of *Prevotella* species compared to the European children [26].

Mounting evidence shows that the composition of the gut microbiota is heavily influenced by diet. However, in addition to changing the makeup of the microbiome, animal models have shown that dietary intake can also affect its function [27]. A diet high in milk fat was found to induce colitis in interleukin 10 (IL-10) knockout mice by facilitating the growth of *Bilophila wadsworthia*. Sulfur is an important nutrient necessary for *B. wadsworthia* to thrive. Milk fat was found to stimulate the secretion of sulfur-containing taurine-conjugated bile acids thereby creating an environment that preferentially promoted the growth of *B. wadsworthia.* Increased populations of *B. wadsworthia* were associated with greater inflammatory cytokine burden and the development of colitis in IL-10 knockout mice. *B. wadsworthia* may also have exerted its effect by the production of hydrogen sulfide leading to disruption of the intestinal epithelial barrier [28]. This indicates that by affecting the composition and function of the microbiome, dietary intake can stimulate immune responses in genetically susceptible hosts, leading to the development of chronic inflammation [29].

Dietary Components and IBD

The typical westernized diet contains high amounts of saturated fats, refined sugars, red meat, and processed foods with limited fresh fruits, vegetables, and fiber [30]. Many studies have investigated the dietary risk factors associated with new-onset IBD and have identified many components of a westernized diet [31]. In particular, a diet high in animal fats, omega-6 (n-6) fatty acids, and refined sugars has been associated with an increased risk of IBD. Conversely, high vegetable intake has been associated with a decreased UC risk and a diet high in fruits and fiber has been associated with a decreased CD risk [32]. The increase in food processing in the western diet has also significantly decreased the amount of microbiota-accessible carbohydrates content—indigestible polysaccharides that provide value and shaping to the microorganisms found within the gut [33]. In a study observing the effects of diet on microbiota changes, a semi-vegetarian diet high in fiber (>30 g/day), low in saturated fat, and low in sulfites that eliminated added sugar, processed foods, carrageenan, and polysorbate 80 was found to provide a significant increase in the microbial diversity in healthy individuals [33]. In a recent analysis of three prospective cohorts, empirical dietary inflammation pattern (EDIP) scores were calculated after collecting data and examining food frequency questionnaires completed by 166,903 women and 41,931 men from the Nurses Health Study, Nurses Health Study II, and Health Professional Follow-up Study. The scores were based on the sums of 18 foods identified within the questionnaires. The analysis found that dietary patterns associated with high inflammatory potential were associated with an increased risk of CD but not UC. Foods associated with a higher EDIP score included processed meats, red meat, organ meat, some fish and seafood, certain vegetables, refined grains, tomatoes, and regular/diet sodas [35]. Below, we review the literature on the relationship between different dietary components and IBD based on in vitro studies, animal models, and epidemiological data (summarized in Table 37.1).

Table 37.1 Dietary components and IBD

Dietary component	Dietary sources	Association with IBD
Saturated fat	Animal fat, milk fat	Increased risk of CD with high intake of saturated fat [32] Milk fat-induced colitis in IL-10 knockout mice [28]
Omega-3-polyunsaturated fatty acid (n-3 PUFA)	Fish, flaxseed	Decreased risk of CD and UC with high intake of n-3 PUFA [36] Decreased risk of CD and UC with high docosahexaenoic acid intake [37, 38] Supplementation with n-3 PUFA not shown to have benefit as maintenance therapy in UC or CD [39, 40]
Omega-6-polyunsaturated fatty acid (n-6 PUFA) Monounsatruated Fatty Acids (MUFAs)	Avocado, egg, nuts, poultry, red meat, vegetable oils Vegetable oils	Increased risk of CD and UC with high intake of n-6 PUFA [32] High ratio of n-6 PUFA to n-3 PUFA associated with an increased risk of CD [36] Conflicting reports for therapeutic potential in IBD Dietary oleic acid intake is inversely associated with UC development [40]
Simple carbohydrates	Candy, refined sugars, sweetened drinks	Increased risk of CD and UC with high intake of simple carbohydrates [32]
Complex carbohydrates/fiber	Fruits, legumes, vegetables, whole grains	High fiber, fruit, and vegetable intake is associated with decreased CD risk [36] and high vegetable intake is associated with lower UC risk [32]
Maltodextrin	Artificial sweeteners, breakfast cereals (selected), candy, infant formulas, processed snack foods	Maltodextrin promoted adhesion of adherent invasive *E. coli* based on in vitro studies [41] Consumption may be a risk factor for the IBD-prone population and a factor promoting low-grade intestinal inflammation leading to metabolic abnormalities [42]
Emulsifiers (e.g., carboxymethylcellulose, polysorbate-80, carrageenan) Sulfites	Bread, coffee creamers, dressings, ice cream, margarine, mayonnaise, processed cheeses, sauces Dried fruits, deli meats, hot dogs, sausages, canned fruits and vegetables	Positive correlation between emulsifier intake and CD incidence [43] Emulsifiers induced mild colitis in wild-type mice and severe colitis in IL-10 knockout mice [44] Carrageenan consumption resulted in the loss of tight junction competence [45] Polysorbate 80 increased bacterial translocation across the intestinal epithelium [43] Sulfites damaged beneficial bacteria, Lactobacillus and S. thermophilus in-vitro [46]
Curcumin	Turmeric, oral supplementation	Supplementation with pure curcumin was superior to placebo for induction of remission [47] and maintenance of remission [48] in UC
Iron	Heme iron (fish, red meat, poultry), non-heme iron (fortified cereals, fruits, vegetables), oral supplementation	Increased risk of CD and UC with high meat intake [32] Increased risk of UC flares with red meat consumption [49] Oral iron supplementation worsened colitis by generating oxidative stress in animal models [50]

Macronutrients

Fat

High total fat intake, a component of the westernized diet, is associated with the development of IBD [32]. Even among healthy subjects, a high-fat diet has been shown to increase markers of systemic inflammation [51]. A study of dietary intake among the Japanese population annually from 1966 to 1985 found that total fat intake was strongly correlated with the development of CD [11].

Although increased total fat intake is associated with IBD, the specific type of fat consumed may be a more important risk factor. Fatty acids are comprised of saturated fats, polyunsaturated fatty acids (PUFA), and monounsaturated fats [31]. Products with animal and milk fat contain a high proportion of saturated fat [28]. In a study completed on mice, a high-fat diet was found to alter the spatial distribution of microbiota in the duodenum, jejunum, and ileum [52]. Multiple studies have found a high intake of saturated fat to be a risk factor for the development of IBD [32]. Likewise, milk fat has been shown to induce colitis in susceptible hosts in other animal models [28]. Moreover, among subjects with known UC, studies have found increased red meat consumption to be a risk factor for disease flares [49]. In a recent cross-over study in 17 UC patients in remission or with mild disease, a low-fat diet resulted in decreased markers of inflammation and reduced intestinal dysbiosis in fecal samples [53]. Conversely, among patients with CD in remission, the Food and Crohn Disease Exacerbation Study trial found that the level of red meat and processed meat consumption was not associated with time to symptomatic relapse [54].

Similar to fat, alcohol is calorie-dense. Alcohol consumption among IBD patients is similar to the general population and is known to be pro-inflammatory and harmful to gut barrier function [55]. Several studies reveal the worsening of IBD symptoms among patients who consume alcohol. However, more studies are needed to identify the exact association between alcohol intake and IBD disease activity and to determine if there is a specific quantity of alcohol that can be safely consumed [55].

Increased intake of PUFA has also been linked to IBD [32, 40]. PUFA are comprised of n-6 and omega-3 (n-3), and it is the relative ratio of these fatty acids that is important [36]. The westernized diet contains an unbalanced ratio of n-6 to n-3 PUFA, which is a risk factor for IBD [30]. In animal and in vitro models, n-3 PUFA has been found to have anti-inflammatory properties, including inhibition of macrophage tumor necrosis factor-alpha (TNFα) production, while n-6 PUFA is broken down into byproducts that are pro-inflammatory [56, 57]. Foods higher in n-3 PUFA include fish and flaxseed [58]. Vegetable oils, poultry, and red meats are high in n-6 PUFA [30]. Among the n-3 PUFAs, docosahexaenoic acid (DHA) may have the strongest anti-inflammatory effects, as several studies have found an inverse association between DHA intake and risk of developing UC and CD, although no association was found with eicosapentaenoic acid, another n-3 PUFA [37, 38]. Despite these promising epidemiological results, systematic reviews of n-3 PUFA supplementation have not shown any benefit as a maintenance therapy of remission for patients already diagnosed with UC or CD [39, 59]. A 2014 Cochrane review found n-3 PUFA supplementation to be ineffective for the maintenance of IBD [59]. Interestingly, a large cohort of women from the high school diet study completed validated dietary questionnaires to further investigate dietary factors that may influence the pathogenesis of CD and UC. This prospective study documented 70 incident cases of CD and 103 cases of UC and found an association between greater fiber and fish intake during high school with a reduced risk of CD. While the study also investigated other specific food groups of an adolescent diet, those with fish intake <10 g/day compared to those with >30 g/day had a 57% lower risk of CD [60].

Carbohydrates

Carbohydrates are comprised of monosaccharides, disaccharides, oligosaccharides, and polysaccharides. Monosaccharides (e.g., glucose and fructose) and disaccharides (e.g., lactose and sucrose) are also called simple carbohydrates, whereas oligosaccharides and polysaccharides are complex carbohydrates [31]. Processed simple sugars are known as refined sugars. There is no association between total carbohydrate intake and the risk of developing IBD. There are also no studies that demonstrate a difference in carbohydrate requirements in pediatric patients with IBD compared to the healthy population [61]. However, studies have found increased consumption of simple carbohydrates to be associated with a higher risk of both CD and UC [32].

Dietary fibers are nondigestible oligosaccharides and polysaccharides and are comprised of insoluble and soluble fiber. Insoluble fibers pass through the gastrointestinal tract mostly undigested, adding bulk and reducing transit time for stool. Cellulose is an important insoluble fiber found in fruits, vegetables, flaxseed, and quinoa. Soluble fibers, such as inulin and pectin, are found in grains and nuts. They are digested via fermentation by the gut microbiota producing short-chain fatty acids, such as acetate, butyrate, and propionate [58]. Not only is butyrate a critical energy source for colonocytes, but it is also felt to help maintain gastrointestinal homeostasis [31, 58]. In vitro studies have shown that fiber can enhance epithelial barrier function [58, 62]. Additionally, multiple epidemiological

studies have associated increased fiber intake with a decreased risk of developing CD and UC [32, 36].

The clinical efficacy of prebiotics in IBD is limited. Prebiotics are types of dietary fiber that promote favorable bacteria in the gut that can benefit the host. Prebiotics include fructans, galacto-oligosaccharides, and can be found in foods such as asparagus, beets, garlic, and lentils [63]. Evolving evidence suggests that prebiotic fibers may be useful in maintenance of remission in patients with UC. Yet, fiber in the form of fructo-oligosaccharide is not effective in CD treatment [64]. A significant increase in colonic butyrate production was found in a study investigating clinical symptom improvement in UC patients who were provided inulin, a soluble fiber found naturally in chicory root [63]. Another study investigating the effect of inulin on inflammation of the ileal reservoir evaluated 20 patients who were provided with dietary supplementation (24 g) of inulin for 3 weeks. Results found those that were provided with supplementation had increased butyrate concentrations, lowered stool pH, decreased numbers of *Bacteroides fragilis*, and diminished concentrations of secondary bile acids in the feces. This was endoscopically and histologically associated with a reduction of inflammation of the mucosa in the ileal reservoir [65].

A low-residue, low-fiber diet has been the historical recommendation for patients with active IBD, including those without stricturing disease [58]. However, there has been no proven benefit to this dietary therapy in non-stricturing diseases. A study comparing a low-residue diet to an unlimited diet among CD patients with a non-stricturing disease phenotype showed no difference in symptoms, hospitalizations, or complications, including the need for surgery [66]. Additionally, a semi-vegetarian diet, high in fiber, has been shown to improve clinical outcomes in a small cohort of adult CD patients [67].

Micronutrients and Trace Minerals

Patients with IBD are prone to micronutrient deficits, especially those with active small bowel disease or previous resections. Vitamin D deficiency is highly prevalent in pediatric patients with IBD due to a number of factors including self-exclusion of dairy products, impaired absorption, bile salt malabsorption, medical advice to limit and protect against sun exposure, seasonal changes, and geographical variation—as IBD is more common at northern latitudes [68]. In a retrospective longitudinal study evaluating vitamin D levels, inflammatory markers, and clinical disease activity in IBD patients, low vitamin D levels were associated with higher fecal calprotectin in UC and CD [63, 69, 70]. A deficiency of vitamin D was correlated with an increase in disease flares, hospitalizations, and steroid use [63]. The findings of a prospective cohort study of 72,719 women enrolled in the Nurses' Health study found a significant inverse association between dietary and supplementary vitamin D and the risk of developing UC and a non-significant reduction in CD risk [69].

Dietary zinc is thought to potentially influence the risk of IBD through effects of autophagy and maintenance of the intestinal barrier [69]. Additional new data suggests that a diet rich in vitamin D and zinc may protect against CD, but not UC [71]. In another study involving two large prospective cohorts from the Nurses Health Data, intake of zinc was inversely associated with risk of CD, but not UC [69].

Several other micronutrient deficiencies have been studied in IBD patients and animal models with varying measures of clinical significance and are featured in Table 37.2. Although these results are promising, large human studies are needed to determine if vitamin and mineral supplementation might offer a therapeutic role in IBD.

Table 37.2 Micronutrient and vitamin deficits in IBD

Micronutrient	Sources	Association with IBD
Biotin	Liver, smaller amounts in fruits and vegetables[a]	Deficiency associated with an IBD-like state in mouse model associated with failure to thrive, microcephaly, alopecia, dermatitis, and conjunctivitis [72] Biotin therapy led to delayed onset and severity of colitis and accelerated healing in mice challenged with dextran sodium sulfate. Oral biotin supplementation (1 mmol/L) was found to prevent the production of inflammatory cytokines and maintain the integrity of the intestinal barrier [72]
Folate	Dark green leafy vegetables, fortified cereals[a]	Folate deficiency hindered the conversion of homocysteine to methionine, which increases oxidative stress in the body. Studies in mice demonstrated a susceptibility towards intestinal inflammation in mice fed diets deficient in folate [70]
Selenium Vitamin D	Fish, meats (organ), eggs, milk, shellfish[a] Fatty fish, fortified milk, cod liver, sunlight[a]	Selenium deficiency worsened experimental colitis by affecting multiple pathways involved in inflammation, oxidative stress, and alteration of the gut microbiota [70 Low vitamin D levels are associated with higher fecal calprotectin in UC and CD [63] Deficiency correlated with an increase in disease flares, hospitalizations, and steroid use [63]
Zinc	Seafood, meats, greens, whole grains[a]	Intake of zinc is inversely associated with risk of CD, but not UC [69] Thought to potentially influence the risk of IBD through the effects of autophagy and maintenance of the intestinal barrier [69]

[a]ASPEN Core Curriculum [73]

Food Additives

Maltodextrin is a polysaccharide food additive commonly found in infant formula, breakfast cereals, candy, artificial sweeteners, and processed snack foods [74]. In animal studies, maltodextrin has been found to interfere with the integrity of the gastrointestinal epithelial barrier [75]. Recently, Laudisis et al., found consumption of foods with maltodextrin leads to the advancement of intestinal inflammation and that maltodextrin adversely affects the intestinal environment by promoting depletion of the protective mucus layer [42]. Adherent invasive *E. coli* exposed to maltodextrin have enhanced biofilm formation and improved adhesion to intestinal epithelial cells. Additionally, in vitro, maltodextrin promotes adhesion of adherent invasive *E. coli* [41].

Emulsifiers are common food additives that have both hydrophilic and lipophilic properties, which allow for the mixture of otherwise immiscible substances. Common emulsifiers include carboxymethylcellulose, carrageenan, and polysorbate-80 [31, 44]. Emulsifiers are found in processed foods, including store-bought bread, processed cheeses, ice cream, dressings, margarine, mayonnaise, sauces, and coffee creamers [76–81]. Carrageenan refers to high molecular weight sulfated polysaccharides extracted from seaweeds that are used to thicken and emulsify foods. In vitro studies have shown that carrageenan decreases gastrointestinal epithelial integrity [82]. Increased intake of emulsifiers has been positively correlated with CD incidence [43]. Consumption of carboxymethylcellulose and polysorbate-80 in wild-type and IL-10 knockout mice was studied over 12 weeks [44]. Emulsifier consumption resulted in low-grade chronic colitis in wild-type mice and severe colitis in IL-10 knockout mice. Intestinal permeability increased as a result of emulsifier intake with bacterial-epithelial distance inversely correlated with severity of inflammation. This suggests that emulsifier exposure is associated with translocation of bacteria, confirming the findings of a previous in vitro study [62]. The importance of host-microbiota interactions was further supported by the observation that colitis did not occur in germ-free mice exposed to emulsifiers. However, when the microbiota from emulsifier-exposed mice was transferred to emulsifier-naïve mice, inflammation resulted [44]. Human intervention studies investigating emulsifier consumption and IBD are needed to better understand the association between emulsifiers and IBD.

Oral Supplements

Curcumin

Curcumin is the major yellow pigment found in turmeric and has historically been used in traditional Chinese medicine to treat a variety of inflammatory conditions [47]. In vitro studies have shown curcumin to have antioxidant and anti-inflammatory properties, while in mice, curcumin has been found to improve colitis via downregulation of TNFα and nuclear transcription factor kappa B [83]. A pilot study of five patients with ulcerative proctitis and five patients with CD who received an oral pure curcumin preparation for 2–3 months found improvement in inflammatory markers and disease activity scores [84]. A multicenter, double-blind placebo trial of 82 subjects with quiescent UC on mesalamine or sulfasalazine therapy showed that curcumin was superior to placebo for maintenance of remission [48]. Another multicenter, double-blind, clinical trial of 50 patients with active mild-to-moderate UC found that the addition of a 95% pure curcumin preparation to mesalamine therapy was superior to combination therapy with placebo in inducing clinical and endoscopic remission [47]. After 1 month of therapy, 14/26 (53.8%) subjects receiving curcumin were in clinical remission compared to none in the placebo group. Likewise, 8/22 (36.3%) subjects who underwent endoscopic evaluation were found to be in endoscopic remission compared to 0/16 subjects receiving placebo. Despite these promising results, the quantity of curcumin used in these studies was much higher than the amount that can be consumed exclusively through diet. In fact, a large trial with 300 patients with mild-to-moderate UC with low-dose curcumin did not find a significant clinical benefit when provided with 450 mg/day [63]. Additional larger clinical trials are needed to confirm these findings in UC and to investigate whether curcumin has a therapeutic role in CD.

Iron

Iron deficiency anemia is a common complication of IBD, and oral iron supplementation is often used for treatment [85]. Iron is a catalyst for reactions that generate reactive oxygen species. In animal models of IBD, oral iron supplementation has been shown to worsen colitis by generating oxidative stress [53]. It is unclear if oral iron can generate oxidative stress and worsen disease activity in IBD patients, as there is conflicting evidence in the literature. A small study of ten CD patients receiving 1 week of ferrous fumarate supplementation showed a rise in oxidative stress and disease activity scores [86]. However, another study of 33 IBD patients supplemented with ferrous sulfate for 4 weeks did not show an increase in reactive oxygen species. Clinical disease activity scores worsened for the UC subjects, but there was no difference in rectosigmoid endoscopic activity or laboratory parameters [87]. As the adverse effects of oral iron supplementation include gastrointestinal symptoms such as abdominal pain, it is unclear if the increases in clinical disease activity scores truly reflect the inflammatory activity.

In terms of dietary sources of iron, heme iron, which is found in red meat, has been found to worsen colitis in animal models [88]. Studies have also found increased red meat consumption to be a risk factor for disease flares in UC [49]. There are no published studies on the effects of non-heme iron sources, such as those found in fruits, vegetables, or iron-fortified cereals, on disease activity in IBD. Avoidance of aggravating, iron-rich foods including beans, red meat, spinach, and seeds among IBD patients may lead to limited oral intake of dietary iron sources.

Probiotics

The use of probiotics in IBD is not a newly-studied concept. Probiotics, live organisms that provide positive health effects in a host, are popular dietary supplements that have been used and studied in a variety of gastrointestinal diseases including IBD. Despite their popularity, there is limited evidence in favor of recommending probiotics in IBD. The strongest data supporting the use of probiotics are among patients with mild UC or among UC patients who have undergone a colectomy and have an ileal pouch-anal anastomosis [69, 89]. In a small study of 40 patients with UC, VSL #3 was found to be more effective than placebo for the prevention of acute pouchitis and improved quality of life [69]. For the treatment of chronic pouchitis, two double-blind placebo-controlled trials in adults demonstrated the effectiveness of VSL#3 in maintaining remission [69]. According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, *Escherichia coli* Nissle 1917, or VSL #3, can be considered for use in patients with mild-to-moderate UC for the induction of remission [69]. It should be noted that the VSL #3 used in previous clinical studies is the original formulation of the product and that this formulation may now be sold under a different brand name. Probiotics have no clear role in the induction or maintenance of remission in CD [63, 89]. Probiotics should be used with caution for patients with central venous catheters [61].

Structured Diets

A number of structured diets have been proposed for the treatment of IBD (Tables 37.3 and 37.4). These diets are based on the exclusion of dietary components felt to be pro-inflammatory. However, with the exception of enteral nutrition therapy, there is currently a lack of robust data to support the efficacy of any structured diet in IBD. This partially reflects the challenges of performing prospective trials of dietary therapies. Because patients in diet trials are often on concurrent medical therapies, the efficacy of the dietary

Table 37.3 Supporting evidence for proposed IBD structured diets

Diet	Description	Supporting evidence
Exclusive enteral nutrition (EEN)	Polymeric, semi-elemental, or elemental formula taken as the sole source of nutrition	Multiple prospective studies support the use of EEN for induction of remission, mucosal healing, and growth impairment in pediatric CD
Partial enteral nutrition (PEN)	Same as EEN except formula is the nonexclusive source of nutrition	Retrospective and prospective studies support the use of PEN for induction of remission and maintenance therapy in pediatric CD
Specific carbohydrate diet	Consumption of monosaccharides is allowed, but disaccharides, oligosaccharides, and polysaccharides are eliminated	Limited evidence. Small, uncontrolled studies that demonstrated clinical improvement and microbiome shifts prospectively
IBD anti-inflammatory diet	Multiple-phase diet derived from the SCD. Certain carbohydrates and fats are restricted and intake of pre- and probiotics is encouraged	Limited evidence. Small retrospective case series of adult IBD subjects demonstrated improvement in disease activity scores
Crohn disease exclusion diet (CDED)	Structured diet that reduces or eliminates exposure to animal fats, dairy products, gluten, and processed foods	Randomized, controlled pediatric trial with mild-to-moderate CD demonstrated CDED plus PEN was better tolerated and equally effective compared to EEN
CD-TREAT	Whole food based diet used to replicate the nutrient composition of EEN	Limited evidence. Three small studies evaluating the effects on the gut microbiome, inflammation, and clinical response in a rat model, healthy adults, and children with relapsing CD
Semi-vegetarian diet	Diet containing fruits, vegetables, dairy, and eggs with limited fish and meat	Limited evidence. A prospective study showed improvement in symptom-based remission compared to a free diet
Low-FODMAP diet	Diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols	Small studies revealing patients with IBD with functional-like gastrointestinal symptoms may have symptomatic benefit
Gluten-free diet	Gluten (found in rice, barley, and wheat) is completely excluded	No published data on the effect of the diet on disease activity in IBD
Paleolithic diet	Exclusion diet allowing foods presumed to be available in prehistoric times, including most fruits, vegetables, and game meat	No published scientific literature

Table 37.4 Allowed and restricted foods in proposed IBD structured diets

Structured diet	Allowed foods	Restricted foods
Specific carbohydrate diet[a,b]	Fresh or frozen meat, poultry, fish, eggs Most fruits (fresh or dried), vegetables (fresh or frozen), and certain legumes Certain cheeses (cheddar, Colby, Swiss, farmers); fully fermented yogurt Oats, flax; nut and legume flours Honey Unsweetened fruit juices	Processed or smoked meats/fish Canned fruits and vegetables, potatoes, chickpeas, soybeans Most forms of dairy Wheat, barley, rye, corn, rice Refined sugars Maple syrup, mayonnaise
IBD anti-inflammatory diet[c]	Lean meat, poultry, fish, omega-3 eggs Most fruits, vegetables, and legumes Certain cheeses (aged, cheddar, farmers), fresh-cultured yogurt, kefir Oats, flax, nuts; legume and nut flours Honey, maple syrup, mayonnaise Unsweetened fruit juices	Non-lean cuts of meat Fruits with seeds and vegetables with stems (depending on diet phase) Most forms of dairy Wheat, barley, rye, corn, rice Hydrogenated oils Refined sugars
Crohn disease exclusion diet (CDED)[d,e]	Fresh fish and chicken breast; eggs; limited fresh beef Select fruits and vegetables (i.e. potato, apple, banana) White rice; rice noodles, rice flour Honey; sugar for cooking Freshly squeezed orange juice	Processed or smoked meats/fish Canned fruits and vegetables, soy Dairy products Wheat, cereals, breads, baked goodsRefined sugars Packaged snacks
CD-TREAT[f]	Macronutrients, vitamins, minerals, and fiber comparable to EEN Full fat milk, rice-based cereals, juices, chicken, salmon, cod, mashed potato All dairy products are lactose-free All cereal products are gluten-free	Gluten, lactose, maltodextrin, and alcohol
Low-FODMAP diet7	Meat, poultry, fish, eggs Low-FODMAP fruits (e.g., banana, orange, strawberry) and vegetables (carrot, celery, potato) Lactose-free dairy, hard cheeses Rice, quinoa, corn, peanut Maple syrup	High-FODMAP fruits (e.g., apple, pear, watermelon), vegetables (e.g., asparagus, cauliflower, garlic, onion), and legumes (e.g., beans, chickpeas, lentils) Most forms of dairy Wheat, barley, rye High-fructose corn syrup, honey, agave nectar

[a] Cohen et al.[90]]
[b] Obih et al. (2015)
[c] Oldenzki et al. (2014)
[d] Sigall-Boneh et al. [91]
[e] Levine [92]
[f] Svolos [93]
[g] Gibson and Shepherd [94]

intervention is more difficult to interpret. Accurately assessing dietary intake and adherence is another challenge for diet studies. Moreover, as opposed to scientifically rigorous pharmaceutical trials, clinical trials involving dietary interventions cannot be double-blinded or have a placebo arm [9]. Whereas many study drugs are only available by enrolling in a clinical trial, structured diets are often well known and can be followed outside the confines of a clinical trial, rendering recruitment difficult.

Exclusive Enteral Nutrition

Exclusive enteral nutrition (EEN) has been extensively studied in pediatric IBD and is an effective treatment modality for induction of remission [95–97]. The formula is the sole source of nutrition in EEN, and the duration of treatment can range from 3 to 12 weeks. There is insufficient evidence for a food reintroduction pattern during the weaning of formula after the induction phase [61]. The formula can be taken orally or through a nasogastric tube with equal efficacy; with nasogastric tube feedings, the formula can be administered while asleep [98]. Additionally, there is no difference in efficacy between polymeric, semi-elemental, or elemental formulas. Polymeric formulas may be more palatable and increase compliance with oral EEN [96, 98]. EEN is widely used in Europe, yet is used by fewer than 4% of gastroenterologists in North America [99]. The exact mechanism of action of EEN is unknown, yet EEN is known to have a profound impact on the gut microbiome [100]. Although early studies had indicated that response to EEN was strongest among CD patients with small bowel disease, more recent

studies have not shown any difference in efficacy based on disease location in CD [101]. Data showing efficacy in UC is lacking.

Meta-analyses have shown that 73% of pediatric CD patients treated with EEN achieve clinical remission [96]. In children with CD, EEN is as effective as corticosteroids for induction therapy [102]. Additionally, EEN is significantly better than corticosteroids at achieving mucosal healing [100, 103]. Whereas corticosteroids are known to impair growth, EEN has been shown to improve growth, bone mass, and lean mass accrual among children with IBD [104, 105]. Based on these data, the latest pediatric CD treatment guidelines by ESPEN and The European Crohn's and Colitis Organization recommend EEN as first-line therapy for the induction of remission in children with active luminal CD [96]. Enteral nutrition has also been studied in CD patients with intestinal strictures. In a prospective observational study, 59 adult CD patients with inflammatory bowel strictures were treated with 12 weeks of EEN. EEN was found to relieve inflammatory strictures with 81.4% of patients achieving symptomatic remission, 53.8% patients achieving radiologic remission, and 64.6% patients achieving clinical remission [106]. Additional studies are warranted to see if EEN can be successfully resued to prevent future relapses, as a study completed by Frivolt et al. found decreased efficacy with a second course of EEN [107].

Partial Enteral Nutrition

Although EEN is an effective therapy for induction of remission in pediatric IBD, it may be too restrictive for many children, as it requires avoidance of all foods. Even among children who do elect to use EEN for induction, it may not be a feasible long-term treatment modality for maintenance therapy. Partial enteral nutrition (PEN) refers to the nonexclusive use of formula for the treatment of IBD with typically at least 50% of calories from formula. Studies have shown that PEN may also be effective for the induction of remission among children with CD [108, 109]. The use of a diet providing 80–90% of caloric needs from formula, with the remainder of calories coming from a free diet, was found to induce remission in 65% of children with CD [108].

In pediatric CD, PEN has also been shown to be an effective maintenance therapy. Children who received PEN that provided 50–60% of caloric needs for 4–5 nights per week were less likely to relapse compared to those on a free diet over a 1-year follow-up period after induction of remission [110]. PEN is also effective as maintenance therapy in adult CD. Patients with CD who received 50% of calories through formula and the remainder of calories via table foods were more likely than those on a free diet to be in clinical and endoscopic remission after 1–2 years [111, 112]. Among adult CD patients, PEN has been found to be as effective as 6-mercaptopurine in maintaining long-term remission [113].

Head-to-head comparisons of PEN and EEN have found EEN to be a more efficacious treatment for pediatric CD [109, 114]. In a prospective study, 90 children with active CD received either infliximab, EEN, or PEN with a regular diet (80% of caloric feeds from formula) and found that infliximab and EEN were superior to PEN in terms of mucosal healing and improvement to quality-of-life [115]. Clinical response was found in 88% of children receiving EEN, 84% of children receiving anti-TNF therapy, and 64% in the PEN group [109]. The PEN and EEN groups were similar in the amount of calories received from formula. However, the amount of table food consumed was significantly higher among the PEN group. This suggests that the mechanism of action of EEN may result from the elimination of table food rather than from any intrinsic therapeutic properties of the formula. Another dietary therapy, known as the Crohn Disease Exclusion Diet (CDED), uses PEN coupled with an exclusion diet and will be discussed later in the chapter.

Parenteral Nutrition

According to ESPEN Guidelines for Surgery 2016, the enteral route should always be favored for supportive nutritional therapy [69]. Parenteral nutrition should not be used as a means to induce remission in pediatric CD [61]. Parenteral nutrition may be indicated if enteral nutrition has failed or if the following contraindications exist: intestinal obstructions or ileus, severe shock, intestinal ischemia, high output fistula, or severe intestinal hemorrhage [69]. In IBD, parenteral nutrition is often a temporary measure provided to severely malnourished patients awaiting surgery. It can also be used to prevent weight loss when calories cannot be consumed orally or enteral nutrition cannot be provided. The risks of parenteral nutrition in IBD patients include line infections when infused in a central venous catheter, catheter-related venous thrombosis, hyperglycemia for patients on steroids, and electrolyte abnormalities among those at risk for refeeding syndrome [115].

Exclusion Diets

Whole food based exclusion dietary therapies to possibly treat IBD includes the Crohn Disease Treatment with Eating Diet (CD-TREAT), Specific Carbohydrate Diet (SCD), the Inflammatory Bowel Disease Anti Inflammatory Diet (IBD-AID), and the Crohn Disease Exclusion Diet (CDED). Restriction diets involving regular food have shown promise, yet shared decision-making is critical for success. Throughout dietary therapy, it is important to assess for improvement in

the clinical and biological condition, as well as adherence to the diet. Completing a nutrition assessment can help determine if the patient is meeting nutritional needs and help identify risks for nutrient deficiencies in restricted diets. The goals of these dietary therapies are to induce and maintain remission, as well as to decrease gastrointestinal symptoms.

CD-TREAT: Crohn Disease Treatment-with-EATing

The CD-TREAT is an exclusion diet designed to replicate the nutrient composition of EEN with the use of ordinary foods for the treatment of CD. This whole foods-based diet was created to see if similar therapeutic results of EEN can be achieved by using ordinary foods compared to a formula-based diet with EEN. The proposed mechanism of action is to mimic the effect that EEN has on the microbiome. The diet eliminates gluten, lactose, maltodextrin, and alcohol, while imitating the macronutrient distribution, vitamins, minerals, and fiber of EEN feeds [93]. The composition of the diet was based on Modulen®formula. CD-TREAT is an individualized dietary plan tailored to the participant's daily energy requirements and also considers food preferences.

The study published by Svolos et al., had three parts including a randomized controlled trial in 25 healthy adult volunteers that investigated the microbial alterations of the prescribed diet, animal experiments that focused on gut inflammation and the microbiome in a disease state, and an open-label trial in five pediatric patients with active CD to test the efficacy of the diet [93]. Results from the 25 healthy adult volunteers found the CD-TREAT to be more satisfying compared to EEN and similar changes to the metabolome and microbiome were identified. Among these findings, participants on both EEN and CD-TREAT were found to consume more total and saturated fat, but less fiber and carbohydrate intake compared to their habitual diets [93]. Among the five children receiving CD-TREAT, four had a clinical response and three entered remission with significant decreases in fecal calprotectin after 8 weeks. In animal studies, similar changes in bacterial load, short-chain fatty acids, microbiome, and ileitis severity scores were similar between CD-TREAT and EEN [93]. Restriction diets involving regular food, such as the CD-TREAT, have shown promise, yet there is a need for additional larger clinical trials.

Specific Carbohydrate Diet

The specific carbohydrate diet (SCD) was developed in the 1920s as a treatment for celiac disease and proposed as a treatment for IBD in the 1990s. The diet allows for the consumption of monosaccharides, but not disaccharides, oligosaccharides, or polysaccharides, which are felt to be poorly absorbed and felt to influence the composition of the microbiota [30]. Fruits, fresh meat and fish, eggs, fully fermented yogurt, and most vegetables are allowed, although potatoes, corn, and some legumes and lentils are not. Grains, including wheat, barley, and rice, as well as most forms of dairy are excluded. Processed foods and refined sugars are also eliminated. Soy is not permitted. Nut flours can be used as substitutes to make baked goods. Because the diet is restrictive and weight loss is common, close follow-up with a dietician is warranted [116].

To examine the nutritional adequacy of the SCD, a small study was performed in eight pediatric patients and found that the majority of participants had nutrient intake comparable to a peer reference group. However, inadequate weight gain was seen in two patients. SCD patients met or exceeded the Recommended Daily Allowance (RDA) for vitamins A, B2, B3, B5, B6, B7, B12, C, and E. Conversely, all patients following the SCD did not meet the RDA for vitamin D and 75% did not meet the Recommended Daily Allowance for calcium [117].

There have been several small studies investigating the use of the SCD in pediatric IBD. Several prospective case series in children have shown improvement in clinical and inflammatory markers in mild-to moderate-disease. A retrospective study of 20 CD and 6 UC subjects on the SCD demonstrated improved clinical disease activity scores and serum inflammatory markers on the diet. Importantly, the authors noted that weight loss occurred in nine subjects (35%) [116]. A prospective study of ten pediatric subjects with active CD starting the SCD showed improvement in disease activity scores after 12 weeks of therapy. Video capsule endoscopy demonstrated mucosal healing in 4/10 (40%) subjects. Seven subjects were followed for 52 weeks with mucosal healing seen in 2/7 (29%) subjects [90]. Another prospective study of 12 patients with mild-to-moderate IBD showed a decrease in mean Pediatric Crohn Disease Activity Index/Pediatric Ulceartive Colitis Activity Index, a decrease in mean C-reactive protein, and significant changes in microbial composition after following the diet. However, diet therapy was found to be ineffective for two patients and another two patients were unable to maintain the diet [118]. In another small study, seven subjects were identified with a modified SCD (SCD plus addition of "illegal foods") and found that complete macroscopic healing of both the ileocolon and upper gastrointestinal tract was not achieved in any patient [119]. In a larger patient survey study, 417 participants perceived clinical benefit with the SCD [120].

The Gut and Psychology Syndrome (GAPS) diet, derived from the SCD, also focuses on the mechanism of removing foods that are considered to be difficult to digest and cause damage to gut flora. The GAPS diet may be popular among

patients, yet there is no published data on the efficacy of this diet in IBD [121].

Larger cohort prospective studies, with a control group, are needed to further study the efficacy of the SCD in pediatric IBD and several larger trials are currently underway.

IBD Anti-inflammatory Diet

The IBD anti-inflammatory diet (IBD-AID) is another structured diet derived from the SCD and was modified to increase the diversity of bacteria that produce short-chain fatty acids [122]. There are four phases to the diet based on disease activity. The diet restricts certain carbohydrates, including lactose and refined sugars. Most grains, with the exception of oats, are also eliminated. The diet encourages the consumption of foods that are prebiotics and probiotics, including fermented foods and those high in soluble fiber. Allowed foods are high in n-3 PUFA and low in saturated fats. In conjunction with a dietician, food intolerances and nutritional deficiencies are identified. Food textures are modified based on clinical disease activity.

There has only been a single retrospective case series reporting experience with the IBD-AID among 27 adult participants with IBD [122]. Self-reported symptoms improved in 24/27 (89%) of subjects. More extensive chart reviews, including disease activity scores, were reported for only 11 subjects (8 CD and 3 UC) among whom all reported improved symptoms and were able to de-escalate medication therapies. All 11 subjects were in clinical remission as defined by the Harvey Bradshaw Index (HBI) and the Modified Truelove and Witts Severity Index for the CD and UC subjects, respectively. Large, randomized, clinical trials with the assessment of disease activity and mucosal healing are needed to define the therapeutic role of the IBD-AID.

Crohn Disease Exclusion Diet

The Crohn Disease Exclusion Diet (CDED) is a structured diet that reduces or eliminates exposures to foods that are thought to aggrevate intestinal permeability and induce dysbiosis. These items include animal fats, certain types and cuts of meats, gluten, maltodextrin, xanthum gum, emulsifiers (carrageenan), sulfites, certain monosaccharides, and several processed westernized foods [123]. The diet, coupled with Modulen® formula, is comprised of allowed, mandatory, and disallowed foods. It was developed for the treatment of pediatric and adult CD, as well as in patients with secondary loss of response to TNFα therapy [92]. Mandatory and allowed foods in the diet provide sources of resistant starch, fiber, pectin, and substrates required to produce short-chain fatty acids. Specific sources of animal protein are considered mandatory [123]. The diet consists of three phases and requires full compliance. Phase 1, the strictest phase, occurs from weeks 0 to 6 with 50% of calorie needs to be provided from formula with the remainder of nutritional needs met from mandatory and allowed foods. Phase 2 occurs from weeks 7 to 12 with 25% of calorie needs provided from formula with the remainder of nutritional needs met from mandatory and additional allowed foods. Phase 3 is considered a maintenance phase which continues with 25% of calorie needs to be met from formula and allows for two free days off from formula consumption plus "cheat" meals that can include restaurant meals [92].

A randomized control trial with two arms comparing CDED with PEN (50%) and EEN (100%) administered orally over 12 weeks in 78 pediatric patients with mild-to-moderate active luminal CD found that the CDED with PEN was better tolerated than EEN alone. The intervention for the CDED arm consisted of 6 weeks of CDED with 50% PEN followed by a Stage 2 CDED with 25% PEN. The EEN arm followed EEN for 6 weeks and then transitioned to 25% PEN with a free diet. Both diets were found to induce remission by week 6. While there was no mucosal healing endpoint, the CDED with PEN protocol was found to induce sustained remission compared to the EEN group and produced changes in the fecal microbiome associated with remission [92].

In an earlier retrospective case series, patients with loss of response to biologics, despite dose escalation or combination therapy, were treated with PEN + CDED for 12 weeks. Twenty one pediatric and adult subjects met study criteria with 81% identified as using combination therapy and 47% had failed a second biologic. Dose escalation failed in 62% of patients. A 62% remission rate was seen in patients in response to diet by physician global assessment and HBI after 6 weeks and 90% displayed clinical response. Improvement in inflammatory markers, including a decrease in mean CRP and an increase in albumin, were observed [123].

Another published study with a small cohort of 47 children and young adults with active CD also followed this diet [91]. Most subjects also received PEN and consumed 50% of calories from formula. Subjects were allowed to be on concomitant immunomodulator therapy, as the primary endpoint was at 6 weeks, prior to the expected full onset of action of such medications. At 6 weeks, clinical remission was achieved in 70% of patients with significant improvements in inflammatory markers and serum albumin. Among the seven subjects who consumed all calories from table food and did not receive PEN, six were in clinical remission at 6 weeks, suggesting that the exclusion diet without PEN may also be efficacious. Fifteen subjects in clinical remission practicing the diet for at least 6 months were assessed for mucosal healing, with 73% found to have evidence of healing based on endoscopy or the combination of imaging and fecal calprotectin. Despite these encouraging results, randomized studies

with a larger cohort, currently underway, are needed to further evaluate the efficacy of the CDED for both induction and maintenance therapy in pediatric CD.

Semi-Vegetarian Diet

There has been one published study on the use of a semi-vegetarian diet for maintenance of remission among 22 adults with CD [67]. This cohort was instructed to consume a diet containing brown rice, vegetables, fruits, yogurt, eggs, and milk. Fish was limited to once a week and meat to once every 2 weeks. During the study period, subjects were treated with either mesalamine or sulfasalazine. The cohort was followed for 2 years with 16 subjects remaining on the diet and six subjects consuming an omnivorous diet. Of the subjects on the semi-vegetarian diet, 15/16 (94%) were in remission compared to 2/6 (33%) subjects on free diet. This study is limited by the small sample size and the definition of remission based on clinical symptoms rather than biochemical or endoscopic parameters. Additionally, all patients were offered this diet, with the treatment group including those who were compliant while the control group was comprised of those who were non-compliant. A study with a larger cohort using established clinical endpoints is needed to assess the efficacy of this dietary intervention.

Low-FODMAP Diet

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) has been shown to reduce clinical symptoms in irritable bowel syndrome [125], but the data are limited in IBD. FODMAPs contain food products that are poorly absorbed by the human body, which leads to an influx of luminal water via osmosis. Additionally, FODMAPs are easily fermentable by the gastrointestinal microbiota into hydrogen byproducts. Together, luminal water and hydrogen production lead to luminal distention and clinical discomfort in patients with functional gastrointestinal disorders [94]. Typically, the fermentable carbohydrates of the FODMAP diet are reintroduced and the patient monitors his/her tolerance in order to expand the diet.

Functional abdominal pain is common in childhood with 13% of pediatric CD patients in remission meeting criteria [125]. About one-third of patients with IBD develop functional gastrointestinal symptoms [126]. Therefore, it is possible that a low-FODMAP diet may have some benefits among IBD patients with overlap functional gastrointestinal disorders. Moreover, since the prevalence of lactose malabsorption is high among patients with small bowel CD [58], a diet low in lactose, such as the low-FODMAP diet, may improve clinical symptoms.

There have been small studies that have investigated the use of a low-FODMAP diet in IBD. A cohort of eight UC patients who had undergone colectomy and started on a low-FODMAP diet was retrospectively found to have decreased stool frequency on the diet. However, a prospective arm of five subjects did not show a dietary effect [127]. A retrospective study of 52 CD and 20 UC patients started on a low-FOMAP diet demonstrated improvement in overall gastrointestinal symptoms in 56% and 55% of CD and UC patients, respectively. Patient-reported improvements in abdominal pain, diarrhea, and bloating were the most common [128]. However, the study had no control group, and disease activity was not objectively measured. Another study among 88 patients with IBD who were referred for low FODMAP diet education found a significant increase in patients having relief of symptoms and improvements in stool consistency and urgency [129]. This study suggests that patients with IBD and functional–like gastrointestinal symptoms (FGS) following a low FODMAP diet may benefit depending upon severity of FGS symptoms. Likewise, among patients with quiescent IBD based on physician global assessment and objective serological markers of remission, but with ongoing gastrointestinal symptoms, a single-blind trial found more patients felt relief (52%) and had a higher quality of life with a low FODMAP diet compared to the control group (16%). Since the patients all had quiescent IBD these results suggest that the clinical improvements were independent of inflammation [130].

Taken together, these studies show that a subset of IBD patients may have symptomatic improvements on a low-FODMAP diet, but it is unclear if these improvements are related to a placebo effect, an underlying functional gastrointestinal disorder, or true improvements in IBD clinical activity. As such, there is currently no data to support the use of a low-FODMAP diet for induction of remission or maintenance therapy in IBD.

Gluten-Free Diet

Adherence to a gluten-free diet is common among IBD patients with a cross-sectional questionnaire study finding that approximately 19% of patients had previously followed the diet. Approximately two-thirds of patients on a gluten-free diet reported improvement in gastrointestinal symptoms [131]. Self-reported non-celiac gluten sensitivity is common in IBD and possibly associated with active disease activity in CD [132]. Gliadin has been shown to increase intestinal permeability even among individuals without celiac disease [133], suggesting that gluten restriction could be a logical dietary target in IBD. Currently, there is no evidence to support the use of a gluten-free diet for induction of remission or maintenance therapy in IBD. Prospective studies are needed to study the effect of a gluten-free diet on clinical disease activity and mucosal healing in IBD.

The Paleolithic Diet

The theory behind the Paleolithic diet is that the increased prevalence of diseases like IBD is due to a change in the human diet from foods obtained by hunting and gathering to agricultural-based foods. Therefore, the diet excludes farm-based foods, such as grains, legumes, and meats from domesticated animals, and allows fruits, most vegetables, and game meat [30, 58]. Although the Paleolithic diet has been promoted in the lay literature, there have been no published studies regarding its use in IBD except for case reports [126]. The autoimmune protocol (AIP) diet is considered an extension of the Paleolithic diet, which removes grains, legumes, nightshades, eggs, dairy, nuts and seeds, coffee, alcohol, refined/processed sugars, food additives, and industrial seed oils. The diet is a phased approach which does allow individuals to identify foods that may be associated with increased symptoms during a reintroduction phase [134]. Recently, a small, uncontrolled clinical trial was conducted in order to examine the efficacy of the AIP among 15 adults with active IBD on concurrent pharmacological therapy. The AIP diet was found to improve quality of life during the elimination and maintenance phases of the diet. Similar to other elimination diets, the AIP diet may have the potential to be an effective adjunct therapy in IBD, but larger, randomized trials, are needed [134].

Conclusion

The westernized diet, consisting of high amounts of animal fat, refined sugars, and processed foods with limited amounts of fresh fruits, vegetables, and fiber, has been associated with the rise in worldwide IBD. Patients with CD typically consume a hypocaloric low-fiber diet. UC patients commonly avoid fiber, especially vegetables, and consume more fat compared to control populations [69]. Patients and families with IBD commonly seek dietary guidance from their medical providers. Unfortunately, there is currently no strong evidence to support the use of any structured diet, with the exception of enteral nutrition, for the long-term treatment of pediatric IBD. Compared to the other structured diets, CDED might have the best data to support a role in the treatment of mild-to-moderate CD. More research is needed and there are several trials underway to study a variety of structured exclusion diets. Until a structured diet is developed that is proven to maintain long-term remission in IBD, clinicians can use data from the epidemiological, microbiome, and animal-model studies to provide general dietary guidelines to their patients. Clinicians can collaborate with a registered dietitian to help educate patients about nutritional therapy, prevent malnutrition and nutrient deficiencies, and assist with individualized diets tailored to the patient's nutritional needs. Pending additional data, a recommendation of a well-balanced diet high in fresh fruits, fresh vegetables, and whole grains with limited processed foods, red meat, and saturated fat may be warranted for pediatric IBD patients.

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Integrative Health Therapies for Pediatric IBD

38

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Introduction

Integrative health is an umbrella term encompassing a broad range of modalities, healing philosophies, and approaches. These therapies are often classified into one of the five domains: (1) whole medical systems, (2) mind-body medicine, (3) biologically based practices, (4) manipulative and body-based practices, and (5) energy medicine. Whole medical systems represent the theories and practices of traditional Chinese medicine, Ayurvedic medicine and homeopathy, for example. Mind-body interventions involve modalities such as prayer and meditation and are meant to facilitate the connection between the mind and body. Herbal products, dietary supplements, and diets comprise the category of biologically based therapies. Body-based practices employ human touch to manipulate the physical body, such as massage or craniosacral therapy. Finally, the domain of energy therapies harnesses the body's energy fields to promote health and healing. Examples include tai chi and reiki. These classification entities encompass a wide range of diverse therapies and may have disparate, but interrelated therapeutic targets.

In the United States, the National Center for Complementary and Integrative Health has moved toward a two-subgroup classification system: mind and body practices or natural products. Furthermore, the identification that most Americans use nonmainstream practices in conjunction with, not as an alternative to, conventional treatments has to lead the development of the term integrative medicine or health. Integrative health (IH) refers to the incorporation and integration of complementary approaches into mainstream healthcare practices.

The use of IH practices is common. The most recent national survey data in the United States suggest that 33.2% of adults and 11.6% of children use complementary and integrative health approaches. The rates of IH use in chronic disease populations frequently exceed those in the general population. The prevalence of IH use in pediatric chronic disease populations also exceeds that of the general pediatric population [1]. In this chapter, we explore the interest, utilization, and efficacy of a subset of IH modalities for the adjuvant treatment of IBD in pediatrics.

Integrative Health Use in IBD

Multiple studies confirm IH use is common among children with IBD, with prevalence estimates ranging between 6.7 and 84% [2]. Pediatric prevalence rates are comparable with or exceed IH use in adults IBD [3–7]. Surveys also suggest that high proportions of IBD patients who do not use IH modalities would consider using them in the future [8]. These surveys indicate that biologically based therapies, including dietary interventions, are the most common IH domain utilized in pediatric IBD populations [6, 7, 9, 10]. The use of IH in conjunction with prescribed medications is also common. In a study by Wong et al., 43.6% of all patients with IBD used both prescription medications and IH therapies in the treatment of their disease [6].

Across surveys, however, the prevalence of IH and predictors of use vary and are inconsistent. Variation in prevalence rates may be attributed to methodologic differences in survey instruments and sampling approaches, regional and

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geographic differences, and ethnic, cultural, and other demographic influences [11]. The high degree of variability in use estimates may also be due to how IH is defined. For example, in surveys where prayer, specifically for health reasons, is included as a mind-body modality, 62% of US adults used IH in the past 12 months. Whereas when prayer was excluded, utilization estimates decreased to 36% [12]. In a survey of IH use among pediatric IBD patients from a mid-Western tertiary care center, 100% of respondents used IH modalities when defined broadly. Yet, when a more narrow definition of IH was applied, removing modalities such as prayer and multi-vitamin use, prevalence decreased to 84% [2].

There are myriad factors associated with the use of IH in pediatric IBD populations. These factors can be categorized into sociodemographic characteristics or disease-related characteristics. Parents' own use of IH, parental education level, parental age, and age of the child may predict IH use in children with IBD [6, 9, 13, 14]. Disease-related attributes associated with IH use may include dissatisfaction with traditional treatment, low self-reported health-related quality of life (HRQOL), desire to have more control over child's condition, symptom management, and to avoid side effects of medicine, the extent of out-of-pocket expenditures on prescription medication, and CD vs. UC [7, 9, 14].

However, disease-related characteristics do not consistently predict IH use. In part, this may be due to how disease severity or activity is defined across studies. In several studies, low HRQOL, increased school absences, greater out-of-pocket spending, and frequency of use of certain conventionally prescribed medications were associated with pediatric IH use [7, 9, 13]. Yet in other studies, school absences, hospital admissions, and prescription medication were not associated with or predictive of IH use [9, 15–19].

Irrespective of whether the child used any IH modalities, parental receptivity toward IH use remains high [14]. Many IH modalities may confer a sense of control over the child's disease as the parent voluntarily chooses which modalities to use, whereas the clinician prescribes a treatment. Interestingly, when parents perceive conventional medical treatment as effective or if they worry about IH interactions, they are unlikely to recommend IH for their child [20].

The remainder of this chapter will focus on the available literature as it pertains to the safety and efficacy of two common IH domains: biologically-based IH modalities (defined as natural herbal remedies and dietary supplements) and mind and body interventions.

Biologically Based Therapies for the Treatment of IBD

The specific role of Integrative Health therapies in the treatment of IBD has not yet been established. Products that have been evaluated in clinical studies for the treatment of IBD include biologically based therapies (herbs and dietary supplements) and mind-body medicine. The use of herbal remedies or nutritional supplements in pediatric IBD has been reported to be high at ~20% and ~36%, respectively. Although research has explored many of these products, scientific evidence regarding their efficacy or safety has not been adequate. The most common biologically based therapies in the treatment of IBD are those stated below (Table 38.1):

Table 38.1 Biologically based therapies in the treatment of inflammatory bowel disease

Biologically based therapy	Year	Indication	Number of subjects	Comparator	Study duration	Response rate (%)	Response on comparator (%)	Author, ref
Oral therapies:								
Aloe vera	2004	UC	44	Placebo	4 weeks	30	7	Langmead [21]
Triticum aestivum	2002	UC	23	Placebo	4 weeks	91	42	Ben-Arye [22]
Andrographis paniculata (HMPL-004)	2011	UC	120	Mesalamine	8 weeks	76	82	Tang [23]
	2013	UC	224	Placebo	8 weeks	60	40	Sandborn [24]
Jian Pi Ling tablet	1994	UC	153	Sulfasalazine (S) Placebo (P)	90 days	53	28 (S) 19 (P)	Chen [25]
Yukui tang tablets	1999	UC	118	Prednisolone, neomycin, vitamin B	40 days	33	17	Chen [26]
Curcumin	2006	UC	89	Placebo	6 months	95	79	Hanai [27]
Curcumin	2015	UC	50	Placebo	4 weeks	65	12.5	Lang [28]
Curcumin	2017	UC	62	Placebo	8 weeks	34.5	30.3	Kedia [29]
Curcumin	2005	CD	5	None	3 months	80	–	Holt [30]
Curcumin—Pediatric study	2013	CD + UC	11	None	9 weeks	–	–	Suskind [31]
Boswellia serrata (BS)	2001	UC	30	Sulfasalazine	6 weeks	70	40	Gupta [32]
BS Extract H15	2001	CD	102	Mesalamine	8 weeks	36	31	Gerhardt [33]
BS Boswelan-PS0201Bo	2010	–	108	Placebo	52 weeks	60	55	Holtmeier [34]
Artemisia absinthium	2007	CD	40	Placebo	10 weeks	65	0	Omer [35]
Artemisia absinthium	2010	CD	20	Placebo	6 weeks	80	20	Krebs [36]
Tripterygium wilfordii	2007	CD	20	Placebo	12 weeks	–	–	Ren [37]
Tripterygium wilfordii	2009	CD	45	Mesalamine	6 months 12 months	82 (6 months) 68 (12 months)	78 (6 months) 61 (12 months)	Tao [38]
Tripterygium wilfordii	2009	CD	39	Sulfasalazine	52 weeks	94	75	Liao [39]
Cannabis (THC)	2013	CD	21	Placebo	8 weeks	90	40	Naftali [40]
Cannabis	2017	CD	20	Placebo	8 weeks	–	–	Naftali [41]
Cannabis	2018	UC	60	Placebo	10 weeks	–	–	Irving [42]
Omega 3 FFA	2005	CD	38	Placebo	12 months	61%	95%	Romano [43]
Plantago ovata seeds	1999	UC	105	Mesalamine	12 months	60	65	Fernandez-Bernares [44]
NAG (Pediatric Pilot)	2000	UC + CD	12	None	Not specified	Oral:8/12 Rectal: 2/9	–	Salvatore [45]
Rectal enema therapies:								
Kui Jie Qing enemas	1997	UC	106	Sulfasalazine, prednisolone (oral and enema)	20 days	72	9	Wang [46]
Xilei-san enema	2013	UC	35	Dexamethasone enema	8 weeks	–	–	Zhang [47]
Xilei-san suppository	2013	UC	30	Placebo suppository	2 weeks	46	0	Fukunaga [48]
Bovine colostrum enema	2002	UC	14	Placebo (albumin)	4 weeks	88	0	Khan [49]
Curcumin enema	2014	UC	45	Placebo	8 weeks	52.5	36.4	Singla [50]

Herbal Therapies

Aloe Vera

Aloe Vera (Xanthorrhoeaceae) is a stemless, drought-resisting succulent plant of the lily family. It is indigenous to hot countries and has been shown to have anti-inflammatory and antioxidant properties. *Aloe vera* gel is the mucilaginous aqueous extract of the leaf pulp of Aloe barbadensis and can act as a barrier such as in patients with colitis. *Aloe vera* contains an abundance of phytochemical substances such as mannans and anthraquinone. Its immunomodulating activity is thought to work through the induction of maturation of dendritic cells and in vitro inhibition of prostaglandin E2 and IL-8. Topical administration of aloe gel is considered safe but if taken orally has been found to cause abdominal cramps, diarrhea, and dehydration. This has also been linked to thyroid dysfunction, acute hepatitis, and perioperative bleeding.

Aloe vera gel has been used in the treatment of mild-to-moderate ulcerative colitis. A randomized double-blind controlled trial from the United Kingdom by Langmead et al. showed that oral aloe vera gel when administered to patients with mild to moderately active ulcerative colitis for 4 weeks, was superior to placebo. Thirty patients were given 100 mL of oral *Aloe vera* gel twice daily and fourteen patients were given 100 mL of placebo twice daily. The primary outcome measures were clinical remission (Simple Clinical Colitis Activity Index < 2), sigmoidoscopic remission (Baron score < 1), and histological remission (Saverymuttu score < 1). Aloe vera gel taken for 4 weeks appeared to be safe, produced a clinical response ($p < 0.05$), reduction in median SSCAI ($p < 0.01$), and reduction in histological disease activity ($p < 0.03$) in comparison to placebo [21].

Triticum aestivium

Triticum aestivum (Poaceae) or better known as **wheat grass** is prepared by sprouting wheat seeds in water for 7–10 days before harvesting the leaves. It has antioxidant properties and is a natural source of vitamins and minerals. It contains agropyrene that has antibiotic activity and apigenin, which has anti-inflammatory properties by inhibiting the adhesion of leucocytes to endothelial cells. It is relatively safe but can cause nausea, anorexia, and constipation.

Wheat grass has shown significant benefit as single or adjuvant treatment for active distal ulcerative colitis. In a randomized, double-blind, multicenter study from Israel, 23 patients with active distal UC were given either daily wheat grass juice or a placebo for 4 weeks. Patients were found to have clinical improvement (reduction in rectal bleeding, abdominal pain, physical global assessment score) in 10/11 patients on wheat grass (91%) vs. 5/12 on placebo (42%). Gross improvement was also seen on sigmoidoscopy in 78% or 7/9 patients on wheat grass vs. 30% or 3/10 on placebo [22].

Andrographis paniculata

Andrographis paniculata (Acanthaceae) is a bitter-tasting annual plant in Asia. This has been marketed in China as Kan Jang, Kold Kare, KalmCold, and Paractin. *Andrographis* has been found to have antibacterial, antioxidant, anti-inflammatory, anticancer, and immune-stimulating properties. Its active constituents are diterpenoid lactones known as andrographolides. Its anti-inflammatory activity works by inhibiting nitric oxide production, cyclooxygenase-2 expression, and TNF-alpha, IL-1b, and NF-kB. Side effects include headache, fatigue, hypersensitivity, lymphadenopathy, nausea, diarrhea, altered taste, elevated hepatic transaminases, and acute kidney injury. *Andrographis* extract may inhibit 1A2, 2C9, and 3A4 and induce CYP1A1. These two properties can affect the intracellular concentration of drugs metabolized by these enzymes.

Andrographis has been found to be an efficacious alternative to mesalamine in the treatment of active UC. A multicenter randomized double-blind, 8-week parallel-group pilot study showed that *Andrographis paniculata* (HMPL-004) was as efficacious as mesalamine in clinical response (76% vs. 82%; clinical response defined as total improvement in clinical symptom scores) in the treatment of mild-to-moderate ulcerative colitis. Furthermore, about 21% of those treated with *Andrographis paniculata* (HMPL-004) achieved complete clinical remission vs. 16% treated with mesalamine (clinical remission defined as 100% improvement in clinical symptom scores). However, there was no difference in endoscopic remission rates at 8 weeks between the two groups, 28% vs. 24% [23]. This was followed up by a larger randomized, double-blind controlled trial in 224 adults with mild-to-moderate ulcerative colitis. HMPL-004 given at a higher dose (1800 mg daily) was associated with a greater clinical response than placebo (60% vs. 40%; $P = 0.018$) although remission rates at 8 weeks were not different between both groups, 38% vs. 34%; $P = 0.101$ [24]. In both trials, the most common adverse events were abdominal pain, diarrhea, and headache. However, the frequency of adverse events was similar in both the treatment and control groups.

Jian Pi Ling

Jian Pi Ling (JPL) tablet and *Yukui tang* tablets are herbal therapies that have been studied in China in the treatment for ulcerative colitis [25, 26, 51, 52]. In a randomized controlled

trial, 153 patients with UC were randomly assigned to three groups: group I, Jian Pi Ling (JPL) tablet with retention enema of *Radix Sophorae Flavescentis* and Flos Sophora decoction; group II, sulfasalazine and retention enema of dexamethasone; and group III, placebo and retention enema of decoction. Remission rates at 3 months in group 1 were significantly higher (53%) than those in the other two groups (28 and 19%, respectively) [25, 26]. Another study evaluated 118 patients with active UC who were treated with oral Yukui tang tablets and herbal decoction enemas, in addition to oral prednisolone 15 mg daily, neomycin, and vitamin B for 40 days. Eighty-six control patients who received only low-dose prednisolone, neomycin, and vitamin B were used for comparison. The remission rates and response rates were 33 and 51%, respectively, in the active group, compared with 17 and 43%, in the control group [25, 26].

Oenothera biennis

Oenothera biennis also known as **evening primrose oil**, night willow herb, fever plant, and king's cure-all. Evening primrose oil is rich in omega-6 gamma-linolenic acid (GLA), which can be converted directly to the prostaglandin precursor dihomo-GLA (DGLA). It has been demonstrated to have anti-inflammatory activity and inhibits platelet aggregation. Administration of the oil may benefit individuals unable to metabolize cis-linolenic acid to GLA, producing subsequent intermediates of metabolic significance including prostaglandins. Side effects include abdominal pain, indigestion, nausea, softening of stools, and headaches. This may cause increased bleeding when taken with anticoagulants or antiplatelet medication. Although there are no interactions reported with antihypertensive medications, evening primrose oil was identified to increase both systolic and diastolic blood pressures, with a clinically meaningful difference for systolic blood pressure in a large population-based study.

Primrose oil has been used in the treatment of ulcerative colitis. In a placebo-controlled study, 43 patients with stable ulcerative colitis were randomized to receive MaxEPA (Omega 3 FFA) ($n = 16$), super evening primrose oil ($n = 19$), or olive oil as placebo ($n = 8$) for 6 months, in addition to their normal treatment. Super evening primrose oil significantly improved stool consistency, and the difference was maintained even after treatment was discontinued. There was no difference in stool frequency, rectal bleeding, disease relapse, sigmoidoscopic appearance, or histology in the three treatment groups [53].

Curcumin

Curcumin is the major phytochemical active ingredient of the **spice turmeric**. It is a herb derived from the ginger family (*Zingiberaceae*) native to India and Southeast Asia. Curcumin is commonly used in Indian traditional cuisine and medicine. It has been found to have anti-inflammatory, antioxidant, and antitumor effects. Curcumin is thought to cause the suppression of the nuclear factor kappa-light chain enhancer of activated B cells (NF-KB). Furthermore, curcumin activity includes suppression of interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF α), two main cytokines that play important roles in the regulation of inflammatory responses. Side effects include dyspepsia, diarrhea, distension, reflux, gassiness, nausea, and vomiting. It also has been found to interact with anticoagulants, hypoglycemic medications, and iron and can increase sulfasalazine levels. Thus, this must be discontinued at least 2 weeks prior to any surgery.

Curcumin has been used in the treatment of both ulcerative colitis and Crohn disease. A 2012 Cochrane review found curcumin is safe and effective therapy for the maintenance of remission in quiescent UC when given as adjunctive therapy along with mesalamine or sulfasalazine. A multicenter randomized double-blind Japanese study evaluated 89 patients who were randomized to receive either curcumin (1 g twice daily) or placebo, in addition to sulfasalazine or mesalamine, for 6 months. The relapse rate was significantly lower in the curcumin group, 4.7% compared to the placebo 20.5%, $p = 0.04$ [27]. This was reinforced by a multicenter double-blind randomized control trial, which evaluated 50 patients with active mild-moderate UC on 5-ASA, who did not respond to 2 weeks of max 5-ASA oral and topical therapy. Patients were randomly assigned to curcumin 3 g/day ($n = 26$) or placebo ($n = 24$) × 4 weeks. Clinical response (reduction of ≥3 points in SCCAI) was achieved by 17 patients (65.3%) in the curcumin group vs. three patients (12.5%) in the placebo group ($P < 0.001$). Endoscopic remission (partial Mayo score ≤ 1) was observed in 8 of the 22 patients evaluated in the curcumin group (38%), compared with 0 of 16 patients evaluated in the placebo group $p = 0.04$ [28]. One study evaluated the efficacy of topical curcumin therapy in the form of an enema. They evaluated 45 patients with mild-to-moderate distal UC who were randomized to oral 5-ASA plus either curcumin enema or a placebo enema for 8 weeks. Curcumin compared with the placebo group showed a superior clinical response (92.9% versus 50%, $p = 0.01$), clinical remission (71.4% versus 31.3%, $p = 0.03$), and endoscopic improvement (85.7% versus 50%, $p = 0.04$) [50, 54].

Curcumin has been also evaluated in Crohn disease. An open label pilot study of five patients with UC proctitis/proctosigmoiditis and five patients with Crohn disease were evaluated. Those with Crohn disease were treated with curcumin, 360 mg (1 capsule) three times daily for 1 month and then 360 mg (4 capsules) four times daily for the remaining 2 months demonstrated a mean reduction in CDAI of 55 points, ESR reduction of 10 mm/h, and CRP reduction of

0.1 mg/dL in 4 out of the 5 patients. All of the proctitis patients improved, with reductions in concomitant medications in four [30]. Despite previously reported results, an RCT done in 2003–2005 showed the failure of low-dose curcumin to induce remission in mild-to-moderate UC using a combination of oral mesalamine and curcumin. Forty-one patients were randomized, either to oral mesalamine 2.4 g daily with curcumin at 150 mg three times a day (16 patients) or oral mesalamine 2.4 g daily with placebo (25 patients). There was no significant difference between the two groups in terms of clinical response, clinical remission or mucosal healing after 8 weeks of therapy [29].

A pilot pediatric tolerability study was performed in 11 patients with mild UC or CD. This had shown overall good tolerability of the drug with only 2 out of the 11 patients exhibiting gassiness. All participants in this pilot study received 500 mg of curcumin twice a day for 3 weeks, and with the use of a forced dose titration design, doses were increased up to 1 g twice a day at Week 3 for a total of 3 weeks and titrated again to 2 g twice a day at Week 6 for an additional 3 weeks. By using the Pediatric Ulcerative Colitis Activity Index (PUCAI) and Pediatric Crohn Disease Activity Index (PCDAI), which are validated measures of disease activity, scores were obtained at Weeks 3, 6 and 9. Three patients had a decrease in their PUCAI or PCDAI scores and none had a relapse or worsening of symptoms [31].

Boswellia

Boswellia (Burseraceae), also known as **Indian frankincense,** is a tree prevalent in India, the Middle East, and North Africa. The gummy exudate or the resin obtained by peeling away the bark is commonly known as "frankincense" or "olibanum." Boswellic acids act as an anti-inflammatory by noncompetitive inhibition of 5-lipoxygenase and decrease in pro-inflammatory makers such as TNF-α. Side effects include gastric irritation and nausea. It has been shown to interact with cytochrome P450 substrates and immunosuppressants and decrease the inflammatory effects of NSAIDs. In addition, this may accelerate menstrual flow and may induce miscarriage in pregnant women.

Boswellia has been used in the treatment of ulcerative colitis and Crohn disease. Two studies had compared the efficacy of herbal therapy to mesalamine. In the first study, 30 patients with chronic active UC were randomized to gum resin of *Boswellia serrata* (900 mg daily in three doses; $n = 20$) or sulfasalazine (3 g daily in three doses; $n = 10$) for 6 weeks. Fourteen of the twenty patients treated with *Boswellia* gum resin and four of the ten treated with sulfasalazine achieved remission. Eighteen of 20 patients treated with *Boswellia* gum resin and 6 of 10 patients on sulfasalazine showed an improvement in one or more of the parameters including stool properties, histopathology, and scanning electron microscopy [32].

In a randomized, double-blind, non-inferiority, parallel-group control trial done in Germany, 102 patients with Crohn disease were randomized. Forty-four patients were treated with *Boswellia* extract (H15) and thirty-nine with mesalamine. CDAI decreased by 90 in the *Boswellia* group and 53 in the mesalamine group [33]. A subsequent double-blind, placebo-controlled, randomized, parallel study from 22 centers in Germany evaluated the long-term efficacy and safety of *Boswellia serrata* extract (Boswelan, PS0201Bo) in maintaining remission in 108 patients with Crohn disease. At 52 weeks, there was no significant difference in the proportion of patients in clinical remission between those who were actively treated or in the placebo group (59.9% vs. 55.3%). The mean time to relapse was also not different between the two groups [34].

Artemisia absinthium

Artemisia absinthium (Asteraceae) is commonly known as **wormwood or sweet sagewort** and has been used in traditional Chinese medicine. Dihydroartemisinin (DHA) is a semisynthetic derivative of artemisinin and has been found to have anti-inflammatory properties. It is believed to attenuate COX-2 production via downregulation of serine/threonine kinase (AKT) and mitogen-activated protein kinase (MAPK) pathways and decrease TNF-α. Side effects include hepatitis and patients with a history of ulcers should not take *Artemisia*. *Artemisia* can also induce seizures resulting from decreased efficacy of antiseizure medications. Extracts from *Artemisia* induce CYP2B6 and CYP3A4 and may affect the serum concentration of drugs metabolized by these enzymes.

Wormwood has been used in the treatment of Crohn disease. A double-blind study carried out at five sites in Germany evaluated 40 patients suffering from Crohn disease receiving a stable daily dose of steroids at an equivalent of 40 mg or less of prednisone for at least 3 weeks. They were randomized to receive either a herbal blend containing wormwood herb (3 × 500 mg/day) or a placebo for 10 weeks. There was a steady improvement in CD symptoms in 18 patients (90%) who received wormwood in spite of tapering of steroids as shown by Crohn Disease Activity Index (CDAI) questionnaire, Inflammatory Bowel Disease Questionnaire (IBDQ), Hamilton Depression Scale (HAMD), and Visual Analogue Scale (VA-Scale). After 8 weeks of treatment with wormwood, there was almost complete remission of symptoms in 13 (65%) patients in this group as compared to none in the placebo group. This remission persisted till the end of the observation period which was week 20, and the addition of steroids was not necessary. This study strongly suggests that wormwood has a steroid-sparing effect on the improvement

of mood and quality of life-based on the HAMD scale, which is not achieved by other standard medications [35].

In a separate controlled trial, 20 patients with active CD were given either dried powdered wormwood or a placebo, in addition to their existing CD therapy. At 6 weeks, 8 of 10 patients (80%) on wormwood and 2 of 10 patients (20%) on placebo achieved clinical remission defined as a Crohn disease activity index (CDAI) below 170 or a reduction in CDAI by 70 points. Six of ten patients on wormwood had a clinical response compared to none on placebo [36].

Tripterygium wilfordii Hook F (TWHF)

Tripterygium wilfordii Hook F (TWHF) known by its mandarin name "léi gōng téng," sometimes called thunder god vine, is a vine used in traditional Chinese medicine that has both immunomodulatory and anti-inflammatory activities. It is a dipterpene tripoxide from an extract obtained from *Tripterygium wilfordii*. Side effects include amenorrhea and nonspecific gastrointestinal symptoms. *Tripterygium* is used in the treatment and in prevention of postoperative recurrence of Crohn disease. A study evaluated 20 adult patients with active Crohn disease who were treated with *Tripterygium* pills for 12 weeks. CDAI scores dropped during the first 8 weeks, and endoscopic improvements were observed at week 12. Furthermore, a significant decrease in serum levels of C-reactive protein and pro-inflammatory cytokines was reported [37].

Two placebo-controlled studies assessed the role of *Tripterygium wilfordii* (GTW) in preventing postoperative recurrence of CD. Forty-five patients with CD were randomly assigned to receive GTW or mesalamine after their operation. No clinical recurrence occurred in both groups at 3 months. There were no significant differences in clinical relapse at 6 months (18% vs. 22%) or 12 months (32% vs. 39%) between the GTW and mesalamine groups. Endoscopic recurrence at 12 months was also similar in the two groups, 46% vs. 61% [38]. This was followed by a subsequent study, which randomized 39 CD patients to GTW ($n = 21$) or sulfasalazine ($n = 18$) 2 weeks after resection for Crohn disease. Clinical recurrence was reported in 6% on GTW and 25% on sulfasalazine, and endoscopic recurrence was reported in 22% on GTW and 56% on sulfasalazine. GTW appeared to be as effective, if not more effective, than mesalamine in preventing recurrence of postoperative Crohn disease [39].

Belladonna

Belladonna (Tincture of belladonna) *Atropa belladonna* or *Atropa bella-donna*, commonly known as belladonna or **deadly nightshade**, is a perennial herbaceous plant in the tomato family Solanaceae. This is native to Europe, North Africa, Western Asia, and some parts of Canada and the United States. The active agents in belladonna include atropine, hyoscine, and hyoscyamine which have anticholinergic properties. Side effects include dilated pupils, sensitivity to light, blurred vision, tachycardia, loss of balance, staggering, headache, rash, flushing, severely dry mouth, urinary retention, constipation, confusion, hallucinations, delirium, and convulsions. This has been used for its anticholinergic properties and symptomatic treatment of pain in inflammatory bowel disease. Its side effect is suppression of gastrointestinal motility and thus can precipitate toxic megacolon. Thus, use is not recommended.

Cannabis

Cannabis is a genus of flowering plants that includes three species *sativa*, *indica*, and *ruderalis*. The plant is indigenous to Central Asia and the Indian subcontinent. D9-tetrahydrocannabinol (THC) and cannabidiol (CBD) seem to be the most active cannabinoids. Two cannabinoid receptors in the gut have been identified, cannabinoid receptors CB1 and CB2. They act mainly through cannabinoid receptor 2 which causes downregulation of cytokines, specifically tumor necrosis factor (TNF)-α and interleukin-1. They also act by suppressing cell-mediated immunity and enhancing humoral immunity. Cannabinoid exposure antagonizes the release of prostaglandins, histamine, and matrix-active proteases from mast cells. Side effects can include dry mouth, drowsiness, palpitations, paranoia, anxiety, memory loss [55], altered state of consciousness, distorted perceptions of time and space, bloodshot eyes, dilated pupils, increased appetite, and impaired coordination and concentration.

Cannabinoids have been used within gastroenterology to treat anorexia, emesis, abdominal pain, gastroenteritis, diarrhea, intestinal inflammation, and diabetic gastroparesis [56]. Endogenous endocannabinoids have been discovered which may modulate intestinal inflammation [57], and animal models suggest cannabis plays a role in the treatment of colitis [58]. THC has been used in the symptomatic relief of inflammatory bowel disease in adults.

Observational data have indicated that marijuana use by patients with CD generally improves their overall perception of health, ability to work, and social function and reduces physical pain and depression, with an increase in weight [59]. This was also echoed in a retrospective study, wherein 21 out of 30 patients with CD had clinical improvement ($p < 0.001$) based upon Harvey-Bradshaw Index and a decreased need for escalation of therapy and surgery after cannabis treatment [60]. A double-blinded prospective study evaluated 21 patients with Crohn Disease Activity Index (CDAI) scores greater than 200 who did not respond to ther-

apy with steroids, immunomodulators, or antitumor necrosis factor-α agents. Patients were randomized to receive cigarettes containing 115 mg of D9 tetrahydrocannabinol (THC) or a placebo containing cannabis flowers from which the THC had been extracted twice daily for 8 weeks. Complete remission (CDAI score, <150) was achieved by 5 of 11 subjects in the cannabis group and 1 of 10 in the placebo group (p 0.43), and clinical response (decrease in CDAI score of >100) was observed in 90% the cannabis group vs 40% in the placebo group ($p = 0.028$). THC-rich cannabis produced significant clinical, steroid-free benefits with active Crohn disease, compared with placebo, without side effects [40].

The most recent trial by Naftali et al., was a small RCT evaluating 20 patients with moderately active CD on various therapies who were randomized to receive cannabidiol 20 mg/day or placebo. No significant difference in CDAI score was noted between the 2 groups after 8 weeks [41]. CBD was noted to be safe but had no beneficial effects. Lastly, a study by Irving, showed that among patients with left-sided or extensive UC stable on 5-ASAs (Mayo scores of 4–10 (endoscopy scores ≥ 1), a cannabidiol-rich botanical extract was superior to placebo in improving QOL outcomes and may be beneficial for symptomatic treatment of UC although remission rates at 10 weeks were similar between the two groups [42].

Indigo naturalis

Indigo naturalis (IN) also known as Qing-Dai is a herbal medicine extracted from indigo plants (*Indigofera tinctoria*) predominantly used in China. IN contains ligands for the aryl hydrocarbon receptor and promotes regeneration of the mucosa by inducing the production of interleukin 22. It has anti-inflammatory properties secondary to the inhibition of TNF-α, interleukin 1, 6, and NF-κB. It has been used as an antipyretic and hemostatic agent. Side effects include diarrhea, abdominal pain, nausea, vomiting, transaminitis, and headaches [61].

In rat models, this has also been seen to reduce myeloperoxidase activity and expression of inflammatory cytokines while increasing the expression of colonic mucosal repair–related cytokines and proteins. A multicenter RCT evaluated the benefit of Indigo in 86 patients with active UC (Mayo score ≥ 6) refractory to conventional treatments. Patients were randomized to receive a daily dose of Indigo at doses of 0.5 g, 1.0 g, or 2.0 g for 8 weeks. The primary endpoint was the rate of clinical response at week 8, defined as a 3-point decrease in the Mayo score and a decrease of at least 30% from baseline, with a decrease of at least 1 point for the rectal bleeding subscore or absolute rectal bleeding score of 0–1. The trial was terminated because of an external reason: a report of pulmonary arterial hypertension in a patient who used self-purchased IN for 6 months. Patients on IN demonstrated significantly higher rates of clinical response, remission, and mucosal healing vs patients in the placebo group. IN should not yet be used because of the potential for adverse effects, including pulmonary arterial hypertension [62].

Non-herbal Therapies

Fatty Acids

Fish Oil (Omega-3 FFA)

Fish oil (omega-3 FFA) is a type of polyunsaturated fatty acid (PUFA) derived mainly from fish oil. It has been found to have anti-inflammatory and immunomodulatory properties. The main components behind its potential therapeutic effects include omega-3 polyunsaturated fatty acids (n-3 PUFAs), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA), the latter 2 being the main bioactive forms synthesized from the precursor n-3 PUFA α-linolenic acid. Recently, n-3 PUFAs have been implicated in favorable shifts in the gut microbiota, including decreases in *Faecalibacterium* and an increase in *Bacteroidetes*.

Fish oil suppresses mediators of immune function by reducing cytokine production (IL-1, IL-2, IL-6 TNF-α), suppressing T and B cell proliferation and decreasing antibody production. Omega-3 fatty acids may also reduce inflammation in patients with ulcerative colitis by reducing rectal dialysate leukotriene β4. This is generally safe but side effects include fishy after taste, nausea, diarrhea, and heartburn. Fish oil can have additive anticoagulant/antiplatelet effects and interact with NSAIDS. This may also potentiate some of the adverse effects of glucocorticoids.

Fish oil has been used in the treatment of both ulcerative colitis and Crohn disease. Despite its generally accepted use, results in clinical studies have been inconsistent. A 2014 Cochrane review of six studies with 1039 patients demonstrated the marginal benefit of therapy for maintenance of remission. The overall quality of evidence was very low, and the two best quality studies showed no benefit. In two systematic reviews, omega-3 fatty acids are not effective for the maintenance of remission in Crohn disease [63]. However, an RCT performed in 2018 examined a cohort of patients in clinical remission (partial Mayo score < 2) but with fecal calprotectin at least 150 μg/g. Patients were randomized to receive EPA (1 g twice daily) or placebo. They found that 63.3% of patients receiving EPA vs 13.3% of patients receiving placebo had at least a 100-point reduction in fecal calprotectin ($P < 0.001$) and 76.7% of patients receiving EPA (vs 50% of patients receiving placebo) maintained remission (odds ratio, 3.29; 95% CI, 1.08–9.95) [64, 65].

Although there is evidence that PUFAs can benefit IBD ex vivo and in animal models, a systematic review and meta-analyses by Turner et al. in 2011 concluded that there are insufficient data to recommend the use of omega-3 fatty acids for the maintenance of remission in CD and UC [66]. Furthermore, a systematic review in 2012 concluded that there is insufficient evidence to recommend n-3 PUFA in IBD [67].

A pediatric study by Romano et al. assessed the use of long-chain omega-3 FFA supplementation, in addition to 5-ASA in pediatric patients with CD. This study included 38 patients 5–16 years of age with CD in remission, randomized to two groups, either receiving 5-ASA and omega-3 FFA or receiving 5-ASA and olive oil placebo capsules for a period of 12 months. Relapse rates were significantly lower in the group receiving omega-3 FFAs, 61% (11/18) compared to placebo, 95% (19/20) ($P < 0.001$) [43].

Blond psyllium

Blond psyllium comes from the husk surrounding the seeds of a herb called ***Plantago ovata*** (Plantaginaceae). When exposed to water, psyllium swells and forms a gel-like mass called mucilage. The colonic fermentation of psyllium in the gastrointestinal tract produces butyrate. Butyrate has an anti-inflammatory effect and inhibits cytokine production. Side effects include transient flatulence, abdominal pain, diarrhea, constipation, dyspepsia, and nausea. Contraindications for its use in IBD include fecal impaction, GI tract narrowing, obstruction, swallowing disorders, and treatment within 2 weeks of surgery.

Blond psyllium has been used to prevent relapse and improve associated ulcerative colitis symptoms. Blond psyllium has been used as a butyrate enema and is effective for the treatment of diversion colitis. In an open-label, parallel-group, multicenter, randomized clinical trial, 105 patients with UC in remission were randomized into groups to receive *Plantago ovata* seeds (10 g twice daily), mesalamine (500 mg three times daily), and *Plantago ovata* seeds plus mesalamine at the same doses. The primary outcome was the maintenance of remission for 1 year. Relapse rates at 12 months were similar in the three groups, psyllium 40% vs. mesalamine 35% vs. combination 30%. There was a significant increase in fecal butyrate with psyllium. Side effects were mild and included constipation and/or flatulence [44].

N-Acetyl Glucosamine (NAG)

N-acetyl glucosamine (NAG) is a chemical that comes from the outer shells of shellfish. It is an amino sugar form of glucosamine. NAG is thought to restore the gastrointestinal protective glycoprotein layer that is broken down with mucosal inflammation. It has been shown to block adherence of *Candida* to gastrointestinal mucosa and stimulates the growth of beneficial *Bifidobacteria*. Side effects include gastrointestinal upset and it is not advised in patients with shellfish allergy. It may interact with acetaminophen, hypoglycemic medication, and warfarin and is contraindicated in asthmatics.

NAG has been used in the treatment of both ulcerative colitis and Crohn disease. A pediatric pilot study evaluated 12 children with severe treatment-resistant bowel disease (10 CD, 2 UC). Seven of the twelve patients had symptomatic strictures. Patients were given 3–6 g of NAG orally as adjunctive therapy. Similar doses were given rectally as monotherapy to nine children with distal UC or proctitis resistant to steroids and antibiotics. Eight of the twelve children who were given oral treatment improved but four required resections. Two of the nine children given rectal therapy achieved remission and three improved, and there was no effect seen in the remaining two patients. Histological improvement was seen in all nine cases biopsied [45].

Chitosan

Chitosan is the N-deacetylated form of chitin extracted from shells of crustaceans and has a structure similar to cellulose. It is a water-insoluble dietary fiber that helps improve bowel habits and prevents colon cancer. Evidence suggests positively charged chitosan polymers bind to negatively charged bile acids in the intestines. This is generally safe but side effects include gastrointestinal upset, nausea, flatulence, increased stool bulk, constipation, and shellfish allergy. It has also been shown to reduce the absorption of calcium, magnesium, selenium, fat-soluble vitamins, and warfarin. This has been studied in the treatment of Crohn disease. A pilot trial of 11 patients with Crohn's was given chitosan and ascorbic acid mixture (1.05 g/day) for 8 weeks. Patients continued their regular therapy. They found that bowel movements slightly increased but nutritional, inflammatory markers, and CDAI did not change. There have been no studies on children. Based on data, this is not recommended in the treatment of IBD [68].

Bromelain

Bromelain (*Ananas comosus*) is a proteolytic enzyme derived from the pineapple stem. It can decrease the expression of mRNAs encoding pro-inflammatory cytokines by human leukocytes in vitro. It has also been shown to decrease the secretion of granulocyte-macrophage colony-stimulating factor, IFN-gamma, and TNF-α in ulcerative colitis and Crohn disease colon biopsies in vitro [53]. Side effects include mild nausea and vomiting, diarrhea, and excessive menstrual bleeding, and it has been seen to interact with anticoagulants, sedatives, and antibiotics. It has been used in refractory ulcerative colitis. There has been a case report of two patients who entered and remained in clinical and endoscopic remission after self-treatment [69].

Rutin

Rutin is a flavonoid with antioxidant properties. It is found in buckwheat, Japanese pagoda tree, eucalyptus, lime tree flowers, elder flowers, hawthorn leaves, St John's wort, *Ginkgo biloba*, and apples. It is safe in small amounts such as present in fruits and vegetables. Side effects include headache, flushing, rashes, and gastrointestinal disturbance. This has shown some benefit in improving inflammatory bowel disease in rats, yet there are no human studies.

Rectal Enema Therapies

Kui Jie Qing (KJQ)

Kui jie qing (KJQ) is a traditional Chinese remedy that has been used as an enema in the treatment of active ulcerative colitis. A randomized controlled trial from China evaluated 95 patients with active UC who were treated with Kui jie qing enemas four times a day. This form of treatment was compared with conventional anti-IBD drugs, including sulfasalazine (1.5 g 3 times daily), oral prednisolone (30 mg once daily), and prednisone enemas (20 mg 4 times daily). After 20 days of treatment, the authors reported a 95% effectiveness rate for KJQ and 62% for conventional drugs, based on the comparison of cure and improvement between the groups. Effective "cure" was shown in 72% of KJQ-treated patients but only in 9% of controls although the definition of "cure" or "improvement" in this study was not clear [46].

Xilei-San

Xilei-san is used in traditional Chinese herbal medicine for its anti-inflammatory properties. This has been used in the treatment of ulcerative proctitis. In an 8-week double-blind randomized study, Xilei-san enema was compared with dexamethasone enemas in 35 subjects with mild-to-moderate active ulcerative proctitis. Subjects were followed up for 12 weeks. Both treatments showed significant improvement in clinical, endoscopic, and histological scores compared to baseline [47].

In another randomized control trial, Xilei-san was used to induce remission in 30 patients with intractable ulcerative proctitis. Subjects were treated with topical mesalamine or corticosteroids for 4 weeks and then randomized into Xilei-san suppositories or placebo for 2 weeks. In the Xilei-san-treated group, significantly more patients achieved remission on day 14 (clinical disease index ≤ 4) compared with placebo ($P < 0.04$). 81.8% of patients on Xilei-san suppositories were without relapse versus 16.7% in placebo ($P < 0.001$) on Day 180. Furthermore, significant endoscopic ($P < 0.01$), histological ($P < 0.02$) and inflammatory bowel disease questionnaire ($P < 0.04$) improvements were observed in the Xilei-san-treated group [48].

Bovine Colostrum

Bovine colostrum is cow's milk secreted during the first few days following calving. It is rich in immunoglobulins, growth factors, and cytokines and confers immune protection to the newborn calf from opportunistic infections. Bovine colostrum is postulated to enhance the immune response. Although the high concentration of immunoglobulins may account for bovine colostrum's effects, the exact mechanism is not known. This may not be used in patients who have cow's milk allergy. Bovine colostrum has been used as an enema in the treatment of ulcerative proctitis. Fourteen patients with mild-to-moderate active UC were treated with bovine colostrum enemas or a placebo containing albumin solution twice daily for 4 weeks in addition to mesalamine. Only the colostrum group showed a mean reduction in symptom score in 7 out of 8 patients and an improvement in the histological score in 5/8 patients vs. 2/6 in the placebo group [49].

Dietary Therapy and Probiotics

Please see separate chapter for this discussion.

Mind Body Therapies for Pediatric IBD

There is an emerging body of literature focused on the use of mind-body therapies to mitigate psychosocial stress and improve HRQOL among IBD patients. Considering that stressful event experiences are perceived as possible triggers for relapse and increased disease activity, the application of mind-body interventions to enhance stress coping skills may enhance the durability of remission [70, 71]. Furthermore, the known association between stress and physical symptom exacerbation and the prevalence of comorbid affective disorders in patients with GI conditions suggest that mind-body therapies may be effective in symptom amelioration [72].

Patients with low-stress levels and those who engage in distraction have shown fewer relapses of disease [73]. Stress has been linked to altering gut permeability, modulating the immune system, and in mice models changing the gut-microbiota leads to a dysregulated colonic inflammatory response by affecting epithelial barrier function [74–76]. In regards to human studies, Mackner et al. showed in a small pilot study that pediatric patients with Crohn disease with high perceived stress had a significantly different composition of their microbiome and metabolome than those with lower perceived stress [77].

Mind-body interventions (MBI) aim to "employ a variety of techniques to facilitate the mind's capacity to affect bodily function" [78]. MBI therapies target stress by affecting the autonomic nervous system and engaging the relaxation response to affect physical symptoms. Mind-body interventions include modalities such as meditation, yoga, and deep breathing, for example, and may be a useful adjuvant treatment for pediatric IBD patients. These MBI modalities are relatively inexpensive, safe, easily integrated, and readily accessible and available. However, there is the paucity of literature in studying these interventions in children with IBD. This section will outline the current body of literature on various mind-body modalities for IBD, focusing on pediatric studies when available, but highlighting adult literature when there are no relevant pediatric studies.

Yoga

Yoga stems from the Indian subcontinent and is a set of practices of physical postures and breathing exercises aimed to promote health. Yoga has been demonstrated to decrease physiologic stress, inflammation, and improve regulation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis by affecting various physiologic parameters [79]. Furthermore, the European Crohn's and Colitis Organization's recent review on complementary medicine and psychotherapy in IBD concludes that yoga improves QOL in adults with IBD [80].

Cramer et al. published that when comparing written self-care advice to a 12-week supervised weekly yoga program in adults with UC in clinical remission, those in the yoga group had significantly higher QOL and lower disease activity scores compared to the self-care advice group in both study outcome time points of week 12 and 24 of the study [81]. In 2015, Sharma et al., compared an 8-week yoga intervention to a control group with standard medical care in both adults with UC (n = 60) and CD (n = 40) [82]. They found that those in the UC yoga group had decreased arthralgias, decreased pain, and significantly reduced anxiety levels in comparison to the UC control group. However, no significant changes were observed in the CD yoga group nor in objective markers such as heart rate variability and immune markers (soluble IL-2 receptor level and serum eosinophilic cationic protein) in either the UC or CD groups in comparison to controls [82].

In pediatrics, to date, there is only one pilot study that assessed the acceptability and feasibility of a combination 8-week in-person and video yoga program for youth with IBD. Arruda et al. recruited nine adolescents with IBD (both UC and CD) who did not have severe disease (as characterized by exclusion criteria of PUCAI <65, starting a recent biologic therapy, and recent hospitalization or surgery in the last two and one months, respectively [83]. The study was well accepted and feasible as both in-person and video yoga sessions had good attendance (all 9 participants attended 2 out of the 3 in-person sessions and 6 completed at least 2 of 3 online sessions weekly) [83]. Qualitative focus group themes from the study revealed that yoga had a calming effect on participants, increased their emotional self-awareness, reduced stress, helped identify and manage their physical symptoms, and was accessible [83]. However, the study was not adequately powered to detect any statistically significant changes in PUCAI, calprotectin, or PROMIS-37 (Patient Reported Outcomes Measurement Information System, which is a validated form assessing six domains of pediatric wellness) [83].

There is more robust literature studying the effect of yoga in both children and adults with Irritable Bowel Syndrome (IBS). Several systematic reviews and randomized control trials have shown that yoga is feasible and safe, helped with the overall reduction in pain and led to global symptom improvement in patients with IBS [84–86]. And, because the report of IBS-type symptoms is as high as 39% in patients with IBD, yoga can be considered as a helpful adjuvant therapy for patients with IBD [87, 88]. However, further robust well-designed research studies are needed to understand the effect yoga may have on objective inflammatory markers, calprotectin, disease activity, etc. in patients with IBD.

Mindfulness and Meditation

The goal of mindfulness and meditation therapies is to increase non-judgmental, purposeful, moment-to-moment awareness of one's thoughts, feelings, bodily sensations and surrounding environment, often practiced via breathing, movement, and meditation exercises [89]. The two most commonly studied mindfulness modalities in IBD are Mindfulness-based stress reduction (MBSR) and Mindfulness-based cognitive therapy (MBCT). MBSR was developed by John Kabat-Zinn at the University of Massachusetts Medical Center in 1970 and consists of an 8-week evidence-based group program taught by a certified teacher. Mindfulness-based cognitive therapy is similar to MBSR and developed by Zindel Segal and colleagues; it is also in 8-week group program that integrates mindfulness and techniques from cognitive therapy [90].

MBSR is beneficial in children with anxiety, depression, and other chronic disease states [89]. Jedel et al. conducted one of the first randomized controlled trials in 2014 examining MBSR in comparison with a mind-body course designed by the study group in 55 adults with UC in remission [91]. The study showed that MBSR was feasible and acceptable but did not impact psychological or disease outcomes, including calprotectin and inflammatory cytokines, compared to the control course. However, among those who flared during the study period, those assigned to the MBSR

group reported a significantly higher quality of life than the control group ($p = 0.0010$) [91]. Feasibility and acceptability of MBSR were again demonstrated in a 2016 randomized trial of 60 adults with IBD conducted by Nielson et al. Significant improvements in anxiety ($p < 0.05$), depression ($p < 0.05$), quality of life ($p < 0.01$), and mindfulness ($p < 0.01$) were reported in comparison to the control group of usual standard medical care immediately post-intervention and significant reductions in depression and improvements in quality of life and mindfulness were sustained at 6 months post intervention [92]. MBCT was studied by Schoultz et al., in a wait-list control study in 44 adults with IBD and found that there were significant improvements in depression, anxiety, and dispositional mindfulness among those who underwent MBCT as opposed to those in the wait-list control group [93, 94].

To date, there is only one pilot study in pediatrics published by Kohut et al., studying mindfulness in adolescents with IBD. They investigated the feasibility and acceptability of an 8-week mindfulness-based intervention, consisting of 2-h in-person group classes. The intervention, labeled MBI-A (mindfulness-based group intervention for adolescents), was developed by members of the study team initially for chronic pain patients and later adapted for youth with IBD and consisted of skill building and mindfulness meditations, exercises, and activities [95]. The mixed-methods study included three groups (16 total participants) studied over 18 months. Significant improvement was found in emotional functioning related to IBD pre- and post-intervention, but overall mean disease activity actually increased though the majority of the participants had mild disease activity [96]. The study did not have sufficient power to detect the statistical significance in their secondary outcomes, which consisted of various questionnaires measuring disease activity, HRQOL, anxiety, depression, self-efficacy, mindfulness, pain acceptance, and social support [96]. While the intervention was well accepted by participants, the authors suggested that feasibility could have been improved by an online delivery method, shorter class time (90 min versus 120 min), and timing of the class in relation to the academic school year [96].

It is important to note that many of the mindfulness studies in IBD are of small populations, so the efficacy is not generalizable. Further studies with more rigorous methodology with higher sample sizes and cohesive outcome measures are necessary in the future.

Acupuncture and Moxibustion

Acupuncture and moxibustion are two forms of Traditional Chinese Medicine (TCM) that have limited data in human studies, but are commonly used. Acupuncture is a modality used to stimulate certain points in the body based on the patient's symptoms as described by TCM, usually with the use of thin needles, to help activate various energy pathways in the body. Acupuncture has been shown to reduce various pro-inflammatory cytokines in murine models with colitis such as TNF-alpha, IL-6, IL-8 [28–30] and increased levels of anti-inflammatory cytokines such as IL-10 and IL-8 [97, 98] in various mouse models. However, the generalizability of this data is limited as the mechanisms used to induce colitis in these mouse models are heterogeneous.

Frequently, moxibustion is used in conjunction with acupuncture as a treatment modality in TCM. Moxibustion is performed by burning dried mugwort (moxa) root in cones or sticks and placing them at certain points on the body, depending on the patient's ailment, like in acupuncture [99]. Joos, et al., published randomized control trials in both UC and CD in comparing control interventions (sham acupuncture and moxibustion) to true acupuncture and moxibustion. For both the UC ($n = 29$, treatment group, $n = 15$) and CD ($n = 51$, treatment group, $n = 27$) populations, baseline disease activity was defined as mild to moderate [100, 101]. In both studies, the treatment groups had a significant mean reduction in disease activity scores as measured by CAI (colitis activity index) and CDAI (Crohn disease activity index), respectively, for UC and CD groups. However, it is important to note that while a difference between the mean reductions between treatment and control groups in both studies was statistically significant, there was also a mean reduction in disease activity in both control (or sham acupuncture/moxibustion) groups. This suggests that there was a large placebo effect in both the studies for these interventions [100, 101].

Exercise and Sleep

There is a growing body of evidence that physical exercise and sleep can positively impact mood, function, and quality of life in patients with IBD. While the quality of the studies looking at various exercise interventions for IBD is mixed and the duration of the interventions was short, the patients who participated in these studies showed an increase in fitness, a decrease in stress and anxiety induced by IBD, and an increased bone mineral density [102]. Long-term moderate-intensity exercise reduced inflammatory markers in patients with IBD [103], but on the other hand, there is some evidence that exercise can also transiently increase pro-inflammatory cytokines and cause mild systemic inflammation that could exacerbate gastrointestinal symptoms [104]. Sleep disturbance is a common occurrence in patients with IBD with one study finding that 67.5% of 166 patients with IBD suffered a sleep disturbance, not associated with active or inactive IBD but rather associated with their psychological state [105–107]. Overall, the importance

of a well-balanced lifestyle with good sleep hygiene and exercise should be encouraged in patients with IBD.

Conclusion

Conventional treatment for IBD focuses on induction or maintenance of remission and symptom management primarily through medication administration. No therapy is curative. The physical and psychological effects of this chronic disease have an enduring impact on HRQOL and may be refractory to treatment. Since conventional treatment may have untoward health effects, parents and patients may seek opportunities to gain a sense of control over the child's disease and therefore may seek out Integrative Health therapies.

Clinicians should be aware of the prevalence of complementary and Integrative Health modality utilization in the pediatric IBD population, parents' receptivity toward these modalities as adjuvant therapies, and the reticence to disclose utilization. Concurrent use of biologically based Integrative therapies, such as herbals and supplements, and prescription medication is common and may cause untoward drug interactions. While the survey literature on IBD IH therapy prevalence rates is robust, there is a dearth of high-quality studies assessing the safety and efficacy of these modalities. Randomized controlled trials are infrequently employed. The methodologic quality of small pilot studies limits the extrapolation of study conclusions. Evidence to support the use of biologically based therapies is still lacking. Stronger randomized control trials are needed in pediatrics to support their use.

Pediatric gastroenterologists should routinely inquire about complementary and integrative therapy use and maintain open, nonjudgmental channels of communication about modality use. The maintenance of a cursory level of understanding and awareness of Integrative Health modalities, including knowledge of efficacy, interactions, and contraindications, is essential to ensure patient safety.

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Part V

Surgical Therapy

39 Management of Intraabdominal Complications of Inflammatory Bowel Disease

Elizabeth C. Maxwell, Peter Mattei, and Andrew B. Grossman

Introduction

While the initial phenotype of Crohn disease (CD) is most commonly inflammatory in pediatric patients, the pathogenesis is characterized by transmural inflammation, which can lead to complications such as fistulae, bowel perforation, and intra-abdominal and pelvic abscesses. This chapter will describe the evaluation for patients with suspected intraabdominal complications of CD and considerations for management, with a focus on intraabdominal and pelvic abscess resulting from internal penetrating disease. In particular, medical and surgical options for treatment will be compared. Surgical emergencies and elective procedures in CD for the indications of perforation, obstruction, and stricture are discussed in more detail in Chap. 41. The approach for managing the penetrating perianal disease is covered in Chap. 35. Surgical treatment of ulcerative colitis (UC) is the focus of Chap. 42, but the complication of toxic megacolon will also be described here.

Intraabdominal and Pelvic Abscess

It is estimated that 10–28% of patients with CD will develop intraabdominal or pelvic abscess, and in some patients, abscess is part of the initial disease presentation [1]. Once recognized, the key principles of treatment are source control of the infection and, if possible, drainage. Traditionally, intraabdominal and pelvic abscesses were treated with surgical drainage, often involving bowel resection and the creation of an ostomy (either temporary or permanent) in an acutely ill patient [1]. More recent evidence has shown that antibiotics and percutaneous drainage, if feasible, may have a more favorable outcome compared to surgery as initial therapy, though this issue continues to be debated. Other treatment considerations include the role of disease-specific medical therapies to control underlying inflammatory disease in the setting of active infection, and how to best optimize nutritional status in these patients.

Pathogenesis

Abscesses tend to form in dependent areas including the paracolic gutters, pelvis, subdiaphragmatic region, and in between loops of bowel [1]. Figure 39.1 illustrates the progression from mucosal ulceration to penetrating disease with abscess formation. Alternatively, abscesses can also be formed via hematologic seeding from a remote section of the diseased bowel or from contamination at the time of bowel surgery [1]. Approximately half of the CD-related abscesses are spontaneous and half result after bowel surgery [1]. Culture from pelvic and intraabdominal abscesses may not always be obtained, but one report found that at least 80% of abscesses are comprised of mixed bacterial pathogens [1]. They may also be sterile and may contain fungal organisms, particularly in the case of immunosuppressed patients and in the setting of chronic abscess [1].

Evaluation

The most common presenting symptoms and signs in patients with the internal penetrating disease include abdominal pain (84%), fever (49%), nausea and vomiting (41%), diarrhea (25%), and the presence of a fistula (14%) [2]. There may also be features of partial bowel obstruction, including a colicky nature of the pain, vomiting, abdominal distention, and/or intermittent constipation [3]. Additional symptoms may

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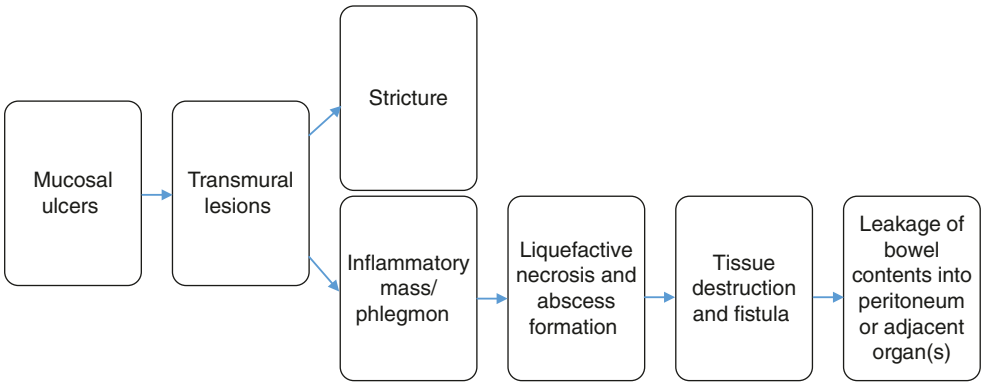

Fig. 39.1 Proposed mechanism of pathogenesis, of internal penetrating Crohn disease [2]

be present depending on the nature and location of the abscess. The right lower quadrant is the most common location of an abscess, followed by the pelvis [4]. If an abscess is adjacent to the bladder, a patient may have urinary symptoms, while local irritation of the psoas muscle from an abscess in the distal ileal region can present as a refusal to walk or bear weight [2].

Physical examination may demonstrate localized tenderness and an abdominal mass may be palpable. Peritoneal signs such as rebound tenderness and involuntary guarding may also be present. Abscess in the right lower quadrant secondary to ileal disease can be difficult to distinguish from acute appendicitis on physical examination. A pelvic abscess may be palpable as a tender bulge on the rectal exam. In a patient with known CD, the development of intraabdominal abscess may also be coupled with other signs of active diseases, such as poor growth or weight loss, extraintestinal manifestations including oral ulcers or arthritis, or perianal findings such as tags or fistulae [2].

Laboratory evaluation will not be specific for an intraabdominal process, but there may be abnormalities in complete blood count (leukocytosis, anemia, thrombocytosis), complete metabolic panel (electrolyte disturbances, hypoalbuminemia), and elevation of C-reactive protein and/or erythrocyte sedimentation rate. It can be useful to compare these values to previous results to establish a trend or deterioration from a patient's baseline. In patients with abdominal pain and vomiting, liver and pancreatic enzymes should be investigated, and urinalysis and urine culture should be obtained in any patient with urinary symptoms. Blood cultures should be obtained in any febrile and acutely ill appearing patient [2].

Cross-sectional imaging is a key component in the evaluation of patients with a suspected intraabdominal complication of CD [2]. Magnetic resonance enterography (MRE) is often considered the optimal imaging modality in pediatrics because it is radiation-sparing (Fig. 39.2). However, in the acutely ill child, standard computed tomography (CT) may be the most readily available and appropriate option [5]. Cross-sectional imaging is able to demonstrate bowel wall thickening, bowel dilation, and mesenteric fat proliferation. Both CT and MR can detect the presence of fistulae, particularly if utilizing oral contrast and performing full MRE or CT enterography (CTE) [2]. Bowel ultrasound (US), which is also radiation-sparing, can be useful in certain clinical scenarios as well, particularly serial monitoring for improvement or disease progression as well as detection of phlegmon or an intra-abdominal abscess if performed and interpreted by an experienced team (Fig. 39.3) [5, 6]. The administration of enteral contrast may improve the quality of bowel US [7]. US can be limited by bowel gas, which is not an issue with CT or MR [2]. Lastly, magnetic resonance imaging (MRI) of the pelvis is usually the modality of choice to evaluate complicated perianal diseases [8]. One challenge is successfully being able to distinguish a phlegmon, which is an inflammatory mass, from a pus-filled abscess cavity, particularly in cases of extensive bowel inflammation. CT, MR, and ultrasound may allow for this differentiation using the presence of gas, fluid, and/or color Doppler signals, though, without these clear features, discerning abscess and phlegmon can be difficult in practice [9]. This can be a clinically critical delineation, as phlegmons cannot usually be drained, while drainage is a mainstay of abscess treatment, as described later in this chapter.

The role of endoscopy in the evaluation of intraabdominal abscess has not been well defined in the literature. In general, endoscopy can be useful to better define overall disease activity, assess for infectious complications of disease or immunosuppression, such as cytomegalovirus, and may provide guidance for overall disease management, particularly when surgery is being considered [2]. However, there is concern regarding the higher rate of complications of endoscopic assessment in the setting of an active abscess secondary to penetrating disease. The optimal timing of endoscopy following treatment of an intraabdominal abscess is also debated, with most sources citing a window of 4–6 weeks after therapy as the ideal interval [1].

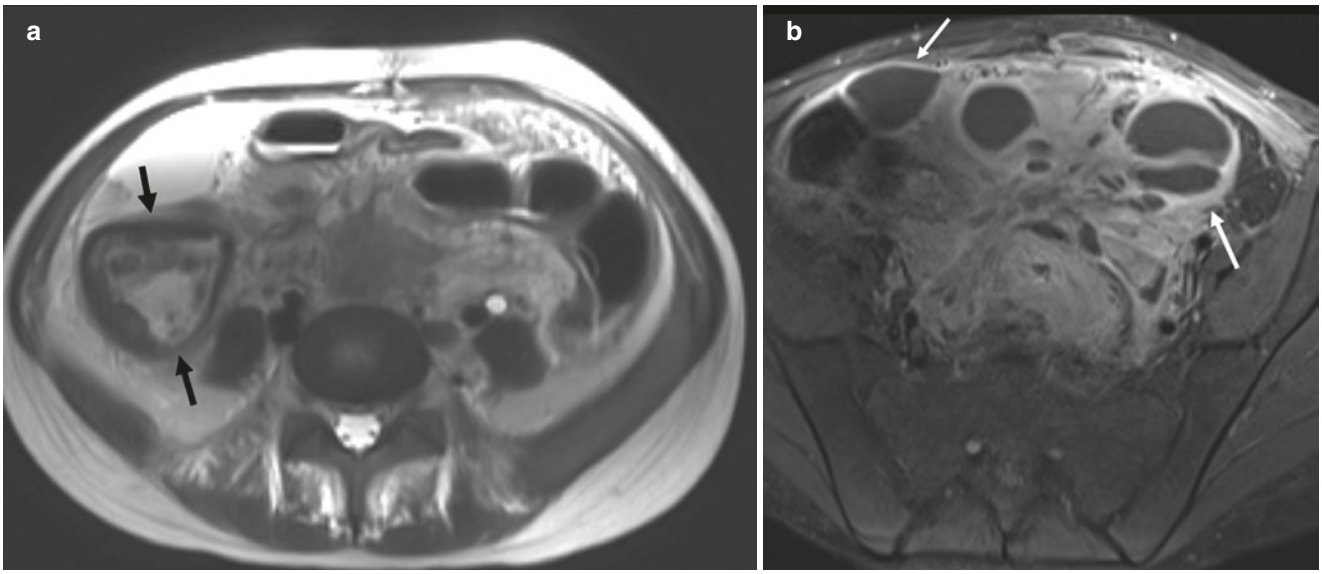

Fig. 39.2 15-year-old female with history of Crohn disease initially evaluated at an outside hospital presenting with prolonged IBD flare and significant weight loss. (**a**) Axial T2-Weighted HASTE sequence from an MR enterography shows marked thickening of the cecum in the right upper quadrant (arrows). (**b**) Axial post contrast t1-weighted image shows marked enhancement and thickening of other segments of the colon in the right and left abdomen (arrows). *Images courtesy of Sudha Anupindi MD, Children's Hospital of Philadelphia*

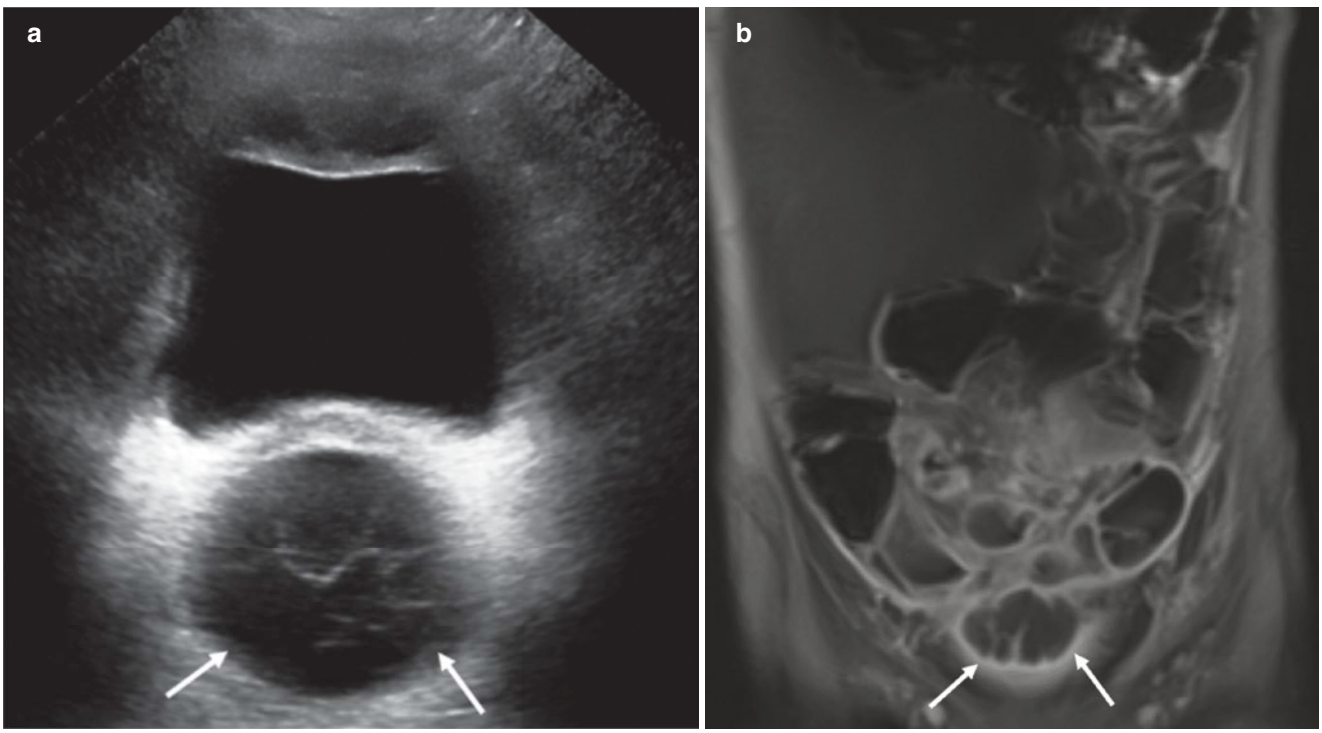

Fig. 39.3 15-year-old female with history of Crohn disease presenting with prolonged symptoms and significant weight loss. (**a**) Transverse ultrasound image shows a complex collection (arrows) representing an abscess in the pelvis behind the bladder. (**b**) The same abscess is seen on the correlative coronal post-contrast T1-weighted image from an MR enterography (arrows). *Images courtesy of Sudha Anupindi MD, Children's Hospital of Philadelphia*

Treatment

Management of intraabdominal or pelvic abscess as a result of internal penetrating CD involves antimicrobial coverage and drainage of the abscess if possible either by percutaneous or surgical approach [10].

Antimicrobial Therapy

Antimicrobial coverage is indicated in all cases of intraabdominal and pelvic abscess and is aimed at enteric gram-negative aerobic and facultative bacilli, enteric gram-positive *Streptococci*, and obligate anaerobic bacilli [1]. Coverage should also target nosocomial pathogens, as many patients with CD and abscess will have had multiple exposures to the health care system [2]. Initial broad spectrum options include a carbapenem, a B-lactam/B-lactamase-inhibitor combination, or an advanced generation cephalosporin, plus metronidazole [2]. Narrowing of coverage may be possible if abscess material is obtained for culture and sensitivity. Consulting with an infectious disease specialist can provide additional guidance related to local resistance patterns and other special considerations such as recent antibiotic exposure [2].

Route of administration of antimicrobials has not been directly compared in the literature, but the decision regarding parenteral versus oral antibiotics is usually determined based on the clinical course and severity [1]. Duration of therapy depends primarily on the ability to successfully drain the collection. Antibiotics are usually continued for 3–7 days after successful drainage [11]. Longer courses are required if the abscess cannot be drained adequately [1].

Some adult studies have shown that antibiotics alone, without percutaneous or operative drainage, can be successful in the treatment of some CD-related intraabdominal abscesses. Cases that may be more likely to respond to medical management alone include abscesses of small size (<3 cm), absence of associated fistula(e), and patients who are immunomodulator-naïve [12–15]. A recent single-center retrospective study of pediatric patients compared medical management vs percutaneous drainage and found that by 1 year follow-up, 67% of the medically managed group and 60% of those managed with percutaneous drainage went on to have surgery [16]. Despite these described associations in several studies, there are no clear indications for which patients will respond to this approach [1]. The recurrence rate after medical treatment for an intraabdominal abscess in CD ranges from 37 to 50% [1].

Percutaneous Interventional Drainage

Percutaneous abscess drainage is performed, most commonly by interventional radiologists, by positioning a catheter or drain into the abscess cavity guided by imaging techniques such as ultrasound or CT scan [12]. In the past, this technique was avoided because of the perceived risk of creating a post-drainage enterocutaneous fistula, but more recent studies have shown favorable results in certain clinical scenarios [2], particularly since the advent of biologic therapies to treat CD [1]. Percutaneous drainage is done in conjunction with antibiotics and can either serve as definitive therapy or as an intended bridge therapy prior to a surgical procedure [12]. There are also cases of failure of percutaneous drainage to fully treat the abscess where surgery is required [12].

Factors related to the success of percutaneous drainage have been described to include abscess size, number, etiology, location, presence of fistula, and proximity to vital structures [12], though studies have shown mixed results when analyzing these variables. In general, a unilocular, well-defined cavity, >2–3 cm in size, without direct contact with major vessels or organs, is most likely to be successfully drained [17]. The expectation is that clinical improvement should be seen within 3–5 days after drain placement, with decreasing volumes of drainage [12]. When drainage decreases to <10 mL/day (5 mL/day in neonates), and the patient is clinically improved, the drain can be removed [2, 18]. If clinical improvement is not seen, reimaging is indicated to reassess if abscess has been drained adequately. If it has not, repositioning of the drain or a plan for surgical intervention usually follows [12].

Persistent drainage raises the concern for fistula formation, in which case an abcessogram can be performed using injected contrast [2]. Studies examining continued treatment with the percutaneous drain combined with medical therapy, bowel rest, and parenteral nutrition have reported varying success in addressing these fistulae [19–21].

Rypens and colleagues published a retrospective series of 14 pediatric patients with CD and intraabdominal or pelvic abscess who underwent percutaneous abscess drainage as an initial intervention. All but two patients eventually had the affected bowel segment resected, though the authors indicated definitive surgical management was the preferred therapy at their institution, thus percutaneous drainage had not been intended to be definitive therapy. They concluded that following the percutaneous drainage, the patients had improved clinical status prior to surgery, which was thought to contribute to a less invasive and technically easier surgical procedure [22]. Another single center retrospective study of 25 pediatric patients with CD who underwent percutaneous drainage abscess drainage found 76% of cases to be clinically successful, defined as no surgery within 1 year of drainage OR surgical resection following drainage with no residual abscess at the time of surgery or on preoperative imaging [23]. Other studies, which were not designed to examine this exact question, have shown reduced postoperative complications in patients who have percutaneous drainage pre-operatively [24–26].

Percutaneous drainage is a relatively safe procedure [17]. Complications have been reported in approximately 5–11% of cases, and include sepsis, small bowel fistulae, colon perforation, and death [17, 22]. Minor complications such as bacteremia or infection at the catheter site have been reported in about 3% of cases [17].

Surgical Intervention

Traditionally, surgical drainage had been the primary treatment option for intraabdominal abscesses in CD [12]. Surgical drainage of intraabdominal or pelvic abscess involves exploration of the region, evacuation of all abscess contents, irrigation and debridement of the abscess cavity, and commonly resection of the affected bowel [1]. Importantly, surgical resection of diseased bowel is not considered curative in Crohn disease as post-operative recurrence of disease, particularly at the surgical anastomosis, is common. Surgical drainage can be associated with significant morbidity, particularly when it is performed in ill patients. Potential complications include wound infections, small bowel fistulae, and anastomotic leakage [12]. Often ostomy creation is indicated or cannot be avoided [12].

As will be discussed in more detail in the following section, surgical intervention may be necessary when medical and percutaneous drainage measures are unsuccessful in achieving abscess resolution, and in some cases, maybe the primary intervention selected along with antimicrobial therapy and CD-specific treatment, based on a variety of factors [2]. General principles of surgical management include preservation of intestinal length and resection with macroscopically disease-free margins [2]. Laparoscopy has become the preferred approach over time due to the benefits of shorter post-operative recovery time, decreased wound-related complications, formation of fewer intraabdominal adhesions, and better cosmesis when compared to an open approach [27]. Laparotomy, however, is still considered a safe and reasonable approach in patients who cannot tolerate or have too many adhesions from prior surgery to allow the insufflation of the abdomen with carbon dioxide needed for laparoscopy [2]. Diverting ileostomy or colostomy may be necessary when there is significant intraabdominal soilage, inflammatory thickening of the intestinal wall, and intraoperative instability precluding safe additional operating time to construct an anastomosis [2]. Ostomy creation may be temporary.

Complication rates vary in the literature but have been reported to be as high as 25% [28] and may be influenced by several factors, including preoperative percutaneous drainage, discussed in more detail in the next section. Otherwise, weight loss, the number of structures involved in the inflammatory mass, peritonitis and free air, smoking, and previous intestinal surgery have also been associated with post-operative complications [29]. Nutritional status and decreasing steroid dose may reduce surgical complication rates [2], and are discussed in more detail in later sections of this chapter.

Percutaneous Versus Surgical Drainage

Drainage in conjunction with antibiotic therapy should be considered for abscesses >3 cm or with other features associated with the likelihood of failing medical therapy alone with the percutaneous approach being regarded as the first line option if feasible [10]. Factors to consider when choosing drainage modality include patient stability, complexity, size, location, accessibility of the abscess, number of abscesses, as well as patient history including prior surgeries and therapies [10]. Abscesses under or near overlying organs or between loops of bowel may not be amenable to safe IR drainage therefore may require surgical drainage [10].

Several studies have indicated success with percutaneous drainage as definitive management of intraabdominal abscesses [19, 30–33], though a larger meta-analysis by He and colleagues found that over one-third of patients treated by percutaneous drainage as the intended definitive therapy did ultimately require surgery [34]. Even when eventual surgery is needed, several studies suggest preoperative percutaneous drainage is beneficial, contributing to less surgical technical difficulty and decreased risk of ostomy creation [1, 22].

Regarding safety, several studies have reported increased complication rates in patients undergoing surgical drainage compared to percutaneous drainage, specifically longer lengths of stay in the hospital [35] and increased need for ostomy creation [34, 36]. Another study noted fewer postoperative complications in patients who first underwent percutaneous abscess drainage, including anastomotic leaks, post-operative abscess formation, intestinal fistula, leaks of intestinal stumps, and leaks of sutured secondary internal fistulae, though these trends (25% vs 11% complication rates) did not reach statistical significance [29]. Again, there are potential biases in these analyses as more severe illness and disability may be present in the patients who were treated primarily surgically [35]. In the large recent meta-analysis by He and colleagues, the initial surgery was associated with a significantly higher overall complication rate compared to initial percutaneous drainage. However, there was no difference in rates of specific complications such as enterocutaneous fistula, wound infection, anastomotic leak, postoperative abscess, and recurrent abscess [34].

To date, randomized controlled trials comparing the two approaches are lacking [1, 12]. Several consensus guidelines including the North American Society for Pediatric

Gastroenterology, Hepatology, and Nutrition (NASPGHAN) [2] and the American College of Radiology [14, 15] have recommended percutaneous drainage as an initial step, provided it is technically feasible [12]. When abscesses are not amenable to percutaneous drainage because of size or location or persist despite percutaneous drainage and antimicrobial therapy, surgical drainage is warranted [12].

Treatment of Phlegmon (Inflammatory Mass)

A phlegmon is an ill-defined inflammatory mass that can form as a result of a sealed-off perforation. Phlegmons in CD typically involve the mesentery and adjacent loops of the bowel. Though it is known that penetrating disease affects 40% of CD patients within the first 5 years of diagnosis, there are no specific data related to the prevalence of phlegmons [37]. One review of about 350 adult patients with CD who had a median duration of disease of about 10 years reported penetrating disease in 20% and phlegmon in 3.4% using CTE [38]. Treatment has traditionally included antibiotics, bowel rest, drainage of an associated abscess collection if present, and eventually surgical resection of the mass. CD-specific medications may also play an important therapeutic role as described in the next section [37]. In the future, radiologic terminology may be moving away from the term "phlegmon," to more illustrative descriptions of findings, such as "inflammatory mass with or without abscess."

Crohn Disease-Specific Therapy

In addition to antimicrobials and drainage of abscess, CD-specific therapy should also be considered as part of the management plan. Aminosalicylates are not effective in the treatment of internal penetrating CD [2]. Corticosteroids should be avoided in the presence of known fistulizing disease because of the increased risk of abscess formation [39]. If a patient is already on steroids at the time an abscess is diagnosed, there does not seem to be additional morbidity associated with continuing the steroids if the abscess is otherwise being addressed [1]. Weaning steroids to a lower dose may reduce the risk of perioperative complications when surgical intervention is required [28, 40], with some recommending reduction to less than 20 mg daily [2, 24].

There are no randomized prospective clinical trials examining the efficacy and safety of biologic agents (infliximab, adalimumab, vedolizumab, ustikinumab), small molecules (tofacitinib) or immunomodulators (6-mercaptopurine, azathioprine, methotrexate) in the setting of acute abscess in CD. Post-hoc analysis of the ACCENT II study explored whether fistula-related abscess formation was impacted by exposure to infliximab; no increased formation of abscess was found in the group treated with infliximab compared to placebo [41]. Nguyen and colleagues examined the role of initiation of anti-TNFα therapy after initial management of intraabdominal abscess in 95 adult patients, 55 of whom underwent image-guided percutaneous drainage and 40 of whom had laparotomy. In the patients who underwent laparotomy as initial treatment of abscess, 30% were not on any therapy for CD at the time. After treatment for the abscess, treatment with an anti-TNFα agent either alone or in combination with a thiopurine was protective against abscess recurrence compared to no therapy [35]. The small retrospective pediatric study by Pugmire et al. also found early resumption of immunosuppressive therapy (within 8 weeks after drainage) to be associated with statistically significant clinical success [23]. There is also data in adults to suggest that 30% of fistulas are partially or completely closed on immunomodulator therapy (azathioprine, 6-mercaptopurine, methotrexate), but require ongoing treatment to maintain closure [39, 42]. Taken together, expert opinion based on this data indicates that immunomodulators and/or biologic agents can be given soon after drainage of the abscess and are beneficial [1].

Cullen et al. retrospectively described the initiation of anti-TNFα therapy following antibiotics in 13 adult patients with CD and abdominal phlegmon [37]. Abscess was detected by imaging in 12 patients initially, but had resolved or was drained prior to initiation of anti-TNFα in all but 5 patients who had small undrainable collections. At a mean of 2.3 years of follow-up, no patients developed an infection or new abscess. Two patients eventually had surgery after failure of anti-TNFα therapy, and 10 of the 11 patients who remained on anti-TNFα therapy were asymptomatic at the conclusion of the study. Although this was a small study in adult patients, the results suggest that initiation of anti-TNFα therapy after antibiotics in patients with intestinal phlegmon can be safe and successful [37].

Nutritional Considerations

Nutritional support and rehabilitation are important in all patients with CD, particularly those with complications of the disease and when surgery is being considered. Nutritional status is one of the few modifiable risk factors related to surgical outcomes and should be optimized whenever possible before proceeding to surgery [2]. Historical and daily weights should be obtained and compared, and serum albumin and prealbumin monitored. Bowel rest and support with total parental nutrition may be considered until drainage of the abscess can be achieved. Once the abscess is drained without evidence of reaccumulation, enteral feeds can be initiated and are usually tolerated [2]. The presence of an actively flowing fistula may be another indication to select

bowel rest over enteral feedings [2]. Some studies, however, have shown a benefit to nutritional rehabilitation with enteral feedings in the setting of internal penetrating disease [25], and exclusive enteral nutrition is a proven therapy to induce remission in CD [43].

Summary

Internal penetrating disease represents a complicated type of CD and leads to several possible complications, including fistulae, phlegmon, and abscess. There are many factors that determine the optimal management approach for each individual patient, including overall clinical status and risk for deterioration, the severity of underlying disease, nutritional status, and features of the collection including size and location. Source control of infection using antimicrobial agents and drainage of the abscess when possible are the mainstays of therapy. CD-specific therapy and nutritional optimization are also important aspects of management in these patients.

Other Complications from Internal Penetrating CD

Perforation

Spontaneous free perforation of the small intestine in CD is rare, with a quoted prevalence of 1–3% in adult patients with Crohn disease over their disease course [44]. One series of 1000 consecutive adult patients found 15 cases of perforation over the course of 20 years. Spontaneous free perforation was the presenting feature leading to CD diagnosis in 9 of those 15 patients (60%) [45]. An older case series in 1415 adult patients with CD over 23 years found a similar incidence of spontaneous free perforation in 21 (1.5%) patients; this series included 10 patients with small bowel perforation, 10 with colonic perforation, and one patient with perforation in both small bowel and colon [46]. There are no large series of pediatric patients with CD and spontaneous intestinal perforation but it has been described in case reports [47]. Perforation is managed operatively, which is urgent in the setting of peritonitis to prevent sepsis. Typically the diseased area of the bowel is resected and primary anastomosis is attempted if deemed safe, or a diverting ostomy, which is often temporary, is performed [45].

Small Bowel Obstruction

Fibrostenotic CD usually presents with obstructive symptoms. The most common location for stricture is the ileocecal region. Obstructive symptoms related to narrowing and stricture formation may be aggravated by superimposed edema from active inflammation [48]. Therefore, a trial of medical management with corticosteroids may be attempted to evaluate whether the obstruction can be relieved without surgery [49]. It was previously thought that pre-existing bowel stenosis was a contraindication for therapy with anti-TNFα agents, but further study has demonstrated that some patients with mixed strictures (both fibrotic and inflammatory components) can benefit from infliximab therapy [50–52].

If medical management is unsuccessful, balloon dilation, stricturoplasty, or surgical resection are considered [48]. One large meta-analysis of 13 studies of endoscopic balloon dilation of mostly post-surgical strictures reported a technical success rate of 86% [53]. In that study, long-term clinical efficacy was 58%, with a mean follow-up of 33 months and a major complication rate of 2%. Short strictures of ≤4 cm were most likely to avoid the need for surgery. Stricturoplasty is a surgical intervention which increases bowel diameter without any resection. It is technically feasible for short strictures [48]. Compared to resection, results are comparable when analyzing the resolution of obstructive symptoms, reoperation rate, and time to recurrence of symptoms [54]. Stricturoplasty may be performed in conjunction with a bowel resection [54]. Limited resection for stenotic CD is effective in relieving obstruction but multiple respective bowel surgeries are avoided if possible, to reduce the risk of short bowel syndrome [48].

Toxic Megacolon

Toxic megacolon is a serious complication of IBD and is a syndrome of systemic toxicity and colonic dilation (>6 cm) in the setting of active colitis with high morbidity and mortality. Toxic megacolon is most often seen in IBD patients with UC, though it has been described in Crohn colitis, as well as other non-IBD entities such as Hirschsprung disease and *Clostridium difficile* infection [55]. Toxic megacolon in pediatric IBD is rare, but the true incidence is not known. A small case-control study of ten pediatric IBD patients with toxic megacolon identified diagnostic features of fever, tachycardia, dehydration, and electrolyte abnormalities to be significantly more common in patients with toxic megacolon compared with hospitalized age-matched controls with UC. Also, a mean luminal transverse colon diameter of ≥56 mm was highly suggestive of toxic megacolon in children. Altered mental status and hypovolemic shock have been described more commonly in adults with toxic megacolon than in pediatric cases [56]. New narcotic requirements in a patient admitted with acute severe colitis can be a red flag sign of evolving toxic megacolon. This and other suggestive symptoms should prompt evaluation of toxic megacolon with an abdominal x-ray (Fig. 39.4).

The goal of the treatment of toxic megacolon is to reduce colitis and the likelihood of colonic perforation [55].

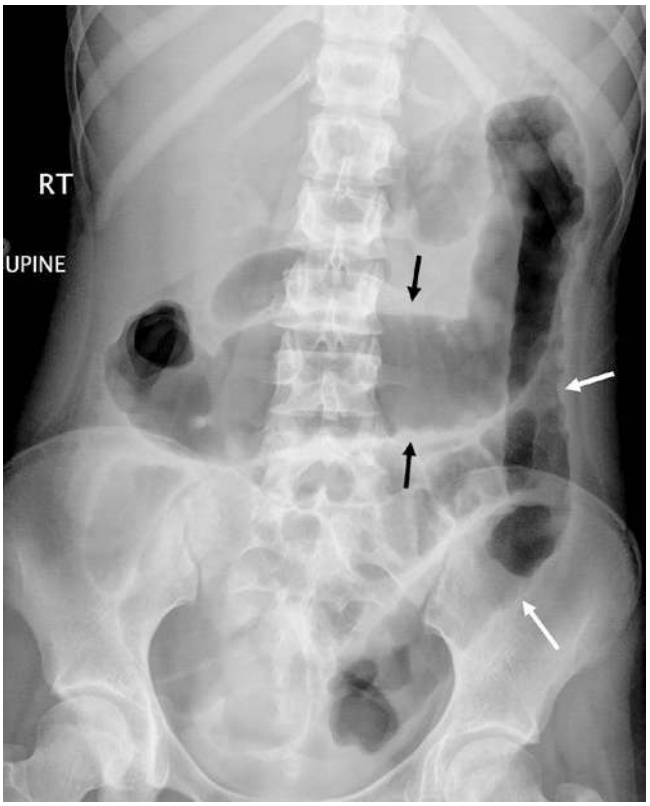

Fig. 39.4 15 year old female with ulcerative colitis: Supine radiograph of the abdomen shows dilated featureless, ahaustral transverse and left colon to sigmoid with thumb printing (white arrows) indicative of submucosal edema or hemorrhage. In addition the transverse colon is disproportionately dilated suggestive of toxic megacolon (black arrows). *Images courtesy of Sudha Anupindi MD, Children's Hospital of Philadelphia*

Immediate surgical consultation should be initiated at the time toxic megacolon is suspected. Medical therapy includes complete bowel rest and NG tube and/or rectal tube for decompression. Patients are frequently monitored in the ICU setting for serial exams and should have laboratory studies (complete blood count, electrolytes) and abdominal radiographs reviewed every 12 h, initially. IV corticosteroids can be used to reduce inflammation and broad-spectrum antibiotics are recommended to decrease the risk of septic complications. Anticholinergic and narcotic medications should be discontinued. Resolution of toxic appearance, decreased fluid and transfusion requirement, improvement in colonic dilation and abdominal distention, and improved laboratory derangements are signs that toxic megacolon is resolving. Absolute indications for surgery are free perforation, massive hemorrhage, increasing transfusion requirements, progression of colonic dilation, and/or worsening toxicity. Subtotal colectomy with end ileostomy is the surgical procedure of choice in urgent or emergent situations [55]. There is a paucity of data regarding the outcome of toxic megacolon for pediatric inflammatory bowel disease; 7 of 10 patients in the aforementioned case series underwent colectomy [56].

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Surgical Management of Crohn Disease in Children

40

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Introduction

Surgery plays an important role in the treatment of Crohn disease. Crohn disease has a major impact on the quality of life in the pediatric population, and, unfortunately, despite the dramatic improvements in medical therapies, 70–80% of patients who carry the diagnosis of Crohn disease undergo some type of surgical procedure at some point during the course of their disease [1–4]. The principles regarding surgical intervention are similar in the pediatric population with the caveat that 50% of patients who undergo an initial operative intervention will require additional surgery in the future. The indications for surgery have evolved over time with a trend toward less invasive procedures and fewer emergency surgery operations because of an acute complication of the disease [5]. Crohn disease cannot be cured in the operating room so procedures are primarily employed to treat complications of the disease including obstruction, perforation, abscess, fistulas, and medically refractory disease. Strategies are employed to preserve intestinal length and minimize scarring. The primary goals of management are aimed at (1) controlling mechanical complications or resecting refractory disease, (2) inducing and maintaining remission of disease, (3) promoting growth and development and (4) preventing short and long-term adverse events. Surgery is not a curative procedure, but, the resolution of disease manifestations can have a tremendous impact on the quality of life in these patients.

As with many diseases in children, studies specific to the pediatric population are not always available making it necessary to extrapolate the results of adult series when considering treatment options for younger patients. Although some differences between the patient populations exist, the philosophy remains the same. Surgical intervention is an integral part of the management of patients with Crohn disease but should be invoked judiciously with a collaborative approach with input from the surgeon, the gastroenterologist, radiologist and pathologist to promote informed discussions with the patient and their family to ultimately aim to avoid the potential for long-term consequences.

History of Surgical Therapy

When Crohn disease was first described in the early 1930s, the disease was thought to be isolated to the terminal ileum [6], and surgical therapy typically involved resection of the terminal ileum with an ileocolic anastomosis. In this era, before the development of antibiotics and sophisticated electrolyte replacement and nutritional support, the mortality for this operation was 25% [7]. In an effort to improve the surgical outcomes and reduce mortality, many surgeons moved to a two-stage approach in which the diseased segment of the bowel was bypassed with an ileocolostomy leaving the diseased segment of the terminal ileum as a blind pouch emptying into the cecum. Months later the patient was returned to the operating room for resection of the diseased segment. Although this approach required a second trip to the operating room to resect the bypassed segment, surgical mortality was substantially reduced. As experience with this approach increased, it became clear that the bypassed segment often improved and ceased causing problems. Many surgeons subsequently abandoned resection of the diseased segment altogether resulting in a dramatic improvement in surgical mortality. In one study mortality in 145 patients was 16% for one-stage operations, 12% for two-stage operations, and 0% in ileotransverse colostomy with exclusion [8]. Unfortunately, it became apparent that there were long-term consequences to bypassing the diseased segment and right side of the colon and leaving it in situ. The function of normal colonic tissue was sacrificed and increased risks of malignant changes in the small bowel were reported [9].

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Fortunately, with improvements in perioperative surgical care, the risk of a primary definitive procedure has been reduced to the point where it has once again become the operation of the first choice and is associated with extremely low mortality rates.

Prognostic Indicators and Operative Indications

The indications for surgical intervention in Crohn disease are varied and often patient-specific, especially in children. However, the principles regarding surgical intervention are similar regardless of the age of the patient. The goal of an operation for Crohn disease is to control one of the many mechanical complications resulting from the inflammatory process in the intestine, and there are many clinical situations that warrant consideration of a surgical procedure during the course of a child's disease (Table 40.1). Surgery is not meant to be curative, but rather to relieve the symptoms or complications of Crohn disease. The timing, indications, and operative procedure performed vary considerably based on the segment of the intestine involved and the specific complication being addressed. The distribution of disease in pediatric patients has been examined in a large cohort of European children. In that study combined ileocolonic disease was found in 53% of patients followed by isolated colonic disease in 28% and limited ileocecal disease in 16% (Fig. 40.1) [10].

Isolated Crohn disease of the foregut is relatively rare [13] and seldom requires surgical intervention. In contrast, terminal ileal and colonic diseases account for the vast majority of surgical interventions in the pediatric patient. Some require an urgent operation, while most are more elective in nature. The most common complications leading to a surgical intervention are obstruction, abscesses, fistulas, and failure or intolerance of pharmacological treatment [14–16].

The indications for surgery have evolved somewhat as medical treatments have improved. A study examining surgical indications in the period from 1970 to 1990 compared to the period from 1991 to 1997 revealed that active disease as an indication for surgery decreased from 64 to 25% of cases, while chronic stricture increased from 9 to 50% of cases. In addition, the time from diagnosis to initial operation increased

Table 40.1 Operative indications in Crohn disease

Intestinal stricture or obstruction	Fistula (bowel to bowel, bowel to skin, bowel to adjacent organ)
Bowel perforation	Urologic complications
Massive intestinal bleeding	Growth failure
Complex perianal abscess or fistula	Fulminant disease refractory to medical management
Neoplastic changes	Intra-abdominal abscess

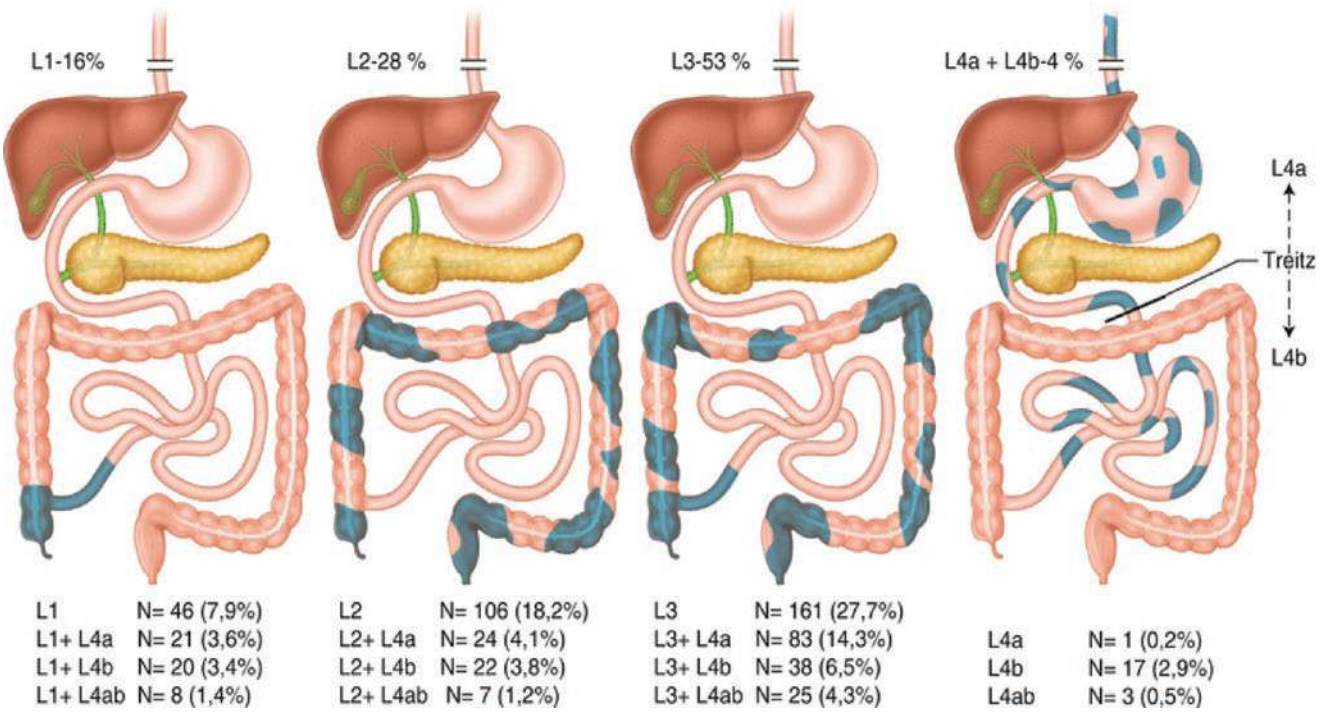

Fig. 40.1 Distribution of pediatric Crohn disease (de Bie et al. [10]) in newly diagnosed pediatric Crohn disease patients who underwent complete diagnostic work up according to Porto criteria [11]. L1: terminal ileal disease (± limited cecal disease). L2: colonic disease. L3: ileocolonic disease. L4: isolated upper gastrointestinal disease. L4A: esophagogastroduodenal disease. L4B: jejunal/proximal ileal disease

from 3.5 to 11.5 years [17] suggesting that medical therapy has been successful in altering the course of the disease but not necessarily preventing ultimate progression in many cases. Fortunately, the shift to less emergent operation likely reduces the morbidity associated with a surgical intervention.

Absolute indications for surgery are rare, and many patients present with multiple relative indications rather than an acute precipitating event. In a large cohort of adults with Crohn disease, the decision to proceed with surgery was distributed as follows: failure of medical management in 47%, obstruction in 20%, intestinal fistula in 15%, mass in 12%, abdominal abscess in 7%, hemorrhage in 2%, and peritonitis in 2% [18].

As our understanding of inflammatory bowel disease has increased, it has become clear that there are different variants of Crohn disease, and some phenotypes are more likely to require operative intervention. The age at diagnosis has an impact on disease characteristics and propensity to progress with younger patients having more extensive and more aggressive disease than adult-onset patients [19]. The complex associations of genetic and epigenetic alterations with specific phenotypes are beyond the scope of this chapter, but our ability to predict patterns of disease and response to therapy continues to improve. As our understanding of the relationship between genotype and phenotype grows in the future, it may be possible to target specific patient populations for specific types of surgical intervention based on response rates and disease characteristics.

In the refractory Crohn disease patient, prior to surgical intervention, nonadherence, inadequate dosing, duration of therapy and other features should be considered prior to surgical intervention as surgery is not curative for Crohn disease (Table 40.2). The indications for surgical intervention in the pediatric population differ from those in adults in many cases. The mechanical complications of obstruction and perforation are the same, but the impact of medical therapy on growth and development is unique to the pediatric population [20]. The indication for surgery may be the failure of medical therapy with growth impairment rather than obstruction or other mechanical complications [21]. Growth failure is observed in 15–40% of pediatric Crohn disease patients with malabsorption, suboptimal intake and increased energy needs leading to this malnutrition [22, 23]. In one study of children who had received extensive medical and/or nutritional treatment before surgery, 26 patients underwent intestinal resections. The indication for surgery was chronic intestinal obstruction in 13 cases and chronic intestinal disability leading to growth failure in 13 cases [24]. Furthermore, the timing of surgery for growth issues is critical in the adolescent. Surgical intervention must occur well before epiphyseal plates close to allow sufficient time for subsequent catch-up growth following the operation [25]. Surgical therapy is associated with significant catch-up growth in 6 months following operation in patients with the treatment-resistant disease [26].

Fortunately, surgical treatments have evolved along with medical therapy, and current surgical procedures are safer and less invasive than at any time in the past. Surgery has progressed from a treatment of last resort for life-threatening complications to therapy for use in conjunction with medical interventions to maximize the patient's quality of life. While the specter of short bowel syndrome must be kept in mind, elective procedures to treat the complications of Crohn disease can be accomplished safely and effectively [27]. While medical therapy may one day render surgical therapy unnecessary, at present, the surgeon remains an integral part of the treatment team for patients with inflammatory bowel disease and Crohn disease in particular.

Table 40.2 Considerations prior to surgical intervention

	Features to consider
CD phenotype	Paris classification: distribution, structuring or inflammatory or both, presence and location of fistulas
Disease severity	Number of affected bowel segments Number of fistulas and locations
Current medications	Compliant? Previous and current response? Effect on the risk of complications—do they need to be discontinued or decreased?
Previous medications	Reason for discontinuation: Loss of response? Nonadherence? Side-effects?
Nutritional status	BMI, deficiencies in micronutrients affecting the immune system and healing process
Growth potential	Age, pubertal status, bone age, height for age and grown velocity over the last 6–12 months
EEN	Previous use, compliance, response, duration of remission
Comorbidities	Infections, genetic immunodeficiencies, other chronic illness

Adapted from [2, 12]

Surgical Emergencies

The most common indication of emergency surgery in patients with Crohn disease is perforation (60.5%), followed by obstruction (22.6%), fistula or abscess (10.3%) and hemorrhage (6.6%) [28]. The operative goal with perforation is to control sepsis and decompress the intestine with as little risk to the patient as possible. In cases of perforation where the process is localized, percutaneous drainage and antibiotics may convert an acute situation into a more controllable elective intervention. When laparotomy is undertaken in the acute setting, the peritoneal cavity may be very hostile with inflammatory adhesions, fistulas, friable bowel, and diffuse peritonitis making extensive dissections and primary bowel anastomosis ill-advised. Rather than proceed with extensive surgery, often the most prudent approach is to divert the fecal

steam with a proximal ostomy [29]. Resection of the involved intestinal segment may be considered when technically possible, but proximal diversion without addressing the actual diseased bowel may be the safest option in severe cases. With emergency surgery, there is a risk of a longer small bowel resection (median length of small bowel resected 30.4 cm), with an additional 10 cm resected compared to an elective surgery for primary Crohn disease (median length of small bowel resected 19 cm, $p < 0.0001$) [30]. Additionally, the incidence of intra-abdominal septic complications with primary anastomosis compared to staged surgery is also higher (15.6% vs 7.5%; $p = 0.04$) [28]. In the setting of perforation, primary anastomosis should only be considered if peritonitis is localized, BMI <18.5 kg/m^2 and/or it was in the setting of iatrogenic perforation as these attributes are associated with a lower risk of post-operative intra-abdominal septic complications.

Proximal diversion with an ileostomy is not without risk. Morbidities most commonly described post-operatively include intra-abdominal fluid collection requiring radiological guided drainage, mechanical bowel obstruction, wound infection and high output stoma [30]. Ileostomies are associated with significant complications at the ileostomy site in addition to the accompanying challenging body image and social stigmata in teenagers [31]. The risk of a diverting ostomy becoming permanent is significant.

Once the intra-abdominal sepsis is controlled and the inflammatory adhesions are allowed to resolve for 6–8 weeks following emergent ileostomy, a more definitive procedure with ostomy closure can be considered. Although no one, especially teenagers and their parents, wants an ileostomy, attempting an extensive dissection or bowel anastomosis in the face of severe inflammation can result in life-threatening complications and potential loss of large segments of the small bowel.

A complete bowel obstruction without accompanying sepsis that does not respond to medical therapy may also require an acute surgical intervention [32]. In a stable patient, aggressive medical management should be attempted to resolve the obstruction before committing to taking a patient to the operating room. This is especially true in cases involving difficult-to-treat intestinal segments like the duodenum where avoiding any surgical intervention is desirable if possible [33]. Recently the pendulum has swung to the more aggressive style of treatment starting with biologics before other milder agents such as immunosuppressants or corticosteroids. In this aggressive medical management model, the MRE is key in helping to identify and differentiate between the inflammatory vs. fibrotic strictures so that we are able to differentiate who has the potential to respond appropriately to biologics and who will need an operation [34, 35].

If the obstruction fails to resolve or evidence of bowel compromise is present, an operation must be undertaken without the ability to prepare the bowel for primary anastomosis. At surgery, the bowel is often inflamed and friable, and although a definitive resection with reanastomosis may be possible, it is imperative that the patient and family be prepared for a diverting ileostomy to avoid the risks of a breakdown in an attempted primary bowel anastomosis.

Patients that have had multiple previous abdominal operations may be particularly challenging because of pre-existing adhesions. Studies suggest that as many as half of the patients undergoing reoperative surgery will require ileostomy formation [36]. In many pediatric patients, this is less of an issue because often patients are making their first trip to the operating room, but one should never hesitate to perform a temporary bowel diversion when primary anastomosis may be unsafe.

Elective Surgery

The indication for surgical intervention is more commonly not emergent, and the timing of the intervention requires the careful consideration of the surgeon, the gastroenterologist, and the family. The typical indications for surgery include failure of medical management, stricturing disease with obstructing lesions, fistulas, and complications related to the side effects of medical therapy.

The preoperative evaluation usually includes both endoscopic and imaging studies. Traditional imaging involves contrast enemas and/or upper gastrointestinal series with small bowel follow-through. More recently, magnetic resonance enterography has been utilized to provide a more complete assessment of the entire gastrointestinal tract [37]. Some recent evidence suggests that CT enterography may provide superior imaging [38] but the differences are not dramatic, and the experience of the radiologist is probably more important when deciding between the two studies. Whichever method is chosen, enterography offers the advantage of cross-sectional imaging of the entire bowel wall rather than being limited to assessing luminal disease (Fig. 40.2). This

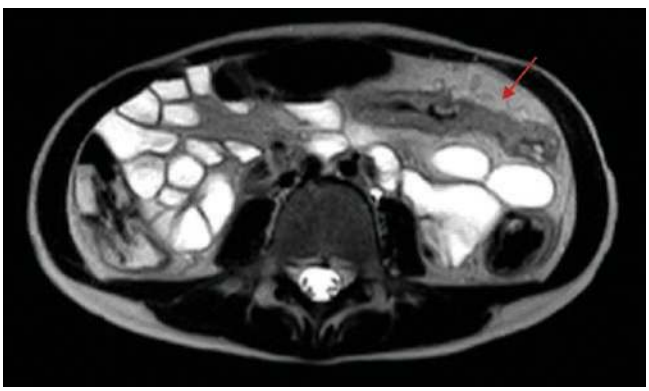

Fig. 40.2 MRE in patient with Crohn pancoltiis with active inflammation involving the entire colon and rectum with prominence at splenic flexure

allows for more accurate surgical planning and facilitates discussions with the patient and family regarding the operative approach.

Efforts should be made to control intra-abdominal sepsis through drainage of abscess and treatment with antibiotics prior to surgery along with supporting the nutritional status of the patient. Percutaneous abscess drainage with prompt resumption of immunotherapy has been associated with avoidance of bowel resection in the pediatric Crohn disease population [39].

Methods to reduce the risk of surgical site infections (SSI) including anastomotic leaks, intra-abdominal sepsis, and wound infections have been extensively studied and remain controversial. The use of intravenous antibiotics, enteral antibiotics, and mechanical bowel preparation have all been advocated for colorectal procedures. The evidence pertaining to the prevention of SSI has recently been evaluated and reported by the Outcomes Committee of the American Pediatric Surgical Association and as with many pediatric surgical procedures, most of the data comes from the adult surgical literature [40]. Parenteral antibiotic prophylaxis should include one of the Surgical Care Improvement Project (SCIP)-approved agents within 1 h of incision and should be discontinued within 24 h of the end of surgery. The use of mechanical bowel prep alone without enteral antibiotics for the indication of reducing infectious complications is not recommended as it provides no benefit over parenteral prophylaxis alone. Additionally, while the evidence for use of enteral antibiotics combined with mechanical bowel prep for reducing SSIs is strongly supported in adults, the data is much more limited in children. Decisions surrounding the use of parenteral antibiotics, mechanical bowel preparation and nonabsorbable antibiotics should be carefully considered within each specific clinical situation.

The presence of a stricture alone is not an indication of operation. Areas of diseased bowel that do not present a mechanical impediment to the flow of the intestinal contents do not require intervention. However, significant chronic obstruction is suggested by dilation of bowel loops proximal to the diseased area (Figs. 40.3 and 40.4). These changes signify a possible impending complete obstruction, and elective resection prior to that allows the opportunity for bowel preparation and resection with primary anastomosis rather than a two-stage procedure requiring temporary diversion with subsequent ileostomy closure. Entero-entero fistulas, chronic phlegmon, and enterocutaneous fistulas are other mechanical indications for operative intervention which can be dealt with after careful radiographic studies to delineate the anatomy and preoperative patient preparation.

Fistulas to the urinary tract with recurrent urinary tract infections may not constitute an urgent indication for operation, but continued soiling of the urinary tract could result in progressive renal dysfunction arguing for earlier rather than later intervention in these situations. Although some patients will respond to medical therapy, the vast majority of patients

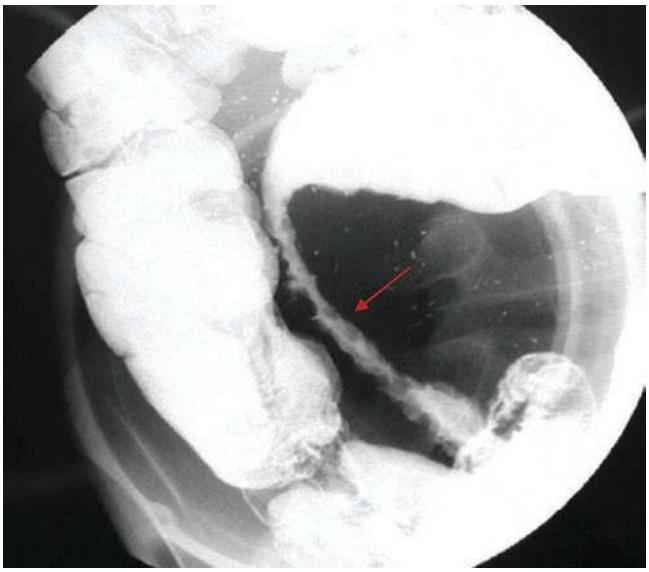

Fig. 40.3 Barium contrast study demonstrating a segmental distal ileal stricture

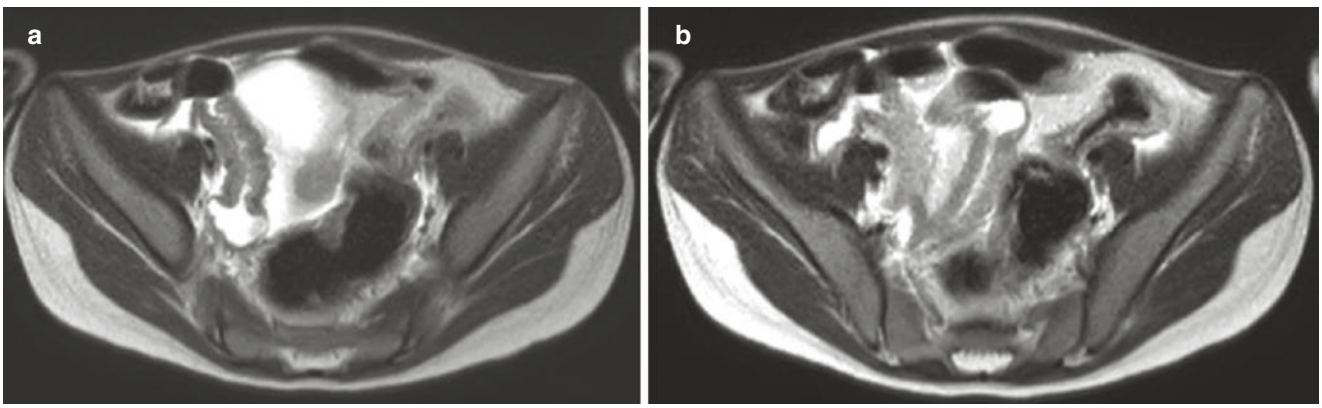

Fig. 40.4 MRE of Crohn disease distal ileum stricture (**a**) and proximal dilation (**b**)

will require surgical intervention [41–44]. Enterovesical fistulas are treated with takedown of the fistula and closure of the bladder, while ureteral fistulas may require resection with reanastomosis or reimplantation of the ureter.

Finally, the progression of the disease with persistent symptoms despite maximal medical therapy may also be the impetus for considering the surgical option. Regardless of the indication, the philosophy of therapy remains the same. The surgical procedure must be tailored to the individual patient with an eye toward preserving all possible small bowel length while providing the most effective palliation of the presenting complication of Crohn disease. Surgical intervention in patients with progressive or chronic symptoms related to stricturing or fistulizing disease in the abdomen is effective in relieving symptoms and can minimize absence from school and improve the overall quality of life when compared to nonoperative therapy [45].

Surgical Therapy

The procedure performed at the time of operation depends on the clinical situation and extent of the disease. As mentioned previously, in a patient that is acutely ill with sepsis or complete obstruction, simple diversion may be the most appropriate response. However, in most patients, a more definitive procedure is performed. In pediatric patients with stricturing disease, the terminal ileum is the most common site involved. Often the disease extends up to include the ileocecal valve, and the most common approach is bowel resection extending from the proximal extent of the disease in the ileum to the ascending colon, which is usually uninvolved. Bowel continuity is restored with a primary anastomosis.

In an effort to preserve as much bowel length as possible, only gross disease is resected since the recurrent disease may require additional surgery, and bowel length may be shorter than normal in patients with Crohn disease leaving less margin for resection before developing issues with poor absorption [46]. The actual technical aspects of the procedure vary somewhat by the surgeon and are largely a matter of training and experience. Bowel resection is carried out in the standard fashion with no need to obtain clear margins or mesenteric lymph nodes as might be required for a cancer operation. The only technical aspect of the procedure that may impact the outcome is the manner in which the bowel is anastomosed.

There are several techniques for reanastomosing bowel with the majority of surgeons performing either a hand-sewn end-to-end anastomosis or a side-to-side, functional end-to-end stapled anastomosis. There is some evidence to suggest that a stapled anastomosis may reduce the time to recurrence in patients with Crohn disease due to the wide lumen configuration and the nonreactive nature of the staples [47–55]. Alternatively, it may have more to do with the anatomic orientation of the anastomosis rather than the manner in which the bowel is re-approximated [56]. The other reported benefit of a stapled anastomosis stems from data to suggest that anastomotic leaks and intra-abdominal abscesses are less common with the stapled anastomosis in some series but not in others [51, 57–60]. Lastly, another anastomotic configuration that has been described is known as the Kono-S anastomosis which combines stapled and hand-sewn techniques with mesentery preservation combined with a supporting column to prevent anastomotic distortion, and an anti-mesenteric anastomosis. Systematic reviews assessing recurrence following Kono-S anastomosis with preservation of mesentery vs mesenteric resection and overall safety and efficacy have found that the Kono-S anastomosis is safe and may reduce endoscopic and surgical recurrence. However, the level of evidence remains poor [61, 62]. A more recent randomized controlled trial with 79 ileocolic Crohn disease patients randomized into Kono-S vs. conventional anastomosis found at 6 months endoscopic recurrence was significantly lower in the Kono group (22.2% vs. 62.8%; $p < 0.001$, OR 5.91) [63]. At 12 months, clinical recurrence was 8% vs. 18% (Kono-S vs. conventional respectively; $p = 0.2$) and at 24 months 18% vs. 30.2% (Kono-S vs. conventional respectively; $p = 0.04$, OR 3.47). There was no difference in surgical recurrence at 24 months (Kono-S 0% vs conventional 4.6%; $p = 0.3$) and no difference in post-operative outcomes [63].

Complications following bowel resection and anastomosis in patients with Crohn disease are common and most often infectious in nature. Wound infections are most common and occur in as many as 20% of patients, while more serious intra-abdominal infections related to anastomotic leaks occur in 3–10% [51, 64]. Wound complications are treated with local care, while anastomotic complications may require reoperation with revision or temporary diversion with an ostomy.

Small Intestinal or Ileo-colonic Disease

For patients with localized ileocecal Crohn disease but no significant evidence of active inflammation, surgical resection is the preferred option. Long-term studies in adults have demonstrated that there is a 50% chance that the patient will never require further operation [65]. With refractory obstructive symptoms after initial medical treatment of ileocecal Crohn disease, surgical resection should be considered as the first option.

Stricturoplasty

Diffuse small bowel disease with skip lesions or strictures that do not involve the ileocecal valve allows for some addi-

tional options in surgical treatment. Short segments are often resected with primary anastomosis when it represents the only area of disease. However, multiple short segments or longer segments up to 20 cm in length may be amenable to stricturoplasty rather than resection in an effort to preserve bowel length.

The most common technique used is the Heineke-Mikulicz stricturoplasty, this technique entails a longitudinal enterotomy through the strictured segment with closure in a transverse fashion to relieve the obstruction and is ideal for short strictures (Fig. 40.5a). For those strictures that are slightly longer (>10 cm but <25 cm), a Finney procedure is indicated and entails taking the strictured segment and folding it on itself. A "U"-shaped incision is made along the length of the stricture it is sutured together thus creating a large diverticulum (Fig. 40.5b). For those that are longer than 20 cm, a Michelassi is indicated and is performed by dividing both the strictured bowel and its mesentery in the

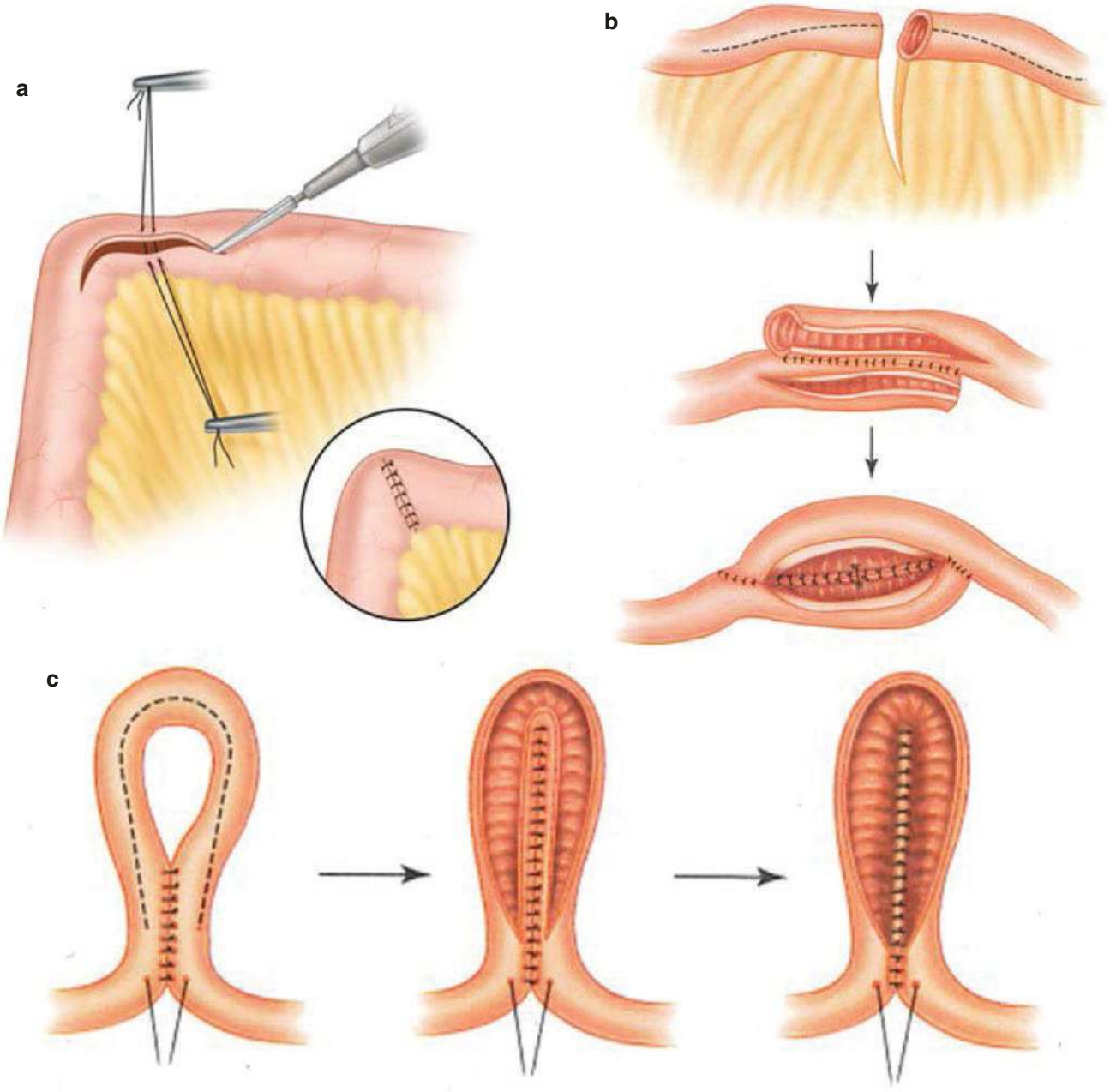

Fig. 40.5 Stricturoplasties: (**a**) Heineke-Mikulicz (**b**) Michelassi (**c**) Finney (Images **b** and **c** reproduced with permission from The ASCRS Textbook of Colon and Rectal Surgery 3rd ed.) [70]

center of the stricture. The bowel is then placed side-to-side and a longitudinal incision is made in both limbs and the stricture is sutured together in a side-to-side fashion (Fig. 40.5c).

While it seems somewhat counterintuitive to leave the diseased bowel in situ, the results following these operations are quite good even when applied to multiple strictures in the same patient [66]. Surprisingly, the rate at which recurrent disease occurs at the stricturoplasty site is low [67], and the technique has been used for many years with results from long-term follow-up studies supporting its use [68]. Recurrence rates following stricturoplasty are on the order of 15% at 2 years and 20% at 5 years [69].

There are a number of technical modifications of this technique that allow for longer segments to be preserved while relieving obstruction [71–75]. In a study of 102 patients undergoing a nonconventional stricturoplasty for a longer segment of the intestine, there were 48 ileoileal side-to-side isoperistaltic stricturoplasties, 41 widening ileocolic stricturoplasties, and 32 ileocolic side-to-side isoperistaltic stricturoplasties, which were associated with Heineke-Mikulicz stricturoplasties in 80 procedures or with short segmental bowel resections or both in 47 procedures. The post-operative complication rate was 5.7% which is consistent with the complication rate from the more common Heineke-Mikulicz stricturoplasty. The 10-year clinical recurrence rate was 43%, and the recurrence rate at the previously affected site was only 0.8% [73]. In another study, long-segment stricturoplasty (>20 cm) was reported to have recurrence rates that are not significantly different from that of shorter-segment disease. Recurrence rates were 20–35% at 3 years, 50% at 5 years, and 60% at 10 years with no difference in complications between the groups [73].

In some very difficult situations such as long duodenal strictures, other modifications of the stricturoplasty technique can be applied. In one such case, a jejunal patch was used to successfully relieve the obstruction and avoid intestinal bypass in a patient with a difficult duodenal stricture [76].

Laparoscopy

Laparoscopy used for Crohn disease was first described by Miller and colleagues in 1996 with the use for a diagnostic laparoscopy to detect the presence of abnormal mesenteric fat (“creeping fat”) in patients thought to have Crohn disease after other studies were inconclusive. Three of the seven suspected who underwent laparoscopy were found to have “creeping fat” and thus underwent resection and the diagnosis of Crohn disease was confirmed [77]. This early implementation of laparoscopy was beneficial and allowed for diagnosis when other studies were not diagnostic [78].

In 2002, Rothenberg was one of the first pediatric surgeons to describe his preliminary experience with laparoscopy for 15 segmental bowel resections in the treatment of Crohn demonstrating the feasibility of minimally invasive surgery for the treatment of inflammatory bowel disease in children [79]. As with many of the other conditions to which laparoscopic techniques have been applied, multiple studies have demonstrated a decrease in hospital length of stay, a more rapid return to regular activity, less postoperative opiod use, and improved cosmetic results. Similarly, multiple studies of laparoscopic techniques applied to surgery for Crohn disease in children and adults have also suggested shorter hospital stays, decreased need for parenteral opiods, and faster return to a regular diet [80–89]. However, a recent Cochrane analysis has shown no difference in length of stay or duration of ileus [90], and the morbidity of the laparoscopic approach is equivalent to open surgery [91]. Thus, although the benefits of the laparoscopic approach may be limited to improved cosmesis at the expense of longer operating time, there is a trend toward increased use of minimally invasive techniques, and the outcomes are at least equivalent to open surgery.

The techniques employed often use the laparoscopic exploration of the abdomen with mobilization of the diseased bowel segment. Various sealer/cutting devices facilitate taking the mesentery of involved segments without additional blood loss and stapling devices allow for dividing the bowel at the margins of disease. The anastomosis may be carried out extracorporeally after the diseased segment is delivered from the abdomen through a small incision or intracorporeally using the laparoscopic stapling devices. These techniques can also be incorporated into the single-site surgical approach to achieve “scarless” operations [92] although the benefit is purely cosmetic and the outcomes have not been tested. The use of the surgical robot has also been reported with the possible benefit of reducing conversions to an open operation but no difference in other surgical morbidities [93].

Although complicated disease involving fistulas or phlegmon was considered a relative contraindication to the laparoscopic approach, many cases are now handled by experienced surgeons without an increase in complication rate [94–99]. One potential benefit of the laparoscopic approach is a reduction in postoperative adhesion formation. This carries added importance in Crohn’s populations where disease recurrence is more the rule than the exception and reoperation is often necessary. Reduced adhesions facilitate subsequent operations [100] and theoretically lower the risk of injury to the bowel and ureters. Approaching recurrent disease laparoscopically is also feasible without an increased complication rate [101, 102].

In the long run, the patients’ quality of life does not appear to be impacted by the technique used at the time of surgery

[102, 103]. However, the advantage of the minimally invasive approach likely extends beyond quality-of-life measurements. Reduced intra-abdominal adhesion formation, possible faster resumption of full enteral nutrition, and perhaps less psychological trauma related to body image issues are all of particular significance to the pediatric patient population.

Colonic Disease

Isolated colonic disease is reported in approximately 27% of cases [10]. In patients with isolated colonic disease, there is a significantly lower risk of surgery (pooled HR, 0.57; 95% CI, 0.43–0.78; $p = 0.0003$; $n = 2289$) [104]. Additionally, this indicates that the presence of small bowel disease increases the risk of surgery. With colonic disease, often the inflammatory behavior, perianal disease and extra-intestinal manifestations are higher when compared to ileal/ileocolonic Crohn disease. However, the overall requirement for surgery is significantly lower in colonic Crohn disease (17.1% vs. 26.1%, $p = 0.032$) and patients with the colonic disease have a lower cumulative probability of first surgery in the first 10 years of follow-up [105].

Crohn colitis requires a different approach than for small bowel disease. The colonic disease is traditionally regarded as being more aggressive, and the colon is not necessary for the nutritional function of the intestinal tract, so some advocate subtotal colectomy rather than segmental resections when colonic involvement requires surgical intervention. However, segmental resection offers the opportunity to preserve colonic function and avoid or delay the potential for permanent ileostomy and has become the more common approach [17]. Fewer symptoms, fewer loose stools, and better anorectal function have been reported following segmental resection, and the re-resection rate did not differ from patients undergoing subtotal colectomy [106, 107]. Conversely, patients with pancolitis or severe distal colonic disease have been reported to have longer disease-free intervals [108] and wean from chronic medications more often when treated with subtotal colectomy or proctocolectomy when compared to those undergoing segmental resection. However, these patients also had a higher incidence of permanent diverting ileostomy [109, 110] suggesting that segmental resection for pediatric patients with colonic Crohn disease is preferable when possible. Additionally, temporary fecal diversion with an ileostomy is an option allowing reversal when their disease burden is better controlled. Laparoscopic techniques are possible and show similar advantages to those described in small bowel resection [111].

Perianal Disease

Approximately 10–62% of patients will develop perianal manifestations of Crohn disease [112, 113]. Patients presenting with perianal disease tend to have a more aggressive disease with higher rates of both perianal and intra-abdominal operations [114]. Perianal Crohn disease falls into three distinct categories: (1) tissue destruction (anal fissures, tags, and deep ulcers), (2) fistula and abscesses, or (3) rectal stricture (Fig. 40.6).

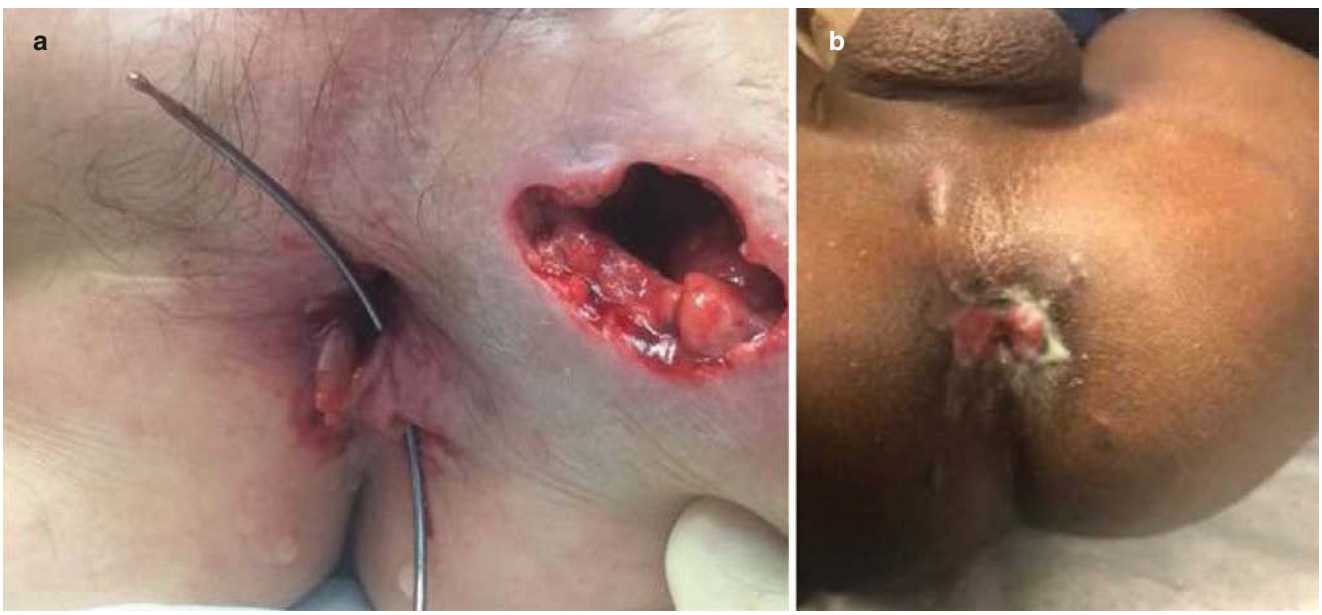

Fig. 40.6 Perianal Crohn Disease: (**a**) Fistula and abscess (**b**) Anal stenosis

Fistulizing perineal disease is an area in which surgical intervention has classically been avoided given the risk of nonhealing wounds and incontinence. However, with newer therapeutics, the goals of treatment have been to completely heal the abscesses and have complete fistula closure. The use of early surgical evaluation has been found to provide important information to help guide the medical management. While fistulotomy and incision and drainage of local abscesses were fraught with long-term complications in the past, the use of new biologic agents such as infliximab has rendered early surgical intervention not only safe but necessary for rapid control of the disease.

Medical therapy for the perineal disease has been greatly improved with the advent of biologic agents yet more than half ultimately require surgical procedures [115]. Two controlled trials support the efficacy of infliximab in achieving closure of perineal fistulas [116], and the combination of infliximab and surgical treatment for the fistulizing perineal disease can result in marked improvement of perineal disease which is superior to infliximab alone [117–119]. Conversely, infliximab treatment does not prevent the need for surgery for fistulizing Crohn disease [120].

Treatment algorithms in pediatric inflammatory bowel disease centers have evolved to include an aggressive surgical approach early. Of children presenting with perianal symptoms, 3% will eventually be diagnosed with Crohn. Those at highest risk are those patients that are males aged 10 years or older who present with a perianal fistula [121]. Additionally, recognizing documented Crohn disease-associated symptoms prior to presentation with perianal symptoms is key to diagnosing these children early.

Examination under anesthesia is particularly useful in the pediatric population. Comprehensive rectal examination is often difficult in the clinic setting for younger patients that are unable to cooperate fully with the exam. General anesthesia in the operating room provides the ideal environment to carefully evaluate the extent of disease with delineation of fistula tracts, abscesses, and rectal strictures. A complete assessment of the extent of the disease is important to help guide medical therapy.

Once the extent of the disease is determined, therapeutic measures can be performed during the same anesthetic. Perianal abscesses should always be evacuated [122]. Most are near the skin and can be drained through a small skin incision. If fistulae-in-ano is present, they can be probed to ascertain the anatomy (Fig. 40.6a). All fistulas are treated with the placement of a non-cutting silastic seton. This allows drainage both internally and externally rather than having an uncontrolled fistula which would be a persistent source of recurring abscesses. Overall setons are well tolerated and can be left in place for long periods of time if there continues to be persistent signs of inflammation or infection. Fistulotomies are discouraged, as muscle division carries a high risk of incontinence and the risk of non-healing perineal wounds [123]. For women with rectovaginal fistulas, any surgical repair should be approached with caution, especially in the presence of active inflammation. Initial surgical treatment may improve the response to subsequent pharmacologic therapy.

With the examination of operative management of perianal Crohn disease, it can usually be divided into simple or complex diseases based on the type of surgical procedure. In a study by Langer et al., the majority of perianal disease was simple (~75%) requiring abscess drainage ± seton insertion while ~25% of pediatric patients had more complex perianal disease requiring loop ileostomy ± more extensive surgery [124]. In those that had a more complex perianal disease, all underwent defunctioning ileostomy and 50% of those patients underwent additional operations including subtotal colectomy, proctocolectomy ± anal sparing, or plastic surgery reconstruction with perineal flap/graft. In this study, ~9% of patients had a such severe perianal disease that they required proctocolectomy compared to adults where severe perianal disease requiring proctocolectomy with permanent ileostomy was seen in as many as 20% of patients [112, 124].

Instillation of fibrin glue into fistula tracts has been attempted following curettage with the thought that fibrinogen and thrombin are able to cause a clot and promote hemostasis and angiogenesis while acting as "scaffolding" for fibroblasts to migrate to and adhere with mechanically sealing of the tract. In a small randomized controlled trial comparing simple or complex fistulas randomly assigned to receive fibrin glue injection or observation alone after seton removal, clinical remission at 8 weeks was significantly better in the fibrin group at 38% compared to observation alone at 16% (OR 3.2, $P = 0.04$) [125]. However, it was also found that fibrin glue may be more effective in those patients with simple fistulas compared to complex fistulas.

Anal fistula plugs have also been attempted. These are usually (a) a cone-shaped device with lyophilized, rolled, porcine small intestinal submucosa or (b) a tubular, multilegged button made from bio-absorbable polymers. Similarly to the fibrin glue, it is used as a matrix in the fistula to allow for the in-growth of collagen and producing fibroblasts. The plug is inserted into the tract with the end of the plug within the anoderm and tapered legs through the tract. In the systematic review, follow-up has been ~3.5–12 months with variable success rates of 29–86% in patients with Crohn disease [126].

The use of autologous adipose tissue-derived stem cells involves curettage of the fistula tract followed by injection of the fistula with stem cells from the patient or a healthy donor. Results from previous studies have reported healing of complex perianal fistulas in 71% of 24 patients that received adipose stem cells mixed in fibrin glue compared to 16% of 25 patients who received fibrin glue alone ($P < 0.001$) [127]. In

patients with transsphincteric fistulas, ligation of the interspincteric fistula tract (LIFT) is a relatively new approach for anal fistula closure that entails creating an intersphincteric incision, isolating and ligating the fistula tract at both the internal and external sphincter, and performing curettage of the external tract with the widening of the external tract at the skin. Results have been promising in patients with a 60% rate of healing at 2 months, and 67% at 12 months with no development of fecal incontinence [128]. Long-term results have demonstrated better healing with laterally located fistulas compared to midline fistulas.

Lastly, an endorectal advancement flap is an attractive and useful option for the closure of a fistula. This procedure is usually performed after the fistula tract has matured through the use of seton drainage. The internal opening is identified within the anus and a "U" or square-shaped incision is made in the mucosa surrounding the fistula with or without muscle fibers of the internal sphincter. This flap of anoderm and submucosa is raised and brought down so that it reached below the muscular internal opening. The internal fistula opening is closed and the new flap is trimmed and sutured close. In systematic review and metanalysis, both the endorectal advancement flap and the LIFT procedure have been excellent options for high perineal fistula disease in Crohn patients. The overall success rate has been 61% (45–76%) with endorectal advancement flap vs. 53% with the LIFT procedure. In comparison, incontinence rates have been significantly higher with the endorectal advancement flap compared to the LIFT procedure (7.8 vs. 1.6% respectively) [129].

Rectal Strictures

Low rectal and anal strictures are usually the result of chronic fibrosis and long-standing inflammation. They generally form extremely slowly which allows patients to accommodate over time to the relative narrowing of the rectum. They can be successfully treated with transanal dilations [116]. Younger pediatric patients may require dilations under anesthesia on a regular basis, while older patients will tolerate dilations in the office or at home. Medical therapies can help to control luminal inflammation, particularly topical therapies. Incontinence can result from over dilation of rectal strictures or operative damage to the muscles during fistulotomy, but it is often difficult to separate the impact of the dilations relative to the underlying disease process. Tight irregular strictures longer than 3–4 cm without a clear lumen are a relative contraindication to dilation because perforation of the rectum is possible, particularly in small pediatric patients (Fig. 40.6b). Initial dilation in the operating room guided by fluoroscopy may reduce the risk of subsequent outpatient dilations. Treatment with dilations may be needed for many months, and ultimately the result is dependent on systemic control of the disease process. Patients with tight, long or refractory strictures may eventually require a diverting colostomy and possible total proctocolectomy. The combination of anal stricture and colonic Crohn disease is a predictor of poor outcomes ultimately leading to fecal diversion in more than 50% of patients [130]. Optimal timing for total proctocolectomy with end ileostomy can be difficult to determine but in patients with worsening anal canal disease and inability to dilate along with significant impairment of bowel function may ultimately require total proctocolectomy with end ilesotomy to improve quality of life [131].

Impact of Medical Therapy

Many of the drugs used to treat Crohn disease have the potential to increase complications following surgical procedures due to their immunosuppressive effects. Steroids significantly impair wound healing, impact growth, and increase infectious complications. Risks of abdominal wound infection, abdominal wound dehiscence, and anastomotic dehiscence are all potentially increased in the presence of steroids. While the risks of operating on Crohn patients being treated concurrently with steroids are likely increased, the data in the literature to support that fear is circumstantial. Studies have demonstrated an apparent increased risk of early complications in patients with ulcerative colitis undergoing definitive surgery while on chronic steroids, while complications were not increased in patients weaned off steroids prior to surgery [132]. Asthma patients treated with steroids during the perioperative period failed to show an increased complication rate over controls [133] suggesting that the impact of steroids on Crohn patients may be cumulative with the other risk factors in these patients. Infliximab therapy does not appear to increase the rate of perioperative complications associated with bowel resections for Crohn disease [64, 134]. With a specific examination of pre-operative infliximab, no significant differences have been found in major complication rate, minor complication rate, reoperation rate or 30-day mortality [135].

Additionally, several studies have demonstrated a reduction in hospitalization and surgery with biologic use. In an observational study, scheduled therapy with infliximab significantly reduced the need for surgery compared to episodic use with the effect more striking in those who achieved mucosal healing [136, 137]. Additionally, anti-TNF therapy has been found to be associated with a significant reduction in the likelihood of surgery (OR 0.26, 95% CI 0.14–0.48) with similar effects for both infliximab and adalimumab with no reduction in likelihood with azathioprine or vedolizumab [138]. One, five and 10-year rates of surgery for Crohn disease patients of 14, 28, and 39% respectively were studied in the 1990s and have not changed during the biological era. Lastly,

the 5 and 10-year re-operative rates are close to 25 and 35% respectively and these have decreased historically from much higher rates but are similar to the pre-biologic era.

Post-operative Recurrence

Early Recurrence Predictors

Recurrence of Crohn disease following surgical resection is common and 30% will develop clinical recurrence during the first year after surgical resection with approximately 80% demonstrating endoscopic recurrence that precedes clinical symptoms [139]. Thus, endoscopic recurrence is the strongest predictor of disease progression [140]. In many cases, medical therapy is discontinued following surgical treatment, but continued therapy with several drugs has been investigated and found to improve disease-free intervals. Establishing the recurrence risk for individual patients and performing endoscopic surveillance is important to help guide therapy [141]. While some studies fail to demonstrate an advantage to prophylactic therapy [142], others have proposed specific algorithms for follow-up and treatment [143, 144].

In an Australian randomized post-operative Crohn endoscopic recurrence trial (POCER), the efficacy of endoscopically tailored treatment was evaluated [145]. There were 174 adult CD patients who all received medical prophylaxis starting immediately after surgery and after randomization (2:1) further step-up in treatment was based on findings at ileocolonoscopy at 6 months (endoscopy group) or clinical symptoms (control group). They found that ileocolonoscopy performed at 18 months following surgery had recurrence of 49% in the endoscopy group vs. 67% in the control clinical group ($p = 0.03$). Thus, ileocolonoscopy continues to be recommended at 6 months following resection to monitor for postoperative endoscopic recurrence [146]. Additionally, there is a poor correlation between post-operative endoscopic recurrence and clinical symptoms, blood inflammatory markers such as CRP and Crohn disease activity index [147, 148].

Lastly in the POCER study, calprotectin was found to be an effective screening tool in patients who require colonoscopy for detecting mucosal recurrence. They found that the level of calprotectin correlated well with endoscopic recurrence but neither CRP nor CDAI. A level of >100 μg/g of calprotectin indicated endoscopic recurrence with a sensitivity of 0.89 and negative predictive value of 0.91, thus colonoscopy could be avoided in 47% of patients using calprotectin as a screening tool. While the POCER study was in adults, a more recent study in pediatric patients found that at fecal calprotectin level >139 μg/g at the time of endoscopy for an increase of 70 μg/g compared to the first post-operative value was also suggestive of endoscopic recurrence while a fecal calprotectin level of >101 μg/g or increase of 21 μg/g indicated histological recurrence [149].

Agents including the 5-aminosalicylate formulations, antibiotics, steroids, and azathioprine have been examined. None of these therapies have convincingly been shown to prevent recurrent lesions [150]. Infliximab has been reported effective in a prospective randomized trial where remission was maintained in 93% of patients in the infliximab group and only 53% of patients in the control group [151]. Importantly, early postoperative treatment with infliximab does not appear to be associated with an increase in adverse events [141]. The use of infliximab to prevent recurrence in children has also been reported [152]. The antibiotics metronidazole and ornidazole have shown efficacy, but cannot be used in the long term because of side effects [153]. 6-Mercaptopurine and azathioprine may be more effective than mesalamine [116, 154, 155].

With examination of biologics at 12 months postoperatively following surgery for Crohn disease, anti-TNF-α therapies have been found to be significantly better than placebo either alone [*P*-score 0.98, RR 0.13; 95% CI 0.04–0.39] or in combination with 5-aminosalicylates [*P*-score 0.81, RR 0.30; 95% CI 0.12–0.75] or 5-nitroimidazoles [*P*-score 0.75, RR 0.40; 95% CI 0.23–0.69] [156]. Similarly, in a meta-analysis of 14 clinic studies examining anti-TNFα agents compared to other conventional therapies, they found that early initiated postoperative anti-TNFα treatment currently is the most effective therapeutic choice in preventing the continuum of histological, endoscopic and clinical postoperative recurrence without increasing the frequency of adverse events [157]. Both infliximab and adalimumab were found to be equivalent in preventing endoscopic postoperative recurrence [157].

Given the risk of recurrent disease, it is important to resect only the grossly involved segment of the intestine at the time of the initial operation. Fortunately, there is some evidence to suggest that the involved segments of the intestine in subsequent operations for ileal disease are shorter than those involved at the initial presentation [158].

Adjuvant Procedures

Finally, there are well-documented complications of growth and development in the pediatric population [159]. Pediatric patients are at particular risk for nutritional complications because of the normal rapid growth and development in children. Malnutrition is highly prevalent in inflammatory bowel disease, especially with active Crohn disease and has the potential to affect the entire gastrointestinal tract. Delayed puberty, short stature, iron deficiency, micronutrient deficiencies and bone demineralization may all be indications for supplemental nutritional support. Malnutrition severity is often influenced by the activity, duration and extent of dis-

ease as well as the magnitude of inflammation which drives catabolism.

Oral nutritional supplements are the first step when improvement in nutrition is indicated in IBD. Sometimes oral intake is not sufficient and enteral feeding with the use of nasogastric tube or surgically placed gastrostomy tube is required. In some cases, exclusive enteral nutrition is effective and is recommended as the first line of treatment to induce remission in children and adolescents with acute active Crohn disease [160]. When enteral nutrition is administered, it should be given via an enteral feeding pump rather than boluses as this has been found to have lower complication rates than bolus delivery.

Total parenteral nutrition is indicated when it is not possible for the child with Crohn disease to receive enteral intake. This may occur if the gastrointestinal tract is dysfunctional if the child has short bowel disease, if there is an obstruction or if there are complications from a previous surgery such as an anastomotic leak or high output intestinal fistula [160]. The parenteral nutrition must fulfil the specific needs of the individual patient.

Surgical adjuncts to care such as gastrostomy tubes and surgically placed central lines for chronic parenteral access may prove to be lifesaving measures for some patients. Compliance with medical regimens in the pediatric population can be challenging, and providing these types of devices early with minimal trauma may help minimize the impact of the disease on these nutritional issues. Low residue diets are frequently used in pediatric patients with progressive stricturing disease in the small bowel. The social impact of an indwelling nasogastric feeding tube may inhibit compliance in the teenage population making these children candidates for percutaneous or laparoscopically placed gastrostomy tubes. The laparoscopic approach allows direct visualization of the stomach to properly site the tube, secure the stomach to the abdominal wall, and place a primary button device without the scarring associated with the open approach.

Patients unable to tolerate adequate enteral feedings are often candidates for supplemental parenteral nutritional support. In these cases, surgically placed central venous access devices may significantly improve the lifestyle by providing stable chronic venous access for infusions and blood sampling. Either cuffed catheters or port devices may be indicated.

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Surgical Treatment of Ulcerative Colitis

41

Peter Mattei

The surgical treatment of patients with medically refractory ulcerative colitis (UC) is often accomplished in multiple stages but typically culminates in the complete removal of the colon and rectum (*proctocolectomy*). Although not a cure in the traditional sense, this effectively removes the target organ of the disease and, with the creation of a neorectum, allows the majority of patients to achieve a very high quality of bowel function and normal activities. Proctocolectomy with ileoanal reconstruction has evolved from the earliest operations that included appendicostomy, which allowed colonic irrigation, and simple ileostomy, which diverted the fecal stream. These allowed some patients relief of their symptoms, but the diseased colon remained an ongoing source of morbidity and a significant risk of malignant degeneration, which meant that most patients would eventually be offered proctocolectomy and permanent ileostomy, which for a long time was the standard of care [1]. More recent advances have included the creation of a functional neorectum using the ileum (*pouch*) and minimally invasive techniques that have improved recovery and cosmesis. There is increasing emphasis on achieving normal bowel function, minimizing complications, and improving the overall quality of life [2]. Today, although most patients can expect to undergo a safe operation with a good outcome, a relatively low risk of serious postoperative complications, and overall excellent functional results, [3] the surgical treatment of UC remains less than ideal, principally due to the threat of undiagnosed Crohn disease, inflammation of the pouch (*pouchitis*), and, in few patients, pouch failure necessitating total proctectomy and permanent ileostomy [4].

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Indications for Surgical Intervention

The primary treatment of patients with UC remains medical [5]. With modern drug treatments, most patients do well and remain largely free of debilitating symptoms for many years. Ultimately, however, it is estimated that approximately 20–30% of adults and 15–20% of children with UC will ultimately require an operation [6, 7]. Indications for surgical intervention generally fall into one of the three categories (Table 41.1): *emergent* (perforation, toxic megacolon), *urgent* (hemorrhage, sepsis, pain) and *elective* (intractable chronic and debilitating symptoms such as bleeding, pain, diarrhea or malnutrition), or concern about malignant transformation. One of the most common indications for surgical referral in children is the persistence of bleeding, severe diarrhea, or pain despite maximal medical therapy. Some patients present acutely with rapidly progressive symptoms (*acute severe colitis*) and unless they respond to aggressive medical treatment are forced to consider having an operation within a few days or weeks of disease onset [8, 9]. Others have symptoms that steadily worsen, requiring more frequent blood product replacement and repeated hospitalizations until they are no longer responsive to even the most aggressive treat-

Table 41.1 Indications for surgery in patients with ulcerative colitis

Emergent indications
Toxic megacolon
Colonic perforation
Urgent indications
Intractable bleeding
Unrelenting pain
Unremitting sepsis
Elective indications
Refractory to or complications of medical management
Chronic malnutrition
Poor growth
Delayed sexual maturation
Colonic stricture
Corticosteroid dependence
Mucosal dysplasia
Malignant degeneration

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ment modalities. Still others, despite otherwise manageable chronic symptoms, will be referred for surgery due to poor growth or delayed sexual maturation due to persistent inflammation and chronic malnutrition. As always, the anticipated benefits and potential risks of an operation need to be weighed carefully against the expected consequences of disease progression.

Indications for urgent laparotomy include perforation, uncontrolled bleeding, or intractable sepsis. In children, a complication of UC or its treatment is an uncommon indication for operative intervention [10]. Colon *perforation*, though rare, is an indication of urgent laparotomy and should be suspected in patients with UC who present with peritonitis or evidence of free intraperitoneal air. The patient with intractable *bleeding* should also be considered a candidate for urgent colectomy. *Toxic megacolon* includes the combination of sepsis and a massively dilated colon (≥6 cm in diameter) [11]. Though often critically ill, these patients can sometimes be successfully treated with fluid resuscitation and broad-spectrum antibiotics [12]. Colonic stricture, debilitating extraintestinal manifestations, and malignancy are complications that result from long-standing disease and are therefore rarely seen before adulthood [13].

Patients are sometimes referred to a surgeon because of complications from medical management or dependence on corticosteroids. Although most of the drugs used in the treatment of UC are well tolerated, and there are few serious complications that would prompt consideration of an operation, long-term high-dose corticosteroid therapy can cause serious sequelae such as diabetes, hypertension, opportunistic infection, or psychiatric complications. They may also develop debilitating somatic changes, acne, obesity, growth failure, and osteopenia. Patients with incapacitating side effects of medication and no effective alternative should be considered for operative intervention.

Although rare in children, mucosal dysplasia identified on colonic biopsy during routine surveillance is an indication of colectomy. Colonoscopic surveillance is recommended for most patients starting 5–8 years after the onset of the disease [14]. As UC is being identified in younger patients, we might reasonably expect to see more adolescents with dysplasia being referred for consideration of early colectomy [15, 16].

The success of currently available medicines has significantly reduced the likelihood that a child with UC will require an emergency operation. One typically begins to consider a surgical option in the patient who is corticosteroid-dependent or whose chronic symptoms are increasingly refractory to medical therapy. As always, the risks of an operation must be considered in the context of the risks of continued nonoperative management. Perhaps more important to consider is the anticipated functional result and lifestyle implications of undergoing proctocolectomy and pelvic reconstructive surgery [17].

Surgical Procedures

Although *proctocolectomy with IPAA* is the definitive operation for patients with medically refractory UC, in current clinical practice it is rarely performed as a single operation (in some centers it is routinely done in a single stage, [18] but in most centers this is reserved for children with familial polyposis who are generally otherwise healthy). Many children with UC who are referred for consideration of surgical intervention tend to be chronically ill with borderline nutrition and some degree of immune compromise due to weeks or months of exposure to biologics and corticosteroids, making them less-than-ideal candidates for a long and difficult operation. In the urgent or acute setting, the first operation considered might be *abdominal* (or "*subtotal*") *colectomy with ileostomy*, in which the surgeon removes the colon, closes the intra-abdominal end of the colon just proximal to the rectum (Hartmann procedure), and creates an ileostomy. The rectum is preserved so that a restorative procedure can be performed electively after the patient has stabilized and can be prepared properly for the more delicate and demanding proctectomy with J-pouch reconstruction [10, 19]. Historically, urgent colectomy was performed through a long midline incision but is now routinely done laparoscopically [20, 21]. The principal risks are surgical site infection and bleeding, but the majority of children do well and recover quickly. The goal of the operation is to remove ~90% of the diseased organ as quickly and as safely as possible and to allow the patient to return to a state of good health until a more definitive restorative operation can be performed. It also provides a surgical specimen that can be examined histologically when the true diagnosis remains uncertain [19, 22].

In some cases, especially in the younger patient whose colitis is of recent onset or unclear etiology—UC vs. Crohn disease—a *diverting ileostomy* alone might be a reasonable consideration [23]. This will sometimes provide an opportunity to conduct a trial of medical therapy and a more detailed diagnostic work-up in a clinically more stable patient. If there is no clinical improvement within a few weeks, abdominal colectomy is usually the next step. Those who improve then require a careful assessment regarding the next steps. A simple reversal of the ileostomy after a period of clinical remission risks a recurrence of symptoms, especially if the true diagnosis remains elusive. In these patients, one should usually consider abdominal colectomy and eventual procto-

colectomy with IPAA. On the other hand, the diagnosis of Crohn disease might be an indication of partial or abdominal colectomy and a restorative operation in which the rectum and/or part of the colon are preserved (*ileocolostomy* or *ileorectostomy*).

After abdominal colectomy, despite the fact that the rectum remains intact, patients usually do quite well. After approximately 6–8 weeks, assuming the patient is doing well and is well-nourished, plans can be made for the completion of proctectomy and construction of an ileal reservoir. In the past, some patients were given the option of *ileorectostomy*, in which the rectum is preserved and anastomosis is created between the ileum and the rectum. This preserves relatively normal rectal sensory and motor function but also retains the rectal mucosa, placing the patient at risk for persistent proctitis and eventual carcinoma. These patients require frequent and meticulous endoscopic surveillance for dysplasia for the rest of their lives. Because of concerns about the risk of cancer and the burden of a lifetime of surveillance, ileorectostomy is generally considered less than ideal for the definitive treatment of UC in children. However, due to a higher risk of infectious complications and fistulizing perianal disease after ileal reconstruction of the rectum, it may reasonably be considered for those with Crohn's or indeterminate colitis [24] (Table 41.2).

Assuming the patient does well after colectomy and the pathology shows no signs of Crohn disease, the second stage of the operation includes removal of the rectum (proctectomy) and a neorectum is created using the ileum: *ileal pouch-anal anastomosis* (IPAA). An anastomosis is created between the ileum and the anal canal. The ileum may be unmodified (*straight pull-through*) or can be fashioned to create a reservoir or *ileal pouch*. The most commonly used pouch configuration is the *J-pouch*, in which the ileum is folded back on itself for a distance of approximately 8–12 cm and the common wall is obliterated using a surgical stapling device (Fig. 41.1). Other options include the *S-pouch*, in which the ileum is folded twice, and the *W-pouch*, in which the ileum is folded yet again, resulting in an even larger reservoir. The type of pouch is determined by surgeon preference and experience. In general, although a larger pouch might allow patients to achieve a pattern of relatively normal bowel habits sooner, it also tends to cause more stasis and bacterial overgrowth, factors that many believe increase the likelihood of pouch inflammation and infection (*pouchitis*). Given its relative ease of construction and proven track record of excellent functional results, most surgeons currently prefer the J-pouch [3].

There are two accepted methods of creating the ileoanal anastomosis, both of which produce excellent results (Fig. 41.2). One involves *mucosal proctectomy* (the outer muscle layers of the rectum are preserved) *with an ileoanal anastomosis*; the other is *total proctectomy with double-stapled anastomosis*, whereby the anastomosis is made between the pouch and the rectum 1–2 cm above the top of the anal canal (Fig. 41.2). Mucosal proctectomy involves dissecting along a submucosal plane and removal of the rectal mucosa all the way down to the anal transition zone, with circumferential preservation of a short portion of the muscular wall of the rectum. This was originally designed as a way to remove the mucosa and submucosa, which is where the inflammation in patients with UC is found while preserving the presumed motor and sensory function of the rectal musculature [25]. The submucosal dissection can be difficult, especially in patients with severe or long-standing rectal inflammation. The ileoanal anastomosis was traditionally created using a hand-sewn technique through the anus, but many surgeons create a circular stapled anastomosis of the

Table 41.2 Surgical options

Operation	Comments
Ileostomy	Occasionally performed as an isolated procedure, especially in very young children
Abdominal colectomy + Hartmann[a] + ileostomy[b]	Usually performed when an operation is needed urgently
Abdominal colectomy + ileorectostomy	Usually performed for indeterminate or Crohn's colitis Requires lifelong surveillance of rectum
Proctocolectomy + end ileostomy	Formerly the standard of care Overall very good results Not popular because ileostomy is permanent
Proctocolectomy + Kock continent ileostomy	Rarely performed except at a few centers with experience Difficult operation with frequent complications
Proctocolectomy + ileal pouch-anal anastomosis	Current standard of care "J-pouch" is most common variation
1. Mucosal proctectomy + hand-sewn IPAA	Good function Leaves no rectal cuff Technically more difficult
2. Proctocolectomy + double-stapled IPAA	Good function Leaves short cuff of rectal mucosa Requires lifelong surveillance of rectal remnant

[a] Hartmann operation: the proximal end of the rectum is sutured or stapled closed; the anus is patent

[b] "Three-stage" approach: (I) Abdominal colectomy/ileostomy, (II) Ileoanal pouch procedure/ileostomy, (III) Ileostomy closure

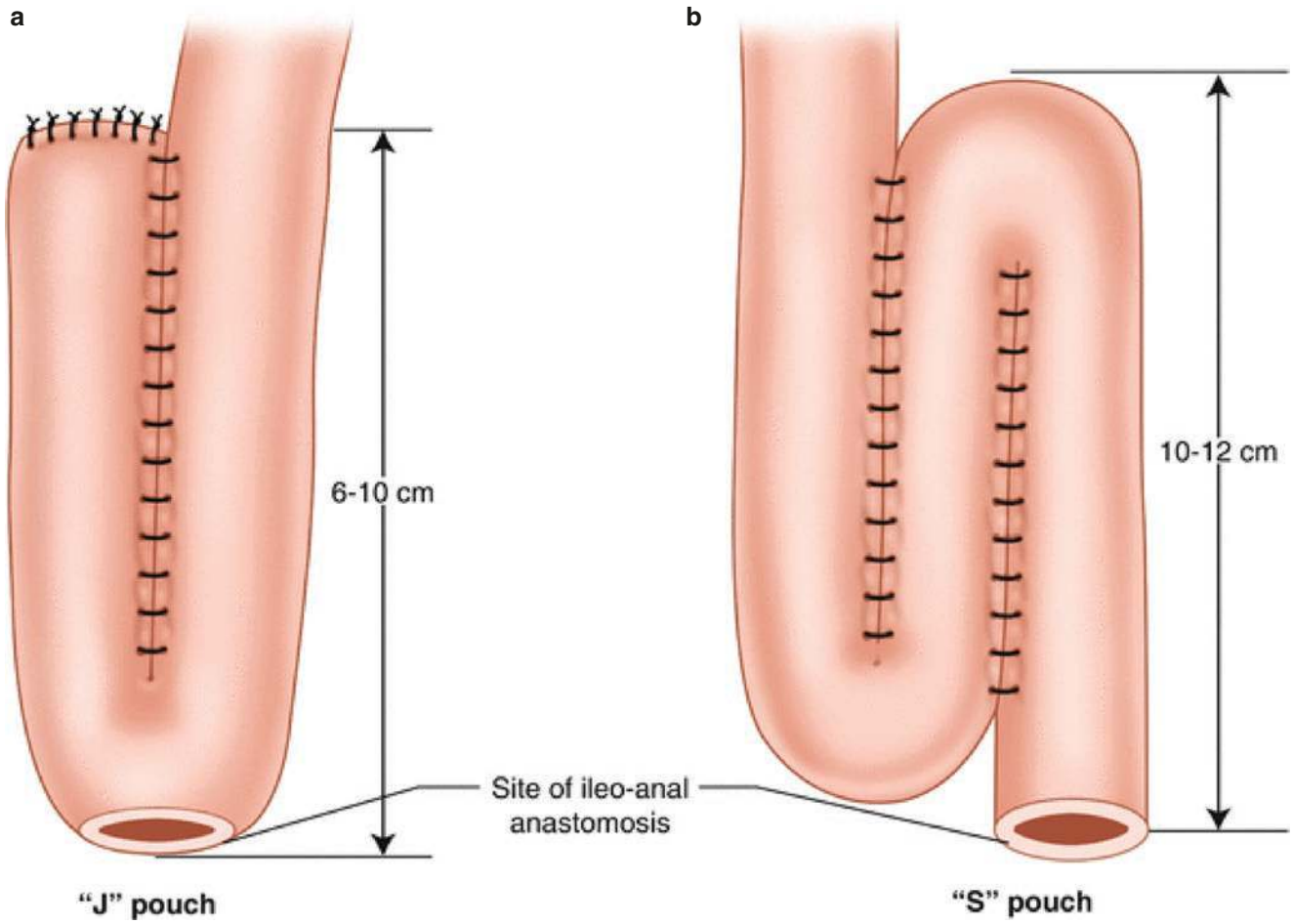

Fig. 41.1 The two most commonly used ileal pouch configurations. (**a**) J-pouch. (**b**) S-pouch. The walls of the jejunal limbs that are brought together are opened using a surgical stapling device so as to create a single lumen that is larger than that of the ileum itself. The ileoanal anastomosis is created by suturing or stapling the lower end of the pouch to the anal canal

pouch to the anal mucosa without having to leave a remnant of the diseased rectum [26].

At the time of ileoanal reconstruction, temporary ileostomy was standard because it was thought to reduce the incidence of anastomotic leak, peritonitis and pelvic sepsis, complications that have been associated with poor pouch function and a significantly diminished long-term quality of life [27, 28]. More recent studies, however, have disproved this idea and many surgeons prefer avoiding diverting ileostomy at the time of the proctectomy and IPAA [29–31]. Ileostomies themselves are also associated with their own morbidity [32]. The ileostomy can usually be reversed after 6–8 weeks, usually after a water-soluble contrast enema confirms good healing, a normal pouch configuration, and good evacuation (Fig. 41.3).

A procedure that is rarely performed anymore but deserves mention is the *Kock pouch* (or *continent ileostomy*) operation [33, 34]. The colon and rectum are completely removed, and the ileum is used to create a reservoir that resides within the abdomen. The end of the ileum is brought out as an ileostomy, but a small intussusception is created just proximal to the outlet, essentially creating a valve that prevents the leakage of stool. The patient does not wear a standard ileostomy appliance and instead uses a plastic tube to evacuate the pouch several times a day. Although the concept is certainly appealing, the functional results of the Kock pouch have been somewhat disappointing and in most centers the complication rate is felt to be unacceptably high [35].

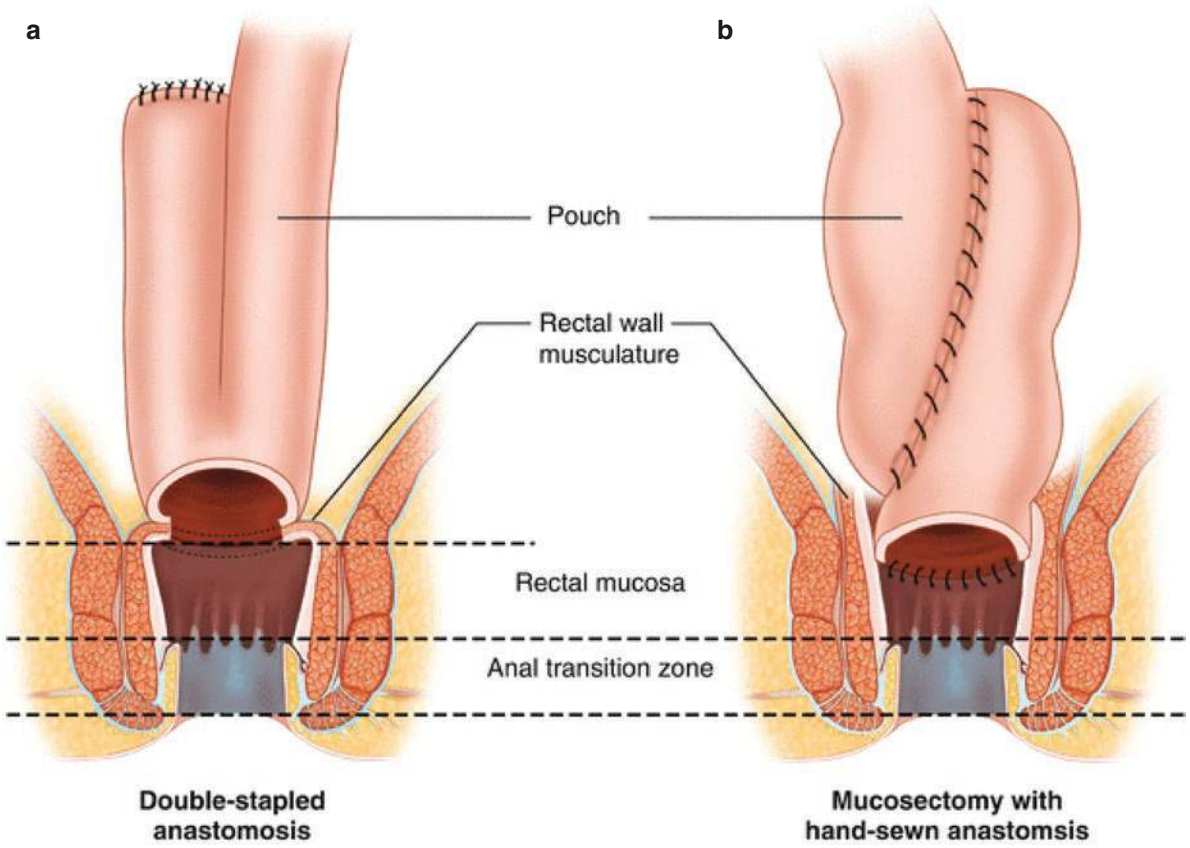

Fig. 41.2 Two commonly used methods for creation of the ileal pouch-anal anastomosis: (**a**) *Double-stapled anastomosis*, so-called because the rectum is first divided and stapled transversely, and then an anastomosis is created between the pouch and the rectum with a specialized stapling device that creates a circular staple line between two hollow viscera (**b**) *Mucosectomy with hand-sewn anastomosis*, in which the mucosa is stripped from the distal rectum, preserving a short segment of rectal musculature, and the anastomosis is performed by hand. Note that with the double-stapled technique, it is unavoidable that a short (1–2 cm) segment of rectal mucosa remains, while after mucosectomy the mucosa is excised all the way down to the anal transition zone. The J-pouch or S-pouch can be used with either method

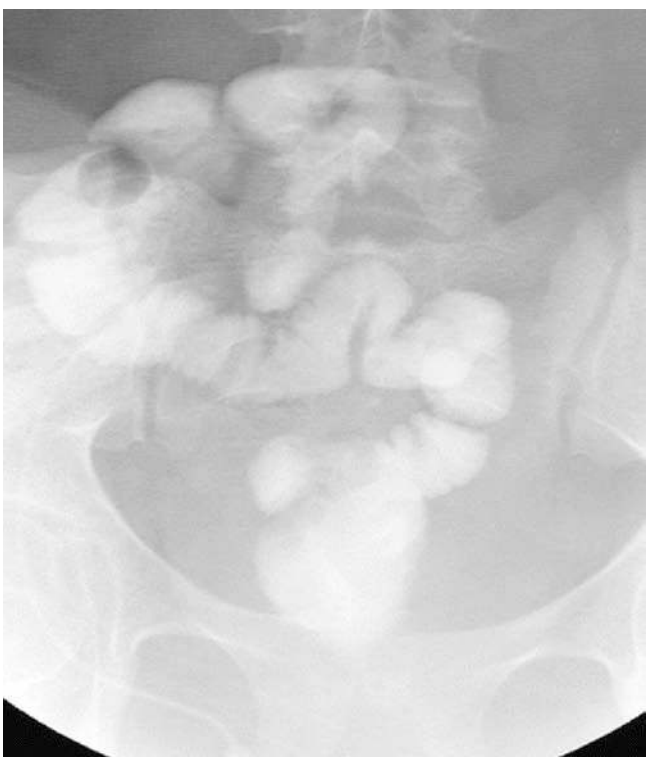

Fig. 41.3 Contrast study performed through mucous fistula of loop ileostomy. The pouch is situated low in the pelvis, is reasonably capacious without evidence of stricture, and is not twisted or volvulized. Functionally, it is important to note that the patient sensed the presence of contrast, was able to hold it for the duration of the study, and at the conclusion of the study was able to evacuate completely and voluntarily

Surgical Decision Making

Proctocolectomy with J-pouch reconstruction initially was routinely performed as a three-staged operation: (1) abdominal colectomy with ileostomy, (2) proctectomy with J-pouch IPAA and another ileostomy, and (3) ileostomy closure. Each phase was separated by 2–3 months or more. It then became fashionable to do it in two stages ((1) colectomy/proctectomy/J-pouch with ileostomy, (2) ileostomy closure) or even one stage, in which an ileostomy is avoided altogether. The more modern "two-stage" approach is gaining in popularity in both adults and children: (1) laparoscopic abdominal colectomy with ileostomy, (2) proctectomy/J-pouch IPAA/ileostomy closure. Most patients with UC who are considering surgical intervention are chronically, and often acutely, ill: they are anemic, malnourished, and exposed to several immunosuppressive medications including corticosteroids, but they can usually tolerate a colectomy and begin to feel better and improve clinically almost immediately. A few months later, most are asymptomatic and gaining weight off all medication—a much better candidate for proctectomy and J-pouch reconstruction and less likely to require ileostomy diversion [36].

Decisions as to which operation to offer and when are complex and involve consideration of several factors: (1) the overall health of the patient, especially nutrition and corticosteroid dependence; (2) whether the operation is being performed electively or emergently; (3) confidence in the diagnosis (UC or Crohn disease); (4) intraoperative factors such as the length and difficulty of the operation, blood loss, degree of soiling of the pelvis with rectal contents, the blood supply of the ileal pouch, and degree of tension at the anastomosis; and (5) recent administration of biologic agents—some [37, 38] but not all [39–41] studies suggest an increased risk of surgical complications for up to several weeks. Therefore, because most pediatric surgeons would consider long-term functional results more important than the short-term inconvenience of multiple operations or time with an ileostomy, they are more likely to err on the side of caution. Nevertheless, the experienced pediatric surgeon evaluates the published data objectively, considers the individual risk factors and the overall status of the patient on a case-by-case basis, and discusses all options with patients and their families frankly but respectfully.

Preparation for Surgery

Patients who need an urgent or emergent operation are prepared for the surgery with intravenous fluid resuscitation and broad-spectrum prophylactic antibiotics. Patients who are anemic may require a blood transfusion, depending on the surgical and anesthetic standards of the institution. Typically, 1–2 units of packed red blood cells are made available for possible use during or after the operation. For patients receiving corticosteroids, it is still standard practice at some institutions to administer a "stress dose" of corticosteroids.

Patients who are being prepared for an elective procedure should have a formal nutritional assessment. Moderate to severe malnutrition prolongs healing and increases the risk of complications after major surgery. Enteral or parenteral nutritional supplementation is sometimes necessary, even if this means delaying the operation for several weeks. Given that chronic, high-dose corticosteroid therapy can also adversely affect wound healing and increase the risks of an operation, attempts should be made to gradually decrease the dose for patients who are scheduled for surgery, preferably down to the equivalent of 15–20 mg of prednisone daily, but not if this causes the inflammation to become severe. Most children do not require mechanical bowel preparation, as these have been shown to increase the risk of complications unless combined with oral antibiotic bowel preparation [42]. Antibiotics are given intravenously immediately before incision but are either discontinued immediately after wound closure or administered for no more than 24 h postoperatively.

Outcomes of Surgery

The technical results of the operations described for children with UC are generally quite good. Infectious complications and bleeding are uncommon and usually easily managed without sequelae. Even after the most complicated operations, most children recover nicely and are able to tolerate a regular diet within a few days of surgery. The short-term results for patients who undergo a minimally invasive procedure might be slightly better, with the added benefit of improved cosmesis. Regardless of the technique, the overall risk of serious complications or death is very low [43, 44].

Functional Results

The functional results of IPAA are also generally quite good, though there is a great deal of variation between patients and in the same patient over time. The ultimate goal of surgical intervention is for the patient to enjoy a normal lifestyle; however, there are inherent limitations in duplicating normal rectal function with a surgical construct [45]. The ideal functional result of IPAA includes (1) fecal continence especially during the day, (2) four or fewer daily stools, (3) preferably no more than one stool at night, (4) the ability to delay evacuation for at least 30 min, and (5) the ability to distinguish between flatus and stool.

The J-pouch IPAA is the most popular operation for children and adolescents with UC who need surgical interven-

tion, and several large studies have confirmed that the majority of patients have good functional results [20, 46, 47]. In most large series, patients report an average stool frequency of 4–5 per day and once or none at night. Fewer than 5% have soiling or staining, most of which occurs only at night [31]. Approximately 90% of patients can delay defecation for at least 30 min, and most report being able to pass flatus without accidents. Many patients are able to participate in a wide variety of normal activities including athletics. Studies using patient questionnaires document a very good quality of life for the majority of patients after IPAA with 90–95% of patients reported to be satisfied or very satisfied with the results of their operation [48].

When mucosal proctectomy with hand-sewn anastomosis is compared to extra-rectal proctectomy and double-stapled anastomosis, the functional results and quality of life parameters appear to be identical, [49, 50] although the relative simplicity of the double-stapled technique may result in improved results in centers where few such procedures are performed [51]. Patients who require a revision of their pouch also tend to do better than expected, [52, 53] although it is certainly preferable for any complex reconstructive procedure to function well after the first attempt. All in all, careful analysis of the collective experience with the IPAA operation over the past three decades confirms that it is a good operation, with excellent functional results and improved quality of life for the majority of patients with UC who need surgery [54].

Complications

As with any complex reconstructive operation, the complication rate for IPAA is not insignificant, occurring in as many as half of all patients [4, 31]. Complications that occur in the immediate postoperative period—surgical site infection, postoperative ileus, and excessive ileostomy output—are usually easily managed. More serious complications such as small bowel obstruction due to adhesions, parastomal hernia, and pelvic abscess often require operative intervention.

A rare but serious complication of ileal pouch-anal anastomosis is anastomotic leak or disruption. This usually manifests as pelvic sepsis, often with an organizing abscess, or with a clinical picture of a perforated viscus, including peritonitis, shoulder pain, free intraperitoneal air, and occasionally frank sepsis. Partial disruptions typically take the form of a tiny leak and can sometimes be managed conservatively with fluid resuscitation, antibiotics, and percutaneous drainage of the abscess. However, patients who are clinically ill, have frank peritonitis or show signs of more than just a small leak should undergo peritoneal washout and ileostomy diversion. The experienced surgeon will resist the urge to perform a repair, which, under these conditions, is futile and dangerous. Much has been made in the past about the subsequent poor function of the pouch complicated by pelvic sepsis, but many will nevertheless have a good long-term function after successful treatment and ileostomy closure. In patients who are well-nourished and whose pouches are under no tension and have a good blood supply, anastomotic breakdown should be rare and well-tolerated. Routine ileostomy diversion does not prevent all leaks but might make patients with a leak less likely to develop sepsis or need another operation [55].

Long-term complications may interfere with the function of the pouch and may result in less than satisfactory function. A number of patients will develop a *stricture* at the ileoanal anastomosis, which increases the risk of pouch stasis and pouchitis. Symptomatic strictures usually respond to anal dilatation and rarely require surgical revision or ileostomy. When an ileoanal stricture is associated with a *perirectal abscess* or *anal fistula*, the diagnosis of Crohn disease must be considered. Prolapse, stenosis, or retraction of the ileostomy may occur, but because the ileostomy is generally temporary, these complications can often be managed by early closure of the ileostomy.

Pouchitis

Perhaps the most feared potential complication after IPAA is *pouchitis* [56]. The patient with *acute pouchitis* typically presents with increased stool frequency, urgency, or pain and sometimes bloody stools, tenesmus, abdominal distension, or fever. The diagnosis is usually made on clinical grounds, though endoscopic examination of the mucosa may reveal mucosal edema, ulceration, or friable granulation tissue. Biopsies often reveal an acute inflammatory process, with polymorphonuclear leukocyte infiltration, crypt abscesses, or ulceration depending on severity. The true incidence and relative severity of pouchitis have been difficult to evaluate consistently between series, perhaps because of the variable presentation and somewhat subjective manner in which the diagnosis is often made.

Of patients who have had an IPAA for UC, perhaps as many as 40% will have at least one bout of pouchitis. Interestingly, the disease almost never occurs in patients who have undergone proctocolectomy/IPAA for familial adenomatous polyposis. At the opposite extreme, it affects as many as 80% of patients with UC who have primary sclerosing cholangitis [57]. Most patients with acute pouchitis respond promptly to a short course of oral metronidazole and/or ciprofloxacin. Chronic or relapsing acute pouchitis is less common but can be debilitating. Approximately 5–10% of patients eventually require permanent ileostomy or removal of the pouch because of intractable pouchitis [55]. The treatment of severe chronic pouchitis is often similar to that of UC or Crohn disease, including anti-inflammatory enemas,

chronic antibiotic therapy, or treatment with a biologic medication [58].

The cause of pouchitis is unknown, though the fact that it occurs almost exclusively in patients with UC would suggest a specific underlying predisposition. A small but significant percentage of patients with severe pouchitis will eventually be identified as having Crohn disease. Regardless of the etiology, stasis appears to be an important factor that increases the risk of pouchitis. This is supported by the observation that pouchitis is less common after straight ileoanal pull-through [59]. Pouchitis is also more common in the presence of an ileoanal stricture or an excessively dilated pouch. Some patients will respond to serial anal dilatations or daily rectal intubation or saline irrigation; however, surgical revision of the pouch needs to be considered in these situations. Some have found that bulking agents in the form of dietary fiber supplements reduce the incidence of pouchitis, [60] perhaps by promoting more complete evacuation of the pouch. Probiotics may decrease the risk of pouchitis; however, thus far the results of clinical trials have been mixed [61, 62].

As many as 15–20% of children who undergo IPAA will eventually be found to have Crohn disease, developing complications after IPAA including pouchitis, sinus tracts, fistulae, and pelvic abscess [63, 64]. Although some respond well to standard medical therapy, many will eventually require the removal of the pouch and permanent ileostomy. Similarly, many consider indeterminate colitis a contraindication to IPAA, though there are some who advocate the use of pelvic pouch procedures in this subgroup of patients, citing an acceptable complication rate [65]. The presence of terminal ileitis ("backwash" ileitis) at operation does not appear to increase the risk of complications, pouchitis, or pouch failure [63, 66]. Patients who develop severe or recurrent pouchitis, anal fistula, or pelvic sepsis after IPAA should be evaluated for Crohn disease with small intestinal imaging, upper and lower endoscopy with biopsies, and serologic analysis for markers of Crohn disease.

Carcinoma

Long-term complications of UC include colorectal carcinoma. Patients with UC are recommended to have a yearly colonoscopy with frequent biopsies starting several years after the onset of symptoms, and cancer is an indication for colectomy in patients with UC [67]. Patients with high-grade dysplasia are at high risk for carcinoma and are also recommended to undergo colectomy. Those with low-grade dysplasia are observed more closely with colonoscopy every 6 months, though there are proponents of colectomy for these patients as well [68]. Although malignancy is rarely an issue in children, there are several important considerations for the pediatric gastroenterologist. First, as the incidence of UC is increasing [69] and increasingly affecting younger patients, it is more likely that patients will need to begin the surveillance in adolescence. Secondly, patients who undergo IPAA using a double-stapled technique invariably have a 1–2 cm cuff of native rectal mucosa distal to the ileal pouch anastomosis, which necessitates lifelong surveillance because of the risk of dysplasia or cancer within the remnant. Because of the obvious long-term implications, this is an important technical detail that should be passed along to the patient. Lastly, there are occasional reports of cancer developing within the ileal pouch itself or at the ileoanal anastomosis, [70, 71] suggesting that the risk of carcinoma can never be completely eliminated in patients with UC. Patients should therefore undergo periodic endoscopic evaluation of the pouch with biopsies, although the frequency of these assessments has not been standardized [72].

Current Trends and Future Considerations

Patients with UC who have undergone IPAA surgery as children are now able to be evaluated as adults. Several series have reported a significant incidence of infertility in women who have undergone ileoanal pouch procedures, [73–75] with some early series suggesting that the risk is double of what is expected for women matched for age and severity of disease who are treated medically. However, more recent studies suggest the effect is smaller now [76]. The risk of infertility is considerably higher for women with UC who undergo IPAA compared to those with familial polyposis and to those who have had an ileorectostomy. The risk is also significantly higher for those who require an intraoperative blood transfusion. The cause of infertility in these cases is unclear. It is thought that the degree of pelvic surgical dissection might generate adhesions, which are known to have a negative impact on fertility. This has led some groups to adopt empirically the use of enzymatic adhesion barriers during IPAA surgery, although there are no data to support that its use reduces infertility [77, 78]. Nevertheless, it is an issue that should be discussed with any young woman with UC who is considering surgical intervention, as they might reasonably choose to delay the operation until after they have children.

Outcomes research generally supports the view that the functional results are better and the complication rate is lower for complex operations performed at high-volume centers. The IPAA procedure is a technically demanding operation with many pitfalls and potential complications. Although there are no large series in which a direct comparison has been done specifically for IPAA in patients with UC, there appears to be a correlation between the experience of the surgeon and favorable outcomes in a variety of complex colorectal procedures [79, 80]. In addition, several studies

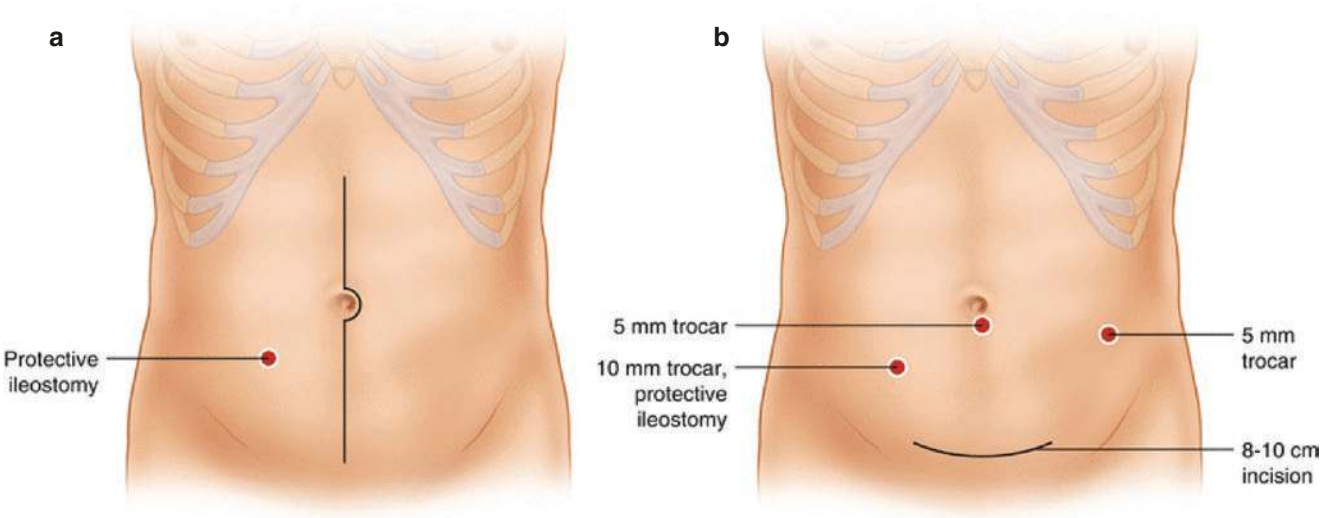

Fig. 41.4 Comparison of (**a**) the long midline incision used for the previously standard approach to open colectomy and ileal pouch-anal anastomosis operation and (**b**) the smaller incisions used during laparoscopic colectomy and ileal pouch-anal anastomosis operation(s). The right lower quadrant laparoscopic incision is used for the creation of an ileostomy. The low transverse incision is a low-transverse (Pfannenstiel) incision used for the creation of the ileoanal pouch after the colon is removed laparoscopically. It can also be used to allow the insertion of the surgeon's hand to facilitate the laparoscopic portion of the operation ("hand-assisted" laparoscopy). The primary advantage of the minimally invasive approach is improved cosmesis; other purported advantages include shorter hospital stay, faster recovery and fewer adhesions

report a significant learning curve for surgeons who perform ileoanal pouch procedures [81]. This suggests that the results of IPAA procedures that are done by experienced surgeons and at high-volume centers are likely to be better overall.

Minimally invasive surgery offers potential advantages such as less scarring, less pain, more rapid postoperative recovery, and improved cosmesis (Fig. 41.4). Many surgeons advocate the use of a laparoscopic-assisted approach, in which the colectomy is performed laparoscopically, while the more delicate pelvic dissection is done through an open incision but one that is much smaller. Although the initial results with this approach have been encouraging, it is too soon to know if the long-term functional results will be the same compared to the more standard open approach. As the technology continues to improve, minimally invasive approaches to complex colorectal surgery in children, including robotic techniques, will eventually become the standard of care for children with UC who need surgery.

Summary

The goals of surgical intervention for UC are to remove the affected organ, restore normal function, and minimize morbidity. The surgical treatment of children and adolescents with UC has improved dramatically over the past 30–40 years, mostly because of technical refinements of the ileal pouch-anal anastomosis procedure. Ileal pouch-anal anastomosis has become the standard of care for patients with UC who require surgical intervention. The majority of patients who undergo IPAA can expect to enjoy an essentially normal lifestyle, although the operation is technically demanding and can be associated with significant morbidity. Surgeons continue to strive to develop restorative operations that more closely duplicate normal anatomy and function with fewer potentially debilitating side effects.

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Postoperative Surveillance and Management of Crohn Disease

42

Benjamin Click and Miguel Regueiro

Risk and Diagnosis of Postoperative Crohn Disease

Early and more frequent use of immunomodulators and anti-tumor necrosis factor (TNF) therapies have reduced but not spared Crohn disease (CD) patients the risk of needing an intestinal resection. Recent biologic era population studies have found that the rate or probability of a first major bowel surgery in CD is still 20–30% [1, 2]. Pediatric CD progresses slower to surgery than adult-onset disease, as the reported 5-year cumulative risk for bowel surgery for pediatric CD patients is less than that for adult patients, but still significant at 13.8–47.2% and 28–34.5% at 10 years [3–6]. While the most common indication for surgery in adult CD patients is stricturing or penetrating complications, in pediatrics, inflammatory behavior, medical failure, or poor growth is cited as the most common surgical indication [7–9].

Unfortunately, CD is rarely curable by surgery, and postoperative recurrence (POR) of CD is inevitable for the majority of patients. In the prebiologic era, natural history studies found that 70–90% of CD patients developed endoscopic evidence of POR within 1 year of their surgery and that 30–60% of postoperative Crohn disease (POCD) patients became symptomatic from the recurrent disease within 3–5 years of their surgery [10–12] (Fig. 42.1). Consequently, 50% of POCD patients in the prebiologic era required repeat surgery within 5 years of their first surgery. Clinical recurrence rates for postoperative pediatric CD are equally high and identical to adult rates, reported to be 60–78% at 5 years [13, 14].

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Postoperative CD recurrence is often clinically silent. Rutgeerts and colleagues found in their initial seminal study of the natural history of postoperative recurrent CD that 72% of examined patients (21 out of 29) had recurrent endoscopic CD within 1 year of curative resection and that a remarkable number of these patients were asymptomatic [15]. In a subsequent prospective cohort of an 8-year follow-up study of 89 patients after resection, Rutgeerts et al. found that only 20% and 34% of patients were symptomatic 1 and 3 years after surgery, respectively, despite endoscopic disease in 73% and 85% of these patients [11]. More recent data from prospective clinical trials similarly demonstrated the endoscopic and clinical discrepancy, finding a kappa coefficient of agreement between the patients' endoscopic scores and their clinical Crohn Disease Activity Index (CDAI) scores was only 0.12 [16]. Thus, relying on symptoms significantly underestimates mucosal disease activity.

The degree of endoscopic disease activity correlates with progression to symptomatic recurrence. Rutgeerts et al. demonstrated that endoscopic activity at 1 year, as judged by the now classified Rutgeerts score (Table 42.1), directly correlated with the and was the most statistically significant variable in predicting outcome [11]. For example, only 8.6% of patients with no or only mild endoscopic disease at 1 year, as defined by Rutgeerts score i0 or i1, had clinical symptoms at 8 years, while 100% of patients with the severe endoscopic disease, as defined by Rutgeerts score i4, had symptomatic recurrence by 4 years. Although the Rutgeerts score has not been validated as a measure of treatment response, most studies now define endoscopic postoperative remission as i0 or i1, and recurrence as i2, i3, or i4.

These findings have largely been replicated in pediatric cohorts with endoscopic recurrence approximating 50% at 1 year, 77% at 5 years, and 94% at 10 years [9, 13]. Clinical recurrence may be more common in pediatric than adult patients with rates of 55% 1–2 years postoperatively and 50–73% by 5 years [6]. Together, these data suggest that POR follows a similar progressive course in pediatric and adult patients.

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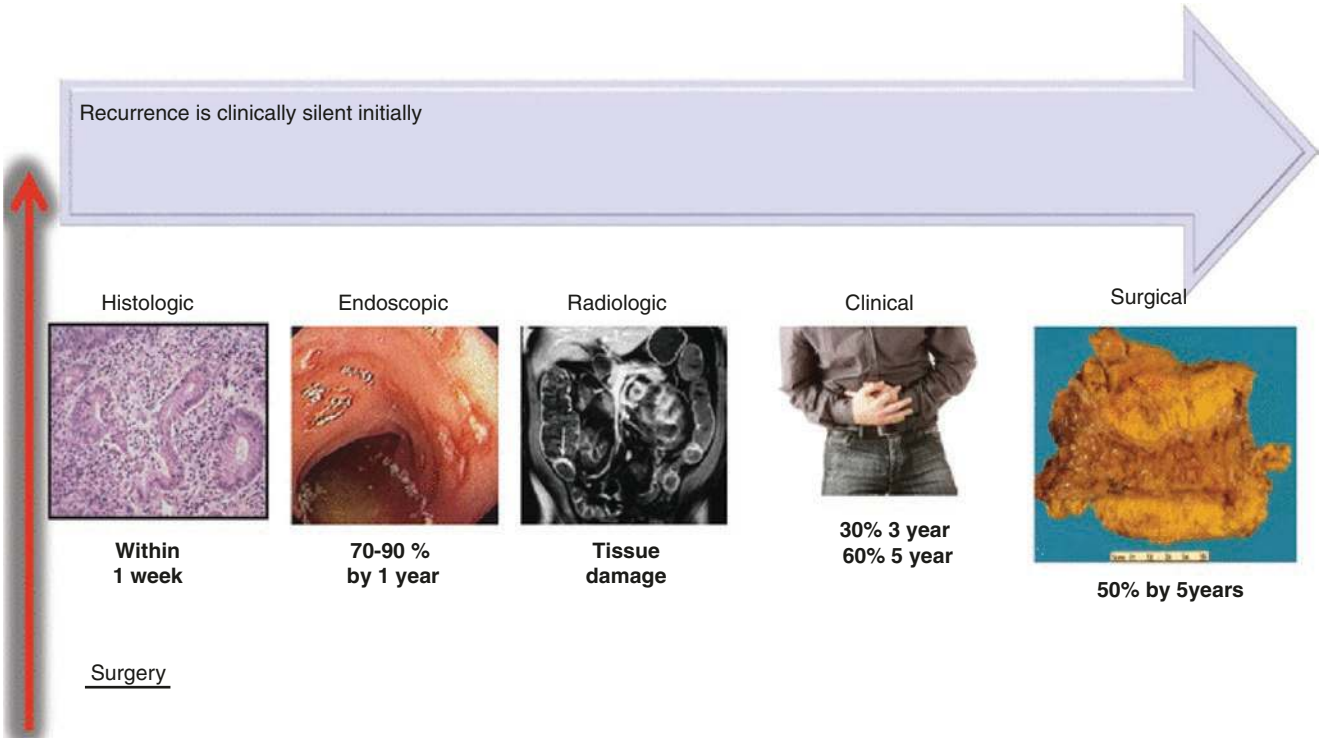

Fig. 42.1 The natural course of postoperative Crohn disease

Table 42.1 Rutgeerts postoperative Crohn disease endoscopic scoring system

Endoscopic score	Endoscopic findings
i0	No lesions
i1	≤5 aphthous lesions
i2	>5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis (i.e., <1 cm in length)
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with already larger ulcers, nodules, and/or narrowing

Since symptom assessment is an unreliable and delayed measure of POR, ileocolonoscopy utilizing the Rutgeerts scoring system is the current gold standard test for POR assessment. The Rutgeerts scoring system defines severity of disease on a 0–4 scale based on the extent of aphthous ulcerations in the neoterminal ileum (Table 42.1) [11]. Complete endoscopic remission with no lesions is classified as i0, while mild disease consisting of five or fewer aphthous ulcers is classified as i1. Moderate disease defined by more than five aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis is classified as i2. Diffuse aphthous ileitis with diffusely inflamed mucosa is classified as i3, and the most severe disease characterized by diffuse inflammation with already larger ulcers, nodules, and/or narrowing is classified as i4 disease.

Debate subsequently ensued regarding the heterogeneity of recurrence outcomes in the i2 category. Recent evaluations have suggested a modification of the Rutgeerts score to differentiate between inflammation confined to the anastomosis only, termed i2a, and disease that extends into the neo-terminal ileum, or i2b [17]. The impact of this distinction is still unclear, as some studies have suggested no difference in the risk of subsequent clinical or surgical recurrence between the two categories, while others have suggested increased recurrence risk with i2b compared to more mild disease [18, 19].

Although ileocolonoscopy is sensitive at detecting POR, the invasive nature of the test is associated with patient discomfort, high cost, and procedural risk. Thus, noninvasive assessments are of particular interest. Fecal calprotectin (fCal), produced by gut leukocytes and epithelial cells at sites of mucosal injury including Crohn disease, has been investigated as a potential noninvasive marker of POR. Early reports from small studies suggested that there was no significant difference in fCal levels between CD patients with endoscopic recurrence versus patients in endoscopic remission at 1 year after surgery [20]. In contrast, recent studies have clarified the value of this biomarker. Boschetti and colleagues examined 86 asymptomatic POCD patients within 18 months after surgery and found that patients with endo-

scopic recurrence (i2-4) had significantly higher levels of fecal calprotectin than patients in endoscopic remission (i0-1) (mean ± s.e.m.: 473 ± 78 μg/g vs. 115 ± 18 μg/g; $P < 0.0001$), and that fCal levels correlate with Rutgeerts scores ($r = 0.65$, $P < 0.0001$) [21]. The correlation of fCal and endoscopic activity has been further supported with more recent work including prospective trials and pediatric populations [22–25]. Based on available data, fCal cutoffs between 100 and 150 μg/g have been proposed, identifying endoscopic recurrence with 70–89% sensitivity, 58–69% specificity, and a negative predictive values >90% [26, 27]. Additionally, data suggest that serial fCal levels can predict early endoscopic and clinical recurrence in both pediatric and adults populations, including data as early as 2 weeks postop and demonstrates treatment response [28–31]. Thus, fCal may have a role in perioperative risk stratification, proactive monitoring, and assessing therapeutic response in POCD. Additional cytokine profiles may supplement fecal calprotectin in more accurately monitoring disease activity but these remain investigational at the current time [32].

Investigators have also studied the utility of fecal lactoferrin, a stable product of activated neutrophils, to detect POR with similar correlations to endoscopic activity as fCal, but slightly reduced accuracy [22]. Serum-derived high-sensitivity C-reactive protein has also been evaluated, but with mixed results and reduced accuracy compared to fCal [27].

Serum measurements of protein/lipid oxidation and total antioxidant capacity correlate to postoperative CD recurrence and may be pathogenic as well [33]. Other serum markers of antibacterial antibodies have been shown to be associated with severe postoperative recurrence [34]. While noninvasive biomarkers have been shown to be useful in monitoring of POR and assessing treatment response, at the current time they remain adjunctive to endoscopic monitoring.

Noninvasive radiographic studies such as small intestine contrast ultrasonography (SICUS), computed tomography (CT) or magnetic resonance (MR) enterography, and video capsule endoscopy have also been investigated to evaluate POR. Calabrese et al. reported that SICUS utilizing oral contrast detected POR, defined by increased bowel wall thickness (BWT) ((>3 mm) for at least 4 cm at the perianastomotic area), in 62 out of 67 patients with endoscopic recurrent disease (i1-4) (92.5% sensitivity), and that BWT strongly correlated with the Rutgeerts score ($r = 0.67$, $P < 0.0001$) [35]. Paredes and colleagues had similar findings in their study of contrast-enhanced US utilizing IV contrast in which they found that BWT > 5 mm or contrast enhancement >46% on US had a sensitivity, specificity, and accuracy of 98, 100, and 98.3% for the diagnosis of endoscopic recurrence (i1-4) [36]. Other reports have generated predictive models of future surgical risk based on SICUS characteristics [37]. Despite these positive findings, the use of SICUS in clinical practice in the United States remains somewhat limited due to equipment, training, reimbursement, and body habitus challenges. Both CT and MR enterography have demonstrated utility in detecting recurrent disease activity and correlate well with endoscopic activity with a correlation coefficient of 0.82 in one study [38–41]. Additionally, cross-sectional imaging can identify more proximal disease recurrence not reachable endoscopically as well as transmural and penetrating complications. Capsule endoscopy had a sensitivity of 100% in detecting POR and only had capsule retention in 2.1% of patients [42].

Risk Factors for Postoperative Recurrence

Given the high rates, but variable severity of POR, many studies have sought to elucidate factors associated with or predictive of POR. These include clinical, disease, surgical, histologic, microbiotic, and molecular characteristics.

Patient-level factors that have been suggested as increasing the POR risk include active smoking, gender, race, and family history of IBD [43]. Of these only smoking has demonstrated mostly consistent associations with disease recurrence. In a meta-analysis of nearly 3000 surgical adult CD patients, active smoking was found to nearly double the risk of clinical and surgical recurrence [44]. Endoscopic recurrence data suggest a similar doubling of recurrence rates (70% smokers at year 1 vs 35% nonsmokers) [45]. Furthermore, it is the only modifiable POR risk factor and data suggest that smoking cessation can reduce recurrence rates [45–47].

Certain disease characteristics have demonstrated association with POR. Younger age at disease onset has demonstrated conflicting findings, potentially related to duration of follow-up [3, 4, 43]. Rapid progression from disease onset to surgical indication has been shown in multiple studies to associate with recurrence risk, though varying timeframes have been proposed, with most data suggesting disease duration <10 years as a risk for POR [48, 49]. A history of prior surgical resections for Crohn's has been shown in multiple retrospective and prospective studies to correlate with POR risk and may impart the strongest risk for POR [43, 50]. Both disease location and length of diseased segment prior to surgery have also been evaluated with conflicting results. Some pediatric studies suggest colonic disease as a risk factor, whereas others concluded distal colonic or upper gastrointestinal tract involvement were protective [3, 4]. High clinical disease activity in pediatric populations has similarly described disparate associations with surgical risk [13]. Preoperative medical therapies including corticosteroids or thiopurines have been associated with increased risk, whereas preoperative infliximab and mesalamine were associated with decreased surgical risk [3, 13, 51]. The latter

finding may be related to disease activity control. Complex disease behavior has been consistently associated with increased surgical risk and in meta-analysis, penetrating disease behavior (fistula, abscess) at the time of surgery was associated with increased clinical and surgical recurrence (HR 1.50; 95% CI 1.16–1.93) [52].

Surgery-related factors including surgical approach, radical versus conservative resection margins, perioperative blood transfusions, and postoperative complications have not demonstrated consistent influence on POR. Emerging data evaluating the role of the resective technique and anastomotic configuration have generated provocative results. In a single-retrospective surgical cohort comparing extended mesenteric excision to conventional mesenteric division flush with the mesentery, Coffey and colleagues found significantly lower rates of surgical recurrence with extended mesenteric excision (2.9% vs 40%, $P = 0.003$) [53]. Prospective trials are underway to validate these findings. A recently described novel antimesenteric functional end-to-end anastomosis technique, termed the Kono-S anastomosis, has been associated with significant reduction in endoscopic and surgical recurrence compared to conventional anastomosis [54–56]. In a prospective randomized clinical trial, the Kono-S group had significantly fewer endoscopic recurrence than stapled side-to-side anastomosis (22.2% vs 62.8% at 6 months, respectively) and those recurrences were less often severe (Rutgeerts score $\geq$ i3) (13.8% vs 34.8%, $P = 0.03$), suggesting a potential role for surgical technique selection in CD [57].

Histologic findings including granulomas both in the resected specimen as well and lymph nodes have been associated with modestly higher recurrence rates (OR 1.37; 95% CI 1.02–1.82) [58, 59]. Myenteric and submucosal plexitis have been associated with recurrence in several studies and the plexitis severity may correlate with subsequent endoscopic activity [59–62]. Histologically positive resection margins have been suggested as a risk factor including several recent prospective cohorts [63]. In the prospective REMIND cohort, transmural extent of proximal margin involvement is associated with increased endoscopic recurrence rate [64]. In an analysis of over 500 primary ileocecal resections, microscopic margin positivity was associated with both clinical (HR 2.16; 95% CI 1.14–2.43) and surgical recurrence (HR 2.99; 95% CI 1.36–6.54) [65].

Serologic markers such as anti-Saccharomyces cerevisiae antibodies (ASCA), E. coli (Omp-C), Pseudomonas (I2), flagellin (cBIR), and the anti-glycan antibodies have been explored largely with negative or mixed findings in adult patients [43]. In pediatric populations, the serologic association has been more consistently demonstrated, with risk conveyed potentially related to immune reactivity as measured by serologic markers [66].

Several studies have sought to elucidate the role of IBD genetic risk loci in influencing POR risk. The *NOD2/CARD15* mutations have been associated with higher surgical recurrence rates (OR 3.29; 95% CI 1.13–9.56) and earlier time to repeat surgery in both adult and pediatric cohorts [67–71]. This affect may be further mediated by smoking [72]. Another study suggested *CARD8* homozygosity may also influence POR risk [73].

The role and influence of the microbiome on POR are being actively investigated. Investigators have described recurrence being associated with elevated levels of Proteus, Lachnospiraceae, Fusobacteria, and reduced Faecalibacterium [74–76]. Recently, interest in a novel *Escherichia coli* strain has garnered interest in POCD. Furthermore, the microbial differences may also be influenced by active smoking, suggesting a risk factor interaction. Adherent-invasive *E. coli* (AIEC) has been implicated in CD pathogenesis in both adult and pediatric populations with a prevalence estimated between 36 and 90% individuals when using mucosa-associated and intracellular detection methods [77]. Unique molecular mechanisms allow AIEC to overcolonize intestinal epithelium, form biofilms, invade the lamina propria, and stimulate immune responses [78, 79]. Prospective trials manipulating AIEC to prevent POR are currently underway (NCT03943446).

Similarly, other "-omics" and their relationship to POR are being evaluated including urinary metabolics, ileal tissue and peripheral blood transcriptomics, and others [80–84]. Thus, the future predictive ability will likely improve with incorporation of these various factors that currently remain investigative.

Risk Stratification for Postoperative Recurrence

Given the natural predisposition for POR and associated risk factors, risk stratification has been proposed by many authors and adopted in recent adult gastroenterological societal guidelines [85]. Patients at high risk for recurrence include those who are younger (<30 years), active smoking, two or more prior surgical resections, penetrating disease, with or without perianal disease. Patients deemed low risk include older (>50 years), nonsmokers, first surgery for short segment (<10 to 20 cm) of fibrostenotic disease, and disease duration for greater than 10 years. Inherently, pediatric patients meet age of onset risk criteria and such strata have not been validated in pediatric cohorts. It is the authors' opinion that similar disease phenotypic criteria apply to pediatric patients. Those with multiple prior surgeries, penetrating disease, active smoking, and perianal disease likely represent a higher risk cohort. Genetic influences may confer a stronger risk for POR in pediatric populations. Such risk stratification can help identify patients warranting more aggressive treatment and monitoring after surgery.

Nonbiologic Treatment Options for Preventing Postoperative Crohn Disease

Medical therapies including antibiotics, aminosalicylates, and immunomodulators have been shown to moderately reduce the risk of clinical and endoscopic disease recurrence [86] (Table 42.2). Mesalamine is a safe but with limited efficacy in preventing POR. A Cochrane analysis by Doherty et al. found that mesalamine does reduce clinical recurrence (RR 0.76; 95% CI 0.62–0.94) and severe endoscopic recurrence (RR 0.50; 95% CI 0.29–0.84) compared to placebo, but with a number needed to treat (NNT) of 12 and 8, respectively [87]. A subsequent systemic review and meta-analysis by Ford et al. concluded that mesalamine is of only modest benefit in preventing POR compared to placebo and should only be considered if immunosuppressive therapy is not warranted or is contraindicated [78].

In the aforementioned Cochrane analysis, thiopurine therapy with azathioprine (AZA)/6-mercaptopurine (6-MP) was found to significantly reduce clinical recurrence (RR 0.59; 95% CI 0.38–0.92, NNT = 7) and severe endoscopic recurrence (RR 0.64; 95 CI 0.44–0.92, NNT = 4) compared to placebo and was found to be superior to mesalamine [87]. Similar findings were reported by Peyrin-Biroulet et al. in a concurrent meta-analysis of four controlled trials, in which AZA/6-MP was determined to be more effective than placebo for preventing clinical recurrence at 1 year (mean difference, 95% CI: 8, 1–15%, P = 0.021, NNT = 13) and 2 years (mean difference, 95% CI: 13%, 2–24%, P = 0.018, NNT = 8) after surgery, and endoscopic recurrence (i2-4) (mean difference, 95% CI: 23%, 9–37%, P = 0.0016, NNT = 4) at 1 year after surgery [88].

Metronidazole (20 mg/kg) may significantly reduce the incidence of severe (i3-4) endoscopic recurrent disease compared to placebo-treated patients at 3 months after surgery (3 of 23; 13% vs. 12 of 28; 43%; P = 0.02), and clinical recurrence at 1 year (1 of 23; 4% vs. 7 of 28; 25%; P = 0.044) [89]. Combining metronidazole with AZA may improve outcomes further. POCD patients treated with metronidazole for 3 months and AZA (100–150 mg qd dependent on body mass) for 12 months had significantly less endoscopic recurrent disease (i2-4) at 1 year after surgery than patients treated with metronidazole alone at 1 year after surgery (14 of 32; 43.7% vs. 20 of 29; 69.0%; P = 0.048) [90]. The limitation of metronidazole is that patients often do not tolerate high doses, can develop neuropathies with prolonged exposure, and long-term prevention of recurrence is lost when the antibiotic is stopped. Recent observational data have suggested that lower dose metronidazole (250 mg TID) may confer similar risk reduction compared to placebo, but still associated with an adverse event rate of 22% and discontinuation in 8% [91]. Ornidazole, a nitroimidazole antibiotic with theoretically lower side effects, has been evaluated the prevention of POR. Ornidazole (1 g/day) compared to placebo reduced endoscopic recurrence at 1 year (OR 0.31, 95% CI 0.10–0.94, p = 0.037,) and clinical recurrence at 1 year (OR 0.14, CI 0.037–0.0546, p = 0.005) [92]. However, importantly, a significant portion of patients dropped out of the study due to side effects, primarily neuropathies and dysgeusia.

Probiotics to modulate the microbiome in efforts to prevent POR have largely been unsuccessful. *Lactobacillus johnsonii* LA1 compared to placebo showed similar rates of endoscopic recurrence at 6 months (64% vs 49%, p = 0.15) [93]. Lactobacillus GG had similar null results (60% endoscopic recurrence vs 35.3% on placebo p = 0.297) [94]. Given that single probiotic formulations were ineffective, a probi-

Table 42.2 Risk factors explored for association with postoperative recurrence

Factor category	Risk factor associated
Patient	Age
	Sex
	Race
	Family history of IBD
	Active smoking
Disease	Age of disease onset
	Time to surgery from diagnosis
	Prior surgical resection
	Disease location
	Anatomic extent involved/length of resection
	Clinical activity at surgery
	Prior medical therapies
	Disease behavior
Genetics	NOD2/CARD15
	CARD8
Serology	Anti-Saccharomyces cerevisiae (ASCA)
	Outer membrane protein C (Omp-C)
	Pseudomonas I2
	Anti-flagellin (cBIR)
	Anti-glycan
Microbiome	Proteus
	Lachnospiraceae
	Fusobacteria
	Faecalibacterium
Operative intervention	Surgical approach (laparoscopic vs laparotomy)
	Blood transfusion requirement
	Excision margin length
	Perioperative complication
	Anastomotic orientation, technique
	Mesenteric excision extent
	Strictureplasty
Histology	Margin involvement
	Granulomas
	Myenteric and submucosal plexitis
	Transmural inflammation
Other "-omics"	Tissue transcriptomics
	Blood transcriptomics
	Urinary metabolomics

otic VSL#3, a formulation of eight different probiotic species, was studied. Endoscopic recurrence was similar in patients treated with VSL#3 for 3 months compared to placebo (9.3% vs 15.7%, $p = 0.19$), despite a reduction in proinflammatory cytokines in the VSL#3 group [95]. Ongoing studies of the characterization and manipulation of the neoterminal ileum and anastomotic microbiome are being conducted.

Other studies have investigated the potential for anti-inflammatory supplements to reduce recurrence rates. Vitamin D deficiency is common in IBD, supplementation is safe, and preclinical studies of high-dose supplementation suggest anti-inflammatory properties. However, Vitamin D at a dose of 25,000 IU weekly failed to demonstrate superiority over placebo to prevent endoscopic (58% vs 66%, $p = 0.37$) or clinical recurrence (18.1% vs 18.6%, $p = 0.91$) at 26 weeks in a prospective randomized trial [96]. Similarly, curcumin, an anti-inflammatory derivative of turmeric with clinical evidence in treating ulcerative colitis, was evaluated in addition to azathioprine to prevent recurrence in a prospective placebo-controlled trial [97, 98]. There was no benefit to curcumin to prevent endoscopic or clinical recurrence and the trial was discontinued early due to futility.

Anti-TNFs for Prevention of Postoperative Crohn Disease

Growing evidence demonstrates that anti-TNF therapy is the most effective treatment to prevent POR and may have the potential to change the natural course of Crohn disease after surgery. Since Sorrentino and colleagues first reported the successful use of prophylactic IFX in a Crohn's colitis patient after a partial colonic resection [99], multiple small randomized and prospective open-label trials have found that IFX and adalimumab (ADA) are superior to placebo, mesalamine, and AZA at preventing POR (Table 42.3) [38, 100–107]. Regueiro and colleagues performed the first randomized placebo-controlled trial examining the ability of IFX (5 mg/kg every 8 weeks) to prevent endoscopic recurrence of Crohn disease at 1 year after ileal resection [103]. In a relatively small study of patients with ileal or ileocolonic disease at moderate to high risk for disease recurrence, the rate of endoscopic recurrence (i2-4) was significantly lower in IFX-treated patients (9.1%, $n = 11$) compared to the placebo group (84.6%, $n = 13$) ($P = 0.0006$). Several other small randomized studies verified that infliximab prevents POR [100, 107]. The protective effects of IFX appear to be a class effect of TNF inhibitors, as ADA has also been found to prevent POR in several small open-label and randomized studies [102, 104, 105]. Overall, anti-TNF therapy is the most effective treatment to prevent POR as verified by recent systematic review and network meta-analysis examining the comparative efficacy of all drugs studied to prevent POR [33] (Table 42.4).

Table 42.3 Summary of nonbiologic postoperative Crohn disease clinical and endoscopic recurrence rates from randomized controlled trials

Intervention	Clinical recurrence (%)	Endoscopic recurrence (%)
Placebo	25–77	53–79
5-ASA	24–58	63–66
Budesonide	19–32	52–57
Nitroimidazole	7–8	52–54
AZA/6-MP	34–50	42–44

Table 42.4 Postoperative Crohn prevention trials investigating the rates of endoscopic recurrence with anti-TNF therapy versus control

	Anti-TNF (%)	Control (%)
Sorrentino (MTX/IFX vs. 5-ASA 2 year)	0	100 (5-ASA)
Regueiro (IFX vs. PBO RCT 1 year)	9	85 (PBO)
Yoshida (IFX vs. PBO Open 1 year)	21	81 (5-ASA)
Armuzzi (IFX vs. AZA Open 1 year)	9	40 (AZA)
Fernandez-Blanco (ADA)	10	N/A
Papamichael (ADA 6 months)	0	N/A
Savarino (ADA 3 year)	0	N/A
Aguas (ADA 1 year)	21	N/A
De Cruz (ADA vs. AZA 6 months)	6	38 (AZA)
Savarino (ADA vs. AZA vs. 5-ASA 2 years)	6	65 (AZA), 83 (5-ASA)

Abbreviations: *MTX* methotrexate, *PBO* placebo, *5-ASA* aminosalicylates

The efficacy of prophylactic anti-TNF therapy to prevent endoscopic POR has been supported by the PREVENT study, the largest randomized placebo-controlled POR-preventive treatment trial to date [108]. The PREVENT study was a multicenter trial that enrolled 297 CD patients who had undergone ileocolonic resection and were at increased risk for POR. One hundred forty-seven patients were randomized to receive IFX (5 mg/kg every 8 weeks), and 150 patients were randomized to receive placebo treatment for a 200-week treatment period. The primary endpoint was clinical recurrence prior to or at week 76 defined by Crohn disease activity index (CDAI) score and endoscopic recurrence (i2-4), or the development of a fistula or abscess. The secondary endpoint was endoscopic recurrence alone (i2-4) prior to or at week 76. The study reported that the proportion of subjects with clinical recurrence was numerically lower in the IFX group compared with the placebo group, but the difference was not statistically significant (12.9% vs. 20.4%, $P = 0.097$) (Fig. 42.2). However, IFX treatment significantly reduced endoscopic recurrence compared to placebo treatment (22.4% vs. 51.3%, $P < 0.001$) (Fig. 42.3). Of patients who had a score of i0, there were more receiving IFX than placebo (83.1% vs. 28.4%). Of patients who had

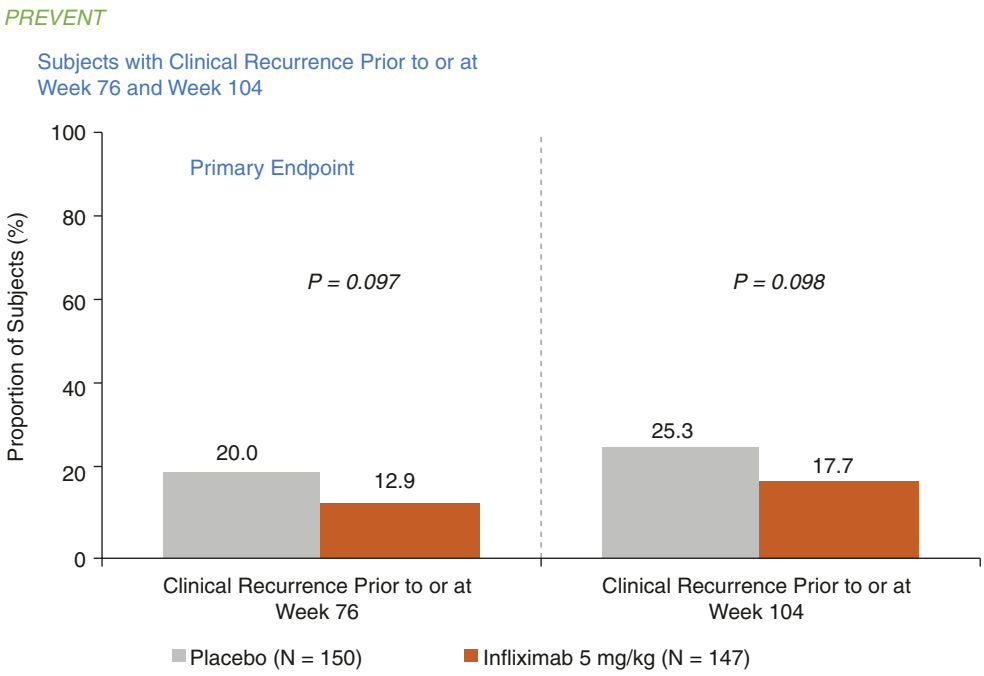

Fig. 42.2 Clinical recurrence was reduced in infliximab-treated patients in the PREVENT study. *P*-values based on the Cochran-Mantel-Haenszel chi-square test stratified by the number of risk factors for recurrence of active CD (1 or >1) and baseline use (yes/no) of an immunosuppressive (i.e., AZA, 6-MP, or MTX)

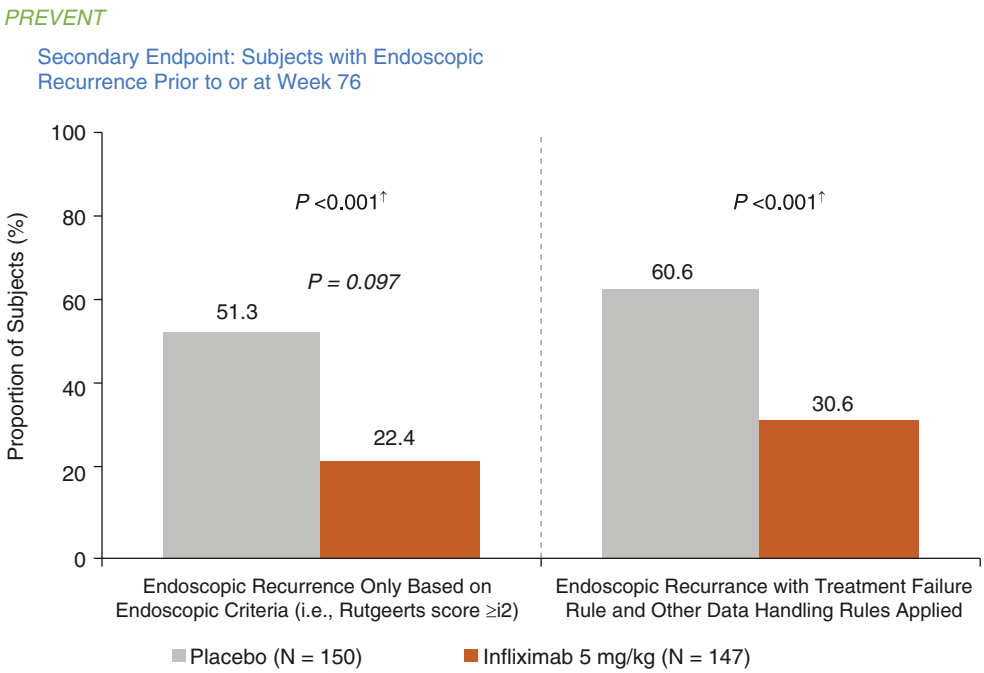

Fig. 42.3 Endoscopic recurrence was significantly reduced in infliximab-treated patients in the PREVENT study. †Nominal *p*-values based on the Cochran-Mantel-Haenszel chi-square test stratified by the number of risk factors for recurrence of active CD (1 or >1) and baseline use (yes/no) of an immunosuppressive (i.e., AZA, 6-MP, or MTX)

more aggressive recurrence, i3 or i4, there were fewer receiving IFX than placebo (16.9% vs. 71.6%). Accordingly, the authors recommend anti-TNF therapy as first-line prophylactic therapy for patients at high risk for POR if no contraindication or documented primary failure previously.

With an increasingly anti-TNF-experienced patient population, there is interest in the efficacy of other monoclonal antibodies to prevent postoperative Crohn disease. In several retrospective studies, postoperative vedolizumab or ustekinumab prophylaxis was associated with higher endoscopic recurrence rates than anti-TNF-treated patients; however, significant retrospective limitations and biases prohibit full interpretation [109, 110]. In a study examining retrospective ustekinumab for POR prophylaxis compared to an azathioprine-treated population as part of a randomized prospective trial, the authors found significantly reduced endoscopic POR at 6 months in ustekinumab compared to azathioprine; however, this risk reduction was not seen for

severe (i3-i4) POR [111]. Prospective studies are underway to better ascertain the role of the alternative mechanisms of action in preventing POR.

Safety of Postoperative Anti-TNFs

The risks versus benefits of continuing prophylactic anti-TNF therapy in patients in long-term remission have also been called into question, considering the cost of treatment and potential for rare, but serious, side effects. Long-term safety data for IFX in the treatment of Crohn disease demonstrate that IFX therapy is associated with a moderate risk for infection, is associated with small increases in the risks of lymphoma and melanoma, but does not increase the risk of mortality [112–115]. Severe Crohn disease and prednisone and narcotic use are associated with a higher risk of infection than IFX therapy, and thus one could argue that the benefits of IFX to prevent severe recurrent disease outweighs the infection risk. In the initial postoperative IFX study, there was no increased risk of adverse events in IFX-treated patients compared to placebo, including postoperative complications up to 1 year after surgery [116, 117]. In the PREVENT trial, rates of adverse events, serious adverse events, infection, and serious infections were similar between infliximab and placebo arms, though more infliximab subjects discontinued therapy due to adverse events [108]. Preventive anti-TNF therapy has been found to be relatively safe in other postoperative studies, including the study of ADA by Savarino and colleagues who reported that ADA-treated patients had fewer adverse events than the azathioprine-treated and mesalamine-treated patients over a 2-year follow-up period [104].

In contrast, the risks of stopping postoperative anti-TNF therapy appear to be higher than continuing treatment, as Regueiro and colleagues found that patients in remission who stop IFX are at high risk for recurrent disease. After completion of the 1-year study, patients were permitted to discontinue (or start) IFX and were then followed for an additional 5 years [117]. Eight of the original 11 IFX-treated patients chose to stop therapy, and all eight developed endoscopic recurrent disease, and five subsequently required repeat surgery. The three other original IFX-treated patients continued their treatment, and none required repeat surgery during the study period. Twelve of the original 13 placebo patients had recurrence and chose to start IFX; seven of these patients achieved endoscopic remission and required no repeat surgery during the study period. Overall, Regueiro et al. found that patients who were treated with IFX for at least 60% of the 5-year study period had a significantly lower risk for repeat surgery, irrespective of their original treatment assignment (20.0% vs. 64.3%, $P = 0.047$). Sorrentino and colleagues found a similar high risk of recurrence, as they reported that 83% of patients ($n = 12$), who were previously in remission for 3 years after surgery on IFX, developed endoscopic recurrent disease 16 weeks after stopping treatment [99].

Enteral Nutrition for Postoperative Crohn Disease

Enteral nutrition in the prevention of CD POR has also been evaluated in several small Japanese studies. One trial of 40 adult patients all receiving mesalamine in the postoperative period, assessed nocturnal self-intubation and infusion of elemental enteral feeding and found that high-volume enteral nutrition (>1200 kcal/day) significantly reduces postoperative endoscopic recurrence compared to low- or no-volume enteral nutrition (<1200 kcal/day) ($p = 0.02$) [118]. A similar non-randomized study of 40 adult Japanese patients found that enteral nutrition significantly reduces endoscopic recurrence at 12 months compared to no therapy (30% vs 70%, $p = 0.027$) [119]. In regards to surgical recurrence, another study found that enteral nutrition compared to placebo reduced recurrence but without statistical significance ($p = 0.08$). The placebo group in this study had a significantly higher cumulative recurrence rate requiring infliximab ($p = 0.03$) suggesting that enteral nutrition may have a role in supplementing or replacing pharmacologic prophylaxis [72, 120]. Limitations to these studies include small and highly motivated adult populations willing to self-intubate nasogastric apparatuses nightly and infuse enteric formulas for indefinite time. It remains to be seen how such findings and management could translate to pediatric or Western cultures. Future large randomized control trials assessing enteral nutrition as a non-pharmacologic therapy are necessary to determine its role in preventing and treating postoperative Crohn disease recurrence (Table 42.5).

Table 42.5 Efficacy of various therapies and knowledge gaps for the prevention and treatment of postoperative recurrence

Therapy/intervention	POR prevention	Treatment of POR
Curcumin	–	?
Enteral nutrition	+	?
Probiotics	–	?
Nitroimidazole/antibiotics	+	–
Mesalamine	–	–
Budesonide	–	?[a]
Thiopurines	+	+
Anti-TNF	+++	+++
Vedolizumab	++?	?
Ustekinumab	++?	?

[a]Authors opinion. Budesonide may be used for short-term induction therapy, but similar to luminal ileal CD, is not likely effective for long-term therapy

Treating Postoperative Crohn Disease: Waiting for Endoscopic Recurrence

Postoperative natural history studies have taught us that most *but not all* patients will develop recurrent disease. Thus, initiating anti-TNF therapy in all postoperative Crohn disease patients would certainly mean overtreating a subset [121]. Relevant to this concern, it is not known whether prophylactic anti-TNF therapy is more effective than waiting to treat recurrent disease. Yamamoto et al. investigated the impact of IFX therapy on Crohn's patients in clinical remission but who had endoscopic recurrent disease 6 months after ileocolonic resection despite prophylactic mesalamine therapy (3 g/day) [122]. Eight such patients were started on IFX (5 mg/kg every 8 weeks), another eight were started on AZA (50 mg/day), and the remainder was maintained only on mesalamine. They found that infliximab induced complete endoscopic remission in 38%, 6 months after starting treatment, compared to only 13% of AZA-treated patients and 0% of mesalamine-treated patients ($P = 0.10$). Sorrentino and colleagues found similar results when they treated patients with endoscopic disease 6 months after surgery with either IFX (5 mg/kg every 8 weeks) or mesalamine (2.4 g/day) [123]. Fifty-four percent of the infliximab-treated patients ($n = 13$) were in endoscopic remission 1 year after starting treatment compared to 0% of mesalamine-treated patients ($n = 11$) ($P = 0.01$). Adalimumab appears to be equally effective in treating early recurrent disease, as Papamichael et al. showed in their study that ADA promoted endoscopic healing in 60% of treated patients ($n = 15$) who had endoscopic disease 6 months after surgery [102]. Overall, these studies suggest that anti-TNF therapy may be effective at treating early recurrent disease in certain patients, but response is often not complete or universal.

The timing of the first colonoscopy after surgery to detect endoscopic recurrence and prevent progression was assessed in the pivotal POCER study [101]. The primary endpoint was endoscopic recurrence at 18 months. In the trial, 174 postoperative patients were randomly assigned in a 2:1 ratio to either a standard care or active care arm. The active care arm had patients undergo a colonoscopy at 6 months, and if there was active Crohn disease (≥ i2), they had a step up in their therapy, for example, starting AZA/6-MP if previously on no medication or adding ADA to AZA/6-MP. The standard care arm did not undergo a 6-month colonoscopy and only had the 18-month colonoscopy. Both study arms were given metronidazole 400 mg twice a day for 3 months. If patients were intolerant, the dose was reduced to 200 mg twice daily, or was stopped altogether. If they were of high risk (smokers or recurrent surgery or penetrating disease) but medication-naive, patients were given AZA 2 mg/kg or 6-MP 1.5 mg/kg once daily, beginning within 1 month after surgery. Patients intolerant to this regimen were administered ADA 160 mg/80 mg induction followed by 40 mg every other week. Patients without any risk factors for postoperative recurrence, that is, nonsmokers, first surgery, and absence of penetrating disease, received no additional treatment beyond 3 months of metronidazole. The 18-month primary endpoint of endoscopic recurrence was significantly lower in the active care arm compared with the standard care arm (49% vs. 67%, $p = 0.03$). Although not an endpoint of the study, it was interesting that the 6-month postoperative endoscopic recurrence rates for patients receiving AZA/6-MP and ADA were consistent to what has been previously reported (45% vs. 21%). This data suggests that early colonoscopy at 6 months with adjustment in therapy based on findings improves subsequent recurrence rates and may alter the course of postoperative Crohn disease.

Strategies for Postoperative Crohn Disease Management

The questions that remain in the practical management of postoperative Crohn disease are: (1) which patients should receive immediate postoperative therapy, and (2) which patients would it be reasonable to wait to treat endoscopic recurrence? The current prevailing strategy for postoperative Crohn disease management is to stratify postoperative treatment based on risk and treat only those patients at high risk for recurrence with prophylactic medical therapy (Fig. 42.4). Low-risk patients would not initiate medical therapy but undergo early monitoring for POR.

In high risk patients who are receiving preoperative biologic therapy and plan to utilize biologic therapy postoperatively, it is imperative to distinguish therapeutic failure (e.g., active disease progression despite adequate drug exposure) from failure due to preexisting damage (e.g., fibrostenotic stricture) or complication (e.g., penetrating disease). It is the authors opinion that with preexisting stricture or complication, the preoperative biologic exposure does not necessarily represent a failure and the agent or class may be continued postoperatively for prophylaxis, particularly for anti-TNFs (+/− immunomodulator) due to the wealth of evidence for their efficacy in POR. In this situation, the authors also frequently continue the biologic dosing throughout the perioperative period after discussing with the surgical team. Despite historical concerns about risk of perioperative complications with biologics, more recent large prospective studies controlling for confounding factors (e.g., malnutrition, steroids) have not seen such an effect [124]. With verified therapeutic failure, the biologic mechanism of action should be changed postoperatively. If anti-TNFs were used preoperatively, one could consider non-anti-TNF agents despite the relative paucity of postop data for either vedolizumab or ustekinumab.

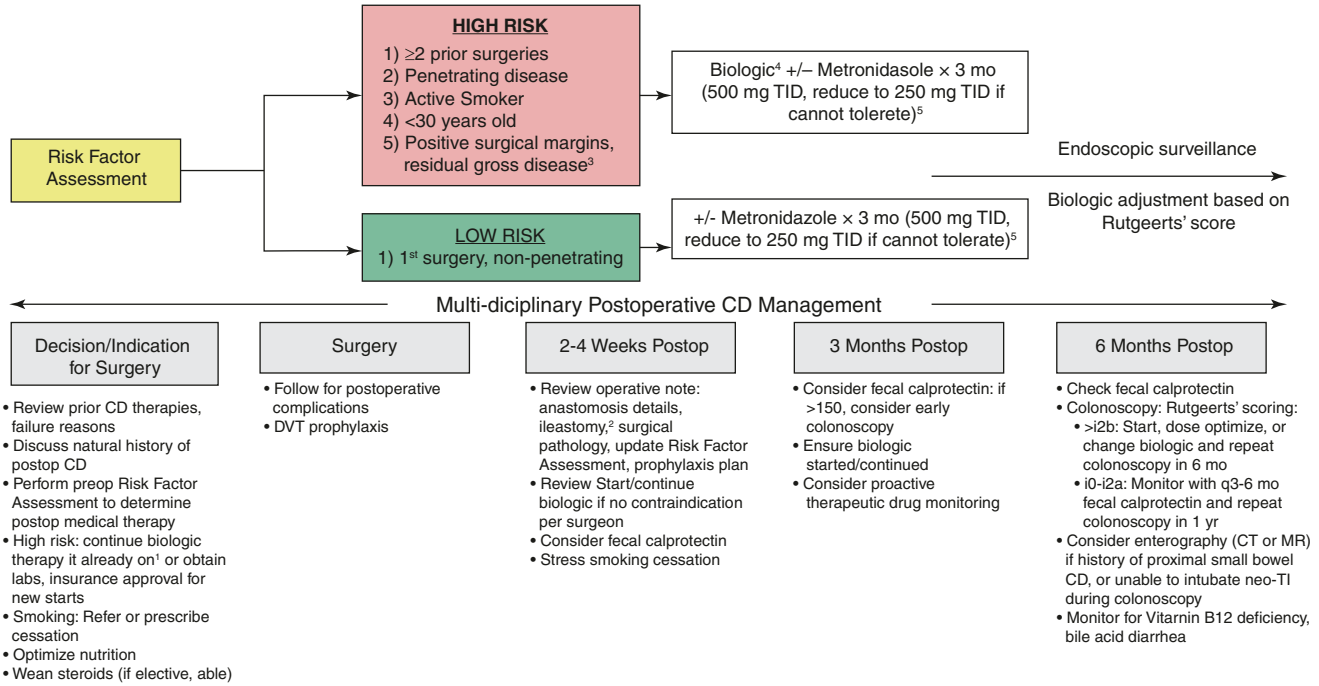

Fig. 42.4 Proposed algorithm for the management of postoperative Crohn disease. Low risk of postop recurrence defined by long-standing Crohn disease, first surgery, and short stricture. High risk defined by multiple prior resections, penetrating disease, active cigarette smoking, young age or with confirmed microscopic or gross disease left in situ. [1]If plan to continue biologic therapy as postop prophylaxis, continue biologic dosing after multidisciplinary discussion with surgeon. If preop biologic deemed failure due to active disease progression while on agent, consider change in biologic class postoperatively. [2]If diverting loop ileostomy present, can delay biologic initiation and postop timeline until ileostomy take down. [3]For other potential risk factors (e.g. myenteric plexitis, transmural involvement), consider early postop monitoring with calprotectin. [4]If no contraindication, prior failure, or other indication, consider anti-tumor necrosis factor therapy ± immunomodulator as first line. Otherwise, consider other biologics despite limited data in postop setting. [5]Authors also consider implementing dietary strategies including Mediterranean diet, Crohn's Elimination Diet, or Specific Carbohydrate Diet based on luminal CD evidence, despite limited data in postop setting

For individuals at high risk, or with surgical or histologic risk factors for recurrence that are awaiting larger validation studies (e.g., myenteric plexitis, transmural lesions, granulomas), one can consider incorporating early biomarker monitoring with fecal calprotectin at 3 months postop. If calprotectin elevated >150 μg/mL, earlier colonoscopy (prior to month 6) to evaluate for recurrence is reasonable though prospective studies have not validated this approach to reduce subsequent recurrence compared to waiting until 6 months.

Individuals identified as low risk for POR would refrain from prophylactic biologic therapy and instead consider metronidazole therapy (20 mg/kg or approximately 500 mg TID) for at least 3 months. If unable to tolerate this dose due to side effects, dosing can be decreased to 250 mg TID. The benefit of postoperative metronidazole appears to be limited to the duration of time the patient is actively taking the medication. As such, POR is likely delayed by postoperative metronidazole rather than prevented. Until the microbiome-altering agent without side effects is identified, and can be sustained long-term, the use of metronidazole beyond 3 months will be limited.

All patients would then undergo a colonoscopy at 6 months from surgery. Concurrent calprotectin measurement is helpful if future biomarker monitoring is desired to align calprotectin levels to endoscopy findings. If the colonoscopy reveals active Crohn disease (≥ i2), untreated patients would be started on biologic therapy, and those receiving prophylactic biologic therapy would undergo therapeutic drug monitoring, dose optimization, or change in biologic agent. Disease activity monitoring with repeat colonoscopy could occur in 6 months to verify mucosal improvement. Those without endoscopic recurrence could be monitored with serial calprotectin every 3–6 months and ongoing colonoscopy surveillance in 1 year with subsequent intervals determined by findings. In individuals with prior proximal CD or incomplete colonoscopies, cross-sectional imaging with enterography (CT or MR) offers a relatively sensitive and accurate detection of POR.

Conclusions

Despite medical and management advances, a significant portion of CD patients require resective surgery. Postoperative recurrence of CD is common, often silent, and requires appropriate therapeutic and monitoring strategies to prevent disease progression. Preoperative risk stratification can help identify patients who may benefit most from prophylactic medical therapy postoperatively. To date, infliximab has been the only biologic prospectively studied for prevention of Crohn disease in high risk patients. Ongoing surveillance with colonoscopy starting at 6 months postoperatively with or without biomarker monitoring allows for early recurrence identification and treatment. There remain many key knowledge gaps in risk factors, biomarkers, and management algorithms for postoperative Crohn disease.

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Perioperative Immunosuppression in Inflammatory Bowel Disease

43

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Introduction

Inflammatory bowel disease (IBD), a chronic idiopathic disease of the gastrointestinal tract, is characterized by two primary phenotypes—Crohn disease (CD) and ulcerative colitis (UC). Given the pathophysiology of IBD remains largely unknown to date, therapeutics used to treat IBD target a number of different immune-mediated mechanisms. While the immunosuppressive effects of these treatment options are necessary to achieve adequate clinical, endoscopic, and histologic disease response, they also pose risk of opportunistic infection [1–3], have been associated with malignancy [4, 5], and have the potential to increase postoperative morbidity [6].

Postoperative morbidity remains a significant concern for a large number of IBD patients. This is because even with optimal medical therapy, 60–80% of patients diagnosed with CD will require intestinal resection and 20% of patients with UC will ultimately need a colectomy for medically refractory disease [7–9]. Due to the ever-expanding repertoire of monoclonal antibodies and now JAK inhibitors, patients are arriving to the operating room with increasingly advanced disease and overall clinical decompensation after trialing numerous medical therapeutics. Therefore, it is not surprising that infectious complications following major surgery for IBD occur in 20–35% of patients in large, contemporary series [10, 11].

Postoperative infectious complications can lead to long-term sequelae including readmission, reoperation, and even pouch failure in restorative proctectomy patients [12, 13]. Given the potentially devastating consequences of infection following IBD surgery, there is an essential need to understand the optimal management of immunosuppressive agents in the perioperative period. While this has been extensively reported on in the adult literature, there is limited data in pediatric surgical patients. The purpose of this chapter is to describe the known mechanisms of immunosuppression from IBD medical therapy and to assess the risk of initiating, continuing, or restarting medical therapy in the perioperative period.

Effects of Immunosuppression on Operative Outcomes in Pediatric Populations

Different pharmacologic classes suppress the immune system via distinct mechanisms and may then theoretically affect immune-related postoperative outcomes differently. Very little formal evidence exists for the impact of immunosuppression on pediatric surgical outcomes, so we have extrapolated presumed effects in children from the published adult literature when necessary.

Glucocorticoids

Glucocorticoids are a potent immunosuppressive medical therapy for IBD that have historically been the primary therapeutic intervention for acute disease exacerbations. Drugs in this class are highly lipophilic leading to excellent bioavailability and easy access to transcription factors located in cells' nuclei. Glucocorticoids bind to the glucocorticoid receptor to form a complex that then interacts with other biochemical pathways that include: inhibits proinflammatory proteins necessary to activate proinflammatory cytokines such as IL-1 and IL-8; upregulating suppressive cytokines like transforming growth factor-β3 and IL-10; and inhibit proliferation of T-lymphocyte, B-lymphocyte, and macrophages through immune tolerance [14].

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The distributed and wide-ranging effects of glucocorticoids on the immune system may explain why this drug class is also intimately associated with postoperative complications. Subramanian et al. conducted a meta-analysis of seven large observational studies combining 1714 patients that demonstrated a 68% increased likelihood of experiencing an infectious postoperative complication in IBD patients undergoing major abdominal surgery when exposed to chronic corticosteroids preoperatively. The study results also noted a dose-dependent response with those taking over 40 mg of oral prednisone experiencing more than double the risk of an infectious postoperative complication [15]. Thus, a daily dose of 20 mg prednisone has been traditionally recommended as the maximal dose of steroid exposure prior to elective IBD surgery.

Observational studies in pediatric surgical patients have also revealed an association of glucocorticoid exposure and adverse postoperative outcomes. Due to the smaller number of patients included in pediatric studies, the findings of these studies have been limited. Markel et al. identified 51 patients at their institution undergoing first-stage colectomies for UC and found that 43% of patients taking steroids preoperatively had postoperative complications versus only 9% of patients not exposed to steroids [16]. However, due to the small study population size, Markel et al. study was not able to perform multivariable analysis controlling for other variables that might explain this difference. Schaufler et al. similarly studied drug-induced immunosuppression's effect in 51 pediatric patients in their own distinct cohort. Since the vast majority of patients were on steroids, it was not possible to compare the association of steroid exposure on postoperative outcomes [17].

Immunomodulators

Immunomodulators have been a core steroid-sparing agent in IBD medical therapy, along with a preventor of antibody formation to monoclonal antibody therapy that results in a secondary loss of response [18]. The most frequently used drugs in this class include the thiopurine analogues, 6-mercaptopurine and azathioprine, and methotrexate. These drugs are grouped together based on their common pathway that leads to the inhibition of T-lymphocyte proliferation. 6-mercaptopurine and azathioprine are both metabolized to 6-thiosine 5′-monophosphate which is then converted by native lymphocyte metabolic processes into thioguanine nucleotides that disrupt normal DNA replication and synthesis [19, 20]. Similarly, methotrexate disrupts folic acid synthesis thereby impairing DNA replication in T-lymphocytes [21]. While immunomodulators have well described adverse events (e.g., hypersensitivity, T-cell lymphoma), the immunosuppressive risks of these agents are typically described as low relative to glucocorticoids. However, the relatively mild side effects of their use due to focused T-lymphocyte proliferation pathways may also explain why these agents are typically considered less effective treatments of IBD [22].

In contrast to glucocorticoids, immunomodulator use is not associated with worse perioperative outcomes. While no meta-analysis exists, surgical outcome studies that included examined immunomodulator use consistently identify no association between perioperative immunomodulator use and short-term complications [23–26]. Mahadevan et al. report one of the largest series of UC patients undergoing colectomy, and found no association of preoperative exposure to immunomodulators and adverse postoperative outcomes. In fact, patients taking immunomodulators such as azathioprine or 6-mercaptopurine preoperatively ultimately had lower complication rates than those not exposed to immunomodulators (43% versus 49%) [25].

In pediatric populations, the effects of immunomodulator use during surgical therapy for IBD has not been formally studied. However, these medications have historically been well tolerated in children, and we would not expect their immunosuppressive outcomes to vary from those of the adult populations reported above.

Monoclonal Antibodies

Monoclonal antibodies have revolutionized the medical treatment of IBD and have led to a decreased need for surgical management of IBD related to medically refractory disease [27]. However, the introduction of this new pharmacologic class with the Food and Drug Administration's (FDA) approval of infliximab over 20 years ago has led to persistent controversy of their safety in the perioperative period. Some of the controversy has resulted from a number of different targeted pathways including antibodies to tumor necrosis factor-α (TNF-α), α4B7 integrins, interleukin-12 and interleukin-23, which have the potential to result in variable infectious complications.

TNF-α inhibitors Increased production of the cytokine TNF-α results in activation of NF-κB-mediated inflammation implicated in IBD [28–30]. Inhibition of TNF-α through monoclonal antibodies (e.g., infliximab, adalimumab, and certolizumab) has had a profound impact on the outcomes and natural history for both CD and UC.

The effect of TNF-α inhibition on postoperative outcomes has been widely studied, and results have been heterogeneous. Moosvi et al. published a meta-analysis of 41 studies including 20,274 patients reported that patients exposed to anti-TNF-α therapeutics were 13% more likely to develop a postoperative complication, equating to an absolute increase in postoperative complications by 5.5% [31]. An important

caveat to these studies included in this meta-analysis is that controlling for the risk of selection bias (e.g., case severity, serum active drug levels) has been inconsistent and limited; thus, it is unclear whether the association found between anti-TNF-α and perioperative complications is a direct result of these agents or that use of these therapeutics is a surrogate marker of increased disease severity [27, 32]. Given the controversial data, if possible, most surgeons will attempt to time surgery in the middle of a dosing interval of anti-TNF-α therapeutics, maximizing the washout period while preventing antibody formation seen with prolonged discontinuation [33, 34].

These findings are similarly supported in the pediatric literature. Lightner et al. described surgical outcomes in a series of 69 pediatric patients with CD undergoing abdominal operative intervention with or without preoperative exposure to anti-TNF-α therapies within 12 weeks of surgery; the authors found no difference in postoperative infectious complications by anti-TNFα exposure [35]. Similarly, Dotlacil et al. described a Czech pediatric referral center's experience of 41 pediatric patients with CD undergoing surgery, and found no association of anti-TNF-α exposure and adverse 90-day postoperative outcomes [36].

Anti-integrins Vedolizumab, a monoclonal antibody targeting the α4B7 integrin expressed on B- and T-lymphocytes, was introduced with great fanfare because the gut-selective mechanism of action was hypothesized to have reduced systemic immunosuppression compared to any other available therapies to date [37]. However, early reports of vedolizumab's effect on postoperative outcomes were concerning. At Mayo Clinic, 94 patients with both UC and CD treated with vedolizumab within 12 weeks of surgery not only had higher rates of complications than the no biologic therapy control group, but vedolizumab-treated patients also appeared to do worse than those treated with traditional anti-TNFα biologic therapies [38, 39]. As more centers reported their results [40, 41], the findings became similarly ambiguous to the context described above for anti-TNFα biologic agents. On balance, early studies of vedolizumab were likely affected by the same selection bias risks affecting anti-TNFα biologic therapy including the potential for increased disease severity or systemic illness that was unable to be controlled for by statistical analysis. As additional time from vedolizumab's introduction has proceeded, the latest evidence suggests that perioperative risks of vedolizumab may be less than anticipated [42].

Currently, vedolizumab is not FDA approved for use in the pediatric age group but prospective trials are ongoing. Hence, even its use as an IBD medical therapy for children has only limited reporting to date [43]. An important area of future investigation will be whether anti-integrins have functional differences in risk for pediatric populations versus adult populations reported above.

Anti-interleukins Ustekinumab's introduction in 2016 led to a new class of an approved monoclonal antibody, this one targeting interleukin-12 and -23. To date, this class appears similar to both anti-TNFα agents and vedolizumab with regard to adverse postoperative outcomes. Although no pooled analyses are yet published, a multicenter study of 44 CD patients exposed to ustekinumab preoperatively was compared to 169 matched patients on anti-TNFα therapy with no statistical difference observed in the rates of postoperative complications [44]. A large single-center series of 30 CD patients taking ustekinumab were compared to 73 matched patients taking vedolizumab, and no differences were seen in postoperative complications [45].

Similar to vedolizumab, the relatively recent introduction of ustekinumab and anti-integrin IBD therapy limits the literature base for its use in pediatric patients [46]. We anticipate wider reporting of its use, and its effect on postoperative pediatric surgical outcomes, in the future.

Clinical Recommendations

Table 43.1 summarizes the clinically relevant details regarding the immunosuppressive effects of pediatric IBD medical therapy in the perioperative period. The current data in children mirrors that in adults. Glucocorticoids are the most deleterious to postoperative recovery. Monoclonal antibody therapies are unlikely to have a major impact on postoperative complications, and some evidence suggests that they have no effect. Immunomodulators contribute essentially no additional clinically significant immunosuppression to the perioperative period. JAK inhibitors remain unstudied due to their very recent approval.

These summary findings are important because they influence our recommendations for IBD medical therapy in the before and after surgery. The critical goal before surgery is to minimize the glucocorticoid burden. Finally, while studies remain ongoing, the effects of monoclonal antibody exposure on postoperative outcomes remains controversial despite an increasing number of papers on this topic. We typically mitigate any remaining monoclonal antibody risk by planning for surgery at the midpoint of a dosing interval to both minimize the circulating drug levels at time of surgery and immunosuppressive effects. However, surgery is not routinely delayed due to the presence of medical therapy alone.

Table 43.1 Drug class

Drug class	Mechanism of action	Degree of perioperative immunosuppression	Recommendation
Steroids	Intranuclear complex inhibits inflammatory cascade synthesis	+++	Ideally avoid, minimize exposure to ≤20 mg prednisone daily
Immunomodulators	Inhibition of lymphocyte proliferation via DNA replication analogues	+	Can be continued pre- and postoperatively
Biologics	Antigen-specific inflammatory cytokine inhibition	++	Schedule surgery to maximize dose-to-dose nadir during postoperative recovery (i.e., surgery at midpoint of dosing interval)

Conclusion

Optimal management of perioperative immunosuppression may minimize adverse postoperative outcomes. Importantly, decisions about perioperative care benefit from multidisciplinary collaboration pre- and postoperatively to either reduce or cease immunosuppressive regimens.Conflict of InterestDr. Lightner is a consultant for Takeda Pharmaceuticals.

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Pouchitis and Pouch-Related Complications

44

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Introduction

Total proctocolectomy with Ileal Pouch-Anal Anastomosis (IPAA) has emerged as the surgical procedure of choice for patients diagnosed with ulcerative colitis (UC) and patients with familial adenomatous polyposis syndrome (FAP) with a high burden of rectal polyps since its introduction in 1978 [1]. In pediatric patients diagnosed with ulcerative colitis, specific indications for proctocolectomy include severe disease refractory to medications, toxic megacolon, perforation, and intractable bleeding. In addition, the histopathologic findings of dysplasia or malignancy are strong indications to proceed with IPAA [2]. The latter two entities, however, are rare in pediatric patients. Patients with indeterminate colitis who undergo IPAA have a complication rate similar to that of UC unless the diagnosis of Crohn disease (CD) is ultimately made [3].

Pouch Anatomy

Initially, restorative proctocolectomy was performed using straight Ileoanal anastomosis (IAA) without the construction of a pouch. The results of multiple subsequent studies have shown the superiority of IPAA in comparison to straight ileoanal anastomosis [4, 5]. In the pediatric population, Telander et al. compared 121 children and young adults with either the straight IAA or the J-pouch procedure [4]. They found the J-pouch to be superior in relation to stool frequency and nighttime stool patterns. The IPAA procedure involves total abdominal colectomy with the upper internal anal sphincter and rectal muscular columnar cuff left intact. A pouch reservoir is then created utilizing the ileum and an anastomotic connection is made to the anus. J-type, S-type, and W-type pouch reservoirs have been fashioned, but the most common and successful procedure involves using the J-pouch (Fig. 44.1). Temporary loop ileostomies are performed at the time of pouch creation in either the two-step or three-step IPAA to facilitate healing of the anastomotic connection and are closed at a later date, typically 2–3 months. Contraindications to IPAA include a preoperative diagnosis of pelvic floor dysfunction and decreased anal sphincter muscle tone. CD is a relative but not absolute contraindication and a pouch procedure can be necessary if control of colonic disease is refractory to medical therapy, recognizing the potential long-term complications including pouch failure requiring excision in up to 40% [6, 7].

Pouch Function

Short-term results are excellent with minimal mortality related to the procedure. A majority of patients are satisfied with the long-term outcomes after the IPAA procedure. Maintenance of bowel continence with a satisfactory functional outcome ranks high with these patients. Lightner et al. reported a mean stool frequency of approximately 6 per day and 2 per night along with one-third having occasional or frequent daytime bowel incontinence and two-thirds having occasional or frequent nighttime bowel incontinence in a large, single-center cohort with up to 30 years of follow-up [8]. In addition, quality of life remains relatively high after recovery from IPAA with little difference between UC, CD, or FAP [9]. However, there can be significant morbidity related to IPAA. Long-term complications include pouchitis, pouch dysfunction, issues related to fertility, stenosis, ischemia, and fistulae related to CD.

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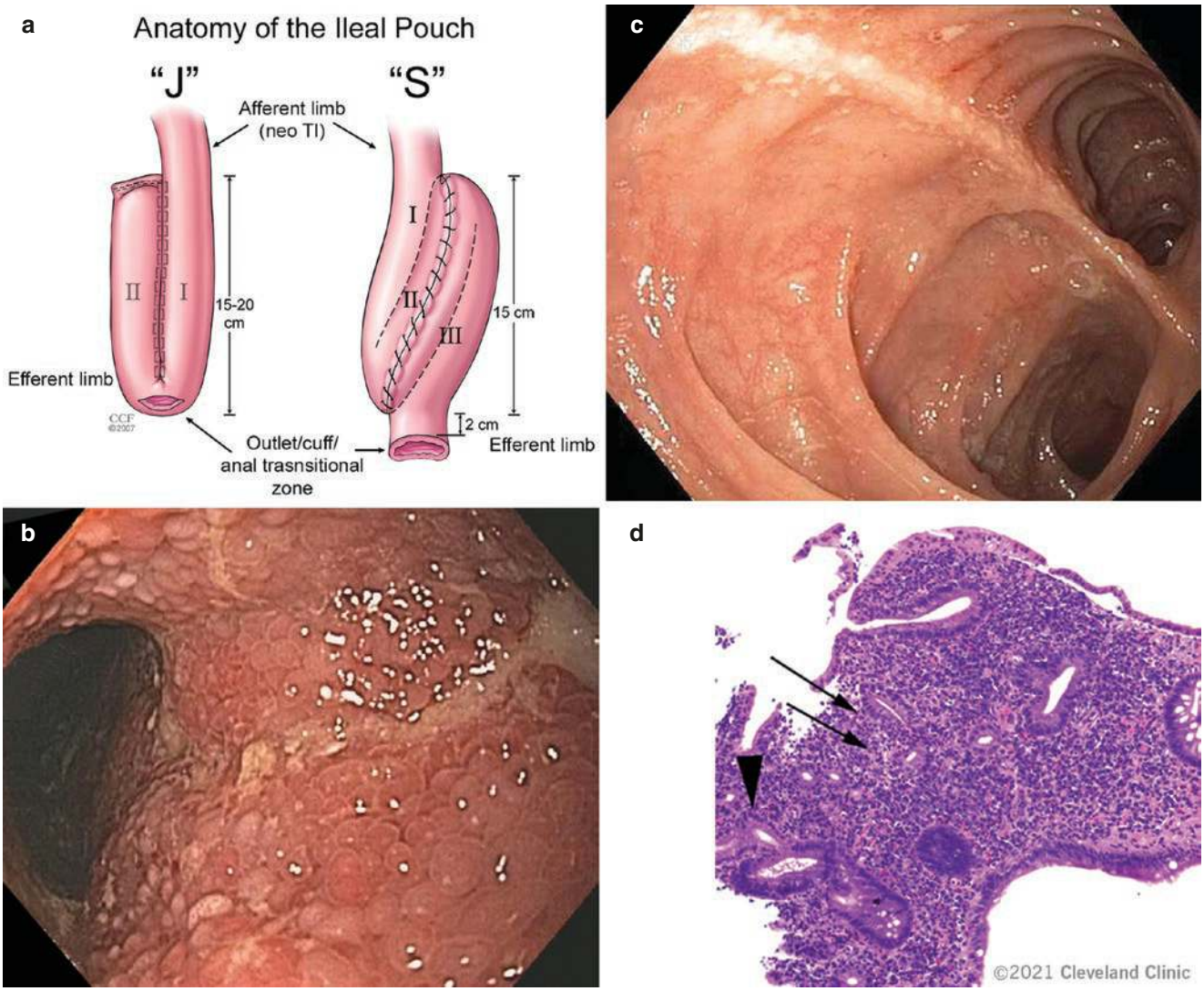

Fig. 44.1 (**a**) Schematic drawing of constructed "J" pouch (left) and "S" pouch (right). (**b**) Normal appearing J-pouch with efferent (top) and afferent (bottom) giving "owl's eye" appearance. (**c**) Inflamed pouch with diffuse erythema, edema, cobblestoning, and ulceration. (**d**) Low-power magnification demonstrates distortion of villous architecture, expansion of lamina propria, and pyloric gland metaplasia (arrows). There is abundant active, neutrophil-mediated epithelial injury (arrowhead) (hematoxylin and eosin stain, ×20). *Drawing and pictures courtesy of Bo Shen, MD. Pathology courtesy of Thomas Plesec, MD*

Pouchitis

Definition and Incidence

Pouchitis is defined as inflammation of the ileal reservoir in patients' status-post proctocolectomy with IPAA. Pouchitis is the most common long-term complication of IPAA and is a significant cause of morbidity related to the procedure. Inflammation in an ileal continence reservoir after proctocolectomy was first described in the literature by Kock et al. in 1977, prior to the first description of the IPAA [10]. This was later coined "pouchitis" when inflammation occurs in the IPAA. Since the initial description, multiple investigators have attempted to characterize pouchitis and delineate the underlying pathophysiology which may be multifactorial. The diagnosis of pouchitis is based on clinical symptoms, endoscopic findings, and histologic findings (Fig. 44.1).

The frequency of pouchitis reported by different groups has varied significantly. However, it is well established that the incidence of pouchitis is higher for patients with ulcerative colitis as compared to patients with FAP. The incidence of reported pouchitis in patients with UC has increased with improvements in medical record data acquisition of both pediatric and adult patients with 10-year rates in both groups in the range of 32–55% and a cumulative incidence at 30 years of 81% [7, 8, 11–15]. In comparison, the incidence

of pouchitis in FAP patients is less than half the UC rate at 22.1% with a median follow-up of 8 years [16].

In pediatric patients, Ozdemir et al. reviewed the outcomes of 433 pediatric patients after IPAA (83.4% with inflammatory bowel disease (IBD), 15.7% with FAP) and found the incidence of pouchitis at 31.9% with a mean follow-up of 9 years [14]. The occurrence of pouchitis was not associated with specific pouch types in this mixed surgical group (J- vs. S-pouch). Shannon et al. reported the incidence of pouchitis incidence at 45% at a mean of 20 years post procedure in pediatric patients along with a change in diagnosis to Crohn disease in 28% [7]. Risk factors for the development of pouchitis in pediatric patients include a high disease activity index at diagnosis of UC, younger age at the time of surgery, and vitamin D deficiency at the time of surgery [11–13].

Etiology and Pathogenesis

Although there has been much interest in defining and classifying pouchitis, the etiology of pouchitis remains unknown. There are a number of proposed factors that may play a role in pathogenesis. It is most likely that the development of pouchitis is multifactorial with several physiological and immunological factors contributing in a susceptible host. The frequency of pouchitis may vary based on the center, surgical experience, and follow-up medical care. Table 44.1 lists the proposed etiological factors that contribute to the development of pouchitis [17].

Fecal Stasis and Dysbiosis

The favorable response of the majority of acute episodes of pouchitis to antibiotic therapy and more recently to the administration of probiotics suggests that bacterial populations are important etiological factors in the development of pouchitis. Pouchitis also rarely occurs until after the takedown of the ileostomy with a resultant resumption of fecal flow to the neo-ileum pouch. However, to date, no single microbial factor has been identified as the causative factor. Fecal stasis in the pouch may also be a contributing factor. A study of rats who received IPAA after colectomy had longer fecal retention and higher rates of inflammation in the pouch compared to rats who underwent straight ileorectal anastomosis [18]. Regarding dysbiosis, 16s ribosomal RNA sequencing has demonstrated altered microbial diversity in patients with pouchitis at multiple taxonomic levels including an increase in the pro-inflammatory Fusobacteria and Enterobacteriaceae species, and a decrease in the anti-inflammatory Bacteroidetes species, similar to that seen in CD [19–21].

Table 44.1 Proposed etiology of pouchitis (Adapted from Macafee et al.) [17]

Immune dysregulation
Dysbiosis
Fecal stasis
Malnutrition
Mucosal ischemia (tension, torsion, or vascular)
Crohn disease, undiagnosed
Colonic metaplasia with associated ulceration
Extraintestinal manifestations of IBD, including primary sclerosing cholangitis
Smoking
pANCA status

Other studies have looked at the role of serological markers, such as antibodies to bacterial and yeast fragments, in the pathogenesis of pouchitis in addition to IBD. Serological markers such as anti-*Saccharomyces cerevisiae* antibodies (ASCA) have been found to be associated with postoperative fistula formation after restorative proctocolectomy [22]. Antibodies to OmpC, an outer membrane porin from *E. Coli,* and I2, an antigen to *Pseudomonas fluorescens*, were found to be predictive of postoperative continuous inflammation of the pouch [23]. In 2001, Fleshner et al. studied the relationship between pouchitis and serum perinuclear antineutrophil cytoplasmic antibody (pANCA), which has cross-reactivity to bacterial antigens including OmpC, in a prospective study [24]. They did not find an overall significant difference in the occurrence of pouchitis in the pANCA-positive versus pANCA-negative groups. They did, however, demonstrate a significant relationship between the development of chronic pouchitis in patients with a high level of pANCA (>100 EU/mL) as compared to patients with a medium level (40–100 EU/mL), low level (<40 EU/mL), or undetectable level of pANCA. Investigating the impact of preoperative pANCA and anti-CBir1 flagellin on the development of pouchitis, a follow-up study by Fleshner et al. showed that patients with a high level of pANCA and positive anti-CBir1 expression have an increased incidence of chronic pouchitis after IPAA [25]. These findings are suggestive of a pathogenic immune response to bacterial antigens.

Infection with *Clostridium difficile* has been increasingly recognized as a problematic cause of diarrhea in IBD patients with both pre- and post-colectomy with IPAA. *C. difficile* as a cause of pathogen-associated pouchitis is diagnosed in up to 10% of adults with an increased risk in patients with recent hospitalization, those receiving antibiotics, and males [26, 27]. When possible, PCR testing for *C. difficile* toxin B is more sensitive than enzyme immunoassay though neither is specific and clinical context needs to be considered for patients who may be colonized with this bacteria [28]. Evaluation with either pouchoscopy or fecal calprotectin levels may help to establish inflammation in the setting of symptoms in patients positive for *C. difficile*. As many of the

patients have already been on metronidazole, vancomycin should be considered first-line treatment. Recurrent or persistent *C. difficile* may also require a fecal microbial transplant to eradicate [29].

Immune Dysregulation

One of the most pursued areas of research is the influence of variations of gene loci on the development of IBD. As cytokines play a major role in the inflammatory pathway that leads to disease manifestations, many studies have focused on the role of cytokines such as Interleukin (IL)-1 alpha, beta, and receptor antagonist (ra) in the etiology of IBD. IL-1 alpha and beta are pro-inflammatory cytokines, whereas IL-1ra is the natural inhibitor of these cytokines. Genetic polymorphisms that lead to a reduction in the ratio of IL-1ra to IL-1 alpha and beta will potentially lead to increased and/or chronic inflammation [30].

It is also possible that an imbalance in the ratio of IL-1 alpha and beta to IL-1ra may influence the initiation of inflammation leading to pouchitis in patients status-post IPAA. In 2001, Carter et al. reported that patients that developed pouchitis had a higher IL-1RN*2 carrier rate as compared with patients that did not have the particular allele, 72% versus 45%, respectively [31]. IL-1RN*2 represents a polymorphism in the IL-1 gene cluster that has been associated with a change in the ratio of IL-1 alpha and beta to IL-1ra and the development of ulcerative colitis. This finding suggests that patients with ulcerative colitis that carry this allele may have an increased tendency of developing pouchitis after IPAA.

More recent studies have identified other genetic polymorphisms and cell-membrane receptors that are associated with pouchitis. The NOD2/CARD15 mutations have been shown to be associated with the development of pouchitis, and in some instances, a more severe manifestation of the primary disease [32–34]. These mutations are also associated with several markers of disease severity in pediatric CD [35]. It is therefore highly probable that these patients may actually have CD involving the pouch.

Intestinal epithelial expression of the innate Toll-like receptors (TLRs) 2, 4, and 5 are activated by bacterial peptidoglycan, lipopolysaccharides, and flagellin and lead to a complex downstream cascade of inflammatory signaling mediated by NFκB. These TLRs have been shown to be upregulated in patients with pouchitis [36]. Lammers et al. showed that patients who possess Toll-like receptor (TLR) 9-1237C and CD14-260T alleles have a higher risk of developing chronic or relapsing pouchitis [37]. Alterations in tight junction claudin-1 and 2 expressions in biopsies of patients with pouchitis also indicate increased barrier dysfunction as a possible cause of the inflammation [38].

A novel concept of immunoglobulin G4 (IgG4) associated pouchitis has been described [39, 40]. Seril et al. demonstrated a high prevalence of IgG4-expressing plasma cells in the pouch of patients with chronic antibiotic-refractory pouchitis (CARP) [41]. Patients with CARP were also more likely to have autoimmune thyroid disease, primary sclerosing cholangitis (PSC), and serum microsomal antibodies suggestive of an autoimmune-mediated pouchitis. Future studies are needed to further investigate the role of IgG4 in the etiology, pathogenesis, and prognosis of patients with pouchitis.

Mucosal Ischemia

During pouchoscopy, if the pattern of inflammation is isolated to a specific limb or wall of the pouch, ischemia should be considered as an etiology of the pouchitis. Ischemia can arise from tension on the pouch when it is pulled into the pelvis during surgery, either from torsion of the pouch when attached to the cuff or by leaving a long cuff resulting in a mobile base for the pouch to rotate on. Ischemia can also occur from decreased tissue perfusion as a vasculitic component of the underlying disease [29]. Ischemic pouchitis can be evaluated under fluoroscopy and by a surgeon for tension-induced ischemia which may require revision. If there is no evidence of tension in the pouch, a more global ischemic process may be the cause. Ischemia has been proposed as a contributing factor in intestinal inflammation after the observation that patients with IBD improved after treatment with hyperbaric oxygen therapy (HBOT). Two studies published in 2020 report the improvement of pouch complications (n = 67) including refractory pouchitis, cuffitis, pouch fistula, pre-pouch ileitis, and ischemic pouchitis in which patients had a significant improvement defined as a decrease in the modified PDAI after a median of 30 treatments with HBOT [42–44]. A 2014 review by Dulai et al. evaluated 17 studies in which HBOT was administered for either UC or CD (including perianal disease) with varying protocols and 86% of patients responded (n = 613, mean 14.6 treatments/patient) [45]. The most common complication from treatment was middle ear barotrauma and tympanic membrane perforation (1.5% of patients, 0.1% of all treatments). More studies including randomized control trials (RCT) should be completed to further evaluate this therapy.

Crohn Disease of the Pouch

Undiagnosed Crohn disease (CD) can present clinically as chronic pouchitis following IPAA. The most common manifestations of CD noted for patients status-post IPAA are fistulizing disease of the pouch, pre-pouch ileitis, and strictures

not related to the anastomosis. In adults, a 2020 single-center study by Kayal et al. reported the development of CD of the pouch in 12% of patients (n = 46/386) at a median time of 2.1 years after completion of IPAA [46]. An additional single-center study by Barnes et al. reported similar results with a 9% cumulative incidence in the development of CD of the pouch in adults (n = 594) [15]. A 2012 study by Coukos et al. also demonstrated the association of ASCA-IgA, ASCA-IgG, and anti-CBir1 flagellin in the development of CD of the pouch or fistula in patients with UC after IPAA [47]. In pediatrics, the rate of CD after IPAA for UC ranges from 5% at 7 years to 28% at 20 years of follow-up [7, 14, 48]. In addition, Shannon et al. reported 28% of pediatric patients with long-term follow-up were ultimately diagnosed as having CD of which 40% required pouch excision [7].

Extraintestinal Manifestations

The presence of extraintestinal manifestations related to inflammatory bowel disease has been studied as possible predictor of the development and severity of pouchitis. One of the first reports in 1990 by Lohmuller et al. looked at extraintestinal manifestations (EIMs) such as erythema nodosum, arthritis, and uveitis to determine a relationship with pouchitis in a retrospective study of 734 patients with IPAA with a mean follow-up of 3.4 years [49]. Their group found that pouchitis occurred in 39% of patients with preoperative EIMs as compared to 26% of UC patients with no preoperative EIMs ($p < 0.001$). They also found an increased risk of pouchitis if postoperative extraintestinal manifestations were later diagnosed. They did not, however, analyze the risk of pouchitis due to individual EIMs.

There are few studies dedicated to analyzing the relationship between primary sclerosing cholangitis (PSC) and the development of pouchitis. In 1996, Penna et al. found that pouchitis occurred in 63% (34/54) of the patients with PSC, while pouchitis only occurred in 32% of the patients without this particular EIM ($p < 0.001$) [50]. This group also reported an increased frequency of chronic pouchitis in patients with PSC versus patients without this disease, 60% and 15%, respectively ($p < 0.001$). In 2010, Wasmuth et al. reported an increase in both acute and chronic pouchitis in those patients with PSC (n = 11), but no increased risk with other EIMs including pyoderma gangrenosum (n = 6) and arthritis (n = 12) [51]. More recently, Barnes et al. reported a 5% incidence of pouchitis in those with PSC compared to 1% without PSC (p = 0.007) and an adjusted odds ratio of 3.94 (95% CI 1.05–14.8) at 2-year follow-up after IPAA; however, this is based on a total of 13/394 patients with PSC in the cohort [15]. Shen et al. also demonstrated that concurrent PSC appears to be associated with a significant pre-pouch ileitis on endoscopy and histology in patients with IPAA [52].

Cuffitis

After IPAA, a region of colonic columnar mucosa remains unless a mucosectomy is performed [53]. It has been shown that patients have markedly better pouch function when mucosectomy is not performed and this is the preferred treatment modality in the absence of dysplasia. As a result, a "cuff" remains above the anal transitional zone (Fig. 44.2). The length of the cuff is dependent on the type of IPAA performed. After a stapled IPAA, the preferred method by adult colorectal surgeons, a region of 1.5–2 cm of diseased mucosa remains. A hand-sewn IPAA has traditionally been performed by pediatric surgeons and leaves a variably smaller cuff region or no cuff when mucosectomy is also performed. Neither method is superior to the other as far as complication rate but the stapled IPAA is typically preferred as it is associated with improved nocturnal continence with higher resting and squeeze pressures of the pouch demonstrated by anorectal manometry [54].

As expected, the remaining diseased columnar mucosa can develop inflammation, a term coined "cuffitis." Patient symptoms include anal pain or discomfort, bleeding, discharge, or diarrhea and endoscopic features typical of colitis in the cuff region (erythema, friability, ulceration). Thompson-Fawcett et al. biopsied the cuff of 113 patients after stapled IPAA and found 13% had evidence of acute inflammation, most of which was mild and 9% were symptomatic [55]. Wu et al. followed 120 patients with cuffitis (12.9%) from their registry of 931 pouch patients over a median of 4 years and found no difference in the demographics, risk factors, extent, or severity of disease compared to controls without cuffitis [56]. Of these patients, 33% responded to topical 5-ASA/steroid therapy, 18% relapsed after initial response to 5-ASA/steroid therapy, and 48% did not respond to topical therapy and required immunotherapy. Sixteen patients (13.3%) with cuffitis ultimately had a failure of the pouch due to CD of the pouch (N = 7; 43.7%), refractory cuffitis (N = 5; 31.3%), or surgical complications (fistula, sinus) requiring diversion or pouch reconstruction (N = 4; 25%) a median of 6 years after IPAA. More recently, Kayal et al. reported the development of cuffitis in 30.1% of patients at a median time of 1 year after IPAA with significant risk factors for cuffitis including a rectal cuff length ≥2 cm and medically refractory disease preoperatively [46]. Cuffitis and greater cuff length were also significant risk factors for pouch failure. As a small segment of colonic mucosa remains in situ, the risk for dysplasia remains equally present in the cuff as in the pouch [57].

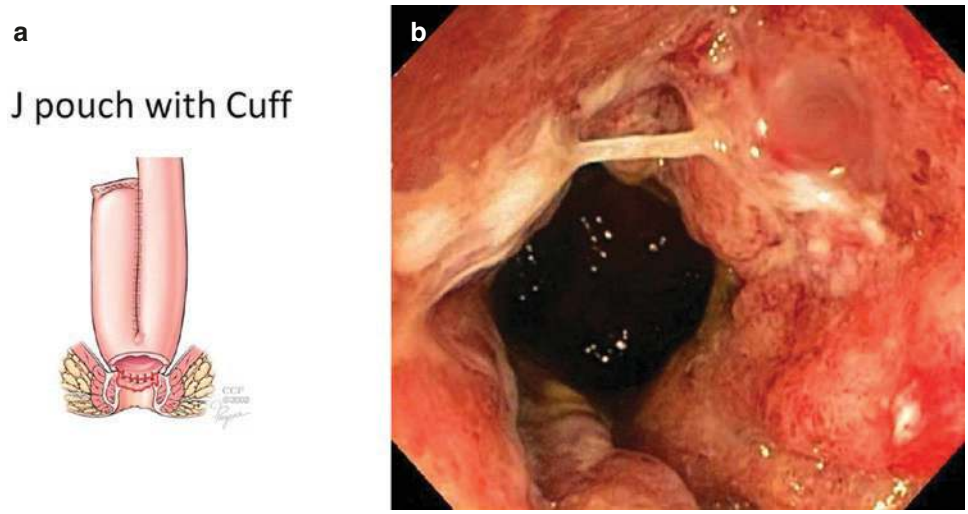

Fig. 44.2 (**a**) Schematic drawing of constructed "J" pouch with cuff outlined in red. (**b**) Inflamed cuff or "cuffitis" at the distal end of J-pouch

Smoking

It has previously been established that cigarette smoking is associated with a reduction in the risk of developing ulcerative colitis. In 1996, Merrett, et al. also described a link between smoking and a reduction in the incidence of pouchitis in patients after IPAA. Their study documented that 18/72 (25%) of nonsmokers were diagnosed with pouchitis, while 1/17 of smokers (5%) were diagnosed with pouchitis. The reason for these findings is unclear, but may be related to the effect of smoking on gut mucosal permeability [58]. Fleshner et al. performed a multivariate analysis of clinical factors associated with pouchitis after IPAA. They showed that smoking and the use of steroids prior to colectomy were associated with acute pouchitis, while smoking in itself appeared to protect against the development of chronic pouchitis [59].

Diagnosis

The first episode of pouchitis occurs most often in the first 6 months after the closure of the loop ileostomy; however, it can occur at any time after IPAA is performed. To accurately make a diagnosis, a combination of clinical symptoms, endoscopic appearance, and histologic findings are typically utilized. The clinical presentation of pouchitis typically includes a combination of increased stool frequency, abdominal cramping, hematochezia, bowel incontinence, and/or low-grade fever. In practice, a presumptive diagnosis of pouchitis is often made based on clinical symptoms alone. However, as in irritable pouch syndrome, the endoscopic and histologic inflammation or lack thereof may not correspond to the degree of symptoms and pouchoscopy is necessary for clinical decision-making. Pouchoscopy still remains the main tool for establishing a diagnosis and also for evaluating other differential diagnoses in suspected cases of pouchitis [60]. Endoscopic findings involve assessing the severity of inflammation of the pouch mucosa. Signs of inflammation include erythema, edema, granularity, mucosal ulceration, and friability. The afferent and efferent limp of the pouch are most often affected and should routinely be biopsied (Fig. 44.1). In addition, if the inflammation of the pre-pouch ileum is visualized, this finding is suggestive of CD, though no standard definition for the extent of inflammation beyond the ileum exists.

Several scales for diagnosing and grading pouchitis have been developed over the last two decades. The PDAI (Table 44.2) is the most commonly used scale encompassing symptoms, endoscopic findings, and histologic grading with a score of ≥7 qualifying as a diagnosis of pouchitis [61]. The modified PDAI was validated to exclude the histologic grading with a score of ≥5 establishing a diagnosis of pouchitis [42].

Histology of the pouch should not classify a diagnosis of pouchitis alone as there is often mild chronic changes including expansion of chronic inflammatory cells, villous atrophy, and crypt hyperplasia even in a normal appearing pouch [62]. These changes are likely the adaptation of the mucosa to its role as a reservoir. Histologic evaluation is invaluable in identifying some of the other secondary causes of pouchitis such as pathogens like cytomegalovirus (CMV) or Candida, ischemia, mucosal prolapse, granulomas, and dysplasia [63].

The histology may be graded on an ABC scale, often used for research purposes. Type A mucosa is described as normal mucosa or mild villous atrophy with no or minimal inflammation. Type B mucosa is described as transient atrophy

with temporary moderate to severe inflammation followed by normalization of the architecture. Type C mucosa is described as persistent atrophy with permanent subtotal or total villous atrophy developing from the early functioning period accompanied by severe pouchitis and thus requires follow-up pouchoscopy to diagnose [64]. Type B and C mucosa are most often found in pouchitis and are discussed as a predictor of outcomes later in this chapter. When a diagnosis of pouchitis is made, evidence of acute and chronic inflammation is typically present on biopsy samples.

Other laboratory tests such as stool studies for *Clostridium difficile* infection may be important, especially in patients with chronic antibiotic refractory pouchitis. Inflammatory markers in the serum may be useful noninvasive adjuncts in the evaluation of patients with suspected pouchitis. Studies evaluating the erythrocyte sedimentation rate (ESR) as a marker of pouchitis have shown that despite its role as a nonspecific marker of inflammation, it does correlate with PDAI and episodes of pouchitis [65, 66]. Elevation of the serum C-reactive protein is a nonspecific marker of inflammation, but this was also found to correlate with the PDAI score and the presence of endoscopic inflammation in the pouch and afferent limb. Fecal inflammatory markers usually are reflective of the presence of intestinal inflammation. Fecal calprotectin and lactoferrin levels have been found to correlate with pouchitis and PDAI scores in a number of studies [67, 68]. These fecal markers could serve as potential adjunctive tests in the initial evaluation of patients with pouchitis but their role in the overall management of these patients still needs to be clearly elucidated.

Table 44.2 Pouchitis disease activity index (PDAI) (Adapted from Sandborn et al.) [61]

Clinical criteria	Score
Stool frequency	
Usual postoperative stool frequency	0
1–2 stools/day > postoperative usual	1
3 or more stools/day > postoperative usual	2
Rectal bleeding	
None or rare	0
Present daily	1
Fecal urgency or abdominal cramping	
None	0
Occasional	1
Usual	2
Fever (>100.5 °F)	
Absent	0
Present	1
Endoscopic criteria	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucus exudates	1
Ulceration	1
Acute histologic pattern[a]	
Polymorphonuclear infiltration	
Mild	1
Moderate with crypt abscesses	2
Severe with crypt abscesses	3
Ulceration per low-power field (mean)	
<25%	1
25–50%	2
>50%	3

Pouchitis defined as a total PDAI score of 7 or above

[a]Modified PDAI excludes the acute histologic pattern with a score of 5 or above defining pouchitis [42]

Classification

The classification of pouchitis can be made based on several different factors (Table 44.3). Severity varies from remission to severely active. Duration varies from acute (less than 4 weeks) to chronic (more than 4 weeks or more than 3 episodes of pouchitis in a 12-month period). Frequency varies from infrequent to continuous. Chronic pouchitis can also be differentiated by the response to therapy including chronic antibiotic-dependent pouchitis (CADP) and antibiotic-refractory pouchitis (CARP). CADP describes those that continue to respond to antibiotics but are unable to discontinue without relapse, while CARP describes those who do not respond to antibiotics and lack features of CD of the pouch. Response to therapy is described as antibiotic-responsive, antibiotic-dependent, or antibiotic-resistant (refractory) [6, 9]. In addition, it must be considered that not all patients status-post IPAA with symptoms of diarrhea and abdominal pain will truly have idiopathic inflammatory pouchitis. Other disease entities that may result in pouchitis include cuffitis, stenosis of the pouch, CD, and infectious bowel disease (most often secondary to *Clostridium difficile* or Cytomegalovirus). Yet, others will have functional symptoms without inflammation as in the case of irritable pouch syndrome.

Table 44.3 Classification of pouchitis (Adapted from Wu and Shen) [104]

Classification	Description
Severity	Remission
	Mildly active
	Moderately active
	Severely active
Duration	Acute (less than 4 weeks)
	Chronic (more than 4 weeks)
Frequency	Infrequent (1–2 episodes)
	Relapsing (more than 3 episodes)
	Continuous
Response to therapy	Antibiotic-responsive
	Antibiotic-dependent
	Antibiotic-refractory

Treatment

Most of the published literature for the treatment of pouchitis is retrospective with fewer than 20 prospective, RCTs, none of which are in the pediatric age group [69]. Therefore, a majority of treatment regimens for both acute and chronic forms of pouchitis are based on empiric data alone. Treatment approaches include both primary prophylaxis and treatment following the development of symptoms.

Prophylaxis

The use of probiotics is proposed to increase the normal, healthy flora of the colon such that concentrations of unhealthy microflora are reduced and the incidence and severity of pouchitis are decreased. The De Simone Formulation (formerly known as VSL#3) (Visbiome®, ExeGI Pharma, Rockville, MD) contains four strains of *Lactobacillus*, three strains of *Bifidobacterium*, and *Streptococcus thermophilus*. One week after ileostomy closure, an RCT demonstrated 10% (2/20) of patients treated with 1 packet of the De Simone Formulation (900 billion bacteria) developed acute pouchitis within 12 months versus 40% (8/20) of patients who received placebo [70]. In a separate study, the first episode of pouchitis has also shown to be delayed in patients given *Lactobacillus rhamnosus* GG following IPAA; however, probiotics have not been found to be efficacious in the treatment of acute pouchitis [71, 72]. There is an ever-growing number of probiotics now on the market while there is a paucity of RCTs to evaluate primary prophylaxis of pouchitis or if one particular brand of probiotics is more effective than another.

Acute Pouchitis

Acute episodes of pouchitis respond to antibiotic therapy most of the time. The first-line antibiotics of choice for acute pouchitis are a 14-day course of metronidazole (15–20 mg/kg/day divided BID or TID) or ciprofloxacin (20–30 mg/kg/day divided BID). In the past, metronidazole alone was considered to be first-line therapy. The first controlled study with this drug was published by Madden et al. in 1994 [73]. They performed a double-blind, crossover trial comparing metronidazole with placebo in 11 patients with chronic pouchitis and reported that patients treated with metronidazole had a decrease of three bowel movements per day as compared with an increase of one bowel movement per day on placebo ($p < 0.05$). Treatment with metronidazole may be limited due to the adverse events of nausea, metallic taste, and paresthesia. Later studies showed the efficacy of ciprofloxacin. In an unblinded RCT by Shen et al., it was reported that both ciprofloxacin and metronidazole significantly improved PDAI scores [74]. In addition, the ciprofloxacin group experienced significantly larger reductions in PDAI scores and decreased side effects as compared with metronidazole. Fluoroquinolones have been associated with arthropathy and tendon rupture in all ages and this should be considered when prescribed to children. Both metronidazole and ciprofloxacin are now considered first-line therapy for acute pouchitis (Fig. 44.3).

Rifaximin, an inhibitor of bacterial DNA-dependent RNA polymerase, has been used as monotherapy in a pilot study by Isaacs et al. [75]. This study showed clinical remission occurred more frequently in patients on rifaximin (2/8) compared to the placebo (0/9), but the difference was not significant ($p = 0.2$). Patients were treated with rifaximin for 4 weeks and there was no difference in adverse events between treatment and placebo.

Chronic Pouchitis

In pediatric patients, Nyholm et al. reported that 19% developed chronic pouchitis with a median follow-up of 6.4 years, an incidence similar to adults [9, 48]. The medical treatment of chronic pouchitis including CADP and CARP is less studied. Shen et al. conducted an open-label trial using rifaximin as a maintenance agent after initial treatment with a conventional antibiotic, for adult patients with CADP ($n = 53$) [76]. After 96% of patients responded to initial therapy, 65% of these initial responders maintained remission at 3 months on a daily median dose of 200 mg rifaximin. Larger trials with long-term follow-up of patients are needed to fully understand the benefits that may accrue from the use of rifaximin in the treatment of patients with pouchitis. The anecdotal goal for the treatment of CADP is to maintain the lowest dose of antibiotics possible.

Tinidazole, a nitroimidazole derivative, has been used in combination with ciprofloxacin in the treatment of CARP [77]. This combination led to a significant reduction in the PDAI scores and also an improvement in quality of life scores after 4 weeks of therapy. In 2004, a study evaluating the effectiveness of combination therapy of rifaximin and ciprofloxacin was published in patients with CARP [78]. Eight patients with chronic pouchitis refractory to ciprofloxacin alone were treated with rifaximin and ciprofloxacin for 2 weeks. Eighty-eight percent (7/8) of the patients responded to therapy and five went into remission for at least 6 months. Additional medications that have been used in the treatment of CARP include 5-ASA products (i.e., oral mesalamine, rectal mesalamine suppositories, and enemas), topical and oral steroids (i.e., prednisone or budesonide), bismuth-containing products, and anti-TNF therapy. In a prospective, open-label study, Gionchetti et al. reported 15/20 patients treated with oral

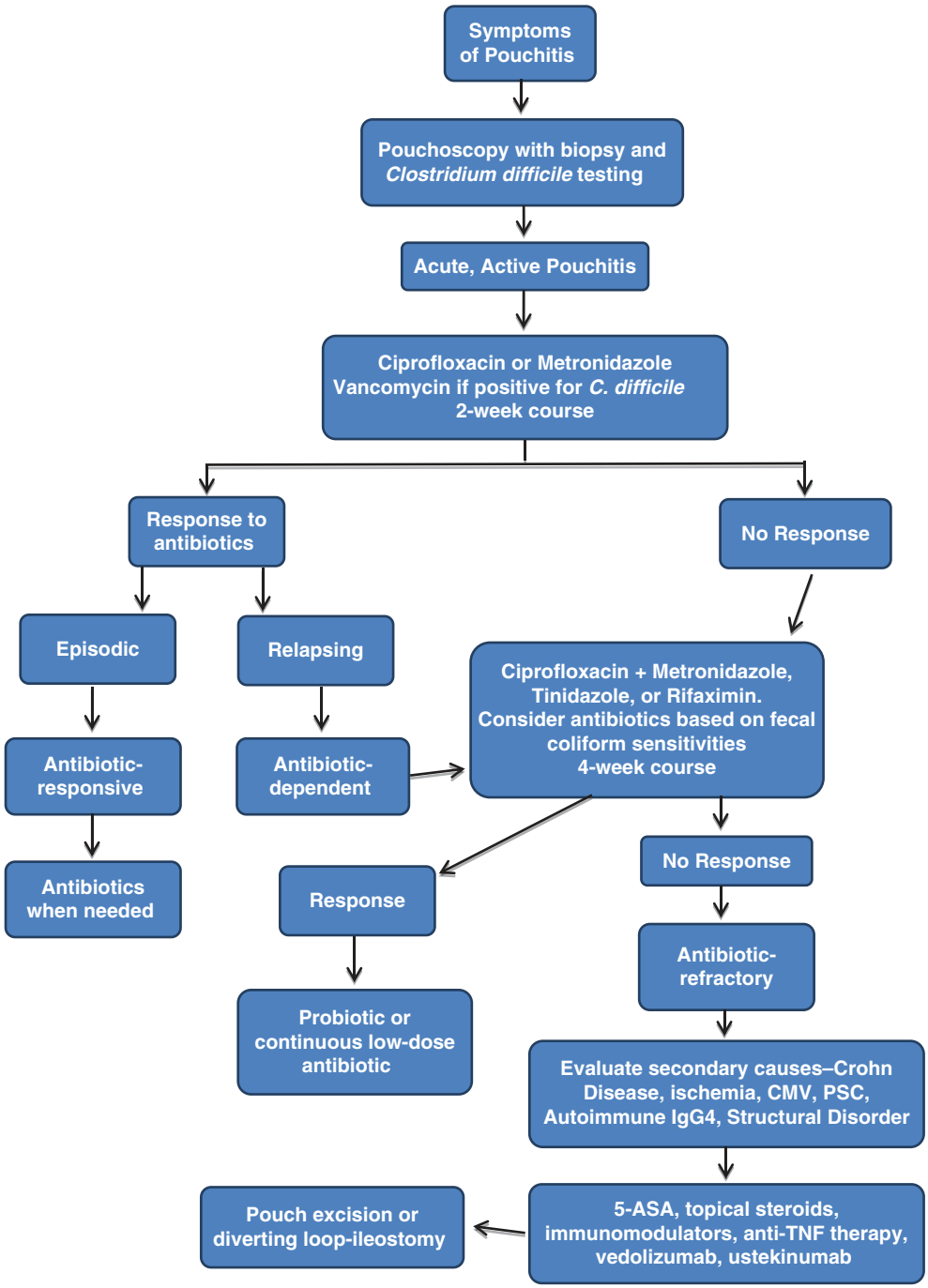

Fig. 44.3 Treatment algorithm for management of pouchitis (Adapted from Shen) [6]

budesonide 9 mg daily achieved clinical remission of CARP at 8 weeks [79]. In a retrospective review, Chopra et al. reported that 8/13 patients had a favorable or moderately favorable response of pouchitis (excluding CD of the pouch) to oral budesonide 9 mg daily at follow-up [80].

In an RCT published in 2000, Gionchetti et al. showed that treatment with the De Simone Formulation for 9 months following antibiotic treatment compared with antibiotic treatment alone was statistically significant in maintaining remission from pouchitis [78]. In 2005, a double-blind placebo-controlled trial examined the expression of pro-inflammatory cytokines in patients diagnosed with pouchitis who were treated with the De Simone Formulation [81]. The results revealed that the expression of mRNA for the pro-inflammatory cytokines IL-1 beta, IL-8, and IFN-gamma in patients treated with the De Simone Formulation was significantly decreased as compared with placebo. The levels of all of these cytokines were decreased at least twofold. A pooled meta-analysis of placebo-controlled RCTs on the use of probiotics showed that probiotics were beneficial in the

management of pouchitis, though each study evaluated patients in different stages of the disease [82].

For patients' status-post IPAA who are subsequently diagnosed with CD of the pouch or CARP, anti-TNF therapy including infliximab is an option that has been utilized as a part of the treatment regimen. In the adult population, a systematic review of papers and abstracts reported a cumulative short-term response of 80% and long-term response of 50% in 140 patients treated with infliximab for chronic pouchitis [83]. There is one case series in the pediatric literature supporting these findings in which 3/4 of patients treated with infliximab for CD of the pouch remained on infliximab therapy at a 2-year follow-up with a significant response [84].

Several reports have been published on the efficacy of vedolizumab for refractory pouchitis [85–88]. The largest study was a multicenter, retrospective cohort by Gregory et al. who reported a 51.8% clinical response, 19.3% remission, and 54% endoscopic response at any point during 12-month follow-up in 83 patients with either CD of the pouch, CADP, or CARP treated with vedolizumab [85].

There have been two reports on the use of ustekinumab for CD of the pouch or chronic pouchitis, one multicenter, the other single-center. Weaver et al. reported a clinical response rate of 83% after 6 months of ustekinumab treatment in 56 patients from four US centers; however, only 11% of patients with CD of the pouch and none with chronic pouchitis were in clinical remission at 6 months [89]. Interestingly, males were significantly less likely than females to respond to ustekinumab (30% vs 83%; $p = 0.014$). There was also no difference in the rate of response in those treated with biologics versus no biologics prior to colectomy. In a single-center retrospective study of CARP only (CD of the pouch excluded) by Ollech et al., 50% of patients had a clinical response on ustekinumab during a median follow-up time of 12.9 months ($n = 24$) [90].

There has been limited evaluation of the use of fecal microbiota transplantation (FMT) in chronic pouchitis. The single RCT of FMT for CADP was halted due to a lack of response. This was followed by a prospective, open-label pilot study in adults who did not find a significant change in the PDAI or endoscopic scores of 19 patients who received a single FMT for chronic pouchitis [91]. At current, there is no evidence of efficacy of FMT for the treatment of acute or chronic pouchitis.

The medical treatment algorithm for acute and chronic pouchitis is shown in Fig. 44.3. The antibiotic treatment of the first, acute episode of pouchitis should be either metronidazole three times per day for 14 days or ciprofloxacin twice per day for 14 days. If a patient is diagnosed with antibiotic-dependent or antibiotic refractory pouchitis, alternative therapies include prolonged antibiotic therapy or a combination of various antibiotic therapies with the option of additional therapy with probiotics such as the De Simone Formulation. Failure of response to these therapeutic options should warrant the consideration of other secondary causes of pouchitis such as *Clostridium difficile* and other pathogens in the stool. The addition of anti-inflammatory or immunosuppressive therapy to the treatment regimen should be considered at this point.

Surgical

Pouch failure is an unfortunate consequence that results from a number of complications with the most common being pouch dysfunction, pouch fistulae, refractory pouchitis, pelvic sepsis, anastomotic leak, pouch prolapse, stricture, and development of Crohn disease. In adults, pouch failure occurs more commonly in Crohn disease than in UC (13.3% vs 5.1%) [9]. In pediatrics, with a mixed series of indications for IPAA over a 27-year period and mean follow-up of 9 years, 9% (39/433) had pouch failure requiring small bowel diversion or excision of the pouch of which 4 were for pouchitis and 3 for Crohn disease [14]. Pouch failure can result in excision of the pouch, diversion with a proximal loop ileostomy, or an inability to reverse a diverting ileostomy from primary colectomy.

Outcome

One of the most concerning potential complications of long-term inflammation of the surgically created pouch is dysplasia and progression to malignancy. Overall, the incidence of dysplasia in the pouch is more common for patients with FAP than for those with ulcerative colitis. For patients with FAP, dysplasia is more often related to the development of adenomas in the pouch. For patients with IBD, the development of dysplasia is related to ongoing chronic inflammation. A 2016 systematic review and meta-analysis analyzing the risk of neoplasia after colectomy for IBD reported a pooled prevalence for dysplasia in the pouch of 0.8% ($n = 7647$) and carcinoma in the pouch of 0.5% ($n = 8403$) [92]. The cumulative incidence of dysplasia in the pouch in that series was 0.6%, 1.5%, and 3.0% at 5, 10, and 20 years post-IPAA, respectively.

No long-term studies have been performed to delineate the overall risk of malignancy in the pediatric patient population. In an early report looking at the incidence of dysplasia after IPAA, Sarigol et al. did not find any evidence of dysplasia in the biopsies obtained during pouchoscopy from 76 children with a mean follow-up of 5 years after IPAA including 5 of which had dysplasia at time of colectomy [93]. Gullberg et al. compared the risk of dysplasia in adult's status-post IPAA with Type A histology of the pouch (normal mucosa or mild villous atrophy) compared with Type C

histology of the pouch (persistent atrophy with severe inflammation). They determined that 5/7 of patients with Type C mucosa developed dysplasia while no patients 0/14 with Type A mucosa developed dysplasia after a median of 9 years with IPAA [94]. These findings are consistent with other research and confirm that patients with Type C mucosa are at a higher risk of dysplasia and possibly malignant lesions in the pouch. There are currently no consensus guidelines for endoscopic surveillance for dysplasia screening for adults or pediatric patients who are status-post IPAA.

Noninflammatory Pouch-Related Complications

Irritable Pouch Syndrome

Irritable Pouch Syndrome (IPS) was initially described by Shen et al. when 42% of adult patients enrolled for endoscopic evaluation of pouchitis symptoms had normal endoscopic and histologic evaluations [95]. The most common symptoms of IPS were increased stool frequency (88.5%) and urgency or abdominal pain (46.1%). In the study by Shen along with a 2007 study by Schmidt et al., IPS could not be differentiated from pouchitis based on clinical symptoms [96]. A follow-up study by Makkar, Shen et al. surveyed those with IPAA and found the quality of life of patients with IPS was similar to those with pouchitis [97]. Patients with IPS were more likely to be taking medication for depression, anxiety, or pain, including narcotics, than those with pouchitis. These findings stress the importance of endoscopy to diagnose pouchitis, as IPS represents a common and significant entity that should be treated as a functional disorder rather than an inflammatory one.

Floppy Pouch Complex

Floppy Pouch Complex (FPC) is a relatively new diagnosis described in 2018 by Khan et al. to characterize a number of mechanical pouch issues related to an elongated and malleable pouch resulting in the folding of the pouch, pouch prolapse, or afferent limb syndrome [98]. FPC typically presents with dyschezia associated with straining and sensation of incomplete evacuation, similar to that of a patient with constipation or proctitis. Pouchoscopy is helpful to evaluate for pouchitis and for signs of FPC, while defecography is often the best test to exhibit abnormal descent, protrusion, or redundancy of the pouch resulting in folding. Pouch prolapse is classified as either full-thickness prolapse, which may be seen on a physical exam with straining, or mucosal prolapse, which requires pouchoscopy and a contrast enema or defecography to visualize. Both types of prolapse may result in ischemia with ulcerations in the region of redundant tissue. Afferent limb syndrome (ALS) occurs when the inlet of the pouch from the small bowel is angulated or twisted without a luminal stricture and results in partial obstruction of the small bowel leading into the pouch. Milder forms of FPC including prolapse are often treated with fiber and biofeedback to avoid straining. Severe and refractory FPC may require pexy of the pouch or pouch reconstruction. It is important to note that none of the treatments for FPC have been validated. Further, recognition of mechanical pouch issues as a significant complication of IPAA is important as these may also have a significant impact on pouch function and quality of life.

Fertility

While fertility has not been shown to be affected in those with UC prior to surgery, issues related to female fertility after surgery are a well-recognized complication. The historical rate of infertility after IPAA has been reported as high as 90%, and a 2019 Cochrane review estimated a fivefold increase in the relative risk of infertility 24 months pre- to post-IPAA [99, 100]. A Danish series examining birth rates over 30 years in women with UC after IPAA reported a 50% decrease in live births (27.6 children/1000 years) compared to those with UC without IPAA (56.8 children/1000 years) [101]. As infertility post-IPAA is often due to the structural impact on fallopian tubes, in theory, a laparoscopic approach to IPAA should offer a decrease in scarring and improvement in potential fecundity. While several studies have been published demonstrating lower rates of infertility with laparoscopic IPAA, the sample sizes have been insufficient to draw any significant conclusions [99].

Assisted reproductive technology (ART) for women after IPAA has a success rate of at least 50%, which is similar to that of the general population [102]. Potter et al. examined rates of pregnancy in women who underwent IPAA before 20 years of age (n = 93) and found that 73% were able to become pregnant of which 21% required ART, and 88% had a successful live birth [103]. While this study included patients with FAP in addition to patients with UC after IPAA, the rates of pregnancy, live birth, and ART were statistically similar in the two groups. Recognizing the potential impact of fertility complications is important when counseling patients, even when the issue may be many years away as in pediatric patients.

Summary

Total proctocolectomy with IPAA is the surgical procedure of choice for pediatric patients with ulcerative colitis. The procedure is generally well tolerated; however, pouchitis is the most frequent cause of morbidity. The majority of patients will experience isolated, acute episodes of pouchitis. Pouchoscopy remains the main tool for establishing the diagnosis of pouchitis, although other emerging noninvasive tests may serve as useful adjuncts in the diagnostic process. Therapeutic guidelines are generally empirically derived. Most patients respond to antibiotic treatment with ciprofloxacin or metronidazole. Others may be treated with a combination of probiotics, antibiotics, anti-inflammatory medications, and/or immunosuppressive medications. Takedown of the pouch is uncommon and is required only in a small minority of patients. There is however an increased incidence in the development of CD in pediatric patients with longer-term follow-up but a change in diagnosis to CD does not inevitably result in pouch failure. Dysplasia and malignancy are concerns for patients with chronic pouchitis and severe inflammatory changes. To date, dysplasia and malignancy of the pouch have not been diagnosed in pediatric-aged patients, although they may be at a higher risk for these complications in their lifetime due to the long duration of disease and other yet undetermined factors. In addition, noninflammatory complications of the pouch including irritable pouch syndrome, floppy pouch complex, and reduced fertility may have a significant impact on quality of life.

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Enteral Feeding Devices and Ostomies

45

Judith J. Stellar

Gastrostomy

Children and adolescents with inflammatory bowel disease (IBD) often suffer the consequences of malnutrition and growth failure. Enteral nutrition as a therapy has been discussed prior to this chapter. Enteral access either via nasogastric tube (NGT) feedings or direct enteral access via a gastrostomy tube (G-tube) is an option for children with inflammatory bowel disease. Once it is clear that a patient requires supplemental calories to support growth and development, a trial of feedings via NGT is often done prior to more invasive percutaneous feeding tube placement. The trial of NGT feedings demonstrates tolerance of supplemental enteral formula and allows the patient and family to become familiar with the feeding delivery system, particularly the feeding bag setup and the pump. It is essential that families are educated regarding NGT placement, feeding administration, and maintenance of the tube and equipment.

Younger children may pose difficulty in keeping the NGT in place. There are products such as the AMT Bridle®, which help prevent the patient from pulling out the tube. Older children and adolescents may choose to place the NGT in the evening and remove it in the morning so as not to have to go to school or do other activities with the tube visible. For many patients and families, nasogastric tube feeding is cosmetically unappealing and difficult to maintain on a long-term basis. Eventually, this approach not only becomes burdensome but also causes daily discomfort. In these instances, if the supplemental feedings appear to be needed on a long-term basis, it becomes necessary to consider percutaneous gastrostomy tube (G-tube) placement.

Gastrostomy tube feeding is appealing for a number of reasons, but particularly because the tube does not require daily or frequent insertions and it is not visible to the outside world. The indications for placement are to provide long-term nutrition to patients who cannot orally ingest sufficient calories for appropriate weight gain and growth and for disease treatment. There are a variety of methods for G-tube placement including open surgical, laparoscopic, percutaneous endoscopic gastrostomy (PEG), or percutaneous radiologic gastrostomy (PRG). Several studies have compared surgical versus non-surgical techniques [1–4]. The type of procedure will depend on a number of patient-related factors including comorbidities, congenital anomalies, and the need for concomitant surgical procedures such as fundoplication. Non-surgical placement of a gastrostomy tube was first described 35 years ago [5, 6], and since that time the technique has been refined, including pre-procedural imaging such as an upper gastrointestinal series and/or abdominal ultrasound to delineate the anatomy. In the past, a percutaneously placed tube, either endoscopic or radiologic, was most often a tube that extends off the abdomen and is approximately 25–30 cm long and consists of an internal bumper and an external crossbar or securing disc (Fig. 45.1). More recently, a procedure for initial placement of a low-profile

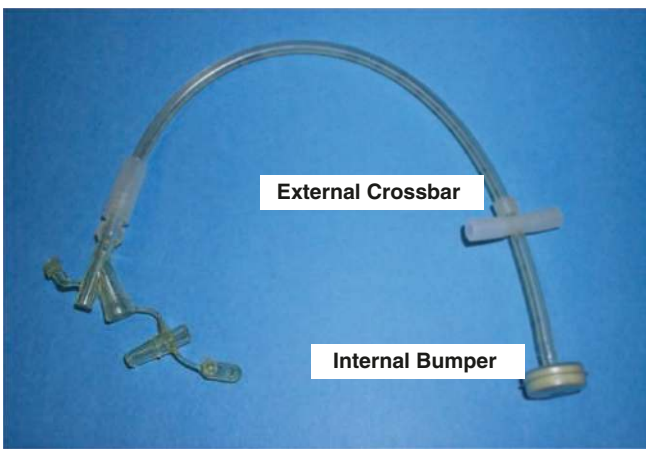

Fig. 45.1 Typical initial PEG/PRG tube with internal "bumper" and external "crossbar"

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percutaneous G-tube has become popular and shown to be safe and effective in pediatric patients [7–9]. These types of tubes are available in a mushroom button style as well as a low-profile balloon style and are manufactured by a number of companies including but not limited to the Boston Scientific EndoVive™ One-step Button™, the Applied Medical Technologies AMT® Initial Placement Gastrostomy (MiniOne®), or Avanos Medical Introducer kit for gastrostomy tubes. A similar technique has also been reported for the primary placement of GJ tubes [10]. With the earlier technique of internal bumper and external crossbar, most centers would recommend waiting 12 weeks before changing an initial PEG or PRG tube to a low-profile device in order to maximize healing of the track and decrease the risk of gastric dehiscence. However, the more recent technique using T fasteners Kimberly-Clark, Roswell, GA; Boston Scientific, Natick, MA) or U sutures for securing the stomach wall to the abdominal wall (Fig. 45.2), combined with the initial placement of a low-profile device, avoid the need for a long tube and can be replaced earlier than the 12 weeks, if needed. There have been some experiences with complications of T fasteners resulting in dislodgement [10, 11].

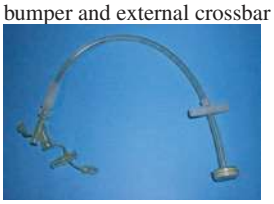
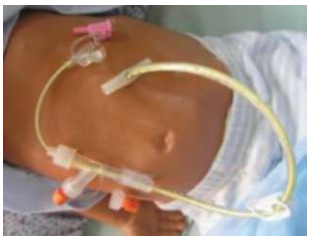
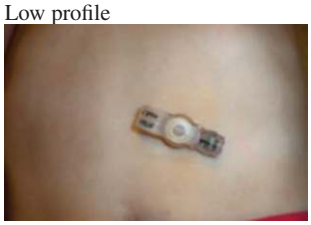
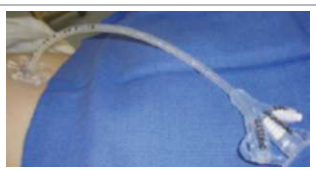
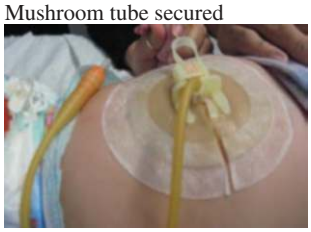
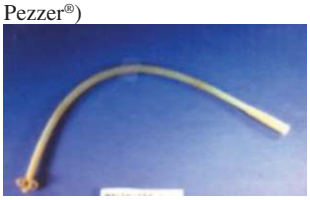
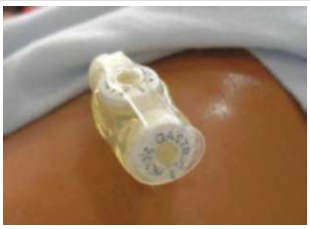
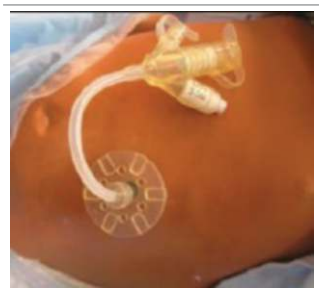
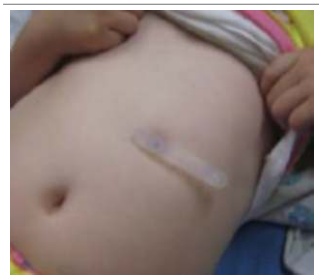
When a G-tube is placed surgically, whether an open technique or laparoscopic, the type of initial tube can vary from a standard mushroom-type tube such as the Malecot or Pezzer, a standard balloon tube with external retention disc, or most often, a low-profile balloon tube, such as AMT MiniOne® or MIC-KEY®. The choice is often based on surgeon's preference while accounting for any clinical benefits of one type of tube or another for a particular patient. An initial surgically placed G-tube could be changed within 4–6 weeks. Regardless of the method of G-tube placement, the timing, method, and personnel involved in initial tube change vary from institution to institution. Commonly an initial PEG- or PRG-placed tube, without T fastener gastropexy, remains in place for 12 weeks then is replaced with a low-profile device or standard replacement tube under fluoroscopic guidance, although some centers do the first change after 6 months of initial tube placement [12]. Thereafter, the tube can be changed by nursing staff or parents who have been thoroughly educated on the G-tube change procedure.

It is essential that families are well educated regarding the care and maintenance of enteral feeding devices and, as mentioned, it is preferable that the success of enteral nutrition via nasogastric tube has been previously documented. Once the decision has been made to pursue gastrostomy tube placement, it is important that the family be familiar with the type of gastrostomy tube being placed, i.e., standard PEG vs. low-profile gastrostomy tube, the length of time that the family can expect the initial tube to be in place and who will perform the first change. All of these vary with institutions and specialties. An example of this is a surgically placed gastrostomy tube that could be a balloon low-profile device, a balloon replacement tube, or a mushroom-type Malecot® tube. Table 45.1 depicts some of the various types of gastrostomy and GJ tubes and securement techniques. The personnel involved in the tube replacement procedure also varies based on who placed the original tube and the direct visualization is now recommended either through radiology or a repeat endoscopic procedure.

Care of the gastrostomy post placement is simple. The skin around the G-tube should be washed daily with mild soap and water. A small amount of serous or mucoid drainage is normal. Use of hydrogen peroxide should be avoided as it causes unnecessary drying and irritation of the skin. It is important for the tube to have a good fit and to be well stabilized. Excessive movement in the tract can cause leakage,

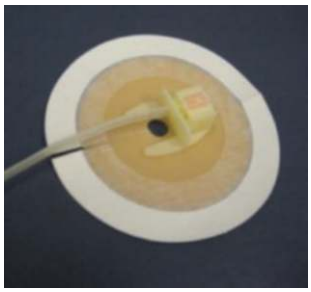
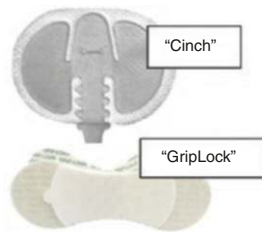
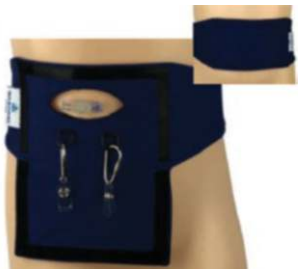
Fig. 45.2 Example of "T fasteners" for initial low-profile G-tube placement

Table 45.1 Examples of types of enteral feeding devices and securement devices

Gastrostomy tubes		**GJ tubes**	
Initial non-surgical G-tube 	Initial PEG/PRG tube with internal bumper and external crossbar 		Initial GJ tube with J limb threaded through G-tube
Low profile 	Low profile balloon tube 		Standard replacement GJ tube
Mushroom tube secured 	Standard mushroom tube (Malecot® or Pezzer®) 		Low profile balloon GJ Tube
	Standard balloon tube Can be initial surgical tube (e.g., Avanos®) 		Low profile balloon trans-gastric jejunal tube
	Low profile mushroom type tube (e.g., Bard®) 		"G-JET" low profile balloon GJ tube (AMT®)

(continued)

Table 45.1 (continued)

Securement devices and techniques		G, GJ-tube belts	
	Hollister Drain/Tube Attachment Device® Can be used to secure and stabilize both G-tubes and GJ tubes Secure tubes in a vertical fashion thus avoiding lateral traction on the stoma		Benik® enteral tube securement belt used to prevent accidental dislodgement of tube https://www.benik.com/peds/wrap/g-tube
	Other commercially available tube holders such as "Cinch®" and "GripLock®" Use these products with caution due to potential for applying lateral traction on the tube thereby causing erosion or "key-holing"		G-tube Wrap-Gus Gear https://gusgear.net/product/g-tube-wrap/
	Four-way tape method for low-profile device For initial securement while track is healing in a vertical fashion		Tuubezz G-tube belt https://www.tuubezz.com/

erosion of the stoma, and hypergranulation tissue formation. Similarly, excess traction on the tube can cause mucosal prolapse and erosion of the tract. Dressings should be minimized and only added as needed. A small amount of serous or mucoid drainage is normal after initial placement and should resolve over time if the tube has a good fit and is well-stabilized. If the patient has a low-profile tube in place, it is important to remove the feeding extension when not in use. Keeping the feeding extension in place at all times defeats the purpose of a low-profile tube and can cause undue lateral traction on the stoma, thereby causing erosion of the tract, "buried bumper syndrome," leakage, and/or mucosal prolapse.

Complications of Gastrostomy/Gastrojejunostomy Tubes

Commonly encountered complications of enteral devices include infection, leakage, hypergranulation tissue, peristomal skin breakdown, stomal prolapse, stomal erosion, tube migration, tube obstruction, and persistent fistula after removal [12–18]. Although there is a paucity of randomized controlled trials, Townley et al [16] present a rapid scoping review of literature regarding tube-related complications in children and treatment methods utilized. Table 45.2 outlines common complications and treatment strategies based on the author's 30-year experience.

Table 45.2 Management of common complications of percutaneous enteral tubes

Problem	Likely etiology	Prevention	Treatment
Dislodgement	Improper or inadequate securement	Adequate securement; use of products such as Griplock® or Hollister Drain Tube Attachment Device® to secure to abdominal wall; use of protective belts such as Benik Belt®; disconnect extension tubing when not in use to avoid lateral traction on tube	Replacement and securement
Leaking, peristomal irritant dermatitis	Inadequate stabilization, poorly fitting tube, inadequate balloon volume; stomal enlargement/erosion	Adequate fit of tube; securing properly; adequate balloon volume	Consider alternative type of tube; secure well; increase balloon volume to maximum recommended; consider removing tube to allow site to contract; peristomal skin protection with silicone sealant, cyanoacrylate, or moisture barriers
Hypergranulation	Inadequate stabilization, moisture, friction	Adequate stabilization, decrease moisture, avoid moist dressings	Silver impregnated hydrofiber or alginate; topical steroid ointment; chemical or surgical cauterization
Infection	Preoperative/pre-procedure antibiotics; treatment of oral, gut or vaginal fungal colonization; immunosuppression	Treatment of oral, gut or vaginal fungal infection; avoid pressure injury from too tight a tube fit which can lead to cellulitis	Topical antifungal powder, sealed in with silicone liquid sealant; topical antifungal ointment or cream; topical antifungal spray; oral or systemic antibiotics
Obstruction	Inadequate flushing, build-up of residue within tube	Consistent flushing schedule before after all feeds and medications; dilute medications, use liquid solutions whenever possible	Flushing, declogging agents (Clog-zapper®)

Infection

Gastrostomy tube infections are more common in the first several weeks following percutaneous placement. It has been estimated that 25–33% of patients develop a peristomal infection [16, 18–20]. Few studies have addressed the issue of peristomal infections in children. The underlying medical condition of the child may influence their risk for infection and hinder wound healing. Antibiotic prophylaxis with the placement of percutaneous endoscopic gastrostomies is recommended [19, 20].

Infection of the peristomal area can present with a variety of symptoms. Fever, spreading erythema, tenderness, pain, induration, and purulent discharge are typical. However, the yellow-brown crusty discharge that is commonly seen around the gastrostomy site is not a sign of infection, a finding that is confusing to families and caregivers. There can be mild erythema from friction at the site which is also not indicative of infection. In case of infection, treatment with a topical antibiotic may be all that is needed; however, oral antibiotics may be necessary. Most infections respond to a first-generation cephalosporin. Abscess formation adjacent to the stoma is another potential complication. These lesions have a rapid onset of a pustule or a red-purple fluid-filled lesion that is tender to the touch. When it ruptures, a punctuate opening is apparent and may drain for several days. Treatment with warm compresses and antibiotic therapy is recommended. Although there is little prospective comparison data available, a retrospective review of surgical vs PEG/PRG G-tube placement technique revealed surgically placed G-tubes had a lower infection rate than PEG/PRG tubes but PEG/PRG-placed tubes had lower costs and length of stay [17]. Fungal infections can occur, characterized by a shiny erythematous rash with satellite lesions. This should not be confused with irritant dermatitis due to leakage of caustic gastric secretions (Fig. 45.3).

It is important to assess the for the proper fit of the tube as a tight-fitting low-profile device can lead to a pressure injury including deep tissue injury and cellulitis at the site (Fig. 45.4). This is especially concerning in patients who have abdominal distention or changes in abdominal girth due to their underlying illness or disease process. Once the tight-fitting tube is removed, the site can usually heal. The tube may have to temporarily be replaced by a standard (long) tube and the low-profile device can be replaced after the injury is completely resolved.

Feeding tubes may become colonized with microbial organisms, yeast, and fungus. There have been more than 100 different microorganisms isolated from gastrostomy tubes with the most common being *Candida, Pseudomonas*, *Escherichia coli*, *Enterobacter cloacae*, *Streptococci*, *Lactobacillus*, *Staphylococcus aureus*, and *Bacteroides.* The significance of gastrostomy tube colonization is unclear; however, in the face of recurrent infections, culture of the site and treatment with the appropriately sensitive antibiotic is recommended.

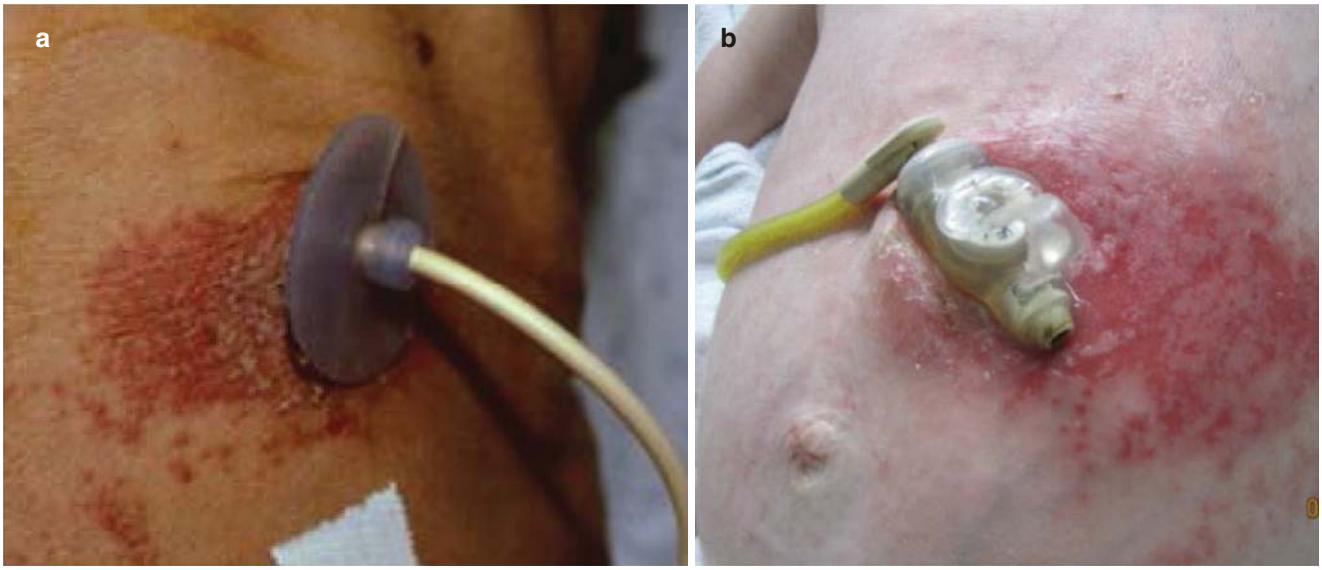


Fig. 45.3 (**a**) Peristomal Candida infection; (**b**) Irritant dermatitis from leakage

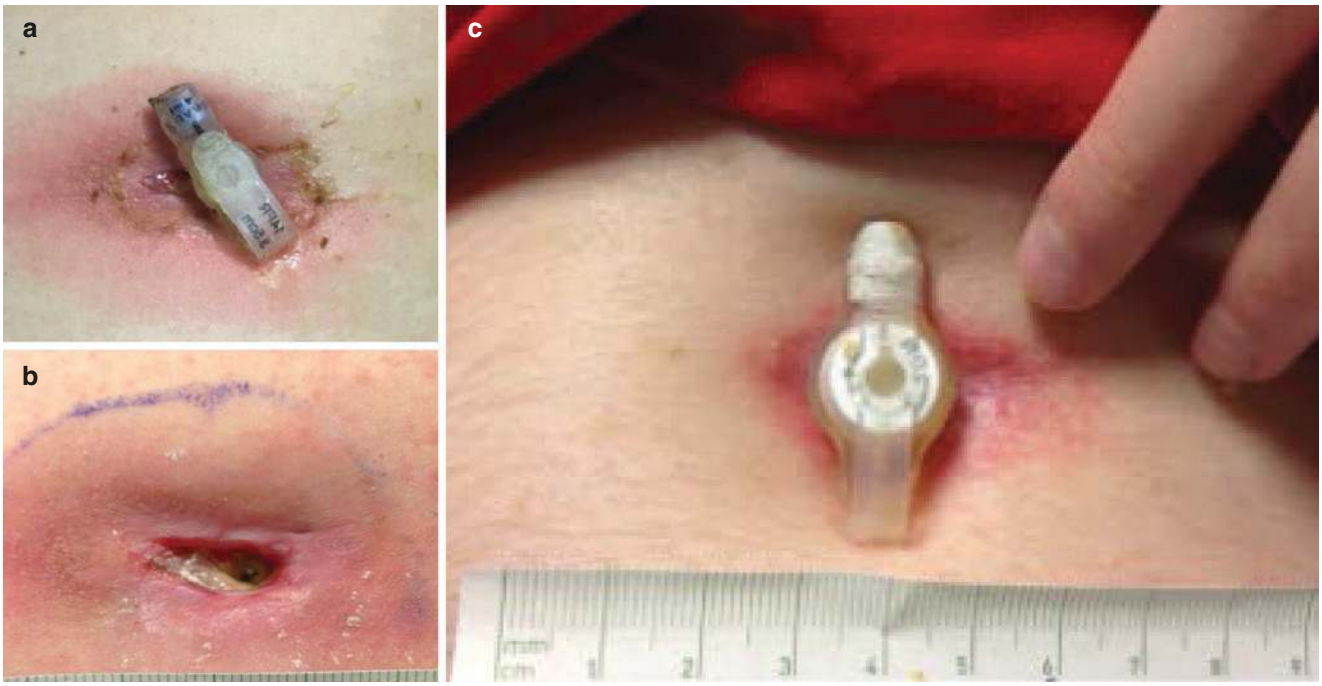


Fig. 45.4 Tight-fitting low-profile tubes. (**a**) Cellulitis, (**b**) Erosion (same patient), (**c**) Tight tube in teen with Crohn disease after gaining weight

Tube Migration and Dislodgement

Migration of the gastrostomy tube is well documented and includes scenarios where the balloon migrates causing gastric outlet obstruction, the jejunal limb of a GJ-tube migrating to the esophagus or retracting into the stomach, and further migration of these tubes into the distal small bowel causing diarrhea with aberrant tract formation has been reported [14]. The buried bumper syndrome (retrograde migration of the gastrostomy tube's internal bumper into the abdominal wall or into the stoma tract) is well described [21–23]. This occurs when there is traction placed on the external portion of the gastrostomy tube that results in excessive tension on the internal bumper at the time of placement. A false tract may develop as a late complication when the shaft length of the low-profile gastrostomy tube is not resized in a growing child [24]. Failure to remeasure the shaft length may result in a too short tube causing the balloon or internal bumper to move up into the tract. Leakage and focal abdominal discomfort may result. Long-term migration of the bal-

loon into the tract may result in the development of a false tract or dilatation of the gastric opening. This allows for drainage of gastric contents onto the skin resulting in peristomal skin excoriation and breakdown. Gastrocolic fistula formation has also been reported due to tube migration [25].

It is important to remeasure the stomal tract correctly and accurately. It is best to measure with the patient in both a supine and sitting position. If the measure significantly differs in either position, the tract length should be the average between the two measurements. It is recommended that tracts be remeasured at least annually. Patients who are gaining or losing weight, however, will need to have the fit remeasured more frequently. Figure 45.4c depicts a teenager with Crohn disease who initially at the time of tube placement was thin and undernourished, then gained weight while undergoing treatment causing a tight-fitting tube.

Tube migration can also occur in children with a GJ tube in place, where the jejunal limb of the tube can migrate proximally or coil backwards. In the latter, instance the child may demonstrate leakage of formula from the gastric limb of the tube or leakage of formula from the stoma. There have even been reports of GJ tube migration into the esophagus. A return trip to the interventional radiology suite is warranted and the tube can then be rewired and repositioned or replaced. If the child exhibits signs of intestinal obstruction, GJ tubes have been identified as a lead point for intussusception and this should be investigated whenever there is a concern for intestinal obstruction [14, 26, 27].

Leakage, Stomal Erosion, and Peristomal Skin Breakdown

Leakage, stomal erosion, and peristomal skin breakdown are all interrelated complications (Fig. 45.5). Chronic leakage is a worrisome complication as it leads to chemical, irritant dermatitis (Fig. 45.3b). Leakage of gastric contents often results in peristomal skin breakdown and pain, and can contribute to potential infection, and proliferation of hypergranulation tissue (Fig. 45.6). The first goal is always to ascertain

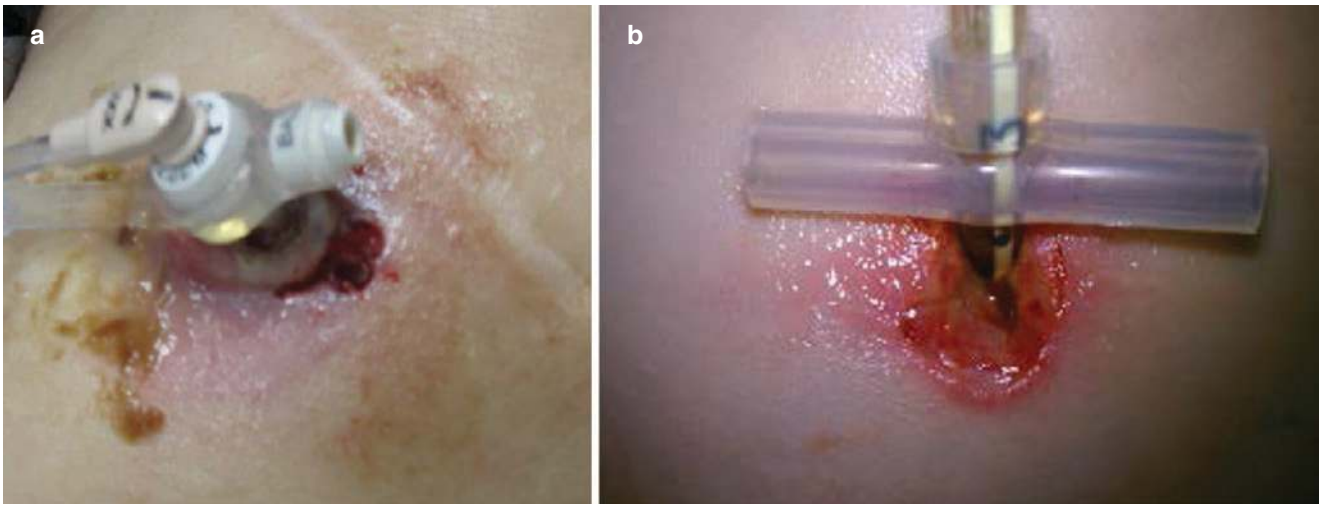


Fig. 45.5 (**a**) Stomal erosion, (**b**) Erosion with "keyholing"

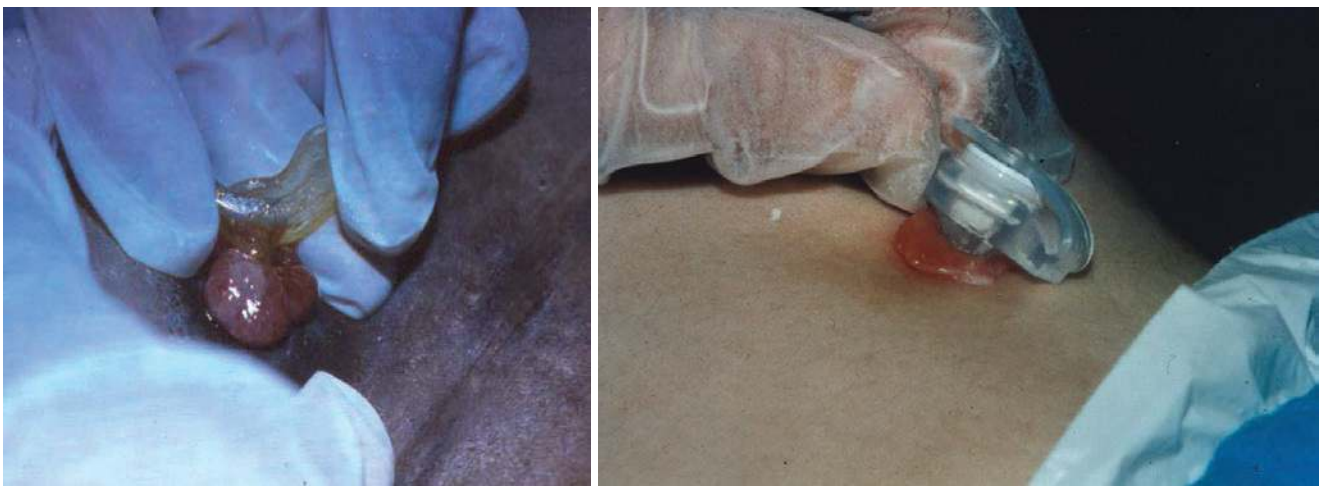


Fig. 45.6 Hypergranulation tissue

the cause of leakage and take steps to stop it. A good fit and proper stabilization are both crucial to preventing leakage. For low-profile balloon tubes, remeasuring the shaft length and ensuring the proper fit of the gastrostomy tube is the first step. Ensuring that there is adequate water in the balloon is important. While most manufacturers recommend that the balloon be inflated with 4–6 mL of water, most can accommodate several additional mLs safely. It is important to be cognizant of the size of the child and their gastric volume, to avoid exceeding gastric capacity. If the leakage is from an enlarged or eroded stoma tract, increasing the diameter of the gastrostomy tube (for example, going from a 14 French to a 16 French) should be avoided. Increasing the lumen size of the tube only further dilates the stoma diameter. Alternatively, removing the gastrostomy tube for a short period allows the stoma to contract. If the gastrostomy is relatively recently placed, often a few hours may be enough time to allow the tract to contract. Longstanding gastrostomies may require removal of the tube overnight or even longer to get the tract to scar down.

For severe leakage and stomal erosion, more aggressive interventions may be warranted. These include temporary removal of the tube and placement of a nasojejunal tube for post-pyloric feedings, while the stoma contracts and the peristomal skin heals. Placement of a smaller caliber balloon tube allows the site to scar down while still utilizing the balloon to stent secretion leakage. The small caliber balloon tube can be secured with manufactured tube stabilizers such as the Hollister Drain-Tube Attachment Device®. This type of device is often used to secure mushroom-type tubes such as Malecot® and Pezzer® tubes. Other strategies for minimizing gastric secretions include placement of an NG sump or placement of an ostomy pouch to help contain secretions while the site contracts. Many patients benefit from changing to a different type of tube if leakage is a chronic issue. If all interventions fail and the site remains enlarged, eroded with profuse leakage, surgical revision may be necessary.

Wound management of the eroded gastrostomy tube site is a challenge. While awaiting improvement in stoma contraction, the peristomal skin must be protected from caustic gastric secretions. The guidance of a wound and ostomy nurse may be necessary. Skin barriers and absorptive dressings are helpful in preventing ongoing damage from gastric secretions. Skin barriers containing zinc oxide and other topical barriers used to treat diaper dermatitis may provide comfort to the patient and protect the skin from further breakdown. Use of silicone skin sealants such as Cavilon No Sting Barrier® (3M), or cyanoacrylate skin sealant such as Marathon® (Medline) can be useful in protecting the skin. There are numerous wound dressings that can support wound healing of the stoma. Absorptive dressings include foams (e.g., Mepilex®), hydrofibers (e.g., Aquacel®), and hydroconductive (e.g., Drawtex®) dressings and have been effective when used around gastrostomy tubes when indicated to address excessive leakage.

Hypergranulation Tissue

Hypergranulation tissue (Fig. 45.6) is a frequent complication of gastrostomy tube [16, 18, 28]. For some patients, it is a minor complication but in others it results in unsightly tissue that is painful and friable where often times there is increased exudate and bleeding. Hypergranulation is a proliferation of capillaries that forms around the external stoma and occasionally within the gastric opening. This excessive, abnormal tissue can also harbor bacterial. Current treatment options are limited. Oftentimes this excessive proliferation of tissue can lead to other issues such as leakage and erosion of the surrounding skin in addition to pain and bleeding. In these more severe cases, it is important to treat the condition. The usual treatment for hypergranulation consists of attempts chemical cauterization with silver nitrate, topical steroid cream, and foams or pectin-based powders. A randomized controlled trial (RCT) comparing hydrogel, saline, and soap and water, with small sample size revealed a hydrogel dressing had best results in deterring hypergranulation tissue [29]. A RCT by Leon et al. [28] investigated the use of a hydrocolloid dressing, with or without silver, and found no difference between standard care, hydrocolloid or silver hydrocolloid. Another option is the topical cream GranuLotion®. Although there are no RCTs investigating this particular treatment, and ineffective results found by the author, there are anecdotal reports from families of a positive response in some cases.

Cauterization of hypergranulation tissue with silver nitrate has been utilized for years. It can result in significant complications if applied improperly. Burns to the surrounding skin are not uncommon and it is essential to protect the peristomal skin. Cauterization is not ideal—it can be painful and may need to be repeated to eliminate the hypergranulation tissue. In addition, chemical cautery causes trauma and inflammation to the tissue, and thus can further exacerbate proliferation of the abnormal tissue. It is important to protect the healthy peristomal skin with a skin barrier, acrylate skin sealant (Cavilon No Sting Barrier® for example) or surgical lubricating jelly. An alternative to chemical cautery is treatment with absorbent silver-impregnated dressings such as hydrofibers or alginates [30]. The silver serves as an antimicrobial to treat the increased bioburden thought to occur with hypergranulation tissue, while the absorptive qualities of the dressing addresses excess moisture.

Although there is little data to support the use of corticosteroid creams in the treatment of granulation tissue, however, dermatologists have used topical steroids in the treatment of postoperative granulation tissue for several years [31]. It is thought that the topical steroids have an anti-

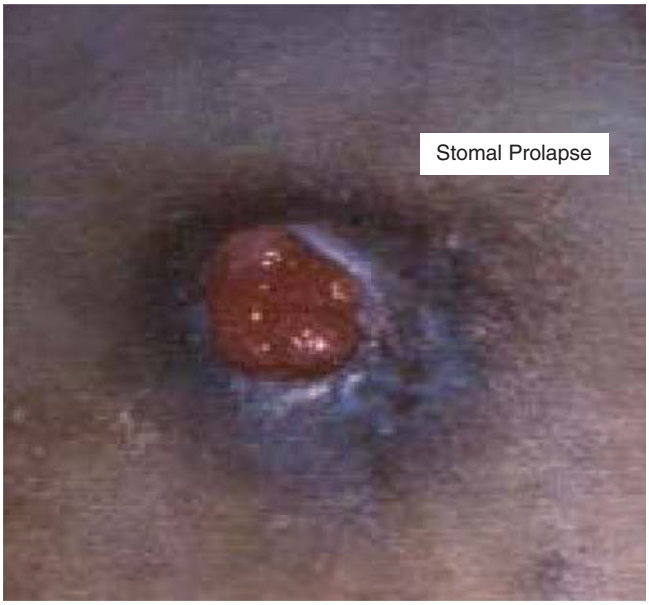


Fig. 45.7 Stomal prolapse

angiogenic effect on the granulation tissue similar to that of systemic steroids in the treatment of large capillary hemangiomas. Anecdotal reports on the successful use of triamcinolone cream in the treatment of granulation tissue are available [16, 18]. The usual dose is 0.1% triamcinolone cream twice daily for 2 weeks has met with some success and some centers implement a short course (2 weeks) of Triamcinolone 0.5%.

Prolapsed gastric tissue (Fig. 45.7) is often confused with hypergranulation tissue. The tissue with gastric prolapse is a deeper red, shiny, and more granular in appearance. Cautery with silver nitrate has no effect on this tissue, which is typically intermittent. Most important in treatment is proper fit of the tube, adequate securement, and avoidance of multiple layers of dressing or excessive traction on the tube.

Tube Obstruction

Obstructed tubes are an issue primarily with gastrojejunal devices. Migration or dislodgement of these tubes is common in children with gastrointestinal dysmotility. To prevent tube clogging, frequent flushing is recommended, before and after bolus feeding or medication administration and every 2–4 h during continuous feedings. Families should be instructed on how to administer medication and which medications are more likely to cause tube obstruction. Water is recommended with a volume large enough to clear the tube, approximately 10 mL with each flush. Vigorous flushing with small volume syringes and warm water may help generate enough pressure to clear the tube. In addition, use of pancreatic enzyme mixed with sodium bicarbonate might help relieve tube obstruction, although there may be concern for tube degradation with these ingredients. There is a commercially made product—Clog Zapper® (Avanos Medical) which is effective in clearing tube obstructions.

Fistula Formation

A persistent gastrocutaneous fistula is one that does not close spontaneously in 4–6 weeks after the gastrostomy tube has been removed. Approximately 25% of all children who had an endoscopically placed gastrostomy tube will suffer this complication [12, 14, 24, 32]. The longer the gastrostomy tube is in place, the less likely the fistula will heal spontaneously. Oftentimes, the track becomes epithelialized which would prevent closure of the track. A variety of techniques for promoting closure have been reported in the literature but all with limited success. Tract cauterization and use of fibrin glue have been reported in adults [13]. If the track has epithelialized, then surgical coring out of the track to create a fresh wound may be warranted. Surgical consultation and closure is usually recommended if the tract has not closed within 4–6 weeks.

Gastrocolonic fistulas may develop after the placement of a percutaneous gastrostomy due to the technique and lack of direct visualization [12–14, 32]. Fecal drainage from the stoma, foul breath or leakage of formula or medications from the rectum or refractory diarrhea should raise the suspicion of a gastrocolonic fistula [25]. Surgical closure of the fistula with a replacement of the gastrostomy tube is necessary.

Ostomy Education and Management

Children and adolescents with inflammatory bowel disease, as with many chronic illnesses, modify many aspects of their lives to gain control of their disease. Medications, dietary changes or limitations, and surgery all play a role in the management of IBD. Activities may need to be limited, and relationships are affected, all of which impact a patient's lifestyle. Many patients who undergo operative intervention ultimately feel physically better after surgery as they gain control they had previously lost. Despite feeling better after surgical intervention, oftentimes the impact of surgery, and in particular fecal diversion, can affect their body image and self-esteem. Preoperative education should occur whenever possible. For those patients who undergo urgent fecal diversion, where preoperative education is not possible or limited, education and support postoperatively becomes essential in assisting the patient and family to adapt to life with an ostomy.

For the majority of children and adolescents with inflammatory bowel disease, having a surgical intervention that results in

an ostomy is associated with fear. For many patients, surgery is recommended either emergently or urgently due to a complication of the disease. It is important that the patient and family be well prepared. David and colleagues [33] describe a qualitative study on perceptions of ostomy educational needs in patients with IBD and their caretakers and found that preoperative education was lacking. Stressing the positives of surgery is important and education can assist in easing anxiety and fear of the unknown. Many have never heard the words stoma or ostomy and the information they have may be incorrect. It is important that the patient and the family understand that living with an ostomy requires a life-style adjustment, and that new skills will be acquired and mastered.

From a healthcare provider perspective, patient/family education prior to the surgery and preoperative marking of the stoma site are essential. The placement of the stoma is important for successful secure pouching and optimal patient satisfaction and outcomes. Ideally, a certified Wound, Ostomy, Continence Nurse (CWOCN) collaborates with the surgeon to select a site that is ideal in terms of creation of the stoma. A joint position statement between the Wound Ostomy Continence Nurses Society and American Society of Colon and Rectal Surgeons outlines key points and patient characteristic factors in stoma site marking [34]. However, there is a small subset of experienced pediatric surgeons who perform a large volume of ostomy surgeries and are expert at stoma siting. The stoma is ideally placed not only within the rectus muscle but also accommodates the patient's body contour, clothing selections, and avoids creases and skin folds. Successful site marking occurs with the patient awake and interactive. The patient is assessed in lying, sitting, and standing positions with typical clothing in place. In many cases, especially in patients with Crohn disease, ostomy surgery is performed on an urgent basis. In these situations, an experienced pediatric surgeon who cares for a large volume of patients with IBD can properly identify the landmarks for stoma siting.

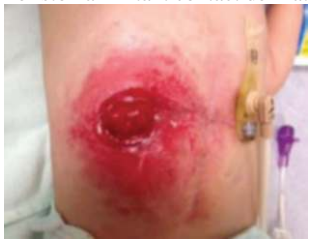
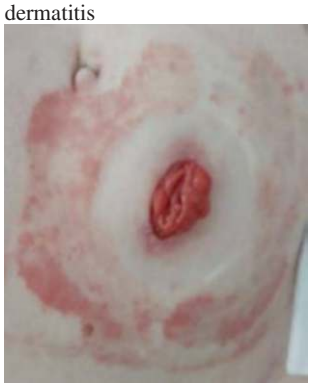
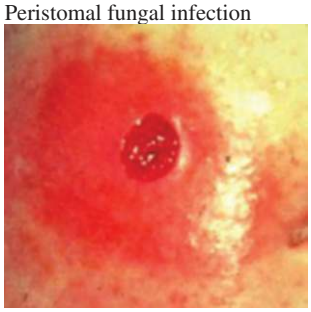
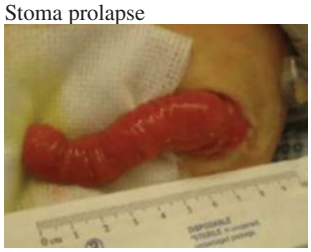
It is important for the patient, with the help and support of their family, to adapt to having an ostomy. Healthcare providers can help educate the patients and family to alleviate common misconceptions. Education should take place within a developmental framework. In 2011, the Wound, Ostomy Continence Nurses Society published a best practices for pediatric ostomy care which includes educational and behavioral intervention for all age groups [35]. More recently, this same professional society published clinical guidelines for management of the adult patient with an ostomy [36] which can be applied to the over 18 years/young adult population cared for within a pediatric setting. Through education and support, clarification and reassurance can be provided regarding such common misconceptions such as ostomies do not smell, they are not visible under clothing, and that sports participation is possible. Swimming, scuba and sky diving, and even professional football are all possible with an ostomy. There are a variety of "stoma guards" on the market which provide protection during contact sports, examples include but are not limited to Stealth Belt, Stoma Guard. In addition, there are several companies who produce clothing and accessories for ostomates, including pouch covers, swimwear, and intimacy clothing. Adolescents fear intimacy with a stoma. This too needs to be addressed up front. If the healthcare professional is uncomfortable with the topic, then arranging a consultation with another provider or a CWOCN who can address these issues is important prior to surgery when possible, or at least during postoperative education in both the hospital and outpatient settings.

Family education and support is important. The preoperative discussion should include what the stoma will look like, how it functions, how it is managed, what the appliance or pouching system will look like. Have the pouching system available so that the patient and family can visualize how the stoma is fitted and how the pouch is emptied. Encourage the patient to wear a pouch prior to surgery so they are familiar with the sensation of the pouch on their abdomen and to be familiar with what to expect after surgery.

One of the most common problem encountered in ostomy management is leakage from around the pouching system. It is important to be able to maintain the seal on the pouching system for a predictable period of time, for most patients 5–7 days, minimum of 3 days. Leakage results in denuded peristomal skin, and more importantly, loss of confidence and frustration for the patient. It is important for the patient to be able to predict the timing for changing the pouching system, thus allowing them to change it on a scheduled day and avoid the worry that the system will fail in the interval.

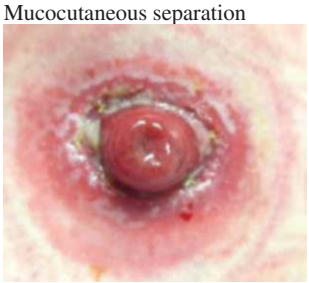
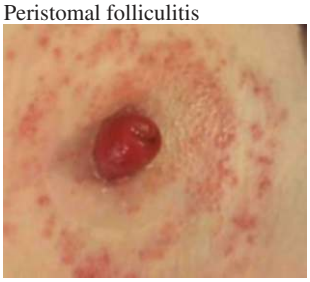
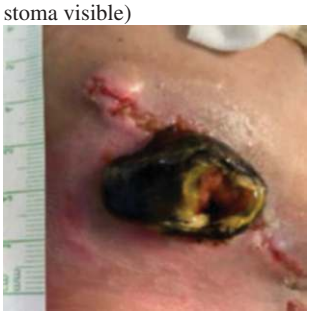
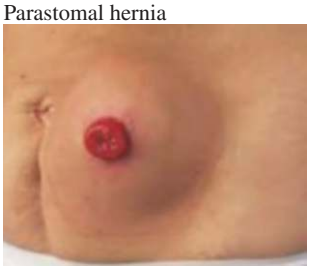
Common stomal and peristomal problems include peristomal skin conditions, poor healing, stomal retraction, or prolapse or parastomal hernias [37]. Prevention and early recognition of peristomal complications is key to achieving patient satisfaction and positive adaptation. Table 45.3 outlines common peristomal complications and recommendations for prevention and treatment. Early intervention and treatment can minimize the long-term complications. One of the more common problems encountered is irritant dermatitis. This often occurs with ileostomies from leakage of caustic stool on the skin under the appliance. Prevention and treatment centers around appropriate appliance selection and sizing. Allergic contact dermatitis is treated by removing the offending product and then using a topical anti-inflammatory in a spray form and replacing the product. Poor wound healing contributes to muco-cutaneous separation. The separated area is filled with an absorptive dressing, then covered with a hydrocolloid dressing in an effort to isolate the wound from fecal output. Candidiasis of the peristomal skin area is best treated with a topical antifungal powder that can then be

Table 45.3 Common stoma and peristomal complications: prevention and treatment

Problem	Likely etiology	Prevention	Treatment
Peristomal irritant contact dermatitis 	Leakage of caustic effluent on peristomal skin	Proper fit of appliance and use of barrier seals as caulking to prevent leakage and undermining of wafer barrier	Alter appliance, sealants and barrier rings or caulking as needed; protect skin with silicone or cyanoacrylate sealants
Peristomal allergic contact dermatitis 	Contact/allergic dermatitis related to appliance and accessory products, in this case the tape border of wafer	Use minimal variety of products necessary for good fit and good seal	Patch testing; switching appliance to alternative product; topical treatment with steroid sprays or powders
Peristomal fungal infection 	Colonization of mouth, gut, vagina; immunosuppression	Keep peristomal skin clean and dry; treat existing infection (oral, vaginal)	Use of antifungal powder and "seal in" with liquid sealant; topical antifungal spray; oral or systemic antifungal agent if needed or if severe in compromised patient
Peristomal pyoderma gangrenosum 	Disease process-extraintestinal manifestation of IBD adjacent to stoma, caused by trauma, inflammation, irritation, abrasion, or pressure	Appliance with good fit Avoid pressure, abrasions, and trauma	Topical, intralesional, or systemic steroids; immunologic or biologic agents; topical dressings of silver impregnated hydrofiber, alginate, or other absorptive dressing with antimicrobial
Stoma retraction 	Short length of intestine for stoma creation; stoma within crease; increased weight gain	Adequate length of stoma	Use of convex wafer and belt to assist in improving stoma profile
Stoma prolapse 	Enlarged fascial opening, increased intra-abdominal pressure	Avoid convex wafers and/or belts in immediate post-operative period; avoid increased intra-abdominal pressure	Protect prolapse; can use lubricant inside pouch to prevent rubbing against prolapse; cut radial slits in wafer barrier to allow to accommodate prolapse

(continued)

Table 45.3 (continued)

Problem	Likely etiology	Prevention	Treatment
Mucocutaneous separation 	Poor healing, mechanical	Maximize medical treatment of IBD, maximize nutrition, whenever possible prior to surgical creation of stoma; consider avoidance of convex wafers in immediate post-op period	For area with depth, pack area with gelling hydrofiber, with silver if there is concern for infection, or alginate and cover with thin hydrocolloid; obtain good seal of appliance to prevent stool coming in contact with wound with the goal of isolating the wound from stool intrusion
Peristomal folliculitis 	Irritation and local infection of hair follicles due to mechanical trauma	Careful shaving of peristomal hair if interfering with appliance adherence	Clean peristomal skin with antibacterial soap, rinse and dry well. Can treat with topical antibiotic powder. Consider treatment with systemic antibiotics if severe or not responsive to cleansing regimen. Reduce frequency of shaving
Stomal necrosis above fascia (pink stoma visible) 	Superficial ischemia, sloughing  Same stoma after sloughing of superficial necrotic layer	Proper position and length of stoma construction to avoid vascular compromise	Monitor/observe if superficial necrotic tissue will slough revealing a viable stoma Emergent surgical revision is required if necrosis is below the fascial level
Parastomal hernia 	Not seen very frequently in pediatric. Occur when there is a defect or weakness in the muscle of the abdominal wall	Proper position and construction of the stoma; avoidance of muscle straining in post-op period	Refer to surgeon Consider use of hernia support belt Instruct patient to report symptoms of incarceration (dark stoma, severe pain, no gas or stool output, vomiting)

"sealed in" with a silicone sealant. More uncommon complications include stomal granulomas, suture granulomas, and peristomal abscess. Peristomal abscesses, though rare, should be treated with systemic antibiotics and topically with an absorptive foam product.

Pyoderma gangrenosum (PG) may occur at or near the stoma of patients with IBD, or elsewhere on the skin. Classically, a full thickness, painful ulcer develops in the peristomal area with a halo of purple discoloration (Fig. 45.8). The etiology is thought to be due to pathergy-trauma such as abrasion, scratching, or pressure. The ulcers are extremely painful with significant drainage. If the ulcer is large, it may interfere with the pouch seal resulting in leakage and further skin breakdown. Treatment of peristomal PG can be difficult and varies. Topical, intralesional, and systemic corticosteroids may be necessary and found to effective as well as immunomodulator therapy and biologic agents. Topical tacrolimus ointment or solution, or cyclosporin has also been reported to assist with wound healing [38–41]. Absorptive dressings such as silver-impregnated hydrofiber (for example Aquacel AG) or a calcium alginate will absorb moisture and exudate [36, 37].

Fig. 45.8 Peristomal pyoderma gangrenosum. (**a**) Intralesional steroid injection, (**b**) Absorptive silver-impregnated hydrofiber dressing

When associated with a fecal stoma, there is the additional challenge of managing stool output and preventing stool intrusion into the wound. Once the wound is dressed, this primary dressing is then covered with a transparent thin hydrocolloid or transparent film and the ostomy wafer is then placed over this. It is important that the PG wound be protected from stool soilage for optimal wound healing. Avoidance of peristomal trauma and pressure is key to minimizing risk of PG. This includes the use of convex wafers and ostomy belts. In addition to modifying the appliance as needed and topical dressings, maximizing medical management of disease process is integral to managing peristomal PG.

Preparing a patient and family for living with an ostomy, whether temporary or permanent, is a planned approach. It should provide them with education regarding the stoma, the skills necessary to care for the stoma, and emotional support. Oftentimes, this is required of families while also managing disease flares, treatments, and side effects. Patients with ileostomies must be taught how to monitor for and treat dehydration. In addition to family preparation, the health care team needs to take the developmental level of the patient into consideration. A school-aged child with an ostomy has different needs and concerns than an adolescent. This age group may pose the most challenge regarding acceptance and adaptation [42]. The adolescent is not only is dealing with biologic and sexual maturation, but they are also striving to achieve independence and autonomy within the greater social environment and often mentoring from others who have gone through ostomy surgery can reassure and guide them in the adaptation process [43]. Transitions from hospital to home and school, and return to sports, work and other activities are important landmarks. The patients and families need support and resources to help guide them through these transitions. There is a wide array of resources and accessories available to ostomates and it is important that the patients explore these options. Figure 45.9 depicts examples of ostomy accessories which can help with these transitions. A supportive healthcare team can be crucial for successful adaptation and positive self-image for the patient, and positive adjustment for the entire family.

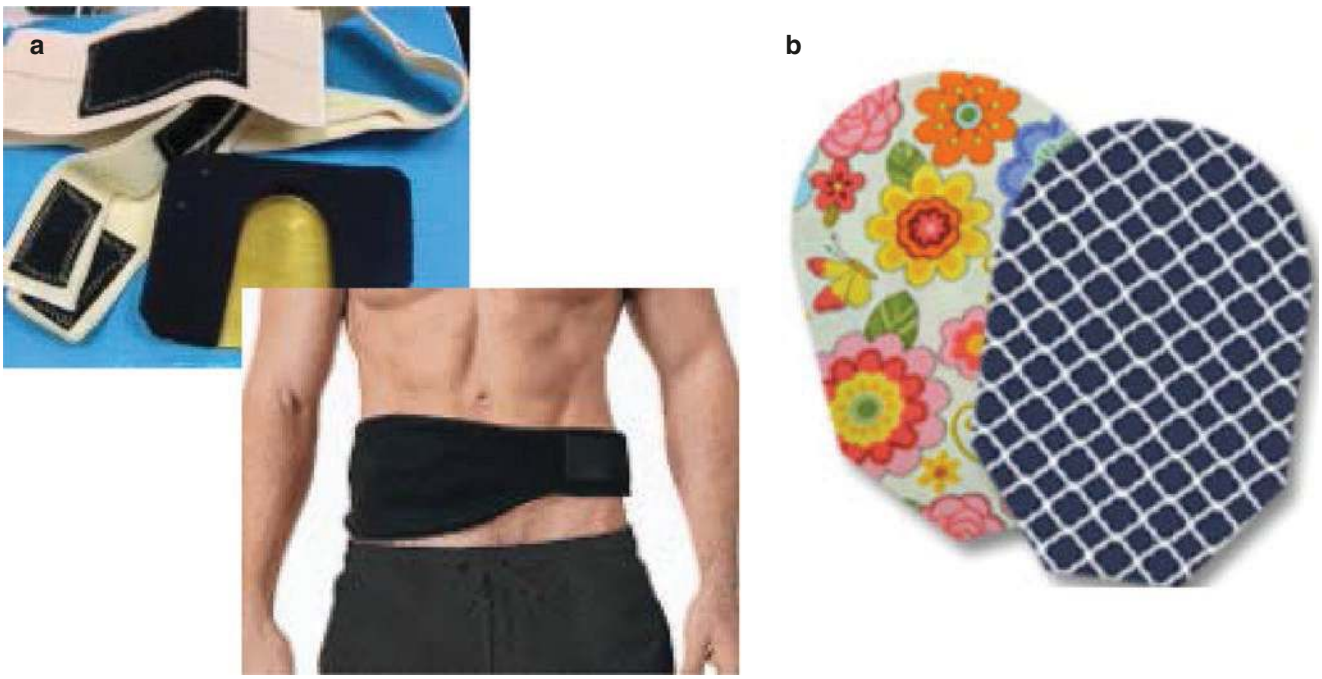


Fig. 45.9 Examples of: (**a**) Stoma protection, (**b**) Pouchcovers

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Part VI

Research

Clinical Indices for Pediatric Inflammatory Bowel Disease Research

46

Oren Ledder and Dan Turner

Introduction

Clinical research relies on standardized markers which accurately reflect a response to interventions. For both practical and ethical reasons, invasive measures are best avoided when possible and thus clinical indices will always play some role in assessing outcomes, both in practice and in the clinical trial setting. Various indices have been developed for pediatric use due to specific aspects of the disease in that population. While some indices were primarily developed for research purposes, many are also widely used to standardize assessment in clinical practice.

Assessment of Instruments Used in Clinical Research

Disease activity is a concept for which no gold standard exists. Even in ulcerative colitis (UC), where colonoscopic examination is highly important in evaluating disease activity, it still cannot be regarded as a gold standard because the degree of inflammation is subjective, mucosal healing lags after clinical improvement, and perhaps other measures are more important, such as histological remission. Therefore, disease activity is best measured using multi-item indices which often incorporate clinical symptoms, laboratory parameters, and, when feasible, also endoscopic findings.

According to accepted standards of health indices development [1], the introduction of a new measure for use in clinical research should follow a multistep process of item generation, reduction, grading, weighting, and evaluation [2, 3]. A list of all potentially useful items is generated by a panel of experts and then reduced to include only the most relevant items. These items are then evaluated for their ability to explain the desired attribute (e.g., signs and symptoms, disease activity, or quality of life); each item is graded and may be assigned a weight according to its ability to reflect the concept which is targeted. The final measure is then evaluated to define cut-off scores that correspond to clinically important disease states such as remission and mild to severe disease activity. For clinical indices that will be used to determine changes over time (evaluative measures), a definition of "response" (i.e., the minimal important difference) is also required.

Once the instrument has been developed, it must be evaluated for validity, reliability, responsiveness, and feasibility [4–6]. Briefly, ***validity*** is the degree to which the instrument measures the concept that it purports to measure [7]. The ***reliability*** of an instrument relates to its stability on repeated measures both over time and by different raters at one point in time [8]. ***Responsiveness*** refers to the instrument's ability to correctly identify change over time in the concept being measured. It is not merely sensitivity to change but rather the ability of the instrument to detect changed from unchanged patients. A highly responsive index is invaluable in clinical trials, as it allows performing the trial with a smaller sample size [9–12]. Finally, ***feasibility*** encompasses both respondent and administrative burden. An instrument is feasible if the participant and researcher report that the instrument is completed within reasonable limits of participant discomfort and both participant and researcher time constraints.

Outcomes in Pediatric Inflammatory Bowel Disease

Crohn Disease Activity Indices

One of the first Crohn disease (CD) activity indices developed in adults was the Crohn Disease Activity Index (CDAI) published in 1976 by Best and colleagues [13]. This index includes clinical symptoms, IBD-related complications,

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physical examination findings, laboratory tests, weight, and use of medications to treat diarrhea. Since its publication, it has been used extensively in most clinical trials in adult Crohn disease, only recently supplanted by patient reported outcomes (PRO) (detailed later in this chapter). The CDAI has been criticized for its complex calculation, potentially poor inter-observer agreement [14, 15] and poor correlation with endoscopic appearance [16, 17] which is becoming an increasingly important outcome. Simpler versions have been developed, the most commonly used being the Harvey–Bradshaw Index (HBI) which incorporates only clinical symptoms and physical exam findings [18]. The respondent burden is significantly lower than the CDAI, with no need for a symptom diary or blood work.

For children, the Pediatric Crohn Disease Activity Index (PCDAI) was developed [19]. This instrument ranges from 0 to 100 points and contains patient symptoms (based on a 7-day recall), physical examination findings, laboratory parameters, and growth measures (Appendix 1.1). Despite its several limitations, the PCDAI performed well in multiple pediatric IBD clinical trials as a measure of disease activity. The weight variable requires a reading at an interval of at least 4 months with weight loss being quantified as a percentage ([current weight—previous weight]/previous weight). The height variable at diagnosis is scored according to the number of channels crossed downward if prior measurement is available and, if not, according to the current centile. The height variable on follow-up visits employs height velocity, measured over a minimum period of 6–12 months [20, 21]:

$$\frac{\text{Height velocity} = 2^{\text{nd}}\,\text{height} - \text{baseline}\left(\text{cm}\right)}{\text{Time}\left(\text{year}\right)}$$

To compare children of different ages and gender, the height velocity is converted to a z-score:

$$\frac{z - \text{score} = \text{Observed height velocity} - \text{Mean height velocity for age and sex}\left(\text{cm / year}\right)}{\text{SD of the mean height velocity}\left(\text{for age and sex}\right)}$$

The z-score corresponds to the standard deviation (SD) of the child's height velocity.

The PCDAI has been evaluated in seven cohorts of children with CD (Table 46.1) [19, 22–24]. In a head-to-head comparison, Otley et al. [22] showed that the PCDAI was highly correlated with physician global assessment ($r = 0.86$), higher than the CDAI ($r = 0.77$), the modified CDAI ($r = 0.76$) and the HBI ($r = 0.72$). In the largest study to date, test–retest reliability on stable patients has been shown to be good [25]. Responsiveness to change was demonstrated and the minimal clinically important change, to define "response," was found to be at least 12.5 points [23], also in the larger study which used several methods to attain this "minimal important difference" corresponding to moderate change [25].

The optimal PCDAI cut-off score that defined remission has been open to some discussion. The initial study found that a PCDAI score of ≤10 points discriminated active from quiescent disease. Other studies found that PCDAI scores of <10 and <15 points were more sensitive and specific, respectively [22, 24]. In a more recent large study of 366 children, the best cut-off values were <10 points or <7.5 without the height item points for remission, 10–27.5 for mild disease, 30–37.5 moderate disease, and 40–100 for severe disease. This yielded the best accuracy (Table 46.1) acknowledging that the growth item is irrelevant in adolescents who passed the growing-tanner stages and that height typically improves several weeks or months after remission has been achieved (i.e., low responsiveness). The PCDAI does not differentiate well between moderate and severe disease activity and the feasibility of the PCDAI is only moderate. In the registry of a pediatric IBD collaborative research group, only 47.6% of the registered visits had a valid PCDAI score, compared to 97.6% with the Pediatric UC Activity Index (PUCAI—see below) [26]. Similarly, data to complete the PCDAI from the ImproveCareNow registry were available in the charts of only 20% of 3643 clinical visits [27]. Besides the low feasibility of the index and the limitations imposed by the growth item, the inclusion of the perianal item is debated as it reflects a different concept than luminal disease activity.

Given these shortcomings of the PCDAI, and since its development was judgmental by a small experts' panel, the PCDAI has been revised by a mathematical weighting on 437 children [28] (Appendix 1.2). This weighted PCDAI, termed wPCDAI, excluded three items shown to be redundant in a multivariable model: height velocity, abdominal examination, and hematocrit, thereby improving its feasibility. The score range of the wPCDAI is 0–125. In the validation cohort, it had higher correlation with physician global assessment (PGA) and ESR than the original PCDAI (0.75 vs 0.67 and 0.58 vs 0.49, respectively). The discriminant validity was better with the wPCDAI: it differentiated those in remission from active disease (area under the ROC curve 0.95), and unlike the original PCDAI, differentiated well between moderate and severe disease (area under the ROC curve 0.87). wPCDAI performed well as a primary outcome measure in recent studies assessing response rates to a sec-

Table 46.1 Validity, reliability, and responsiveness of Pediatric Crohn Disease Activity Index

Instrument	Study population	Validity	Reliability	Responsiveness
PCDAI Hyams et al. [19]	*n* = 131 prospective cohort	PCDAI to HBImod *r* = 0.81 PCDAI to PGA *r* = 0.80 Score cut offs: No disease 0–10 Mild 11–30 Moderate/Severe >30 } 69% correct classification	Inter-observer *r* = 0.86	N/A
Otley et al. [22]	*n* = 81 prospective cohort	PCDAI to CDAI *r* = 0.86 PCDAI to PGA *r* = 0.86 PCDAI to HBI *r* = 0.84 Receiver operating curves to select PCDAI cut-offs for no versus mild disease: Sensitivity Specificity ≤10 0.75 0.905 <15 0.83 0.905	N/A	Correlation of the difference PCDAI score, between the two visits was highly correlated with the difference in the CDAI in 17 patients. No other responsiveness measures are provided and time of follow-up visit not specified
Hyams et al. [24]	*n* = 181 from Pediatric IBD Collaborative Research Group Registry	Validation of previously defined score cut-offs: Sensitivity Specificity No disease vs mild: <10 0.81 0.68 Mod/severe vs mild: >30 0.71 0.83	N/A	Clinically significant change in PCDAI predictive of change in PGA = 12.5 points (sensitivity 0.87, specificity 0.73)
Kundhal et al. [23]	*n* = 25 and 63 (from 2 prospective cohorts)	N/A	N/A	Minimal clinically significant change in PCDAI predictive of PGA at 1-month follow-up = 12.5 points (sensitivity 0.83, specificity 0.92) High effect size statistics in 15 patients who responded to therapy (SES = 1.78, SRM = 1.41)
Turner et al. [67, 68]	*N* = 437 4 prospective cohorts	PCDAI to PGA *r* = 0.67 PCDAI to CRP *r* = 0.26 PCDAI to ESR *r* = 0.49 PCDAI to Alb *r* = −0.37 PCDAI to Hb *r* = −0.40 PCDAI to Plat *r* = 0.58	*N* = 90 ICC: 0.74–0.8	The PCDAI showed good responsiveness to change (*r* = 0.54–0.83, distributional 0.8–1.4, diagnostic utility analyses AUC ROC 0.79–0.85); minimal important difference >12 points
Turner et al.	*N* = 322 (from 2 prospective cohorts)	PCDAI to PGA *r* = 0.67 PCDAI to SES-CD *r* = 0.42 PCDAI to Calprotectin *r* = 0.26	Test-retest reliability *N* = 25 ICC: 0.85–0.97	PCDAI showed good responsiveness to change compared to PGA (*r* = 0.71) and differentiated clinical improvement from those with poor response (AUC ROC 0.86–0.96)
Grover et al.	*N* = 24 prospective cohort	PCDAI to SES-CD *r* = 0.33	N/A	PCDAI demonstrated poor responsiveness between pre- and post-treatment measures in comparison to SES-CD

CDAI Crohn Disease Activity Index, *HBI* Harvey–Bradshaw Index, *PCDAI* Pediatric Crohn Disease Activity Index, *abPCDAI* abbreviated PCDAI, *PGA* Physician Global Assessment, *CRP* C-reactive protein, *ESR* Erythrocyte sedimentation rate, *Alb* Albumin, *Hb* Hemoglobin, *Plat* Platelets, *SES-CD* Simple Endoscopic Score—Crohn Disease

ond biological agent [29] and repeated courses of nutritional therapy in CD [30] in which remission was defined as wPCDAI <12.5 and response as decrease in wPCDAI >17.5.

In addition to the wPCDAI, a number of abbreviated PCDAI instruments have been proposed to increase the feasibility of the PCDAI for use in retrospective chart reviews [31, 32]. The abbreviated PCDAI (abbrPCDAI) retained the three history variables (abdominal pain, general well-being, and stools per day), weight variable, abdominal exam, and perirectal disease. A larger study presented a short version of the PCDAI (shPCDAI), excluding items with a low frequency of completion in a patient registry [27]. The difference between the shPCDAI from the abbrPCDAI is that the extraintestinal manifestation item has replaced the perianal item and new weights have been mathematically assigned to each item, reflecting their relative importance to PGA of disease activity. The exclusion of the lab items in both indices increased their feasibility but at the expense of reduced validity when compared head-to-head with the other PCDAI versions [33]. Nonetheless, these versions may be used in retrospective studies when not all items required for the full index are available. A third abbreviated version, a modified PCDAI (modPCDAI), aims to provide a measure of disease activity in pediatric Crohn disease when only blood tests are available (e.g., in administrative databases) [34].

PCDAI has a poor correlation with endoscopic assessment of mucosal healing both at diagnosis (r = 0.33) and following induction therapy (r = 0.34) and is an inferior

marker than both CRP and fecal calprotectin [35]. Further analysis on two large prospectively collected cohorts (ImageKids and GROWTH studies) showed that all four PCDAI versions (i.e., PCDAI, wPCDAI, abbrPCDAI, and shPCDAI) had at best, fair correlation (r = 0.42–0.45) with mucosal healing [33].

A validated non-invasive marker of subclinical inflammation and mucosal healing is becoming an increasingly critical need given the increasing recognition of progressive intestinal damage even in the absence of clinical disease [36–40]. Nonetheless, repeated endoscopic evaluation is not feasible in children. Significant progress was made to address this gap with the recent development and validation of the Mucosal Inflammation Non-invasive (MINI) Index for pediatric Crohn disease [41] (Appendix 1.3). Utilizing clinical, biochemical, endoscopic, and magnetic resonance enterography data from the large dataset of the prospective ImageKids study, and validated on three independent patient cohorts, an index was developed in a blended mathematical judgmental clinimetric approach to identify children with mucosal healing. The MINI index incorporates stool frequency and character, fecal calprotectin, ESR and CRP in a weighted categorized index. A MINI index score below 8 identified children with mucosal healing with 88% sensitivity and 85% specificity. Among the 12% of children with MINI ≥8 with active mucosal inflammation, 86% of these had merely mild inflammation [41].

Perianal Crohn Disease

In classification of perianal CD, a distinction should be made between the detailed anatomic description of perianal fistulas and an assessment of fistula activity [42]. There are two disease activity measures traditionally used in adult clinical trials to follow perianal CD activity: the Perianal Disease Activity Index (PDAI) and the Fistula Drainage Assessment (Appendix 2.1). The PDAI contains 5 items, each scored 0 to 4, with higher scores representing more severe disease [43]. In the validation cohort, it had moderate correlation with both physician and patient assessment of perianal disease activity (r = 0.72 and 0.66, respectively). In the Fistula Drainage Assessment, [44], a fistula is considered closed when it no longer drained, despite gentle finger compression. A response has been defined in clinical trials as a reduction of 50% or more in the number of draining fistulas, and remission as absence of any draining fistulas on two consecutive visits [45–47]. Its high feasibility is an advantage, but a major limitation of the PDAI is the subjectivity in "gentle finger compression." In addition, the main drawback of both clinical indices is the dependency on external appearance rather than the real status of the fistula. Therefore, MRI-based indices are gradually replacing these legacy scores.

van Assche et al. generated an index, subsequently referred to as the van Assche index, which scores number of fistula tracks, location (extra/intersphincteric, transsphincteric, or supra sphincteric), extension (infralevatronic or supralevatronic), hyperintensity on T2-weighted images, collections, and rectal wall involvement [48, 49]. The MRI-based index is relatively simple to calculate with high interobserver concordance and acceptable responsiveness, yet has only been partially validated [50, 51].

More recently, a newer MRI index for assessing perianal fistulas, termed the magnetic resonance index for fistula imaging in CD (MAGNIFI-CD), was developed and validated utilizing paired baseline and week 24 MRI scans from 160 patients [52]. The index consists of weighted scoring of eight items: number of fistula tracts, hyperintensity of primary tract on T2-weighting, hyperintensity on T1 weighting, dominant feature (fibrous, granulation tissue or fluid/pus), proctitis, fistula length, extension, and presence/features of inflammatory mass. This index has yet to be externally validated.

Of MRI features of perianal disease, recent pediatric data suggest that perianal fistula length assessed by MRI was found to be the best predictor of treatment response [53], yet there lacked a unique perianal disease indices developed or validated in children. Utilizing the ImageKids study dataset, a pediatric-specific MRI index of perianal CD, termed Pediatric MRI-based Perianal Crohn disease index (PEMPAC) (Appendix 2.2), was recently developed and validated [54]. Ninety-five pelvic MRI's on 80 children were centrally read by two readers and scaled for perianal disease severity on a visual analog scale. Radiological items selected by a Delphi group were assessed in different multivariable statistical models whereby fistula number, length and location of the fistulas, hyperintensity on T2-weighted imaging, and collections >3 mm were identified as the items with the greatest correlation to radiological global assessment. The PEMPAC correlates strongly with radiological global assessment and performed comparably with the van Assche index in its ability to differentiate remission from active disease, and demonstrated good responsiveness to change.

Ulcerative Colitis Disease Activity Indices

The earliest classification of UC disease activity was a qualitative scale published by Truelove and Witts in 1955 [55]. Arbitrary quantitative indices have since been introduced, including the Powell-Tuck Index [56], the Mayo Clinic score [57], Rachmilewitz Index [58], and Lichtiger Score [59] with the Mayo score which has been until recently in widespread use [60]. The recent shift away from these indices relates to their more subjective nature, with regulatory bodies requiring more objective indices such as endoscopic scores (as

described below). Additionally, there has been a recent trend, also encouraged by regulatory agencies, to utilize patient reported outcomes instead of, or in addition to physician-derived indices.

The first three scores include an endoscopic evaluation of the rectosigmoid as part of the global assessment. Their validation has been largely a side product of clinical trials in which they have been used and developed. Seo and colleagues developed and evaluated an UC disease activity index [61, 62], weighted against the Truelove and Witts classification but it is hardly used. Walmsley and colleagues developed a Simple Clinical Colitis Activity Index that removed all laboratory parameters [63]. Given its high feasibility, it has gained popularity especially in retrospective research studies. The Endoscopic Clinical Correlation Index (ECCI) was developed prospectively in 137 adults with items chosen based on their ability to predict endoscopic outcome [64]. The ECCI is highly correlated with the endoscopy colitis score ($r = 0.81$), higher than the Seo, Truelove and Witts, Powell-Tuck, and Walmsley's simple colitis index; however, separate validation is not available to assess reliability and responsiveness. In a prospective head-to-head study in adults of all non-invasive UC disease activity indices, the Walmsley index and PUCAI (see below) were best in assessing disease activity when compared to a number of parameters including the Mayo score [65] (Appendix 3.1).

Endoscopic evaluation of the colonic mucosa in UC is invaluable in questionable clinical cases, before major treatment changes and for cancer surveillance, but is not routinely needed to confirm mucosal healing, especially in the presence of low fecal calprotectin [66]. Unlike CD, UC has a more homogenous presentation and thus 80–90% of patients in complete clinical remission will also have mucosal healing or near-mucosal healing [26, 65]. Endoscopic assessment is not without limitations. It is subjective with low inter-observer reliability [67]. Endoscopic appearance lags after clinical improvement, thereby underestimating response to treatment [68]. Furthermore, limited sigmoidoscopy may not reflect the entire disease burden (i.e., the product of severity and extent) especially in children in whom extensive disease is the most common phenotype.

The PUCAI was developed with the aim of reflecting disease activity and mucosal inflammation without invasive measures, hence making it attractive for repeated use (Appendix 3.2) [69]. The feasibility and reliability of the PUCAI were demonstrated on 2503 pediatric UC patients in the ImproveCareNow registry; all items in PUCAI were satisfactorily completed in 96% of visits [70]. PUCAI demonstrated good discrimination between remission, mild and moderate disease, good correlation to PGA ($r = 0.76$) with PUCAI score changes correlating well with PGA score changes over follow-up visits.

The PUCAI is tightly correlated with endoscopic appearance of the colonic mucosa [65, 71] and the correlation with the Mayo score is as high as 0.95 [65, 71, 72]. Predictive validity of the PUCAI is high as per multiple studies. The T72 infliximab trial in children with UC showed that PUCAI-defined remission was not inferior to sigmoidoscopy in predicting 1-year steroid-free sustained remission [72], a finding replicated also in ambulatory UC children [73]. The PUCAI strongly predicted the need for short-term treatment escalation in pediatric UC [26] and the type of surgical intervention, when needed [74]. In two independent cohorts of children requiring admission for intravenous treatment of corticosteroids for UC exacerbations, the PUCAI has shown strong predictive validity of outcomes important to patients, accurately identifying those who will require treatment escalation to second-line medical therapy or colectomy [75, 76]. In this setup, the PUCAI has shown to have superior predictive validity to five fecal biomarkers, including calprotectin [65, 77]. These findings were recently replicated in a large retrospective cohort of adults hospitalized with acute severe colitis, showing superiority of the PUCAI over the legacy adult tools in this setup—the Oxford and the Lindgren criteria [78].

The corresponding PUCAI cut-off scores of remissions (<10 points), mild (10–34 points), moderate (35–64 points) and severe (≥65) disease have been validated in several cohorts and found to have sensitivity, specificity, and area under the ROC curve of >95% [26, 65, 71]. In the regulatory T72 trial evaluating the effectiveness of infliximab in pediatric UC, the PUCAI determined week 8 remission rate was 33%, identical to the rate of complete mucosal healing found by sigmoidoscopy [79]. Similarly, the week 12 remission rate in a clinical trial evaluating Beclomethasone 17,21-dipropionate (BDP) in children with UC, was similar whether determined by sigmoidoscopy or the PUCAI [80], as well as when comparing sigmoidoscopy, ultrasound, and the PUCAI [81].

The PUCAI has also demonstrated predictive abilities regarding surgical management of patients with UC requiring restorative proctocolectomy with ileal pouch-anal anastomosis. A high preoperative PUCAI was significantly predictive of the likelihood of a staged procedure [74]. Beyond its use purely as a marker of disease activity, PUCAI has also been shown to correlate with both children and parents health-related quality of life scores [82].

The recent ESPGHAN-ECCO guidelines on the management of pediatric UC incorporated the PUCAI in evaluating response to treatment, while combining this score with fecal calprotectin results [83]. Specifically, while the goals of treatment in active UC should be clinical remission as defined by PUCAI, since ~20% of these children have endoscopic inflammation, the guidelines recommend fecal calprotectin as a tool to help select those patients requiring endoscopic evaluation.

Patient-Reported Outcomes

Patient-reported outcomes (PRO) involves the report of health status coming directly from the patient without interpretation of the of the patient's response by a clinician or anyone else [84]. There has been developing interest over recent years in PRO as a tool for IBD research, led by the US Food and Drug Administration (FDA). Since PROs capture signs and symptoms of the patients not necessarily related to disease activity and endoscopic appearance, any PRO should be supplemented by an objective measure of inflammation such as fecal calprotectin or endoscopic evaluation. The accuracy of self-reported IBD medical history in comparison to medical records was shown in one study to be fairly good for major factors such as disease type and previous surgical procedures; however, it was poor when more detailed medical information was assessed [85].

An inventory PRO in adults with UC includes stool frequency, bleeding, and general well-being and was shown to correlate well with the Simple Clinical Colitis Activity Index (SCCAI) ($r = 0.71$). However, the patient-generated assessment under-reported active disease in 10% of the study cohort [86].

PRO in the pediatric population presents several unique challenges such as age-related vocabulary, comprehension of health concepts, unclear determination of lower age limit for which responses would be reliable and valid, and the appropriate use of parents or carers to contribute to the reportable outcomes [87]. Recently, a PRO measure of signs and symptoms for pediatric UC, the TUMMY-UC index, has been developed following nearly 150 concept-elicitation and cognitive interviews with children with UC and their caregivers. This work identified good correlation between children and their caregivers regarding the order of importance of various symptoms reflective of perceived disease activity [88]. The TUMMY-UC has a PRO version for adolescents older than 12 years of age and an observer-reported version for younger children who have shown poor understanding of the questions. Each version is composed of eight items which were graded as most important by children and caregivers, including abdominal pain, stool frequency, stool consistency, nocturnal stooling, amount of blood, frequency of bleeding, fatigue, and urgency [89]. The TUMMY-UC has shown high correlation with global assessment of children, caregivers, and physicians, as well as will the PUCAI. In pediatric CD, the development of a corresponding PRO, the TUMMY-CD, is also underway.

Gastrointestinal Endoscopy Indices

Crohn Disease

Mucosal healing in CD has been associated with better long-term outcomes [90]. Indeed, the recent ECCO/ESPGHAN position paper recommends mucosal healing, as a desired treatment target [91]. Two groups have developed standardized approaches to endoscopy findings in CD. The first designed the Crohn Disease Endoscopic Index of Severity (CDEIS) by incorporating endoscopic findings, previously shown to have high inter-rater reliability [92], into a regression model using the physician global assessment of endoscopy severity as the dependent variable [93] (Appendix 4.1). The index was found to have high inter-rater reliability ($r = 0.96$), and was highly correlated with the physician endoscopy assessment in an independent cohort ($r = 0.81$). It has subsequently been used in multiple clinical trials evaluating endoscopic endpoints [94–96]. However, due to its complexity, Daperno and colleagues developed the Simplified Endoscopic Activity Score for Crohn disease (Appendix 4.2) [97]. The SES-CD had high inter-rater reliability (ICC = 0.98) and was highly correlated with the CDEIS ($r = 0.92$). Lower correlations were found between both the SES-CD and CDEIS and other parameters of disease activity including the CDAI (0.39 and 0.36 respectively) and C-reactive protein ($r = 0.47$ and 0.45 respectively) confirming that in CD, mucosal findings do not necessarily reflect the patient's clinical status.

There is no unique endoscopic instrument for pediatric CD but there is no evidence that endoscopic characteristics differ in children. The SES-CD seems to be a valid alternative to its more complicated counterpart also in children.

There is a lack of a universally accepted definition of endoscopic healing (EH) and endoscopic response (ER). Based on a systematic review, a recent Delphi group consensus of the IOIBD defined ER as a 50% decrease in the SES-CD or CDEIS, and EH as SES-CD ≤ 2 or CDEIS < 3 and a lack of any ulcerations including aphthous ulcers [98].

Upper gastrointestinal (UGI) CD is associated with earlier onset and more severe disease [99] and its identification may assist in predicting disease course and directing appropriate therapy. Recently, an UGI SES-CD score was developed, by applying the SES-CD to the UGI tract, specifically scoring the esophagus, stomach body, antrum, and duodenum [100]. The score was assessed on the ImageKids dataset of 202 children among whom 81 were followed for 18 months. Identification of UGI CD involvement by the UGI SES-CD index was associated with higher wPCDAI, PGA of inflammation, ileocolonoscopic SES-CD, fecal calprotectin, and radiological global assessment of damage on MRE. There was, however, no association between initial UGI SES-CD and disease course over follow-up [100].

In recent years, data are accumulating on the value of histologic healing over endoscopic remission, with the assumption that deeper healing improves outcomes. Histological healing in CD, as opposed to in UC as described later, is complicated by a lack of a well-validated index and insufficient data justifying the added benefit of treatment escalation to obtain this endpoint. This was formalized by the recent STRIDE-II guidelines which did not adopt histologic remission as a formal treatment target [98].

Endoscopy is an important outcome in assessing postoperative interventions in CD [101]. Rutgeerts and colleagues [101] proposed a scoring system for recurrent endoscopic disease at the surgical anastomosis (Appendix 4.3). Although quite subjective, higher Rutgeerts scores consistently predicted a more severe clinical course [101]. Patients with no or mild endoscopic lesions (termed i0 and i1, respectively) at 1-year postoperative endoscopy had good long-term outcomes, as opposed to those with clearly progressive disease (i3 or i4) who developed early clinical recurrence and were more prone to a complicated disease outcome in subsequent years. Rutgeerts score i2 is a heterogenous group defined as moderate lesions in the terminal ileum (i2a) or lesions confined to the ileocolonic anastomosis (i2b); however, recent data demonstrate equivalent rate of postoperative occurrence in both subgroups, hence calling into question the benefit of subdividing i2 [102].

Standard endoscopic indices are limited to assessment of the colon, terminal ileum, and developing indices of the upper GIT. Full small bowel assessment was made possible by the introduction of the wireless capsule endoscopy. The Lewis score was developed as a measure of mucosal inflammatory activity based on villous edema, ulcers, and stenosis [103]. (see Appendix 4.5) The Lewis score was validated for the evaluation of small bowel CD, demonstrating strong inter-observer agreement [104]. The Lewis score has been shown to correlate with fecal calprotectin and CRP, [105] serve as a useful clinical tool for patients with suspected CD, [106] and to assess the true inflammatory burden and extent of mucosal healing in patients with clinically quiescent disease [107]. A Lewis score of 135 is designated normal or clinically insignificant, a score between 135 and 790 defined as mild inflammation, and ≥790 is moderate or severe [103]. The Lewis score has also been shown to be the sole predictor of both short-term and long-term (out to 2 years) disease exacerbation in patients with quiescent CD [108]. A Lewis score ≥350 predicted subsequent flare with greater accuracy than fecal calprotectin and MRE, while an increase in Lewis score of ≥383 on follow-up capsule studies predicted imminent disease exacerbation within 6 months.

A second capsule index in use is the Capsule Endoscopy Crohn Disease Activity Index (CECDAI) was developed [109] and validated [110] yet the correlation with fecal calprotectin was found to be stronger in the Lewis score than the CECDAI [111]. While both of these scores incorporate similar parameters, the Lewis score is derived from the most severely involved of the three tertiles, whereas the CECDAI is a cumulative score that represents the summation of segmental scores for proximal and distal small bowel.

More recently, a new pan-enteric video capsule was developed to assess the entire bowel in Crohn disease [112]. The software for this system incorporates a novel quantification system for both small bowel and colonic inflammation assessing "most severe lesion," "most common lesion," and "extent of involvement." This intuitive index has yet to be assessed for validity against clinical, biochemical, or radiological indices. In the interim, it is reasonable to quantify the small bowel using the traditional Lewis score and the colon—by lack of ulceration, as described above.

Ulcerative Colitis Endoscopic Assessment

No endoscopic index in UC has been developed in children but yet again, there is no reason to believe that adults are different than children in assessing the bowel mucosa. Two endoscopic indices used in clinical trials are the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) [67] (see Appendix 4.4) and the Mayo endoscopic subscore (MES) [113]. The MES is a four-point scoring system in which patients with normal/inactive, mild, moderate, or severe disease are given scores 0–3. The UCEIS was only recently validated and demonstrated high intra-investigator and inter-investigator reliability (0.96 and 0.88, respectively) [114]. Subsequently, a Modified Mayo endoscopic subscore (MMES) was developed which factored both severity and distribution of mucosal inflammation [115]. While the UCEIS and the MES have been extensively evaluated, they have only recently been validated for disease responsiveness with the MES performing poorly compared to the UCEIS [116–118].

Despite the lack of consensus, most commonly defined endpoints for these indices are Mayo endoscopy subscore ≥1-point decrease or UCEIS ≥2-point decrease to define endoscopic response. Recent consensus recommends Mayo endoscopic subscore of 0 points and UCEIS of ≤1 point to define endoscopic healing [98, 119]. Some endoscopic assessments have shown to have low reliability [120, 121].

The benefit of histological remission over macroscopic endoscopic healing has been demonstrated in UC both for predicting long-term remission [122, 123] and in cancer prevention [124]. While numerous histologic indices have been developed, the Nancy index [125] and the Robarts histopathology index (RHI) [126] have been most extensively validated. The RHI is significantly more complex and time consuming than the Nancy index yet both have been recommended for clinical trials, whereas the Nancy index may be more suitable for observational studies an potentially in clinical practice [127]. What remains to be determined is the number needed to treat to achieve clinically meaningful outcomes over endoscopic healing alone and hence the utility of these indices in clinical practice remains uncertain [98, 127].

Quality of Life, Disability, and Other Related Instruments

Both adults and children diagnosed with IBD are at increased risk of emotional distress, disability, depression, fatigue, and

decreased social functioning [128, 129]. Thus, quality of life (QOL)-related assessment has been increasingly recognized as an important and independent clinical outcome in IBD research and can be scored by both generic- and disease-specific instruments. A thorough discussion of QOL instruments available for pediatric IBD research is found in Chap. 51. In brief, health-related QOL (HRQOL) is impacted by actual and perceived disability, fatigue, work/school absence, and other factors relating to the physical, psychological, familial, and social sequelae of the disease. Several indices have been developed and validated in adults, including the IBD Disability Index (IBD-DI), a survey relating to 19 items scaled for severity from 1 to 5 [130]. The IBD-DI has been validated and found to have high intra- and inter-rater reliability, strong construct validity, and excellent responsiveness [131]. More recently, the IBD Disk was developed as a shortened, patient-administered survey, adapted from the IBD-DI [132]. Ten items are scored based on level of agreement with the overall score illustrated on a multicolored disk with the area outlined by "joining the dots" reflecting the extent and aspects of QOL-related burden. Pediatric-specific QOL studies have been less well developed, with most data utilizing generic, rather than disease-specific QOL measures [133].

Radiographic Indices

Brief mention should be made about currently available radiographic modalities which are now part of the mainstay of measuring disease in IBD, more so in CD. These modalities were described in greater detail in an earlier section of this book. As outcomes shift from clinical response and remission to mucosal healing, subtle findings of inflammation and intestinal damage may only be detected by use of various imaging techniques. Transmural healing has not yet been included as a formal treatment target but nonetheless, it is well recognized as a vital adjunct measure in CD, both in clinical practice and in the research setting [98]. Moreover, the assessment of bowel damage as an important disease endpoint is increasingly incorporated using validated multi-items tool. The advent of bedside abdominal ultrasound (US) assessment has increased the feasibility of measuring this concept repeatedly. It is non-invasive, lacks radiation, and relatively cheap, but it is operator-dependent [134]. In a large prospective trial comparing small bowel US to MRE, while MRE outperformed US in sensitivity and specificity, both were found to have high sensitivity for detecting small bowel lesions and could be considered valid first-line investigations [135]. Recently a Simple Sonographic Score was developed and validated, derived from the two US findings of greatest correlation with disease activity: bowel wall thickness and color Doppler signal, and found to accurately reflect CD activity [136].

For MRE in adults, the MaRIA and Lémann scores have been developed to assess inflammatory activity and damage, respectively [137–139]. More recently, a simplified MaRIA score (sMaRIA), which lacks the need for gadolinium injection has been developed [140] for quantifying treatment response in luminal CD [141]. Most recently, a pediatric MRE-based disease activity index has been developed: the Pediatric Inflammatory Crohn's MRE Index (PICMI) [142, 143]. The PICMI was developed and validated as part of the ImageKids study, a multicenter international study which recruited 240 children (5–18 years) diagnosed with CD, undergoing MRE, ileocolonoscopy, and upper tract endoscopy within 14 days. PICMI was developed specifically for pediatric CD and includes the entire small and large bowel and does not require colon preparation or enema. The weighted items retained following multivariable regression modeling are wall thickening, DWI, ulceration, edema, and comb sign: 3 × Wall thickness (>3 mm) + 9 × DWI (0/1) + 6 × Ulcers (0/1) + 6 × Edema (0/1) + 9 × Comb sign. The PICMI was highly correlated with the MaRIA and the sMaRIA (0.79 and 0.77, respectively, unpublished). The PICMI does not require the use of the T1 sequences pre- and post-enhancement, and thus can be calculated without the use of Gadolinium.

Summary of Clinical Outcome Measures

Various instruments are available to measure clinical outcomes in pediatric IBD (Table 46.2). Valid pediatric clinical indices and quality of life-related measures exist for both UC and CD as well as recently developed PRO's and MRE-related indices. The evaluation of health-related indices is

Table 46.2 Clinical indices for research in pediatric inflammatory bowel disease

Clinical trial outcome	Instrument	
	Crohn disease	Ulcerative colitis
Disease activity index	Physician global assessment PCDAI/wPCDAI TUMMY-CD (future) MINI index	Physician global assessment PUCAI TUMMY-UC
Perianal disease activity index	Fistula Drainage Assessment PEMPAC	N/A
Endoscopic scores	CDEIS (assessed only in adults) SES-CD (assessed only in adults) UGI-SES-CD Lack of ulcerations Lewis score (adults)	UCEIS (adults) Mayo endoscopic subscore (adults)
Quality of life instruments Generic Disease-specific	Multiple (e.g., PedsQL, Child QOL questionnaire) IMPACT-III	Multiple (e.g., PedsQL, Child QOL questionnaire) IMPACT-III

an ongoing process and therefore, the development of new indices and the re-evaluation of the performance of existing indices will continue to be explored in different clinical and research settings. Furthermore, each index should not be seen in isolation—combining different indices can often provide a more complete assessment of the patient. For example, combination of wPCDAI or TUMMY-CD (as a PRO measure) with the MINI index or fecal calprotectin would provide a more complete picture of the patient, relating not only to clinical sequelae of the disease but also reflecting attainment of mucosal healing. Additionally, HR-QOL indices helps formulate a more holistic assessment of the patient to better implement multiple aspects of the management plan.

Appendix 1

Appendix 1.1: Pediatric Crohn Disease Activity Index [19] History (Recall, 1 week)

Abdominal pain						**Score**
0 = None	**5** = Mild: Brief, does not interfere with activities			**10** = Moderate/Severe: Daily, longer lasting, affects activities, nocturnal		_____
Patient functioning, general well-being						**Score**
0 = No limitation of activities, well	**5** = Occasional difficulty in maintaining age appropriate activities, below par			**10** = Frequent limitation of activity, very poor		_____
Stools (per day)						**Score**
0 = 0–1 liquid stools, no blood	**5** = Up to 2 semi-formed with small blood, or 2–5 liquid			**10** = Gross bleeding, or ≥6 liquid, or nocturnal diarrhea		_____
Laboratory						
Hematocrit (HCT)						**Score**
<10 years:			11–14 years (Male):			
0 = ≥33%	**2.5** = 28–32%	**5** = <28%	**0** = ≥35%	**2.5** = 30–34%	**5** = <30%	
11–19 years (Female):			15–19 years (Male):			
0 = ≥34%	**2.5** = 29–33%	**5** = <29%	**0** = ≥37%	**2.5** = 32–36%	**5** = <32	_____
Erythrocyte sedimentation rate (ESR)						**Score**
0 = <20 mm/h	**2.5** = 20–50 mm/h	**5** = >50 mm/h				_____
Albumin						**Score**
0 = ≥35 g/L	**5** = 31–34 g/L	**10** = ≤30 g/L				_____
Examination						
Weight						**Score**
0 = Weight gain or voluntary weight stable/ loss	**5** = Involuntary weight stable, weight loss 1–9%			**10** = Weight loss ≥10%		_____
Height at diagnosis						**Score**
0 = <1 channel decrease	**5** = ≥1 to <2 channel decrease			**10** = >2 channel decrease		_____
Height at follow-up						**Score**
0 = Height velocity ≥ −1SD	**5** = Height velocity < −1SD, > −2SD			**10** = Height velocity ≤ −2SD		_____
Abdomen						**Score**
0 = No tenderness, no mass	**5** = Tenderness, or mass without tenderness			**10** = Tenderness, involuntary guarding, definite mass		_____
Perirectal disease						**Score**
0 = None, asymptomatic tags	**5** = 1–2 indolent fistula, scant drainage, no tenderness			**10** = Active fistula, drainage, tenderness, or abscess		_____
Extraintestinal manifestations						**Score**
(Fever ≥ 38.5 °C for 3 days over past week, definite arthritis, uveitis, E. nodosum, P. gangrenosum)						
0 = None	**5** = One			**10** = ≥Two		_____
Total Score:						

Appendix 1.2: Weighted Pediatric Crohn Disease Activity Index (wPCDAI) [68] History (Recall, 1 week)

Abdominal pain			**Score**
0 = None	**10** = Mild: Brief, does not interfere with activities	**20** = Moderate/Severe: Daily, longer lasting, affects activities, nocturnal	_____
Patient functioning, general well-being			**Score**
0 = No limitation of activities, well	**10** = Occasional difficulty in maintaining age appropriate activities, below par	**20** = Frequent limitation of activity, very poor	_____
Stools (per day)			**Score**
0 = 0-1 liquid stools, no blood	**7.5** = Up to 2 semi-formed with small blood, or 2–5 liquid	**15** = Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea	_____
Laboratory			
Erythrocyte sedimentation rate			**Score**
0 = <20 mm/h	**7.5** = 20–50 mm/h	**15** = >50 mm/h	_____
Albumin			**Score**
0 = ≥3.5 g/dL	**10** = 3.1–3.4 g/dL	**20** = ≤3.0 g/dL	_____
Examination			
Weight			**Score**
0 = Weight gain or voluntary weight stable/loss	**5** = Involuntary weight stable, weight loss 1–9%	**10** = Weight loss ≥10%	_____
Perirectal disease			**Score**
0 = None, asymptomatic tags	**7.5** = 1–2 indolent fistula, scant drainage, no tenderness	**15** = Active fistula, drainage, tenderness, or abscess	_____
Extraintestinal manifestations			**Score**
(fever ≥38.5 °C for 3 days over past week, definite arthritis, uveitis, E. nodosum, P. gangrenosum)			
0 = None		**10** = One or more	_____
Total Score (0–125):			

Appendix 1.3: The MINI Index

Item	Points
1. Stool	
0–1 Normal or liquid stools, no blood	0
≤2 Semiformed with small blood, or 2–5 liquid	4
Gross bleeding, or ≥6 liquid, or nocturnal diarrhea	8
2. Fecal calprotectin	
<50 µg/g	−3
50–99.9 µg/g	0
100–299.9 µg/g	5
300–599.9 µg/g	7
600–899.9 µg/g	9
≥900 µg/g	12
3. ESR and CRP	
ESR < 10 mm/h and CRP <5 mg/L	0
30 > ESR ≥ 10 mm/h or 10 > CRP ≥ 5mg/L	1
50 > ESR ≥ 30 mm/h or 30 > CRP ≥ 10mg/L	2
ESR ≥ 50 mm/h or CRP ≥ 30 mg/L	5
Sum of MINI	−3 to 25

User guide:

1. While it is possible to score the MINI index with either CRP or ESR, both are preferred
2. Score the highest of CRP or ESR
3. The stool item: The intent is to score the stool pattern during the preceding week. First categorize the subject as having blood in the stool or not

If there is no blood in the stool, score as follows:

- Formed stools or up to 1 loose stool daily = 0
- 2–5 liquid or very loose stools on 1 or more days = 4
- 6 or more liquid or very loose stools on 1 or more days or any nocturnal diarrhea = 8

If blood is present in the stool, score as follows:

- Small amounts of blood (on toilet paper or small spots in stool) = 4
- Any gross bleeding (large amounts on stool or colors the water in the toilet) = 8

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *MINI* Mucosal-Inflammation Non-invasive

Appendix 2

Appendix 2.1: Perianal Crohn Disease Activity Index [43]

Discharge	
0	No discharge
1	Minimal mucous discharge
2	Moderate mucous or purulent discharge
3	Substantial discharge
4	Gross fecal soiling
Pain/restriction of activities	
0	No activity restriction
1	Mild discomfort, no restriction
2	Moderate discomfort, some limitation activities
3	Marked discomfort, marked limitation
4	Severe pain, severe limitation

Restriction of sexual activity	
0	No restriction sexual activity
1	Slight restriction sexual activity
2	Moderate limitation sexual activity
3	Marked limitation sexual activity
4	Unable to engage in sexual activity
Type of perianal disease	
0	No perianal disease/skin tags
1	Anal fissure or mucosal tear
2	<3 perianal fistulae
3	≥3 perianal fistulae
4	Anal sphincter ulceration or fistulae with significant undermining of skin
Degree of induration	
0	No induration
1	Minimal induration
2	Moderate induration
3	Substantial induration
4	Gross fluctuance/abscess
Total score = sum of total score per category	

Appendix 2.2: Fistula Drainage Assessment [44]

	Definition
Remission	Fistula closure or absence of any draining fistulas for at least 4 weeks
Response	≥50% decrease in draining fistulas for at least 4 weeks

Appendix 2.3

Parameter	Score
Maximal hyperintensity on T2-weighted imaging	
None	0
Mild	2
Pronounced	4
Total length of fistulas	
None	0
Short (1–25 mm)	2
Medium (26–50 mm)	4
Long (>51 mm)	6
Number of fistulas	
None	0
Single	4
Multiple	8
Collections (>3 mm)	
Absent	0
Present	11
Location	
None	0
Inter-sphincteric	3
Trans-sphincteric	6
Extra-sphincteric	9
Trans-sphincteric and inter-sphincteric	12
SUM OF PEMPAC (0–41)	

- **Cut-off values**: PEMPAC<10 (*Remission*), PEMPAC 10–15 (*Mild disease*), PEMPAC 16–29 (*Moderate disease*), PEMPAC ≥30 (*Severe disease*)
- A change of at least 4 points denotes the minimally important difference
- In case of more than one fistula, the location should be scored according to the highest scored fistula

Appendix 3

Appendix 3.1: Ulcerative Colitis Disease Activity Indices (Adult)

Instrument items	Mayo-Clinic score [57, 144]	Powell-Tuck index [56]	Rachmilewitz score [58]	Lichtiger index [59]	Seo index [61]	SCCAI [63]	ECCI [64]
Clinical signs and symptoms	0–6	0–6	0–7	0–9	Frequency: 1–3 (×13)	0–11	No. nocturnal × 16
Stool characteristics	–	0–2	0–3	0–3	Blood: 0–1 (×60)	–	Blood 0-4 × 17
Abdominal pain	0–3	0–3	0–3	0–5	–	0–4	–
General well-being	–	0–2	0–9	–	–	1/ complication	–
No. of complications					–		–
					–		–
Physical exam	–	0–3	–	0–3	–	–	–
Abdominal tenderness	–	0–2	0–3	–	–	–	0–1 × 39
Body temperature							

Instrument items	Mayo-Clinic score [57, 144]	Powell-Tuck index [56]	Rachmilewitz score [58]	Lichtiger index [59]	Seo index [61]	SCCAI [63]	ECCI [64]
Laboratory variables	–	–	Hgb 0–4 ESR 0–2	–	Hgb (g/dL) × −4 ESR (mm/h) × 0.5 Alb (g/dL) × −15	–	Alb (g/dL) × −26
Sigmoidoscopy	0–3	0–2	0–12	–	–	–	–
Other		Nausea, anorexia 0–2		Use of anti-diarrheals 0–1	Total score added to constant = 200		
Score cut-off for disease activity	Remission: ≤2 and all subscores ≤1 Response: decrease of 3 (and 30%) from baseline and decrease in rectal bleeding score	Remission: 0 Improved: decrease ≥2 No change: ±1 Worse: increase ≥2	Remission ≤4	Improved: 50% decrease in score (short-term) and ≤4 total score (long term)	Mild < 150 Moderate 150–220 Severe > 220	Remission < 5 Relapse ≥ 5	Severe endoscopic disease >55

SCCAI Simple clinical colitis activity index, *ECCI* Endoscopic-Clinical Correlation Index, *Hgb* Hemoglobin, *ESR* Erythrocyte sedimentation rate, *Alb* Albumin, *PGA* Physician global assessment

Appendix 3.2: Pediatric Ulcerative Colitis Activity Index

Item	Points
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in less than 50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 h	
0–2	0
3–5	5
6–8	10
>8	15
5. Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
SUM OF PUCAI (0–85)	

Appendix 4

Appendix 4.1: Crohn Disease Endoscopic Index of Severity [93]

	Rectum	Sigmoid and left colon	Transverse colon	Right colon	Ileum	Total
Deep ulceration (12 present, 0 absent)						1
Superficial ulceration (6 present, 0 absent)						2
Surface involved by the disease (/10 cm)[a]						3
Ulcerated surface (/10 cm)[a]						4

$$\frac{\text{Total A} = \text{Total}1 + \text{Total}2 + \text{Total}3 + \text{Total}4}{\text{No.of segments explored}(1-5)}$$

CDEIS = Total A + 3 (ulcerated stenosis present) + 3(non-ulcerated stenosis present)

Adapted from Daperno and colleagues [97]

[a]Analog scales converted to numeric values

Appendix 4.2: Simple Endoscopic Score for Crohn Disease [97]

	Score per segment			
Variable	0	1	2	3
Size of ulcers	None	Aphthous ulcers (0.1–0.5 cm[a])	Large ulcers (0.5–2 cm[a])	Very large ulcers (>2 cm[a])
Ulcerated surface	None	<10%	10–30%	>30%
Affected surface	Unaffected segment	<50%	50–75%	>75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

SES-CD = Total score from each segment (rectum, sigmoid and left colon, transverse colon, right colon, ileum)
Final score = Total SES-CD score − 1.4 (number of affected segments)
[a]Diameter

Appendix 4.3: Rutgeerts Score for Postoperative Endoscopic Disease Recurrence [101]

Grade	Endoscopic finding
0	No lesions in the distal ileum
1	≤5 aphthous lesions
2	>5 aphthous lesions with normal mucosa between the lesions or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis
3	Diffuse aphthous ileitis with diffusely inflamed mucosa
4	Diffuse inflammation with already larger ulcers, nodules, and/or narrowing

Appendix 4.4: Ulcerative Colitis Endoscopic Index of Severity (UCEIS) [65]

Descriptor (score most severe lesions)	Likert scale anchor points	Definition
Vascular pattern	Normal (1)	Normal vascular pattern with arborization of capillaries clearly defined
	Patchy loss (3)	Patchy loss or blurring of vascular pattern
	Obliterated (5)	Complete loss of vascular pattern
Mucosal erythema	None (1)	The color of the mucosa is normal
	Light red (3)	Some increase in color of the mucosa that is probably abnormal, but would be best compared side by side with a normal examination
	Dark red (5)	Red or crimson color of the mucosa that is similar to blood—that is, clearly abnormal even if not compared with a normal examination (does not include intramucosal hemorrhage)
Mucosal surface (Granularity)	Normal (1)	Smooth mucosa with a sharp light reflex, similar to a polished surface
	Granular (3)	Mucosal surface diffuses reflected light causing minor variation in the surface
	Nodular (5)	Evident nodular variation in mucosal surface
Mucosal edema	None (1)	Normal appearance: no white or yellow substance visible
	Probable (3)	Slight swelling and thickening of mucosa
	Definite (5)	Marked thickening and edema of the mucosa with blunting of the mucosal folds
Mucopus	None (1)	Normal appearance: no white or yellow substance visible
	Some (3)	White or yellow deposits on the mucosa unrelated to any bowel preparation
	Lots (5)	Mucopus substantially covering the mucosal surface unrelated to any bowel preparation
Bleeding	None (1)	No visible blood
	Mucosal (2)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (3)	Some free liquid blood in the lumen
	Luminal moderate (4)	Frank blood in lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood
	Luminal severe (5)	Frank blood in the same lumen with visible oozing from a hemorrhagic mucosa
Incidental friability	None (1)	No bleeding or intramucosal hemorrhage before or after passage of the endoscope
	Mild (2)	No bleeding at the site of assessment before, but minor bleeding or intramucosal hemorrhage after, passage of the endoscope
	Moderate (3)	Intramucosal hemorrhage without overt bleeding before passage of the endoscope
	Severe (4)	Overt bleeding after passage of the endoscope
	Very severe (5)	Overt bleeding from the mucosa

Descriptor (score most severe lesions)	Likert scale anchor points	Definition
Contact friability	None (1)	No bleeding from the mucosa after light touch with closed biopsy forceps
	Probable (3)	Intramucosal hemorrhage or minor bleeding after light touch with closed biopsy forceps
	Definite (5)	Overt bleeding mucosa after light touch (within 10 s) with closed biopsy forceps
Erosions and ulcers	None (1)	Normal mucosa, no visible erosions or ulcers
	Erosions (2)	Tiny (≤5 mm) defects in the mucosa, of a white or yellow color with a flat edge
	Superficial ulcer (3)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial
	Deep ulcer (4)	Deeper excavated defects in the mucosa, with a slightly raised edge
Extent of erosions or ulcers	None (1)	None seen during endoscopy
	Limited (2)	<10% of the affected mucosa
	Substantial (3)	10–30% of the affected mucosa
	Extensive (4)	>30% of the affected mucosa

Appendix 4.5: Lewis Score [103]

Parameters	Number	Longitudinal extent[a]	Descriptors
Villous appearance (worst-affected tertile)	Normal—0	Short segment—8	Single—1
	Edematous—1	Long segment—12	Patchy—14
		Whole tertile—20	Diffuse—17
Ulcer (worst-affected tertile)	None—0[b]	Short segment—5	<1/4—9[c]
	Single—3[b]	Long segment—10	1/4—1/2—12[c]
	Few—5[b]	Whole tertile—15	>1/2—18[c]
	Multiple—10[b]		
Stenosis (whole study)	None—0	Ulcerated—24	Traversed—7
	Single—14	Nonulcerated—2	Not traversed—10
	Multiple—20		

Lewis score: Score of the worst-affected tertile [(villous parameter × extent × descriptor) + (ulcer number × extent × size)] + stenosis score (number × ulcerated × traversed)

[a] Longitudinal extent: short segment:<10% of the tertile; long segment: 11%–50% of the tertile; whole tertile:>50% of the tertile

[b] Ulcer number: single: 1; few: 2–7; multiple:≥8

[c] Ulcer descriptor (size): proportion of the capsule picture filled by the largest ulcer

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Clinical Trials (Clinical Perspective)

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Marina Aloi and Salvatore Cucchiara

Introduction

Several epidemiologic studies report that up to 30% of new inflammatory bowel disease (IBD) cases are diagnosed in childhood [1]. Pediatric IBD (PIBD) seems to be more extensive and severe than the adult-onset forms, with a frequent need for second-line therapies, including immunomodulators and biologics, and a more complicated disease course [2, 3]. However, excluding most patients with very early-onset IBD (VEOIBD) receiving the diagnosis when younger than 6 years, particularly those with the infantile-onset IBD (patients younger than 2 years), pediatric and adult-onset disease seem to share mechanisms, diagnostic work-up, endoscopic, and histopathological features [4]; moreover, not uncommonly, therapeutic pediatric strategies are simply "extrapolated" from adult trials in "off-label" use. Indeed, randomized clinical trials (RCTs) in children could be more difficult for several reasons: first of all ethical concerns, due to the natural vulnerability of this population, and for the relative paucity of eligible patients, because of the lower number of incidents and prevalent cases compared with adults. Moreover, parents, worried about possible therapy adverse events and/or additional invasive tests and visits, are more hesitant to have their children recruited in interventional trials than adult patients. Similarly, physicians hesitate to enroll young patients in interventional studies involving invasive procedures.

The other side of the coin is that children with IBD represent a unique cohort of patients to be explored, as far as aspects such as the initial host immune response, the need for early treatment, genotype-to-phenotype relationship, and the natural disease course, are concerned. Above all, because of the higher impact of environmental factors that may influence adult-onset disease (e.g., comorbidities, disease duration, drugs, smoking), the knowledge of the pathogenetic pathways of pediatric IBD can provide insights into the initial mechanisms underlying the disease [5].

A crucial factor when evaluating the efficacy of different treatments in children with IBD is the ability to compare new drugs to known therapies in a meaningful way. Randomized clinical trials lead to gold-standard evidence on the efficacy of pharmacologic and nonpharmacologic treatment of IBD. An ideal clinical trial should answer to well-defined primary research endpoints in specific study populations and should provide significant results both statistically and clinically. Steps that describe RCTs are: clear definition of the primary (and secondary) outcomes; definition of the eligible population; randomized assignment to the treatment regimen; and standardized and well-defined interventions. Moreover, a well-defined study population, based on explicit outlined inclusion and exclusion criteria, is mandatory when designing an RCT. The trial design should be sufficiently linear to fulfill the trial's questions; on the other hand, it must not be so weighty that patients and physicians cannot complete the study. Furthermore, clinical trials conducted in children must balance quality with feasibility while considering unique age-specific ethical considerations. Enrolling children in clinical trials of drugs that are already widely used in adults is, therefore, particularly challenging, and a placebo-controlled design in this circumstance is most often untenable for many investigators and parents. Very recently, several PIBD experts published a comprehensive review to highlight the pediatric challenges in regulatory trial design [6]. The authors underlined the importance of avoiding unnecessary and irrealistic endpoints in designing pediatric trials (i.e., too many invasive procedures, unrealistic sample power, etc.), and tried to identify easily attainable outcomes combining objective disease measures as well as patient clinical symptoms. At the same time, pharmacokinetic/pharmacodynamic (PK/PD) pediatric data, along with specific dosing and safety, should be always evaluated in pediatric-conceived drug trials. Furthermore, the authors claimed that no placebo studies should be performed in children if the

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study drug was previously shown to be superior to placebo in children and/or in adults. Indeed, one of the main barriers to perform a pediatric RCT is the potential need for a placebo arm. Although a randomized, double-blind, parallel-group trial is regarded as the ideal study design for assessing the efficacy of a new drug, this can prompt ethical and feasibility problems for pediatric studies [7]. Placebo-controlled trials are indeed hardly suitable for clinical trials for the vulnerable population of children with IBD. According to an evidence-based, expert-driven practical statement paper of the pediatric ECCO committee on the outcome measures for clinical trials in pediatric IBD [8], a placebo may only be considered for pediatric trials when evaluating additional treatments, provided that both study groups (treatment and control) receive effective therapy. In line with this position, a recent joint position paper from ESPGHAN, ECCO, the global PIBDnet, and the Canadian Pediatric IBD network, further states that placebo should only be accepted in children with IBD when true equipoise exists against the active therapy. In contrast, it should not be used when previous adult trials have already shown the efficacy of the active treatment, supported by clinical experience in children [9].

Identifying the correct endpoints when designing pediatric clinical trials is also crucial to achieve significant results. The ECCO experts identified several important outcomes for RCTs in pediatric IBD, the first being the recommendation to define steroid-free mucosal healing (MH) as assessed by endoscopy as the primary end-point for all preauthorization trials for a new drug authorization. Mucosal healing has emerged as a specific treatment endpoint in adult IBD, both in clinical trials and in clinical practice, as it is associated with a reduced risk of disease exacerbations in the long-term, treatment escalations, hospitalization rate, and colectomy [10, 11]. Prospective studies in children have rarely been performed using MH as a primary outcome so far [12]. In the case of therapies already demonstrated to induce MH in adult trials, ECCO experts recommend using objective measures of disease activity [weighted Pediatric Crohn Disease Activity Index (wPCDAI) or Pediatric Ulcerative Colitis Activity Index (PUCAI)] as primary endpoints. However, very recently, adulthood and pediatric gastroenterologists, on behalf of the International Organization for the Study of IBD (IOIBD), have recommended that even in children the long-term therapeutic goal is deep remission (which includes endoscopic healing of the mucosa, normalization of biohumoral, and fecal markers of inflammation in addition to the disappearance of symptoms), while the goal of a deeper remission (including transmural and histological healing) requires further research, mainly to define whether these targets justify more aggressive and expensive methods, with associated additional risks [13].

Recently, the Food and Drug Administration (FDA) has declared that pediatric studies are not necessarily required for all new treatments. However, "extrapolation" from adult trials should always take into account drug pharmacokinetics, pharmacodynamics, and evaluation of potential and real side effects/toxicities. It is still emphasized that the pharmaceutical industry should focus on pediatric pharmacokinetic studies for those medications with a strong potential impact on children. On the other hand, specific pediatric outcomes, including the effect on growth and bone-related variables, cannot be evaluated based on adult studies. Therefore, an accurate balance between the concerns of conducting a pediatric trial and the advantages of having well-defined data should be always be sought for any proposed trial.

Summary

Up to now, only few RCTs in children with IBD have been performed. Although pediatric and adult IBD probably share their pathogenetic mechanisms, histopathological damage, and response to therapies, an accurate balance between the usefulness of the data from adult studies and those required for the optimal knowledge of efficacy and safety of new drugs for pediatric IBD must always be considered. Partial extrapolation of adult data is reasonable and tolerable, if including data on drug pharmacokinetics, pharmacodynamics, and safety. A placebo should not be used in pediatric clinical trials when the superior efficacy of a new drug has already been documented in adults. However, pediatric RCTs are needed to identify specificities of treatment strategies in children, as well as to understand the long-term impact of new treatment strategies on specific outcomes (growth and bone-related issues), thus ensuring that children with IBD can access new treatments in a reasonable time frame.

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Global Regulatory Industry Perspective of Clinical Trials

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Timothy Cripps and Andrew E. Mulberg

Key Stakeholders in Drug Development Process

Pediatric drug development presents novel challenges and opportunities. The following chapter will review relevant laws guiding drug development in the USA and EU, provide an overview of the drug development process in general, and highlight some of the specific challenges for pediatric patients in clinical trials, utilizing inflammatory bowel disease as an example.

The drug development process in the USA and EU is guided by regulations. With particular respect to children, the goal of these regulations is to improve the health of children aged 0–17 years by promoting the study of therapeutic agents in pediatrics, while establishing protections for this vulnerable population. Drug development involves a collaborative effort among regulators, industry sponsors, academic researchers, and individual investigators.

Regulatory Agencies

In the USA, each step in the drug development process is regulated by the Food and Drug Administration (FDA). The agency regulates a wide variety of products, including food products, drugs for human and animal use, cosmetics, biologic agents, medical devices, radiation-emitting products, and animal feed. The agency's actions, under current US laws, regulate all phases of the drug development process.

In the EU, the regulatory network of Member States' national regulatory agencies, the EMA, and the EC regulates all phases of drug development and post-authorization lifecycle management. National regulatory agencies and the EMA cooperate and share expertise in the assessment of new medicines and of new safety information. They also rely on each other for the exchange of information in the regulation of medicine. This is underpinned by EU legislation which requires that each Member State operates to the same rules and requirements regarding the authorization and monitoring of medicines.

Efforts to standardize the drug development process across countries and promote international cooperation have been increasing, augmented through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The mandate of ICH is to bring together regulatory authorities and the pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines. Since its inception in 1990, ICH has gradually evolved, to respond to increasingly global developments in the pharmaceutical sector and these ICH guidelines are applied by a growing number of regulatory authorities. Given the difficulty in enrolling sufficient numbers of pediatric patients into trials in general, this is of particular relevance for pediatric drug development as outlined in the ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population.

Industry Sponsors

Industry sponsors conduct research to identify potential therapeutic targets and seek biological or chemical agents that will affect a target to treat disease. Once a suitable target is identified, the sponsor will begin a rigorous process of preclinical, followed by clinical development, with the goal of ultimately identifying a product that can be brought to market. Close collaboration between industry sponsors and global regulatory health authorities is vital to expeditious development of new drugs and biologic molecules. Some sponsors will choose to utilize a contract research organization (CRO) to handle the planning and implementation of some or all of a clinical trial. This is particularly helpful for

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smaller companies that may not have the required experience, infrastructure, or resources to successfully run a large clinical trial.

Academic Researchers

Apart from private firms, scientists and physicians at academic institutions also participate in various steps in the drug development process. Both university-based and government-funded research laboratories conduct vital basic science investigations to identify molecular mechanisms of disease, which may ultimately result in new drug target identification. Physician-scientists often participate in this work and provide clinical context which allows for a more direct translation of basic science concepts to clinical care. Additionally, social science research into optimal methods to measure the clinical outcomes of importance to patients (development of patient-reported outcome tools or PROs) may also be conducted by academic staff and have direct implications on clinical trials.

Investigators

Once a proposed product has been rigorously tested in nonclinical studies and models, it must then be tested in patients. Clinical trial investigators are typically physicians treating patients with the condition of interest. They may be located in an academic or private practice setting. In collaboration with industry sponsors, individual investigators will share the responsibility for enrolling suitable patients into drug trials, monitoring the safety of those patients, and generating data that will ultimately be used to make a final determination of the safety and efficacy of a given new drug product.

Regulations Guiding Pediatric Drug Development

This section will briefly review some of the major legislative changes in the US and EU which guide the pediatric drug development process today.

In the early 1900s, global regulations pertaining to the manufacturing, marketing, and distribution of drug products were minimally restrictive. The existing US regulations at that time, under the Food and Drug Act of 1906, did not prohibit false therapeutic claims, nor did they provide FDA significant power to enforce the regulations that did exist [1]. Thus, the US market was filled with products that lacked adequate safety or efficacy testing.

Sulfanilamide Tragedy 1937 and the Food, Drug, and Cosmetic Act of 1938

"Elixir of Sulfanilamide" was a liquid preparation of a commonly used antibiotic, manufactured and distributed widely without adequate safety testing. After the deaths of more than 100 people in 1937, many of them children, it was ultimately discovered that the manufacturer had utilized ethylene glycol, a poisonous substance, as a solvent [2]. It was in part this tragedy that spurred Congress to pass new legislation imposing stricter regulations on the industry and providing FDA with increased authority to regulate the pharmaceutical industry. This came in the form of the **Food, Drug, and Cosmetic Act (FDCA) of 1938**, which President Roosevelt signed into law.

One of the critical provisions in the law mandated premarket approval of all new drugs. This meant that a drug manufacturer was required to prove to the FDA that its product was safe for use prior to marketing. The new law also contained provisions that extended FDA control to cosmetics and devices; provided safe tolerances be set for unavoidable poisons; authorized standards of identity, quality, and fill of container for foods; authorized factory inspections; and added penalties for those who violated these laws [1]. The passage of FDCA was an important step in improving the safety of the drugs available in the marketplace, as previously there had been no standard requiring demonstration of the safety of pharmaceutical products. The FDCA was subsequently updated with the **Durham–Humphrey Amendment of 1951**, which established the need for medical supervision in the use of certain drug products and defined for the first time which drugs would be available by prescription only.

Thalidomide Tragedy 1957–1961, the Kefauver–Harris Amendments of 1962, and the European Directive 65/65/EEC

Thalidomide was launched in Europe in 1957 and proclaimed a "wonder drug" for insomnia, morning sickness, coughs, colds, and headaches, by the manufacturer. At this time, drugs were not thoroughly tested for potential harm to the fetus and use during pregnancy was not strictly controlled. While initially considered safe, it was ultimately concluded that thalidomide was responsible for teratogenic deformities in children born after their mothers used it during pregnancy, prior to the third trimester, resulting in the drug being withdrawn from all markets in 1961. By this time, *thalidomide had been introduced into 46 different countries worldwide resulting in the estimated* deaths of

approximately 2000 children and serious birth defects in more than 10,000 children [3].

The Thalidomide tragedy has arguably had the most profound effect in shaping medicines regulation in the modern era. Although thalidomide was never approved for marketing in the USA, it spurred a major change in the history of US drug regulation with the passage of the **Kefauver–Harris Amendments (KHA) of 1962** to the FDCA [4]. The KHA first introduced into law the requirement that a drug product be proven efficacious. They led to the requirement of two adequate and well-controlled trials for demonstrating efficacy of a new drug product. Additionally, these amendments provided a number of other safeguards, including formal rules guiding good manufacturing process, provision of a 180-day period for FDA to review a new drug application, requirement of an affirmative decision by the agency to approve a drug before marketing, and requirements of drug manufacturers to report adverse events associated with drug use to FDA [5].

In Europe, **Directive 65/65/EEC** on the approximation of provisions laid down by law, regulation, and administrative action relating to medicinal products was established as a direct result of the thalidomide disaster to further develop harmonization in the Community. In 1975, two further Directives were introduced, the first on approximation of the laws of Member States relating to analytical, pharmacotoxicological, and clinical standards and protocols in respect of the testing of proprietary medicinal products (**Directive 75/318/EEC**), and the second on the approximation of provisions laid down by law, regulation, and administrative action relating to medicinal products (**Directive 75/319/EEC**). The introduction of these directives represents a milestone for initiating EU harmonization with the final long-standing aim of creating a "common market" for medicines. The ensuing Council Regulation EEC/2309/93 established the European Medicines Agency (formerly known as the European Medicines Evaluation Agency) in 1993 and its Committee for Human Medicinal Products (formerly known as the Committee for Proprietary Medicinal Products) which formulates the opinion of the Agency on questions relating to the submission of applications and granting marketing authorizations in accordance with the centralized procedure.

Orphan Drug Regulations

Orphan Drug Regulations are particularly relevant to the pediatric population, as many orphan diseases are conditions that affect children disproportionately, including certain cancers, cystic fibrosis, sickle cell disease, and inflammatory bowel disease. In the US, the **Orphan Drug Act of 1983** was established, whereas in Europe, the **Orphan Regulation (EC) No 141/2000** was adopted in 1999. The regulations have introduced incentives for companies to develop drugs for rare diseases such as fee reductions on regulatory submissions, access to accelerated/fast track regulatory pathways and the EU centralized procedure, rare pediatric disease priority review vouchers in the US, research grants in the EU, and grants for the costs of clinical testing expenses in the US. By providing significant incentives, the regulations have resulted in an increased interest in conditions previously overlooked by many pharmaceutical companies, due to perceived lack of financial benefit [6].

Pediatric Drug Regulations (US)

Legislation guiding pediatric drug development in the US was first established with the **Pediatric Labeling Rule of 1994** issued by FDA, to further promote access to drugs for children. The rule introduced the concept of pediatric extrapolation—allowing the agency to label drugs for pediatric use in some limited circumstances based on less than the standard of two adequate, well-controlled clinical trials.

The **Food and Drug Modernization Act (FDAMA)** reauthorized the FDCA and focused on reforming and modernizing many facets of the regulation of food, drugs, and cosmetics and represented the next major development in pediatric legislation in the US. One important facet was a financial incentive offered to companies for pediatric drug development. The law allowed FDA to grant 6 months marketing exclusivity to drugs which were studied appropriately in a pediatric population. However, despite companies starting to take advantage of marketing exclusivity, there remained a major deficiency in the availability of strong clinical evidence to support the safe and effective use in children of many prescription drug products [7].

Despite additional benefits for companies developing drugs for orphan indications and FDAMA incentives, the gap between high-quality evidence informing the use of many drugs for children, compared with adults, remains wide. Even when pediatric studies are conducted, there is often a lag of many years between the approval of a new drug for adults and the availability of adequate data to support labeling in children. To further bolster pediatric research, the **Best Pharmaceuticals for Children Act (BPCA) of 2002** was enacted. In addition to extending the financial incentive of 6 months of market exclusivity from FDAMA, BPCA established a program to promote pediatric drug development, through the National Institutes of Health (NIH). The act was reauthorized in 2007 and later permanently reauthorized in 2012 and provided additional measures including a process through which FDA can issue a request to a manufacturer to conduct specific trials in children, if deemed necessary by the NIH. If the manufacturer chooses not to conduct those trials, the NIH may do so [8].

More recently, the **Pediatric Research Equity Act (PREA) of 2003** was passed. The most comprehensive piece of legislation regulating pediatric drug development to date, PREA provides authority to the FDA to require sponsors to conduct studies in pediatric patients when a marketing application is first submitted to FDA for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. However, under certain circumstances (e.g., if the disease for which the drug is used does not occur in children), FDA may grant a waiver for studies under PREA [9]. PREA was reauthorized in 2007 and expanded as part of the **Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012**.

Pediatric Drug Regulations (EU)

Pediatric development is governed in Europe by the EU Pediatric Regulation (EC 1901/2006). All applications for a Marketing Authorization for a new medicinal product must include the results of studies as described in an agreed upon Pediatric Investigation Plan (PIP), unless the pediatric development is exempt because of a deferral or waiver. This requirement also applies when a Marketing Authorization holder pursues a new indication, pharmaceutical form, or route of administration for a drug that is already authorized and covered by intellectual property rights.

Pediatric Drug Regulations (Rest of World)

Beyond the requirements outlined for the US and EU, pediatric development is also mandated in Switzerland to support adult development and is a prerequisite for the submission of adult Marketing Authorization Applications, although exemptions do exist. Special regulations for obligatory pediatric development do not exist for any other region/country, although rewards and incentives may be available.

Overview of Clinical Trials

Once a pharmaceutical company has identified a compound of interest, non-clinical studies will be conducted. This typically includes animal pharmacology and toxicology studies, to assess the potential therapeutic benefit of the drug in a disease model and to permit an assessment of whether it is reasonably safe for initial testing in human subjects. Depending on the targeting of an individual new molecular entity to the pediatric population, juvenile animal toxicity studies may also be required to asses for potential effects on growth and development and assessment of effects on specific developmental systems and are especially important in the development programs for drugs that will ultimately be used in children.

Clinical trials are typically divided into four phases.

Phase I Clinical Trials

Phase I clinical trials typically involve the first exposure of humans to the new drug. Typically, these studies are conducted in healthy adult volunteers and may enroll very small numbers of patients (often less than 50 patients). For ethical reasons, pediatric subjects are typically excluded from phase I clinical development programs, until the risk–benefit profile in human subjects is more clearly understood.

Phase I trials often involve the administration of a small, single dose to a small number of subjects in order to understand various aspects of its pharmacokinetics in the human body. Particular interest is paid to collecting multiple blood samples over time, in order to assess the pharmacokinetic (PK) profile of the drug. These data will be compared with PK data collected in animal models, to help direct the testing of further doses and to determine safe starting doses for use in the clinical trials. These studies may provide additional insight into the metabolism, clearance, elimination half-life, etc. of the drug in humans. Specific attention is paid to any safety concerns, including changes in vital signs, laboratory parameters, and subject symptoms [10]. Further investigation may include dose escalation strategies to test larger doses, once initial safety is confirmed. A major goal of a phase I study is to obtain sufficient understanding of pharmacokinetics to inform the design of a phase II trial which will allow safe initial evaluation of efficacy in patients.

Phase II Clinical Trials

A phase II clinical trial utilizes the background information obtained from the phase I trial to adapt the development program toward the patient population of interest. Goals of phase II studies include demonstrating proof of concept in a specific disease population, determining the optimal drug dosing regimen for a given disease, and exploring the exposure–response relationship [11].

Phase II trials are designed to be relatively short in duration and small in size and may use an early clinical response or biomarker as the endpoint of interest. They often enroll 100–200 patients, or sometimes less. The ultimate goal is to confirm that the drug will likely be successful in further development, before undertaking a large, long-term phase III program, and to obtain the needed supportive information to inform the design of those pivotal trials.

Phase III Clinical Trials

Phase III trials are designed to utilize the previously determined effective dose to demonstrate efficacy in a specific patient population. Phase III trials are typically large (may include hundreds to thousands of patients), aim to enroll a diverse patient population, and will be statistically powered to demonstrate efficacy of the study drug in the given population. Various trial designs can be employed, including comparing the new drug to a previously approved alternative (to demonstrate non-inferiority or superiority) or to a placebo (to demonstrate initial efficacy). Apart from efficacy, safety measures are assessed carefully to determine if infrequent but serious adverse events may occur [12].

Phase IV Clinical Trials

In the USA, phase IV trials are those conducted after initial approval of a new drug. This may include studies mandated by the regulatory agency for a variety of reasons. FDA routinely issues post-marketing requirements (PMRs) for studies to obtain additional safety and efficacy data after the initial approval. This may include further studies to better assess the safety and effectiveness of the drug in various subpopulations, such as specific age groups or ethnicities that were not well represented in the original trials that supported approval. Deferred pediatric studies required by PREA are also included. Other phase IV studies may be conducted to understand the long-term safety and/or efficacy of a product (which can be done via a long-term observational study or registry protocol). They may assist in the detection of very rare but serious adverse events. Due to the low incidence of these types of events, it may take thousands of patients and follow-up over many years to obtain the required data to fully understand the risks [13].

Key Concepts in Clinical Trial Conduct

Good clinical practice (GCP) refers to a collection of rules, regulations, and standardized procedures which are designed to protect participants in clinical trials. These standards are designed to ensure that the trial is conducted such that the credibility and accuracy of the data generated are maintained. Required components of GCP include an institutional review board (IRB), specific requirements for informed consent documents, a standardized approach to evaluation and reporting of adverse events which may occur during clinical trials, and use of a data monitoring committee. This section will describe each of these components in more detail.

Institutional Review Board (IRB)

The statutes governing the regulation of an Investigational New Drug (IND) in the USA specify that clinical investigations must be approved by an IRB. An IRB is a group of individuals designated to carry the responsibility of reviewing a proposed clinical study to ensure that it will be conducted in accordance with standard ethical principles. An IRB may be specific to one hospital or healthcare institution, or, more commonly in large multicenter trials, a centralized IRB may be utilized to oversee the study at multiple cooperating sites.

Informed Consent

A key component of good clinical practice is obtaining the research subject's informed consent to participate. As specified in the Code of Federal Regulations (21 CFR 50.2), "no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence."

The informed consent document (ICF) is a written form prepared by the investigator or sponsor which details the risks, benefits, and responsibilities of the research participant and the sponsor of the clinical trial. The form serves to document the discussion that the consenting investigator must have with the participant, allowing him/her the opportunity to ask questions and ensure that the subject understands what is involved in participating in the trial.

Required components of the informed consent document include (1) a statement that the study involves research, explanation of the research, and a description of the procedures involved in the study and expresses explanation of what is considered "experimental," (2) a description of known or anticipated possible risks or discomfort that a subject may experience, (3) a description of any benefit that the study may provide to the subject or to other patients in the future, (4) an explanation of other reasonable treatment options/alternatives that are available to the patient, (5) an

explanation of confidentiality of the study records, and (6) an explanation of any compensation and, if more than minimal risk is involved, what remedies or treatments are available in the event of illness or injury and who to contact/how to report any injury or illness that might result from participation. The ICF should specifically detail if required care would be billed to the patient's insurance, covered directly by the sponsor, and what would occur if study participation was terminated due to an adverse event [13].

Pediatric Considerations

For pediatric patients, both parental permission and patient assent are required in most cases. The risks and benefits of proposed pediatric participation in a research study should be discussed in detail with the parent or legal guardian of the pediatric subject. The parent or guardian must provide their permission on an informed consent document, to permit their child to participate in research. Assent refers to the willingness of the child to participate. The IRB, when considering procedures for enrollment in a given study, will determine the age at which pediatric subjects' assent will be required. Typically, some degree of assent should be solicited once the child possesses the intellectual and emotional ability to comprehend the concepts involved. The age at which this occurs varies based on the clinical situation and research in question. However, the guiding principle is that when a child is capable of understanding the nature of participation, assent must be sought. Waiving the requirement for assent should only be considered in well-defined circumstances, such as if the child's capacity for understanding is so limited that they cannot be consulted, if the intervention holds the prospect of direct benefit or well-being to the child and is only available in the context of the research, or if the research meets other conditions for waiver of informed consent for adults, as specified in the regulations [14].

Adverse Event Reporting

The clinical trial protocol should provide specific guidelines for the collection and reporting of adverse events that may occur during the trial. Adverse events will generally be reported by the investigator to the IRB, and a subset of such events must be reported promptly to the FDA. Reportable events include serious adverse events (SAEs), defined in the Code of Federal Regulations, including death, life-threatening illness, hospitalization, disability or permanent damage, congenital anomaly or birth defect, or other serious events such as those where intervention was required to prevent permanent impairment [15]. In general, events must be reported to the IRB if they are unanticipated and serious and may have implications for the continuing trial. For clinical trials conducted under an IND application, a sponsor is also required to notify the FDA in a written safety report of "any adverse experience associated with the use of the drug that is both serious and unexpected [16]."

Data Monitoring Committee

An independent data monitoring committee (DMC) may be formed to assist in the conduct and analysis of data in a clinical trial. A DMC may be appropriate for trials of long duration (when interim analysis would be appropriate and important), for trials with endpoints that include survival/mortality (where a finding of futility may require early termination of a study), in trials that involve vulnerable populations (such as elderly patients, children, or patients with disabilities), in trials involving treatment that is high risk to subjects, and in large multicenter trials. The goal of a DMC is to evaluate incoming/cumulative data on an ongoing basis and provide feedback to the sponsor regarding the continuing safety of the trial participants, as well as the ongoing validity and benefit of continuing the trial [17].

Highlights of the Regulatory Review Process

In the USA, the first regulatory step in drug development is the submission of an Investigational New Drug (IND) application to the FDA. They are categorized as commercial (utilized for a drug that will ultimately seek marketing approval) and noncommercial research.

Current Federal law prohibits transportation or distribution of unapproved drugs across states lines. The IND provides an exemption from that legal requirement for investigational drugs. Further, the IND provides the FDA with the necessary data to ensure the potential safety of investigational products. Once an IND application is submitted, current regulations require that the applicant not commence clinical trials until 30 days of elapse; during that time, the FDA makes a determination regarding the safety of the planned clinical trials. IND applications must provide animal pharmacology and toxicology data, manufacturing information, clinical protocols, and investigator information.

For the purposes of developing a new drug that will ultimately seek marketing approval, a commercial investigator IND is submitted. This type of application seeks permission to begin the first human trials of an investigational drug in the USA.

Non-commercial INDs are used to gain access to an investigational drug for research or limited treatment purposes. This may occur under a non-commercial investigator, emergency use, or treatment IND.

An investigator IND is submitted by the person who actually conducts the investigation and under whose immediate

direction the investigational drug is administered or dispensed. This type of application may be utilized when an academic researcher wishes to study the effects of an investigational drug in a particular patient population, though he/she is not necessarily connected to the pharmaceutical company that is developing the drug.

An emergency use IND allows the FDA to authorize limited use of an experimental drug in an emergency clinical situation that does not allow time for submission of an IND. This situation may occur when there is no acceptable approved medical treatment for a given condition, and a prescribing physician wishes to seek permission to treat a patient or limited number of patients with an unapproved agent.

A treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions, while the final clinical work is conducted and the FDA review takes place. A treatment IND may be utilized to allow patients who are completing a phase III trial access to continue the drug, until final approval is obtained [18].

Once a sponsor has completed all investigations, the next step in the regulatory process is the submission of a new drug application (NDA). Utilizing the information submitted as part of the NDA, the FDA reviewer must reach the following conclusions:

- *Whether the drug is safe and effective in its proposed use(s) and whether the benefits of the drug outweigh the risks*
- *Whether the drug's proposed labeling (package insert) is truthful and not misleading and what it should contain*
- *Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity* [18]

Similar to the NDA, used for approval of drugs, a biologics license application (BLA) is a request for permission to "introduce, or deliver for introduction, a biologic product into interstate commerce [19]." The BLA should contain enough information for an FDA reviewer to reach the same conclusions (listed above) for drugs.

Regulatory Safeguards for Pediatric Patients Involved in Clinical Trials

Pediatric patients are considered a vulnerable population, and their participation in clinical trials requires specific safeguards that are detailed in regulation. For any clinical research involving pediatric patients, the Code of Federal Regulations provides specific criteria that an institutional review board (IRB) must rely upon to make decisions regarding the approval, monitoring, and review of biomedical and behavioral research. These criteria are listed below.

Criteria for IRB Approval of Pediatric Research

1. Research not involving greater than minimal risk to the children [20].
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research [21].
3. Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition. This type of trial must only represent a minor increase over minimal risk [22].
4. Research that the IRB believes does not meet the other conditions but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children (this trial requires a special level of governmental review beyond that provided by the IRB) [23].

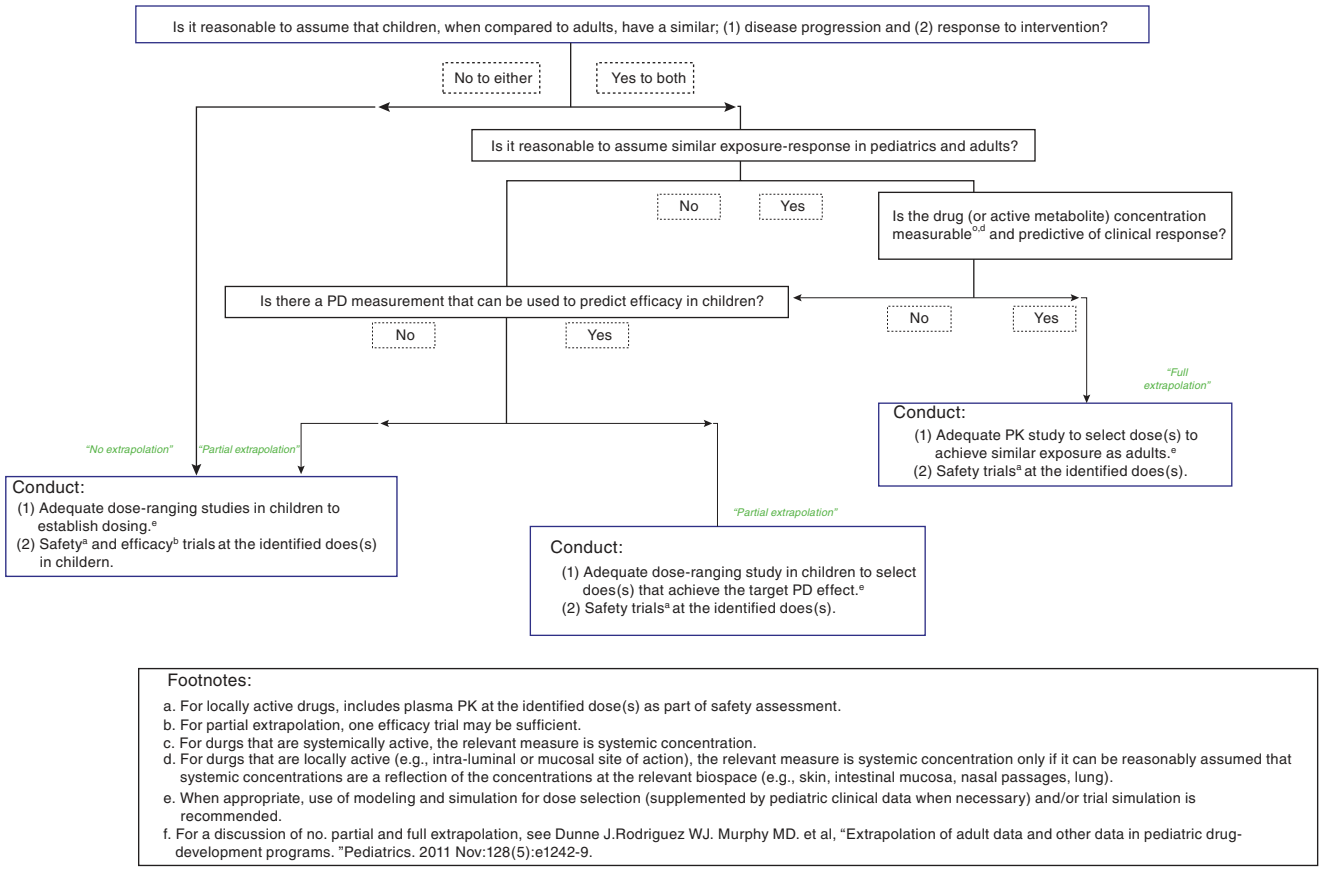
As a general rule, children should not be enrolled in a clinical investigation unless their enrollment is necessary to achieve important scientific and/or public health objective(s) directly benefiting children.

Pediatric Extrapolation

Given the unique challenges of conducting pediatric clinical trials, including the vulnerabilities of the pediatric population, ethical limitations on participation, and logistical challenges of studying children, the concept of pediatric extrapolation was developed. The goal of extrapolation is to leverage the available data from adult trials and to minimize the size and scope of the trials needed in pediatric patients, while still maintaining a standard of evidence to support safe use of drugs in pediatric patients.

The Pediatric Research Equity Act of 2007 states that "if the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies." It should be noted that only effectiveness (not safety) can be extrapolated.

The following algorithm illustrates the pathway used to determine if and when extrapolation may be appropriate [24].



From FDA's Draft Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, Dec 2014.

For conditions where the disease progression and response to intervention are expected to be similar between pediatric patients and adults, extrapolation may be appropriate. In this setting, depending on the degree of similarity and availability of exposure-response data in children and adults, a determination will be made as to how much additional safety and efficacy data are needed to support use of the drug in pediatric patients. Applying the extrapolation approach may reduce the burden on pediatric patients, by requiring fewer efficacy studies or smaller studies, and/or pharmacokinetic and safety studies only, depending on the disease process in question.

Pediatric-Specific Issues in IBD Trials

Using the general pediatric drug development principles described above, the development of drugs for the treatment of IBD in pediatric patients continues to evolve. In the USA, approvals for IBD products in adults continue to outnumber pediatric approvals. Pediatric approvals lag behind those for adults by a number of years, effectively restricting access to the newest advances in therapies for pediatric patients. Important pediatric IBD drug development program considerations include, but are not limited to, use of extrapolation, adequate dose selection, use of placebo arm, the burden of repeat endoscopies, and measuring outcomes that matter to patients.

A claim of efficacy requires a product demonstrate a meaningful change in a prespecified measurable endpoint. In inflammatory bowel disease, there have been a variety of different indices utilized to measure clinical response to therapy in drug trials. For example, a published review of pediatric trial data submitted to the FDA from 1950 to 2008 of products used to treat patients with ulcerative colitis (UC) identified three disease activity indices utilized as endpoint measures for the three pediatric UC products approved during that time (Colazal, Remicade, and Azulfidine). The Modified Sutherland UC Activity Index (MUCAI) was used for the Colazal pediatric trial (2006) [25]. The Mayo score and the Pediatric UC Activity Index (PUCAI) were used for the Remicade pediatric trial (2011) [26]. It should be noted that Azulfidine was initially approved for UC in 1950 and granted pediatric approval in 2009 based on full extrapolation of efficacy from adult trials; therefore, no pediatric trial was conducted. The results of this review suggest that there exists a lack of consensus on the most appropriate primary endpoint for pediatric UC trials, and the same problem exists

in the study of Crohn disease [27]. Considerable debate continues in the field as to the definition of clinical response and/or remission and how best to measure it. Historically, endoscopic appearance of the mucosa was considered the gold standard for evaluating response to therapy in an IBD trial. Others have suggested that mucosal healing, as described on histology specimens (and so requiring biopsy), is the preferred endpoint of interest. Particularly in pediatric patients, where it is necessary to limit the number of endoscopies during a trial, less invasive measures of disease activity are becoming increasingly important. However, from a regulatory standpoint, the use of a non-invasive endpoint, or biomarker, introduces additional complexity. A biomarker must first be clearly demonstrated to correlate well with the outcome of interest, before it can be qualified for use in a trial that will support product labeling [27].

To quantify meaningful changes in signs and symptoms, patient-reported outcome (PRO) and observer-reported outcome (ObsRO) instruments can be used. Changes in symptoms are subjective, however, so standardization of the definitions of the symptoms of interest and carefully designed tools for their measurement are crucial. FDA has recently published guidance for industry on their development and use ("Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims") [28].

The gold standard of evidence to support a claim of efficacy involves a double-blind, placebo-controlled clinical trial. However, inclusion of a placebo arm in a pediatric trial, particularly for patients who have a serious chronic medical condition such as inflammatory bowel disease, is controversial. Trial design is evolving over time to minimize exposure to placebo and risk from lack of treatment for patients. This may include use of an open-label induction period, followed by randomized withdrawal phase, use of an active comparator instead of placebo, or the use of randomization rates of more than 1:1 to minimize the number of subjects receiving placebo.

Given the lack of consensus across countries and regulatory agencies, international consensus regarding pediatric IBD trial outcome measures would facilitate drug development. In an attempt to develop a consensus statement regarding pediatric UC trial outcome measures, the *i*-IBD Working Group was convened in 2012 by scientists from the US Food and Drug Administration, European Medicines Agency, Health Canada, and the Pharmaceuticals and Medical Devices Agency of Japan. The *i*-IBD Working Group "concluded that outcome measurements in pediatric UC trials must account for both endoscopic disease activity of UC and improvement of signs and symptoms." The group also recommended that assessment of signs and symptoms be used as a co-primary endpoint in pediatric UC trials in conjunction with endoscopic parameters of mucosal appearance to assess disease severity [29]. A similar approach should be taken for Crohn disease.

Studying drugs to treat IBD in children presents a number of challenges, though they are not unique to this disease process. Careful assessment of study design, judicious use of placebo arm, limiting invasive procedures during the trial, consideration of patients' reported symptoms, and increasing collaboration internationally and across various regulatory agencies are all measures that will contribute toward advancing drug development in the field.

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Part VII

Special Considerations

Infectious Complications of Pediatric Inflammatory Bowel Disease

49

Monica I. Ardura and Sandra C. Kim

Introduction

The role of infections in the pathogenesis of inflammatory bowel diseases (IBDs) remains incompletely understood. Current hypotheses suggest that pathogenic or commensal gut flora act as potential cross-reactive antigens leading to a dysregulated immune response that may trigger both primary disease and relapses in IBD [1]. Animal models have demonstrated that bacterial colonization is a prerequisite for the development of intestinal inflammation in susceptible hosts, but proof of causation in humans is lacking [2, 3]. Although the exact role of microbes in causing IBD remains to be clarified, infections do play an important role in the clinical course and management of patients with IBD. Infections may be a presenting manifestation of IBD and may exacerbate disease activity. Herein, we will focus on the infections that may occur as complications of the primary inflammatory disease or secondary to therapeutic modalities, including surgery and pharmacologic therapies that modulate immune system activity.

Much of the data regarding infections in patients with IBD are extrapolated from reports of clinical trials and population-based observational studies in adults; the pediatric data are limited to reported adverse events in pharmacoepidemiological and registry studies, as well as case series that are specific for a pathogen or immunomodulatory therapy [4–6]. The lack of large, population-based cohort studies in the pediatric IBD population makes it difficult to reliably calculate and compare rates of infections. Factors predisposing patients with IBD to infectious complications include severity of underlying IBD, medical co-morbidities, malnutrition, abdominal surgery, and immunosuppressive medications. When compared with adults with IBD, children with IBD have more extensive luminal disease, are more likely to require systemic steroids, and typically have a more severe disease course [7, 8]. These differences, coupled with a higher likelihood of acquiring primary infections during childhood and increasing use of combination immunomodulator and biologic therapies, may place pediatric patients with IBD at risk for infectious complications.

Antibiotic Use for Treatment of IBD

Based on the rationale that antibiotics could potentially medically modulate and suppress the host inflammatory response to commensal or pathogenic gut flora [9], their clinical use has preceded evidence-based data. Antibiotics have been utilized broadly for the treatment of IBD luminal and fistulizing disease, maintenance of disease remission, treatment of abscesses, and as prophylactic therapy to prevent postoperative recurrences. Much of the data are derived from patients with Crohn disease (CD); the presence of transmural inflammation in CD is an inherent risk factor for formation of fistulae and possible perianal disease. Indeed, the incidence of perianal CD in children is estimated to be 10–62%, but the exact role of putative bacteria and data for therapeutic benefit of antibiotics for non-suppurative perianal disease are unclear. Perianal fistula and abscesses may represent sterile inflammation or be infectious; small studies describing the microbiology of perianal fistulas have differing results with important antibiotic implications [10–12].

In US tertiary pediatric centers, there is a wide practice variation of antibiotic prescribing for children hospitalized with IBD exacerbations, ranging from 27 to 71% [13]. This heterogeneity in antimicrobial use is likely a reflection of lack of robust efficacy data in the published literature. Systematic reviews of the available small, randomized trials in adults evaluating the efficacy of antibiotic therapy in

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helping to induce remission or prevent relapse in IBD have variable results given distinct methodologies, early and differing endpoints, case definitions and disease severities, and utilization of different antibiotics (single or dual), sometimes in combination with other therapies [14–16]. When evaluating pooled antibiotic use, patients who received antibiotics, compared with placebo, were more likely to have induction of remission of active UC and CD, and fewer relapses in patients with colonic but not isolated small bowel CD [16]. However, the varied antibiotics used in these trials (predominantly metronidazole and ciprofloxacin) preclude firm conclusions. A recent Cochrane review evaluating the efficacy of antibiotics (analyzed individually or pooled by antibiotic class) for both the induction and maintenance of remission in CD among published randomized trials failed to confirm robust evidence of clinically meaningful efficacy [17].

In three randomized controlled trials (RCTs) evaluating antibiotics to treat perianal fistulas, the use of metronidazole or ciprofloxacin demonstrated a trend towards reducing fistula drainage in patients with CD (RR 0.8, 95% CI 0.66–0.98, not statistically significant) [14]. Despite lack of controlled studies and conclusive efficacy data in children, pediatric treatment algorithms also recommend antibiotics for perianal fistulizing disease [18, 19]. The role of antibiotics to prevent post-operative recurrence of ileal or ileocolonic CD is unclear, though there is a trend of reduced risk for clinical and endoscopic recurrence in patients who received metronidazole over those who received placebo [20]. The optimal approach to prevention of post-operative recurrence is unknown, and no clear prophylactic strategy is preferred. There is evidence to suggest that initiation of immunomodulatory therapies for patients in higher-risk disease categories may decrease post-operative CD recurrence [21, 22].

There are less data regarding efficacy of antibiotics for UC than CD. In clinical trials of adults who presented with severe UC, there were no differences in outcomes when intravenous empirical antibiotics were used as adjuncts to steroid therapy [23]. Recently, the PRASCO study showed that hospitalized children with acute severe colitis (ASC) who received a quadruple antibiotic cocktail (amoxicillin, vancomycin, metronidazole, and doxycycline/ciprofloxacin) along with intravenous corticosteroids (versus IV corticosteroids alone) had significant improvement clinically by day 5. While overall clinical response since this initial study has been reported to be 20–50%, those who do respond do so fairly rapidly. These findings suggest a potential unrecognized infectious trigger leading to the clinical response [24]. There have been limited studies in adult patients with UC which suggest a limited role of a multi-antibiotic regimen in patients with UC. Given these results, antibiotics should not be routinely used in patients with UC unless an infection, such as *Clostridium difficile,* is suspected, pending diagnostic testing results, or in the presence of toxic megacolon.

Clinical benefit of antibiotics (ciprofloxacin alone or in combination with metronidazole or rifaximin) has been observed in some trials for pouchitis, the most common complication after ileal pouch–anal anastomosis in patients with UC [25]. In addition, there is evidence to suggest that VSL#3, a probiotic preparation, decreases pouchitis in patients with UC post-colectomy [26].

To further illustrate the complex interplay and immunopathogenesis of antibiotics, the microbiome, mucosal immunity, and IBD, a genome-wide association study demonstrated that in a small subset of children with newly diagnosed CD, short-term (<3 months) antibiotic use prior to IBD diagnosis amplified the microbial dysbiosis associated with CD by decreasing presumed protective bacterial species [27]. The complexity of the potential gut microbiome–host association has been corroborated by other population-based studies noting that higher cumulative exposure to systemic antibiotics, particularly broad-spectrum antibiotics, may associate with the development of new-onset IBD [28–31]. These studies provide some circumstantial evidence of an association between antibiotic use and later IBD diagnosis, that requires additional study and consideration of judicious antibiotic use in young children.

While there are insufficient data to recommend universal use of antibiotics for inducing or maintaining remission in active IBD, there may be some benefit as adjunct therapies as outlined above; antibiotics may provide potential benefit because of their immunomodulatory properties, including suppressing tumor necrosis factor (TNF)-alpha synthesis, and not by direct antimicrobial effects on the microbiome [32]. Altering the gut microbiome with the use of antimicrobials may indeed have a role in modulating primary IBD activity, but requires further rigorous prospective, controlled studies in larger populations of patients with IBD.

Infections Associated with Underlying IBD

Antimicrobials have an established role in the management of patients with IBD for microbiologically proven infectious complications of underlying disease, including intra-abdominal abscesses. Evidence-based guidelines for empirical antimicrobial therapy of intra-abdominal abscesses have been put forth by multiple professional societies [33, 34]. In high-risk patients with complicated intra-abdominal infections, including those who are considered immunocompromised, empiric therapy with cefepime and metronidazole or piperacillin–tazobactam monotherapy are appropriate; a carbapenem (e.g., meropenem) is preferred in patients with a prior history of infection with extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*. Targeted

antimicrobial therapy should be further guided by microbiologic culture data, local epidemiology, and patient's history of bacterial colonization and resistance patterns. Visceral abscesses, frequently in the liver, have been described, particularly in patients with CD; these may occur alone and unrelated to hepatobiliary disease or as a complication of an intra-abdominal infection or cholangitis [35]. Results of aerobic and anaerobic bacterial cultures obtained from drainable abscesses help guide antimicrobial therapy. Duration of antimicrobial treatment will ultimately depend on ability to achieve source control, and a composite of clinical improvement, normalization of laboratory values, and resolution on follow-up imaging studies.

Patients with IBD may also be at higher risk for urinary stone formation leading to urinary tract infections and have a higher disease severity than patients with urinary stones who do not have underlying IBD [36]. In addition, some infections may mimic IBD lesions or occur concurrently in patients with underlying IBD. In particular, sexually transmitted infections, like syphilis and lymphogranuloma venereum, can cause proctocolitis and lead to rectal lesions resembling CD [37]. Thus, a high index of suspicion and appropriate diagnostic testing should be performed in sexually active adolescents with IBD who are not responding to standard therapies.

Patients with IBD may be more prone to infections of the gastrointestinal (GI) tract due to microbial dysbiosis or impaired epithelial barrier function [38]. Enteric infections may mimic, be a presenting symptom of, or lead to exacerbation of IBD; most cases of infectious colitis are caused by bacterial enteropathogens. For example, *Yersinia* spp. can classically cause an acute ileitis indistinguishable clinically from acute Crohn ileitis. As such, it is recommended that patients with a clinical presentation concerning for IBD or with previously diagnosed IBD presenting with diarrhea, especially if bloody, should have diagnostic testing performed for bacterial pathogens, including *Clostridium difficile (C. difficile),* and receive appropriate antimicrobial therapy [19, 24].

Rates of infection in children with IBD are difficult to discern given diverse testing modalities of varied sensitivities, overall prevalence of disease, and clinical indications for testing (screening or worsening colitis symptoms). Further, there is a wide variation in diagnostic practices among gastroenterologists caring for children with IBD. A survey of pediatric gastroenterologists confirmed that 29% of children undergoing an initial evaluation for colitis symptoms and possible CD did not have stool testing performed [39]. In a large study of US children presenting with newly diagnosed UC, the diagnostic yield of routine enteropathogenic stool testing was retrospectively evaluated; testing included bacterial stool culture, including *Yersinia*, ova and parasite examination, Giardia and *Cryptosporidium* antigen, *C. difficile* toxin A/B by PCR, and viral testing (by culture, rotavirus EIA, quantitative adenovirus PCR, viral culture for adenovirus, cytomegalovirus (CMV), and enterovirus) and electron microscopic examination [40].

Clostridium difficile

In the same study 863 test samples from 152 pediatric patients with UC, *C. difficile* was the most commonly detected organism in 13.6% of samples, followed by adenovirus (1/13, 7.7%), non-typhoidal *Salmonella* species (4/220, 1.8%), and parasites (2/151, 1.3%). In retrospective cohort studies from the US and Europe, children with IBD and diarrheal relapse in whom stool was evaluated by a combination of microscopy, bacterial culture, and/or detection of *C. difficile* toxin, 10–20% of relapses were associated with infections, most commonly *C. difficile* and *Campylobacter* spp. [41, 42]. When evaluating for parasitic infections in 149 children presenting with IBD flares, systematic testing detected *Cryptosporidium* by enzyme immunoassay in 4.6% of patients (7/149) [43]. More unusual enteric infections with mycobacteria, including *Mycobacterium tuberculosis,* which has a proclivity for the terminal ileum and cecum and nontubercular mycobacteria, or fungi, such as histoplasmosis, require additional diagnostic testing (culture, staining, and PCR evaluation) to distinguish the granulomatous inflammation of infection from underlying IBD. Although the diagnostic yield of testing for enteric pathogens seems to be low, a high index of suspicion and eliciting epidemiological risk factors are important so targeted antimicrobials can be prescribed when needed.

Lack of judicious antibiotic use may also promote proliferation of resistant bacterial strains or increase the risk of other infections. *C. difficile* is an important cause of antibiotic-associated diarrhea and a frequent cause of healthcare-associated infection in the United States, with a rising incidence in pediatrics [44–46]. Patients with IBD have been found to be at increased risk of *C. difficile* infection (CDI) [47]. Risk factors for CDI in adults and children with IBD include hospitalization, previous antibiotic therapy, immunomodulatory medications, use of proton pump inhibitors, and presence of severe colonic disease. Patients with IBD receiving immunomodulators and corticosteroids may be at higher risk of CDI (corticosteroid use RR 3.4, 95% CI 1.9–6.1); TNF antagonists do not seem to increase this risk [48]. However, some patients with IBD develop CDI without any identifiable risk factors.

In children with IBD, CDI is prevalent, as documented by the disproportionate increase in *C. difficile*-associated hospitalizations. Additionally, risk factors in this pediatric subpopulation may differ [49, 50]. In addition to increased *C. difficile* detection, pediatric patients with IBD who are diag-

nosed with CDI were also found to have active colonic disease and a more severe disease course [51]. Currently, it is recommended that all patients with IBD who require hospitalization for disease flare undergo testing for *C. difficile* and, if severe colitis is present, empirically start on antimicrobial therapy; further, escalation of immunosuppression should be avoided in the setting of symptomatic and untreated CDI, if clinically possible [52, 53].

Although the increasing incidence and severity of CDI has been related in part to the emergence of the North American pulsed-field type 1 (NAP1) strain that produces more toxin, some of the increase in CDI incidence may be related to changing diagnostic modalities from cell culture cytotoxicity neutralization assays to enzyme immunoassays (specific, but lacking sensitivity), and most recently to highly sensitive molecular assays. Clinicians should be aware of the method and details of *C. difficile* testing performed at their institutions to improve the clinical interpretation of results in pediatric patients [54].

The detection of *C. difficile* by PCR methodology, although sensitive for infection, may not be specific for disease [55]. The majority of molecular tests detect *C. difficile* toxin genes (A, B, or both) that are present, but do not detect actual toxin production which is required for CDI disease pathogenesis. Thus, in children *C. difficile* toxin gene detection by PCR does not reliably distinguish between *C. difficile* colonization (detection of *C. difficile* in an asymptomatic patient) and *C. difficile* disease (detection of *C. difficile* in a patient with symptoms consistent with CDI, varying from mild diarrhea to fulminant colitis). In a non-controlled trial, application of the recommended two-step testing in children, including a subpopulation with IBD, was inadequate to differentiate colonization from disease [56]. Indeed, interpretation of *C. difficile* PCR testing is even more challenging in children with IBD, in whom worsening colitis may be from underlying disease, CDI, or both. *C. difficile* colonization in the US healthy adult population has been estimated to be 3–7%, with rates of 4–20% for individuals that require hospitalization [57]. High *C. difficile* colonization rates are known to occur in infants <1 year of age and young children; thus, testing for CDI is discouraged. Colonization rates in children older than 3 years of age have been estimated to be <5% [58]. However, in asymptomatic patients with IBD, *C. difficile* carriage has been detected in 8% of adults and 17% of children and may be higher in patients with UC versus CD [59–61]. The possibility of over-diagnosing patients with CDI through the use of molecular testing has been corroborated in a large, prospective observational study of hospitalized adults, in whom *C. difficile* detection by molecular PCR results but a negative toxin immunoassay had outcomes similar to patients with negative *C. difficile* testing by either method [62]. This represents a clinical conundrum to clinicians faced with a child with IBD, worsening colitis symptoms, and detection of *C. difficile*, where distinguishing colonization from disease in a time-sensitive fashion may not be possible. Evolving data applying multiomics suggest potential biomarkers that may help distinguish disease processes [63]. Additional prospective studies are required in pediatric IBD patients to reliably and accurately understand colonization from disease and diagnose CDI. The optimal treatment of CDI in patients with underlying IBD is another area of ongoing study, including the use of fecal microbiota transplantation for recurrent CDI [53, 64].

Cytomegalovirus

The exact role of CMV infection in patients with IBD remains poorly defined, and CMV infection (detection of CMV) must be distinguished from disease (detection of CMV in the presence of clinical signs, symptoms, and end-organ involvement). Several studies have established an association between severe IBD (in particular steroid-refractory UC) and CMV-induced disease with reported prevalence rates of 21–36% [65, 66]. The diagnosis of active CMV colitis in patients with IBD is challenging and requires additional testing. Histopathology continues to be the gold standard for diagnosis, but this may not always reveal the enlarged viral inclusion cells that are classic of CMV infection. To improve diagnostic sensitivity, immunohistochemical staining for CMV should also be performed on tissue specimens. In patients with steroid-refractory UC with unremitting symptoms who undergo lower endoscopy with biopsy, specimens should be sent for histopathology and immunohistochemical staining for CMV [24]. Similarly, detection by nucleic acid amplification testing (NAAT) alone is insufficient to confirm CMV disease. Prospective studies are required to better define disease, establish prevalence, and to determine which patients may benefit from antiviral treatment.

Coronavirus 2019 (COVID-19)

Since the initial case patient with coronavirus disease 2019 (COVID-19) in the United States reported GI symptoms, including pain, nausea, vomiting, and diarrhea, GI manifestations have been increasingly described and SARS-CoV-2 has been detected in stool and GI tract tissue specimens [67–71]. Early observations from the COVID-19 pandemic reported that symptoms, including diarrhea and enteritis, were more frequent in children compared with adults, both during acute COVID-19. In addition, GI manifestations have been associated with Multisystem Inflammatory Syndrome in Children (MIS-C), also referred to as Paediatric Multisystem Inflammatory Syndrome temporally associated

with SARS-CoV-2 (PIMS-TS) [72–75]. Given these implications, there has been an urgent need to understand the role of SARS-CoV-2 in the pathogenesis of infections in children with underlying IBD and receiving immunosuppressive therapies. Mechanistically, SARS-CoV-2 has been found to enter host cells via ACE2 receptors, with reports of a 100-fold higher ACE2 expression in the GI than respiratory tract [71, 76, 77].

Emerging data demonstrate that children of any age can be infected with SARS-CoV-2 and that they generally have less severe disease than adults. Currently, preliminary data in patients with underlying IBD suggest that having a diagnosis of IBD alone is not a risk factor for neither acquiring SARS-CoV-2 infection nor worsening disease severity [78–82]. Initial pediatric data from case reports and voluntary reporting to registries are also reassuring. As of early May 2021, there are a total of 672 patients ≤19 years of age with underlying IBD reported to have COVID-19 in the SECURE-IBD registry, comprising 11.3% of the total 5959 reported COVID-19 cases in patients with IBD [83]. In addition, reported outcomes in patients ≤19 years of age have been reassuring; the majority have been managed as outpatients (94.6%), 29 (4.3%) required hospitalization, 6 (<1%) required admission to the intensive care unit, and 3 (0.4%) required mechanical ventilation. Importantly, there are no reported deaths in children and young adults ≤19 years of age to date, compared with the overall mortality of 2% in adult patients with IBD and COVID-19. Among those adult patients with IBD who have worse outcomes, rates of hospitalization were highest in older age groups (starts increasing to 22% in individuals 50–59 years, with increases to 44% by 70–79 years of age), in those with ≥2 co-morbidities (41%) and with moderately to severely active IBD disease (24%) [83, 84]. Despite concerns for the impact of immunosuppressive therapies on underling COVID-19 infection in patients with IBD, patients on TNF antagonist monotherapy did not have increased risk for adverse outcomes with COVID-19 infection. However, receiving systemic corticosteroids for underlying IBD at the time of COVID-19 diagnosis has been associated with worse SARS-CoV-2 disease and outcomes [aOR 6.9 (95% CI, 2.3–20.5)] along with immunomodulators (methotrexate) and 5-aminosalicylates/sulfasalazine [84]. The optimal therapy and management of underlying IBD in patients with COVID-19 remains unknown, but an individual approach that takes into consideration underlying host factors and co-morbidities, severity of infection, and net state of immunosuppression seems prudent to consider and weighed against the risk of IBD disease exacerbation [82, 85, 86].

There are still many questions regarding the relationship between infection and disease activity in patients with IBD. Further research that help delineate host and microbiome immune profiles may allow for improved diagnostic and management strategies, including prognosis and therapies [87, 88]. Recent genome-wide association studies link IBD to host–microbe pathways central to sensing/signaling and mucosal-initiated effector responses [89].

Increased Risk of Infections Secondary to Therapies

The benefits of immunosuppressive treatment for IBD should be weighed against the potential risks, including infectious complications, in each individual patient before starting immunosuppressive therapies. This may be particularly important for patients with a history of chronic, recurrent, or opportunistic infection, for those with identifiable risk factors for infection, and for patients with other co-morbid medical conditions that may predispose them to infections.

Infections have been associated with all immunosuppressive therapies for IBD, most frequently with systemic corticosteroid therapies but also with anti-metabolites, purine analogues, alkylating agents, and more recently given an increase in their use, with TNF antagonists [90, 91]. Serious infections are defined as infections requiring hospitalization or parenteral antimicrobial therapy and any opportunistic infections. Risk factors for severe infections in patients with IBD include young age, severity of underlying disease, and time-dependent exposure to immunosuppressive therapies, including immunomodulators and TNF antagonists. In patients with IBD, monotherapy with corticosteroids (odds ratio, OR 3.4, 95% confidence CI 1.8–6.2), azathioprine or 6-mercaptopurine (OR 3.1, 95% CI 1.7–5.5), and infliximab (OR 4.4, 95% CI 1.2–17.1) were associated with increased risk for opportunistic infections in univariate analysis [92]. Multivariate analyses confirmed this finding and importantly noted that the risk for infection was further increased 14-fold in patients receiving two or more of these immunosuppressive medications concomitantly (OR 14.5, 95% CI 4.9–43). An increase in adverse infectious events, including opportunistic infections in patients receiving combination immunosuppressive therapies has been confirmed in other IBD studies [93, 94]. Pediatric patients are considered to be severely immunocompromised if they have a known primary immunodeficiency disorder that affects phagocytic, cellular, or humoral immunity or have a secondary immunodeficiency from receipt of immunosuppressive therapies, including high-dose systemic corticosteroids (defined as ≥2 mg/kg/day of body weight or ≥20 mg/day of prednisone for ≥14 days), methotrexate >0.4 mg/kg/week, azathioprine >3 mg/kg/day, 6-mercaptopurine >1.5 mg/kg/day, and biologic agents (e.g., TNF antagonists, anti-CD20), or are receiving combination immunosuppressive medications [95, 96].

Purine Analogues

Mercaptopurine and azathioprine are used for maintenance of remission in IBD. Purine analogues can directly alter cell-mediated immunity, resulting in viral and fungal infections. The incidence of infections in case series of patients receiving these therapies ranges from 0.3 to 7.4%, most frequently with viral infections, particularly herpes viruses, like varicella zoster virus (VZV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) [92, 97–99]. These agents may also cause myelosuppression; the presence of leukopenia itself, even without thiopurine use, is associated with an increased risk of infection and sepsis. The duration and severity of neutropenia can also predispose to infections with bacteria (e.g., *Pseudomonas* spp.) and fungi (*Candida* and *Aspergillus* spp.), while severe lymphopenia (<600/μL) can lead to severe primary viral infections or viral reactivations [100–102]. The highest rates of infection, and most serious infections, were reported when thiopurines were used in combination with other immunosuppressive therapies.

Corticosteroids

Corticosteroids have a broad range of anti-inflammatory activities and have historically been a mainstay in IBD treatment. However, corticosteroids have been shown to be a major independent risk factor for the development of infections and infection-related mortality (OR 2.1, 95% CI 1.15–3.83) [103]. In one study, the relative risk of infection in IBD patients receiving corticosteroids was 1.4 (95% CI 1.1–1.9), with increasing risk at higher corticosteroid doses (>10 mg/day of prednisone) and duration of therapy beyond 14 days [104]. Not surprisingly, infections with multiple pathogens have been reported in association with corticosteroid use. In IBD patients, the use of systemic corticosteroid therapy has also been associated with increased rates of intra-abdominal abscesses in patients with both perforating (OR 9.03, 95% CI 2.4–33.8) and non-penetrating disease (OR 9.31, 95% CI 1.03–83.91); this effect seemed to be dose dependent, with increasing abscess rates in patients receiving >20 mg of prednisone/day [105, 106]. Similarly, post-operative complications were increased in patients receiving corticosteroids (pooled analysis OR 1.68, 95% CI 1.24–2.28) and are up to twofold higher in patients receiving greater than 40 mg of oral corticosteroids prior to surgery [107].

Worsening severity of primary viral infections or reactivations are well-described complications of systemic corticosteroid use. In IBD patients, both primary varicella and zoster infections have been reported most frequently. In pediatric IBD patients, the use of corticosteroids as monotherapy (prednisone >10 mg/day) or in combination with other immunosuppressant medications (TNF antagonists or thiopurines) was associated with an increased risk of VZV infection, including severe infection, with a case fatality rate of 25% [108]. Ideally, patients with IBD who have not received varicella vaccine or are known to be seronegative (VZV IgG negative) should receive the two doses of vaccine (with appropriate intervals) at least 4 weeks before any immunosuppressive regimen is initiated [95]. Due to the prolonged interval recommended between the first and second dose, necessary vaccinations should ideally be provided at the time of IBD diagnosis to allow sufficient time to both mount a serologic response and not interfere with timing of immunosuppressive therapies. Infection prevention by optimizing vaccine-preventable infections is discussed further in Chap. 55.

Tumor Necrosis Factor Antagonists

TNF antagonists is crucial to intracellular pathogen defense and ensuring a robust cell-mediated immune response. The majority of data regarding infections in patients receiving TNF antagonists have been extrapolated from adults with IBD and other autoinflammatory diseases [109, 110]. TNF antagonists have a differential infection risk that depends on the agent and other host or environmental factors [111, 112]. It is not surprising that granulomatous infections secondary to *Mycobacteria* spp. and fungi (e.g., endemic species; *Candida; Aspergillus* and other molds; *Pneumocystis jirovecii*) and infections with intracellular bacteria (e.g., *Bartonella; Brucella; Listeria; Salmonella; Legionella; Nocardia*) have been reported in patients receiving TNF-α inhibitors [113, 114]. The majority of these infections occurred in the first 6 months of starting infliximab, and in the case of mycobacterial infections, likely reflected reactivation of latent infection. Infections or reactivations with viruses, including Hepatitis B, Hepatitis C, and herpesviruses have also been described [108, 115–118].

The TNF antagonists most commonly used for the treatment of IBD in children in which there are sufficient published data related to infection are infliximab and adalimumab. When compared with adults with IBD receiving TNF antagonists, the overall incidence of reported serious infections in children with IBD receiving TNF antagonists was significantly lower [90]. A recent systematic literature review of infections in children with IBD receiving TNF antagonists reported a predominance of mild and mostly viral infections, with incidences of 3–77% of cases; severe infections occurred less frequently, but were varied, with incidences of 0–10% [118].

An increased risk of mycobacterial and fungal infections has been associated with TNF-α inhibitor therapy. *Mycobacterium tuberculosis* is the most frequent granulo-

matous infection reported in patients treated with infliximab and the risk is further increased when the TNF antagonist is combined with other immunomodulators [119–121]. Infections with *M. tuberculosis* are more common than non-tubercular mycobacterial infections. However, it is unknown to what extent TNF antagonist therapy increases the risk of *M. tuberculosis* disease in children. Two cases of *M. tuberculosis* presenting with disseminated disease have been reported in children with IBD during infliximab therapy despite baseline non-reactive tuberculin skin testing [122, 123]. Current guidelines recommend screening for tuberculosis prior to initiating therapy with TNF antagonists though the optimal testing strategy is unknown [19, 24, 96, 124]. Immunodiagnostic screening with both a tuberculin skin test (TST) and an Interferon-Gamma Release Assay (IGRA) at the time of IBD diagnosis and before initiation of any immunomodulatory therapies, particularly steroids and TNF antagonists, will increase diagnostic sensitivity and allow for more optimal patient management [114].

Histoplasmosis is the most common endemic mycosis in the US, prevalent in the Ohio and Mississippi River valleys, and is the most common fungal infection associated with TNF-α therapy in adults and children, either as a newly acquired infection or by reactivation or reinfection [110, 125]. Histoplasmosis has been described in pediatric patients with IBD receiving TNF antagonists [126–128]. Importantly, IBD patients with histoplasmosis (and similarly with other endemic fungi) most frequently presented with non-specific symptoms indistinguishable from IBD (fever, malaise, weight loss, abdominal pain) or had a pulmonary clinical manifestation similar to community-associated pneumonia, not responding to conventional antimicrobial therapy; thus, a high index of suspicion is warranted in patients receiving TNF antagonists [128]. Diagnostic testing should involve multiple testing modalities if possible, including histopathology, fungal tissue cultures, serologic testing, and antigen detection (in both blood and urine). The sensitivity and specificity of the different tests will depend on the clinical presentation (e.g., pulmonary vs. disseminated), infection severity, and timing of infection. In a patient with compatible signs and symptoms, a high diagnostic sensitivity may be achieved when both urine and serum antigen testing are performed concomitantly, as well as serology (by immunodiffusion and complement fixation) [129]. Other fungal infections in patients with IBD receiving TNF-α inhibitor therapies have also been reported [113, 130, 131].

Pneumocystis jirovecii pneumonia (PCP) has been described in patients with IBD, most commonly CD, who receive high-dose steroids (even during the tapering phase), calcineurin inhibitors, and TNF antagonists [132]. The crude incidence of PCP in IBD patients was estimated to be 10.6/100,000 in a health claims database; although PCP cases have been reported in children with IBD, the overall pediatric incidence is unknown [133]. However, given the higher mortality from PCP in the non-HIV population, PCP prophylaxis should be considered in high-risk children with IBD, including those receiving multiple immunosuppressive agents (TNF antagonists plus a calcineurin inhibitor, TNF antagonists as part of a triple immunosuppression regimen, or combination therapies that include high-dose corticosteroids), malnourished children on combination immunosuppression therapies, and in young children <6 years of age with severe IBD in whom an underlying immunodeficiency disorder is possible [96, 134, 135].

TNF-α inhibition may facilitate the risk of primary viral infection and reactivation [136]. Reactivation of hepatitis B, hepatitis C, or progression of viral liver disease have been described in patients receiving TNF antagonists. Therefore, it is recommended that all patients with IBD be screened for hepatitis B prior to receipt of any TNF antagonist; patients with risk factors or evidence of elevated transaminases should also be screened for hepatitis C [96, 117, 124, 137, 138]. In particular, reactivation of HBV after initiation of immunosuppressive therapy has been associated with significant morbidity and mortality. High- and moderate-risk patients who require therapy with TNF antagonists and are Hepatitis B surface antigen positive (or Hepatitis B surface antigen negative but Hepatitis B core antigen positive) and do not have liver injury may be candidates for antiviral prophylaxis and viral monitoring during biologic therapy [139]. In addition, VZV infections with rates of 11.3/1000 patient years have been reported in patients with IBD receiving TNF antagonists [140]. Primary varicella seems to occur more frequently in susceptible patients with CD than those with UC, and risk of disseminated disease is increased in patients receiving highly immunosuppressive therapies, with case fatality rates of up to 25% [108]. Similar varicella screening recommendations are recommended before starting TNF antagonist therapy as described under the corticosteroid section (see above).

Conclusion

The use of biological agents and immunomodulatory therapy has improved IBD management. Infections, including serious infections, albeit rare, are increasingly being described in patients with IBD receiving immunosuppressive therapies. A heightened index of suspicion, timely diagnostics, and targeted therapies are needed for optimal patient management. Given the limited pediatric data, there are ample opportunities for robust pediatric studies to improve our understanding of infectious burden in this population, optimize preventative strategies, and improve patient outcomes.

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Psychological Aspects of Inflammatory Bowel Disease in Children and Adolescents

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Introduction

Youth with pediatric inflammatory bowel disease (IBD) are at greater risk for psychosocial challenges, including deficits in health-related quality of life, symptoms of anxiety and depression, poor social, academic, and family functioning, and suboptimal adherence and self-management. Many of these psychosocial issues are related to the unpredictable relapsing and remitting disease course as well as the embarrassing nature of the symptoms. Treatments can also cause side effects and it may take time for newly diagnosed children to find the treatments that work best for them, which can be frustrating for children and their families. Frequent medical appointments and procedures may also interrupt day-to-day life. As a result, youth with IBD may withdraw from peers, limit their activities, and miss school, all of which are critical, developmentally normative activities that promote psychosocial adjustment during childhood and adolescence. Concerns with appearance (e.g., short stature, changes in weight), pressure to engage in risk behaviors, and the perceived stigma of having a chronic gastrointestinal illness also impact psychosocial functioning. In response to these concerns, pediatric IBD care has emphasized a multidisciplinary approach involving psychologists and social workers as core members of the care team. The following chapter will provide an update on the psychosocial literature in pediatric IBD from the previous chapter on the topic written in 2017 by Drs. Bonney Reed-Knight, Laura Mackner, and Wallace Crandall [1]. Several psychological aspects of IBD will be reviewed, including health-related quality of life, pain and symptom management, emotional functioning, social functioning, academic functioning, body image, family functioning, adherence and self-management, and health behaviors (e.g., physical activity, sleep, and substance use). Evidence-based efforts to address psychosocial aspects of IBD will also be reviewed, and recommendations for future research and intervention will be provided.

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Health-Related Quality of Life

Health-related quality of life is a critical aspect of psychosocial functioning in pediatric IBD and is also the most well examined due to the rigorous development of both general and disease-specific measures (e.g., PedsQL, IMPACT-III [2]) and robust evidence of associations with demographic characteristics and disease activity in addition to anxiety, depressive symptoms [3], social functioning, school functioning, family conflict, poor self-image, and suboptimal medication adherence [4, 5]. Emerging research continues to confirm that increased psychosocial difficulties (e.g., distress and pain catastrophizing [6], illness perceptions, anxiety, and depressive symptoms [7]), gastrointestinal symptoms [8], and disease severity are associated with poorer health-related quality of life [9–11].

Findings from a recent study suggest that disease activity may be the main correlate of quality of life in youth with IBD, with extra-intestinal manifestations (e.g., musculoskeletal pain, liver disease) associated with even more impaired quality of life [12]. However, this study was cross-sectional and longitudinal research examining health-related quality of life in pediatric IBD is limited. One study confirmed that this association may hold over time and found that health-related quality of life at baseline, disease activity at baseline, and changes in disease activity predicted changes in health-related quality of life over time [13]. An additional longitudi-

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nal study found that changes in disease activity and health-related quality of life may be also assessed via change in other patient-reported outcomes, including the PROMIS pediatric measures of anxiety, depressive symptoms, pain interference, fatigue, and peer relationships [14].

Pain and Symptom Management

Abdominal pain is a primary, prevalent symptom of pediatric IBD, yet literature examining the psychosocial correlates of this construct is relatively limited. Pain is most often associated with active disease, but it can also be present during periods of clinical remission. A recent systematic review concluded that several psychosocial factors are associated with pain in pediatric IBD [15]. Given that pain can also be heavily associated with functional disability and reduced health-related quality of life across youth with chronic medical conditions, it is critical that pain be considered as a component of psychosocial functioning in pediatric IBD. Most adolescents report abdominal pain regardless of disease activity, females reported abdominal pain more often than males, and abdominal pain is significantly associated with poorer health-related quality of life and increased activity limitations [15, 16]. Although pain may significantly decrease during the first year after diagnosis, it is important for providers to recognize risk factors for increased pain and the impact of pain on the child or adolescent's overall well-being [17].

Pain catastrophizing, or the tendency to magnify or exaggerate the threat or seriousness of pain, has also been shown to predict increased functional disability in youth with IBD [18]. Additionally, coping abilities, anxiety, depression, and beliefs about what symptoms might mean (e.g., "My stomachaches mean I'm really sick") were strongly associated with increased symptom reporting and not related to disease severity [19]. The unpredictable nature of the disease course and the experience of pain and IBD symptoms can bring about psychological distress in children and adolescents in the form of anxiety and depression, which in turn can lead to increased reporting of IBD symptoms and related functional disability [5]. Given that treatment decisions are often in part based on symptom reporting, it is also important to consider the impact of psychosocial functioning when assessing pain and symptoms in pediatric IBD.

Social Functioning and Peer Relationships

A diagnosis of IBD during childhood or adolescence can significantly affect social functioning, including spending time with friends and maintaining friendships. Friendships are critical for normative adolescent development and may be challenging to develop and maintain for youth with IBD due to discomfort around disclosing their diagnosis and symptoms [20, 21], missing out on activities due to dietary restrictions or fatigue and worrying that their friends just "feel sorry for them" [22]. A study examining belongingness found that youth with IBD who perceive that others are stigmatizing their illness report less social belongingness, which may have implications for increased depressive symptoms [23]. However, positive social support may ameliorate the effects of peer victimization in this population [24]. Therefore, youth with IBD may benefit from cognitive behavioral treatments that address perceived stigma and belongingness and promote peer relationships to support social functioning.

Youth with IBD often seek peer support from other youth with IBD. Online support groups are increasingly popular with adolescents and young adults seeking this type of peer support [25]. A recent study examined how young people with IBD utilize online support groups (e.g., sharing personal experiences, sharing information about IBD [26]); however, data do not yet exist on how participation in these groups may affect psychosocial outcomes.

Camps for youth with IBD are available across the country and can be another way for youth with IBD to meet one another and access social support. Research suggests the benefits of camp include improvements in health-related quality of life, social functioning [27], and overall psychosocial adjustment [28]. Focus groups suggest that peer mentoring may also be another way by which youth with IBD can access social support from other patients. Findings from these groups suggest that youth with IBD are seeking support, role models, and information/education from their peers [29].

Academic Functioning

School functioning includes academic performance, school attendance, educational attainment, and psychosocial functioning in the school setting, and children and adolescents with IBD are at risk for poor school functioning [30, 31]. Several studies suggest that school functioning is more consistently predicted by demographic and psychosocial factors. Specifically, older age, socioeconomic status, parent marital status, and mental health diagnoses have all been associated with poorer aspects of school functioning [32–35].

The majority of studies in this area have focused on school attendance, with most suggesting that youth with IBD have significantly more absences from school compared to healthy peers [30, 32, 36, 37]. Increased school absences have been associated with internalizing problems (e.g., anxiety, depression) [32], as well as concerns with not feeling well at school, not having access to bathrooms, not being able to keep up with assignments, and their teachers' understanding of IBD

[35]. Despite increased absences, there appear to be no differences in educational attainment [34], academic performance [33], or other aspects of school functioning [32] when compared to healthy peers. This discrepancy may be due to increased rates of special education supports, including Individualized Education Plans or 504 plans. These supports offer accommodations for youth with chronic medical conditions, including additional time to complete assignments. Common accommodations for youth with IBD may include "any time" bathroom passes, a place to rest during the day if needed, access to medication, and access to snacks or water throughout the day, among others [38]. Children with IBD and their families often require support from the medical team in establishing these plans with their school systems. Accommodations provided may promote academic success both in elementary and high school and may also promote success in higher education as well [39].

The transition to and experience in college is also challenging for adolescents and young adults with IBD, especially since this transition may often involve moving away from home or transitioning to another medical team. Several elements of the college experience pose unique challenges to those with IBD (e.g., bathroom access, dining options, medication storage) [40]. College students with IBD reported greater difficulty adjusting to college compared to healthy peers. College adjustment, which consists of academic functioning, social adjustment, emotional adjustment, and school attachment, is not only linked with success during college (e.g., retention) but also graduation rates and even future economic success. Poorer college adjustment in young adults with IBD has been associated with poorer health-related quality of life [41, 42]. Class attendance is lower for older college students with more severe disease as well [42]. Although most college students with IBD report average college adjustment, one study indicated that nearly half of students reported social-emotional adjustment to college within the very low to low range, and reported that having IBD impacted their choice of college [39]. College-bound youth with IBD may benefit from support from their medical team, school counselors, disability support services, and other psychosocial support during the college application process to avoid inappropriately perceiving their IBD as a limiting factor [39]. Providers can also be helpful with putting plans in place to support adjustment to college and providing resources for how to navigate the college experience while still best managing their IBD [40, 43].

Body Image

Body image is a significant concern for children and adolescents with IBD, especially with respect to growth, development, and changes in weight due to disease processes or treatment (e.g., steroids). Since the previous version of this chapter, two studies have examined body image dissatisfaction: one utilized an item from the IMPACT-III (e.g., "I look awful", "I look bad") and another administered the Adapted Satisfaction with Appearance questionnaire. Across both studies, patients with body dissatisfaction were older, reported more active disease, and reported greater depressive symptoms [44, 45]. Body image has been examined in adults with IBD as well as with a recent systematic review suggesting female gender, older age, fatigue, disease activity, and steroid use were most commonly associated with body image dissatisfaction [45]. Given that body image is so closely related to overall health-related quality of life, interventions designed to improve health-related quality of life should include aspects related to improving body image.

Emotional Functioning

Adjustment to and coping with a diagnosis of pediatric IBD can be difficult for both youth and their parents. A recent qualitative study with patients and their parents identified several challenges related to their IBD diagnosis, including the unpredictable nature of the disease, a disrupted sense of normalcy, and increased difficulties with treatment decisions, managing relationships, and life transitions [46]. They reported coping through social support, maintaining a positive attitude, behavioral strategies for managing emotions (e.g., deep breathing), and maintaining confidence in their medical team [46]. Emerging research has also examined specific aspects of adjustment in youth with IBD and their parents, specifically illness uncertainty and illness intrusiveness which have both been associated with youth and parent overall psychological adjustment [47].

Youth with IBD exhibit higher rates of anxiety and depressive disorders compared to both healthy youth and youth with other chronic medical conditions [4, 48]. Recent prevalence rates drawn from a systematic review suggest 16.4% of youth with IBD report anxiety symptoms and 4.2% report anxiety disorders. 15% of youth with IBD report depressive symptoms and 3.4% report depressive disorders [49]. Findings have been mixed regarding factors influencing elevated anxiety and depressive symptoms: one study indicated that perceived functional disability was the primary influence [50], while others cite demographic factors such as disease severity, lower socioeconomic status, corticosteroid treatment, parent stress, and older age at diagnosis [51]. Since emotional functioning can impact pain, sleep, substance use, adherence, and negative illness perceptions [51], both anxiety and depression have been studied extensively in pediatric IBD.

Anxiety symptoms reported by youth with IBD frequently are around school anxiety, separation anxiety, and general anxiety [52]. Emerging research in anxiety in pediatric IBD has incorporated the IBD-Specific Anxiety Scale [53] which measures how often respondents worry about using the bathroom, experiencing pain, medication taking, medical procedures, and IBD symptoms. Notably, IBD-specific anxiety is associated with overall poorer psychosocial functioning and increased healthcare utilization [54, 55], yet patient health communication may explain the link between anxiety and symptoms in this population [56]. Therefore, improved patient–provider communication about aspects of IBD-specific anxiety (e.g., symptoms) may alleviate some anxiety symptoms and interventions to manage anxiety in this population may require tailoring to include aspects of both IBD-specific anxiety and generalized anxiety depending on the patient's needs [57].

Depressive symptoms are very commonly reported by youth with IBD; however, most youth with IBD do not experience clinical levels of depressive symptoms [58]. One of the largest studies of youth with IBD and depression found evidence for three subtypes of depressive symptomology: 75% fell within a mild subtype characterized by low depressive symptoms and highest quality of life; 19% fell within a somatic subtype characterized by fatigue, changes in appetite, loss of interest in activities, and depressed mood with highest disease activity; and 6% fell within a cognitive subtype characterized by the highest depressive symptoms, anxiety, and functional IBD symptoms [59]. Youth with IBD may be more at risk for experiencing depressive symptoms due to a combination of neurobiological (e.g., inflammation, pain, sleep disturbances) and psychosocial factors (e.g., illness perception, illness-related stressors) [60]. Increased depressive symptoms have been associated with disease severity [61], symptoms and functional disability [19], how family stress contributes to pain-related distress [62], nonadherence and risk of relapse [63], increased length of inpatient hospital stays [64], and overall health-related quality of life [7, 65]. However, many symptoms of depression are confounded with common symptoms of IBD, including changes in appetite, changes in sleep, and low energy which may make it difficult for providers to determine whether symptoms can be addressed via psychosocial intervention, medical intervention, or a combination of both. Multi-disciplinary teams, including behavioral health providers, are equipped to assess for comorbid depressive symptoms and support adaptive coping with both IBD and depressive symptoms [66]. As such, guidelines have recently been developed around screening all children and adolescents with IBD for depression starting at age 12 [67].

Family Functioning

Family functioning, or the dynamics within the family environment, have been related to both parent and child health and psychosocial outcomes in pediatric IBD [68]. Suboptimal family functioning may be characterized by difficulties with family communication, family problem-solving, delineating roles and responsibilities within the family, and family conflict, all of which have been reported by families of youth with IBD [69, 70]. These difficulties may arise throughout the disease course and the child's development. For example, a flare-up or introduction of a new treatment regimen may disrupt existing routines within the family, which may lead to family dysfunction. Additionally, as a child develops into an adolescent and subsequently into a young adult, their desire for independence may increase and they may want to take more ownership over their IBD treatment, which may be difficult for families to navigate [71]. Broadly, family functioning has been found to be an important predictor of both parent and child health-related quality of life [3]. Family functioning can also be affected by the child's behavioral difficulties [70], emotional symptoms [72], and pain [73], or fatigue.

Parent functioning is a critical component of family functioning and is often found to be driven by their child's disease course [74]. Parenting stress has been most commonly examined with the Pediatric Inventory for Parents, which assesses both the frequency and intensity of a variety of stressors that come up when caring for a child with chronic medical condition [75]. It is critical to assess parenting stress in caregivers of youth with IBD since it has the potential to negatively affect disease management, which can result in poorer health outcomes [75] as well as child depressive symptoms [72, 76] and poorer child health-related quality of life [74]. Greater parenting stress has also been associated with increased disease severity; however, most studies examining this are cross-sectional, suggesting that this relationship may be bidirectional [72, 74].

Adherence and Self-Management

Medication nonadherence rates vary widely, ranging from 2 to 93% in pediatric IBD [77] with poorer adherence associated with negative health outcomes (e.g., treatment escalation [78]) and increased healthcare costs [79]. Many studies have documented the association between poorer psychosocial functioning and poorer medication adherence in pediatric IBD [63, 80, 81]. Managing pediatric IBD is complex and may include any combination of daily oral medications, weekly or bimonthly subcutaneous injections, or periodic

infusions in addition to surgical procedures and various healthcare maintenance tasks (e.g., routine lab work, immunizations, bone density scans) [63]. This complexity can put a strain on various aspects of psychosocial and behavioral functioning [82], including health-related quality of life [83], emotional functioning (e.g., anxiety, depression) [81], social functioning (e.g., missed activities), academic functioning (e.g., missed school days), and family functioning (e.g., family conflict) [84]. Given that adherence can also be influenced by psychosocial functioning, interventions to improve aspects of psychosocial functioning closely linked to adherence, such as motivational interviewing, problem-solving skills training, and family-based interventions are likely to also improve adherence [85].

Clinical practice around adherence monitoring varies widely; 25% of responding pediatric GI providers reported using a screening tool, approximately half cited using objective measures (e.g., lab values), and most reported using patient and caregiver reports [86]. The most commonly identified barriers to adherence include forgetting, interference with activities, and being away from home [77, 87], and both cross-sectional and longitudinal research suggest that barriers to adherence impact medication adherence [88, 89]. Therefore, adherence promotion interventions in pediatric IBD have primarily utilized a problem-solving approach that helps patients and their families first identify barriers to adherence and work to test various solutions to those barriers [90], while others have taken a multicomponent approach by also incorporating education, behavior modification, and family functioning [91].

Self-Efficacy and Disease Knowledge

Self-efficacy and disease knowledge are important skills for the long-term management of IBD. Self-efficacy refers to one's belief in their capacity to perform behaviors that are needed to meet a goal, which is why this concept has been examined with respect to disease management in pediatric IBD. The IBD Self-Efficacy Scale for Adolescents and Young Adults (IBDSES-A) is a validated, disease-specific measure that assesses disease management self-efficacy [92], and several measures have been used to assess disease knowledge with the most recently validated being the Inflammatory Bowel Disease Knowledge Inventory Device 2 (IBD-KID2) [93]. Notably, both self-efficacy and disease knowledge are suboptimal in adolescents with IBD [94, 95]. Specific areas of knowledge deficits include medications (e.g., dose, side effects, refill frequency), appointment management (e.g., frequency, how to schedule), and the effects of substance use (e.g., smoking, drugs, and alcohol) [94, 95]. These constructs are related with greater self-efficacy being linked to greater disease knowledge [95]; therefore, as adolescents with IBD become more responsible for their care and prepare to transition to adult care, they may require interventions to promote self-efficacy and disease knowledge, such as problem-solving skills training and increased involvement in their clinic visits and treatment decisions [95].

Health Behaviors

In addition to medication taking, there are several other health behaviors that are impacted by psychosocial functioning in youth with IBD. The three that have garnered the most attention in recent years have been sleep, physical activity, and substance use. Broadly, sleep is critical for both physical and psychosocial health for all children and adolescents; however, youth with IBD often report sleep difficulties and fatigue. Those who report difficulty sleeping also report increased anxiety, depression, somatic complaints, and aggressive behavior [96]. Impaired sleep has also been associated with active disease in multiple studies, suggesting an association between sleep disturbances and inflammatory pathways [97, 98]. Adolescents endorse that symptoms interfere with their sleep (e.g., waking to use the bathroom, abdominal pain), resulting in fatigue [99] which is a common symptom reported by youth with IBD. Yet, improved health-related quality of life is associated with better sleep [100]. Therefore, sleep ought to be routinely assessed and considered in the context of disease activity. Whether sleep is affected by symptoms or psychosocial functioning, youth with IBD may benefit from behavioral sleep intervention to increase overall sleep quality.

Physical activity is another health behavior that may impact health outcomes in pediatric IBD and has been linked with psychosocial functioning. Although one study suggests that most patients continued to exercise and participate in sports after their IBD diagnosis [101], several studies report that most children and adolescents report that their IBD has interfered with their participation in sports [102, 103] and physical activity [104, 105]. This can result in poorer exercise capacity [106], which may impede future physical activity endeavors. Decreased physical activity may not only be a result of pain or fatigue [105] but may also be associated with disease symptoms [104] and body image concerns [103]. Addressing these barriers to sports participation and physical activity in general may help promote this health behavior in youth with IBD.

Substance use, including alcohol use, tobacco use, and marijuana use, is a developmentally normative adolescent behavior, yet has been understudied in adolescents with IBD. Given the rise in the use or cannabis to manage IBD, medical providers are encouraged to recognize the perceived

benefits (e.g., symptom reduction) and understand the potential detrimental effects and risks of its use [107–109]. Prevalence of marijuana use appears to be particularly high in young adults with IBD with most not disclosing their use to their medical team and approximately half without knowledge of adverse effects [110]. Broadly, adolescents and young adults with chronic illnesses use substances at similar or greater rates than their healthy peers [111, 112], and may experience more adverse health outcomes as a result. In addition to marijuana use, alcohol use is also common in adolescents with chronic medical conditions and was found to be associated with poorer medication adherence in a study that included youth with IBD [113]. Adolescents and young adults with IBD endorsing multi-substance use in the last 30 days were older, more likely to be male, more likely to have active disease, and more likely to have been hospitalized in the past year compared to those who abstained [114]. Additionally, they reported greater barriers to adherence, lower disease management self-efficacy, and poorer health-related quality of life [114]. Although this group likely represents a small percentage of adolescents and young adults with IBD, it is notable that substance use can be associated with health and psychosocial outcomes.

Psychotherapy and Other Resources

Increased recognition of the psychosocial impact of pediatric IBD has led to increased resources in pediatric IBD centers to provide multi-disciplinary care to children and their families [115]. These efforts have included additional personnel (e.g., psychologists, social workers) and most recently, implementation of mental health screenings as a standard of care [116]. One recently published approach describes this integrated model as well as data collected from newly diagnosed patients with IBD. Recommendations include routine surveillance via developmentally appropriate psychosocial data collection to inform referrals and close ongoing collaboration between psychosocial providers and the medical team to address the biological, psychological, and social needs that may impact treatment [117, 118]. Screening efforts examining health-related quality of life have shown associations with healthcare utilization such that those reporting poorer health-related quality of life had more IBD-related hospitalizations, clinic visits, emergency room visits, telephone contacts, and psychosocial referrals [119]. Annual depression screening is recommended for all adolescents 12 and older as well [67].

Cognitive behavioral interventions continue to be effective for addressing anxiety and depression. Pilot data suggest that youth with comorbid IBD and anxiety benefited from a 13-session cognitive behavioral treatment program compared to those receiving standard care with significant and sustained reductions in IBD-specific anxiety [120]. Cognitive behavioral therapy has also been examined in adolescents with IBD and comorbid subclinical anxiety and depressive symptoms; however, disease-specific cognitive behavioral therapy did not appear to perform better than standard medical care in reducing these symptoms [121, 122] or improving medical outcomes (e.g., relapse) [123]. Therefore, cognitive behavioral interventions are likely most appropriate for youth with IBD who meet full diagnostic criteria for anxiety or depression and other, less intensive interventions may be more appropriate for those reporting subclinical psychological symptoms.

Mind–body interventions have also emerged as a potentially effective adjunct to the standard medical treatment for IBD. These interventions include not only psychotherapy as described above but also relaxation, mindfulness, biofeedback, yoga, and hypnosis. These therapies may be especially helpful for those in IBD who experience associated symptoms consistent with irritable bowel syndrome (IBS) (e.g., when a patient in clinical remission is reporting significant symptoms) due to the bidirectional brain-gut connection [124]. Preliminary evidence suggests that relaxation and mindfulness techniques are feasible [125, 126] and can improve psychological functioning in adults with IBD, and that heart rate variability biofeedback and yoga may help with pain management and improve anxiety [127]. Many adolescents report using mind–body techniques (e.g., relaxation, guided imagery, meditation) to manage their symptoms, and those with more severe disease and poorer health-related quality of life were more willing to consider using relaxation or meditation in the future [128].

As digital health and mHealth tools are becoming more widely used by adolescents and young adults with chronic illnesses, several mobile apps have been developed to assist with adherence and self-management as well as other psychosocial aspects of pediatric IBD (e.g., pain and symptom tracking, coping, tracking health behaviors). One existing review of mobile apps for IBD self-management assessed 26 apps; however, the majority do not have professional medical involvement and therefore do not include evidence-based guidelines [129]. It is important that future development of these tools include medical professionals, psychosocial professionals, and patients in the design and development process.

Summary

Overall, children and adolescents with IBD experience psychological difficulties across a variety of domains with research suggesting significant risk for impairments in health-related quality of life, increased anxiety and depressive symptoms, school absenteeism, parenting stress, and

suboptimal adherence and self-management. Despite this association between psychological issues and IBD, research examining psychotherapy and the use of psychopharmacologic treatment is limited in pediatrics [130]. This may in part be due to a disruption in psychosocial development; a recent study suggested that youth with IBD achieved fewer social and psychosexual developmental milestones compared to healthy peers [131]. This can have important implications for adult functioning, especially related to work-related productivity and disability status [132, 133].

Given the prevalence of psychosocial challenges in this population, providers are increasingly recognizing the value of routine psychosocial assessment and the inclusion of behavioral health providers (e.g., psychologists, social workers) in routine clinical care [115]. Yet, a recent survey suggests there are still significant gaps in the psychosocial care of youth with IBD. Specifically, 30–40% of youth surveyed indicated family/peer relationships, school/extracurricular activities, and mood were not addressed by their healthcare team. Many also reported that substance use, sexual health, and body image were also not discussed [134]. A multidisciplinary approach to treating pediatric IBD will allow for these psychosocial issues to be addressed, which will have a positive impact on health outcomes broadly.

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Measurement of Quality of Life in Pediatric Inflammatory Bowel Disease

51

Amy Grant and Anthony Otley

Introduction

The burden of disease imposed on children and youth by Crohn disease (CD) and ulcerative colitis (UC) may be considerable, as manifested by clinical parameters, such as symptoms, number of hospitalizations, growth retardation, and frequent need for surgery [1–5]. However, increasingly the psychosocial burden of inflammatory bowel disease (IBD) on young patients is being considered alongside these important clinical parameters [6–8]. One means of assessing the psychosocial burden is through evaluation of health-related quality of life (HRQOL). The purpose of this chapter is to provide the reader with an understanding of the concept of HRQOL, the approaches to its measurement in children, more specifically in pediatric patients with IBD. Finally the gaps in knowledge of HRQOL in pediatric IBD and the future directions for research in this area will be discussed.

Quality of Life: Concepts/Definitions

In 1948 the World Health Organization defined health as being not only the absence of disease and infirmity but also the presence of physical, mental, and social well-being [9]. Since that time quality-of-life issues have been increasingly recognized as important parameters in determining health status. A single definition of quality of life is difficult to find [10, 11]. Without a clear definition, multiple interpretations of what quality of life "is" have evolved. This has led to the development of a number of different measures which assess varying aspects of quality of life. This failure to achieve a unifying definition has hampered the ability to make comparisons between quality-of-life outcomes. Most current definitions include the concept of the multidimensional nature of quality of life and incorporate domains of social, physical, and emotional functioning of the individual [12]. With HRQOL one is attempting to ascertain the impact of the disease, concentrating on the health-related aspects of quality of life. Quality-of-life outcomes have been conceptualized by viewing the domains in two dimensions: objective assessments of functioning or health status (the *y* axis in Fig. 51.1) and more subjective perceptions of health (the *x* axis) [13]. While the objective assessment is integral for describing an individual's degree of health, the individual's subjective perceptions and expectations modify the objective assessment into the real quality of life experienced (or Q, as expressed in Fig. 51.1 by the intersection of the *x* and *y* coordinates). Because perceptions and expectations may vary from individual to individual, two people with the same health status may have very different qualities of life [13].

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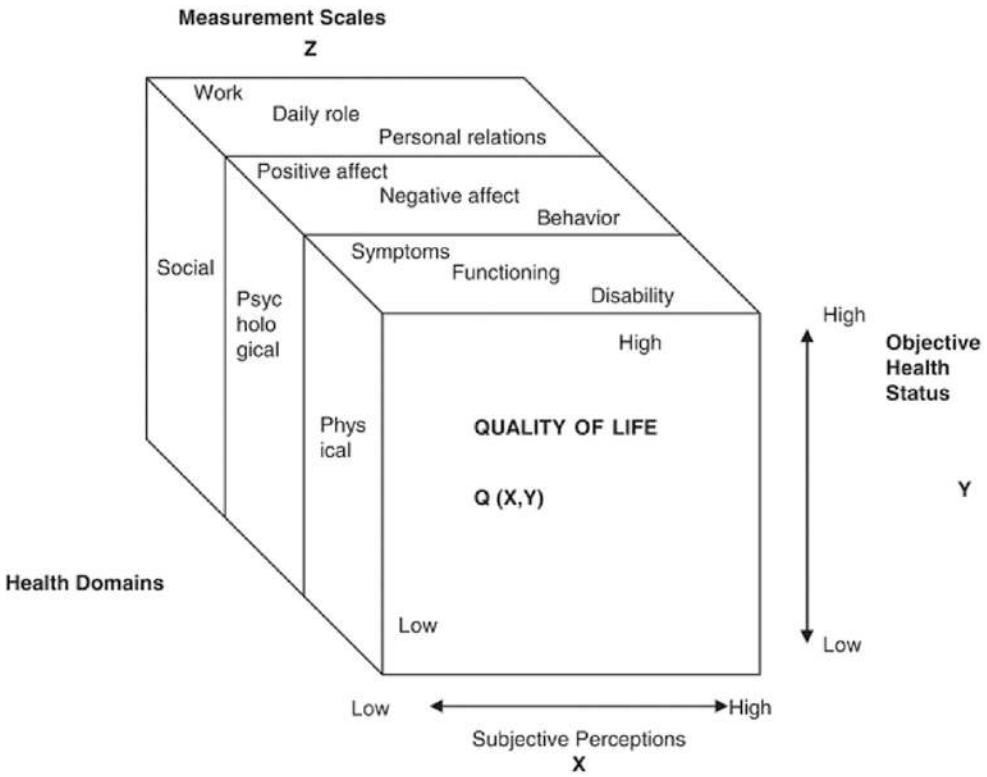

Fig. 51.1 Conceptual scheme of the domains and variables involved in a quality-of-life assessment. The *x* axis represents subjective perceptions of health, the *y* axis represents objective health status, the coordinates Q(*X, Y*) represent the actual quality of life, and *Z* represents the measurement of the actual quality of life associated with a specific component (i.e., positive affect) or domain (i.e., the psychological domain) (Adapted from Testa and Simonson [13])

Why Measure Health-Related Quality of Life?

Over the past several decades, a dramatic increase in the employment of quality-of-life outcome measures has been evident in the adult and pediatric clinical trials' literature. In part, this is a result of the trend to expand the traditionally selected, "objective" outcome measures of morbidity (i.e., days hospitalized, number of infections) and/or mortality to include assessment of the emotional and functional status of participants. The single-minded focus on mortality and morbidity as outcomes in health is being steadily superseded by broader considerations of quality of life. This broader consideration is currently being espoused by the Food and Drug Administration (FDA) which is now mandating inclusion of patient-reported outcomes (PROs) alongside more objective measures (i.e., endoscopic evaluation) in the design of clinical trials to evaluate new drug therapies in IBD [14–16].

One of the first stages in evaluating a new measure is to determine the "phenomenon of interest," to define the conceptual framework underlying the measure [17]. In IBD the primary outcome measure traditionally selected for use in clinical trials has been a multi-item disease activity index [18], such as the pediatric Crohn disease activity index (PCDAI) [19, 20]. However, measures, such as the PCDAI, have concerns around feasibility (i.e., difficulty collecting all required laboratory data) [21], short-term responsiveness to change in clinical status based on the inclusion of questions that do not show short-term change (i.e., height velocity) [22], and construct validity given the low correlation with objective markers of inflammation or fecal calprotectin levels [23, 24]. For disease activity measures, the concept is to use the degree of intestinal inflammatory activity as a surrogate measure of the patient's health status. This framework is based heavily on physician perceptions, with little input about the patient's perception of the disease on their health status [18]. There is now consensus around a desire to move away from sole reliance on objective measures of disease and to develop co-primary endpoints using concurrent endoscopic or less-invasive objective measures (e.g., MR enterography, fecal calprotectin) and quality of life assessment [15]. Use of quality of life addresses this deficiency of focusing only on physician perceptions. Because existing measures of disease activity are not sensitive enough to assess the full impact of the disorder, HRQOL measures have been developed to do this [25].

Approaches to Health-Related Quality-of-Life Measurement

The ideal assessment of HRQOL would involve lengthy, detailed interviews between the patient and an independent interviewer, an impractical procedure in day-to-day clinical care or a clinical trial. A self-administered questionnaire that is easy to understand, complete, and covers all the important aspects of the patient's HRQOL is a more attractive means of

assessing HRQOL. The questionnaire should include all relevant elements or "domains," of HRQOL. These domains may cover physical, functional, emotional, and cognitive well-being and, in case of disease, disease-related aspects. Each domain consists of a number of "dimensions" or questions. A balance needs to be struck between including a sufficient number of dimensions so that a complete assessment of HRQOL can be made, while being careful not to create a questionnaire so lengthy that it becomes burdensome for the respondent to complete. The advantage of combining questions into domains is that interventions can be directed at these domains, attempting to ameliorate that aspect of HRQOL.

There are two basic types of HRQOL measures: generic and disease specific. A generic measure is designed to measure all aspects of health and related quality of life and can include items and domains that are broadly applicable to various diseases and populations. Although disease-specific questionnaires include some of these same issues, they also address issues specific to the particular disease. Disease-specific questionnaires are more sensitive to disease-related changes in patients' health status than generic questionnaires.

Generic measures can take several forms, from instruments with global assessments using single indicators (e.g., "What is the quality of your life on a scale of 1–10?"), utilities (e.g., standard gamble, time trade-off, Child Health Utility 9D CHU) [26], or multi-item measures which give a health profile, such as the Pediatric Quality of Life Inventory (PedsQL) [27–29]. One of the advantages of a generic measure is its generalizability. Generic measures permit comparisons between "healthy populations" and different disease groups, interventions, and demographic and cultural groups [30, 31]. Generic questionnaires, such as the Medical Outcomes Study Short Form (SF-36) for adults [31, 32] or the Child Health Questionnaire for children [33], have been applied to groups with no defined illness, allowing normative values to be generated for these healthy populations. When such normative data are available, it offers the potential to make comparisons as to burden of illness between populations affected with and without chronic illness [34]. The chief disadvantage to generic measures is their insensitivity to important clinical change. This stems from their inherent lack of specificity, a result of the inclusion of many items which may not be relevant to the individual patient with an isolated disease. This can be addressed by the use of a disease-specific measure that focuses on concerns relevant to a particular patient group. "Specificity" is achieved by the inclusion of dimensions and domains which are targeted to the disease in question. For example, in the Pediatric Asthma Quality of Life Questionnaire, a measure developed by Juniper et al. [35], the symptom domain includes questions, such as "How much did tightness in your chest bother you during the past week?" and "How often did your asthma wake you up during the night in the past week?" This specificity makes the questionnaire more sensitive to important clinical change in asthma, which is an important criterion when choosing an outcome measure in a clinical trial. In the adult literature, disease-specific questionnaires have been developed for a number of diseases, including IBD [36], rheumatoid arthritis [37], breast cancer [38, 39], and asthma [40, 41]. Increasingly disease-specific questionnaires have been developed for use in the pediatric population as well [40, 42–48].

Any measurement tool should be tested prior to use to ensure it fulfills the fundamental psychometric characteristics of a good measure. A HRQOL questionnaire would be one example of a measurement tool. The psychometric characteristics to be assessed include sensibility, reliability, validity, and responsiveness to change (Table 51.1).

Table 51.1 Four fundamental measurement characteristics to be assessed of any measure

Measurement characteristic	Definition	Examples of what to look for
Sensibility	Do the components of the instrument make sense and is it feasible to administer and complete?	• Readability statistics • Number of questions left blank • Inappropriate inclusions or important omissions of items
Reliability	Are similar scores obtained on subsequent assessments if no change in disease status has occurred?	• Test–retest reliability most commonly reported (either as intraclass correlation coefficient or Kappa value) • Instruments with good reliability require smaller sample sizes
Validity	Is the instrument measuring what it was intended to measure?	• Criterion validity testing when a gold standard exists to compare to • Construct validity testing when no gold standard exists, and hypotheses are generated and tested on how the instrument would be expected to function
Responsiveness	Does the instrument score change with a change in disease status?	• No one accepted way to evaluate • Want to know over what time period an instrument is responsive (i.e., short term, 4 weeks, or longer term, 6 months)
Minimal Importance Difference	What is the smallest difference in score that is perceived as important, that could lead to a change in patient management or outcomes?	• Can be evaluated using multiple approaches (anchor based or distribution based) • Anchor-based methods may be more conservative • Distribution-based methods do not take into account patient perspectives

Sensibility is a measurement characteristic with many aspects and for a questionnaire should include assessment of feasibility for both the person administering and completing the questionnaire (i.e., time to complete and mark, readability), as well as a critical review of the appropriateness of items included or omitted. *Reliability* looks at whether a measure has reproducibility, (i.e., if the same result is obtained when the same (unchanged) entity is measured again) [30]. For example, assuming that HRQOL is influenced by disease activity or medication use, one would expect a reliable HRQOL questionnaire to show very similar scores when given to a patient at time one and again at time two if no interval change in disease activity or medication has occurred. *Validity* is concerned with whether a questionnaire actually measures what it is intended to measure. Ideally one would like to measure the validity of an HRQOL measure comparing it with a gold standard. Unfortunately, HRQOL is a concept for which no gold standard exists. Thus, a process of construct validity testing must be carried out. This involves generating hypotheses, called constructs, and studying whether the measure acts as one would expect. The final characteristic, *responsiveness* to change, relates to the ability of the questionnaire to detect change over time, characteristics important for use in clinical settings. A very responsive HRQOL questionnaire should be able to detect even a small change in disease status. Last but not least is the importance of measuring not only the statistical difference in scores when there is a change in disease status as per responsiveness but also understanding the clinical significance of the change in HRQOL scores. This clinical or meaningful difference is represented methodologically by the "Minimal Important Difference," which measures the degree of change corresponding to a clinical change as perceived by a patient, physician or caregiver [49]. Both responsiveness and the related minimal importance difference characteristics are especially important in determining the sample size for studies in which HRQOL is a main outcome, as the expected amount of change determines how many participants are needed to show a statistically and/or clinically significant change.

Health-Related Quality-of-Life Assessment in Pediatrics

Making quality-of-life assessments in a pediatric population requires the awareness of several key methodological issues: whether to ask children directly [50, 51] and how to allow for varying developmental level and age [10, 52]. It is not always possible to obtain the child's assessment of their quality of life, whether due to age and/or developmental or disability limits to comprehension. In these instances a proxy is sought. The proxy reporter of the child's quality of life is most often their parent/caregiver but in some cases may be another individual, such as a teacher or physician [51]. The wide developmental spectrum seen across the pediatric age group can affect both children's perception of their own quality of life and the relationship between a child and proxy score. The quality of a child's self-report is highly dependent on their expressive and receptive language abilities [10]. As well, differences in time perception and memory related to their developmental stage will affect a child's ability to respond to questions based upon experiences during a specific time period [51]. Within a given culture, developmental tasks can vary by age such that some quality-of-life items may be appropriate for a specific age range but not for another. For example, perceptions on relationships with the opposite sex will vary with age. Other issues likely related to developmental age include position bias, the tendency to choose the first answer; acquiescence response bias, the tendency to agree with the interviewer; and limited understanding of negatively worded items [53].

When both a child and parent are able to complete an assessment of HRQOL, research has generally shown that proxies tend to have a low-to-moderate agreement [54] between child and parent HRQOL reports, while others have found moderate to high agreement. Despite differences in the degree of concordance across studies, most find greater concordance on more observable measures (e.g., physical well-being [54]) and lower concordance on more subjective measures (e.g., emotional well-being). Pantell et al. showed that parents and teachers agreed fairly well in reporting on child functioning but markedly less well for recent functional status, certain types of subjective feelings in regard to illness, information needs, emotional states [55], and family functioning [56]. Agreement among raters may differ as a result of factors, such as child sex, age, condition [57], as well as both child psychosocial [58, 59], and parent psychosocial comorbidities [60], such as anxiety, depression, and post-traumatic stress related to a child's condition.

Realizing that the degree to which there is agreement for proxy ratings in some areas of response varies, it is unclear to what extent differences in response pattern are due to limitations in abstract reasoning, differential influences from demographic or psychosocial influences, or true differences in perspective or opinion. Further research should seek to disentangle these effects in order to appropriately identify young patients who may benefit from interventions to improve HRQOL.

Health-Related Quality-of-Life Assessment in Inflammatory Bowel Disease: Adult IBD Perspective

Measurement of HRQOL in IBD has received a lot of attention over the several decades, with the result that there are now validated outcome measures that have been used in clinical trials or cross-sectional studies (Table 51.2). Early attempts at assessing HRQOL in IBD, however, were hampered by a number of methodological issues: healthy or medical comparison groups were not used, studies were done by retrospective analyses [61, 62], non-standardized instruments [62–65] and unskilled interviewers were used to obtain the data, and insensitive outcome factors (i.e., ability to work) [61, 65, 66] were used as measures of HRQOL.

The main disease-specific HRQOL instrument currently used is the Inflammatory Bowel Disease Questionnaire (IBDQ) which was developed for IBD patients and to be used in clinical trials [36, 67, 68]. It is a 32-item questionnaire, consisting of 30 items chosen most frequently and rated most important by adult IBD patients and two items added based on feedback obtained by clinicians who had practices heavily weighted with IBD patients. The four domains covered in IBDQ include bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). Responses are based on a seven-point Likert scale in which 1 represents the worst function and 7 represents the best function. Thus, the higher the score, the better the quality of life. The questionnaire can be self-administered [69, 70] and takes approximately 15 min to complete. The IBDQ has undergone extensive testing of its measurement characteristics, including several randomized controlled trials [67, 71, 72] and cross-sectional studies [73]. From a large multicentered Canadian trial of maintenance therapy, an intraclass correlation coefficient of 0.70 was calculated for test–retest reliability in 280 patients with stable disease over an 8-week period [67]. Responsiveness testing using a modified responsiveness index developed by Guyatt et al. indicated that all IBDQ indices reflected deterioration for those patients whose condition worsened during the study [74]. Construct validity testing in the original publication of the measure, and with subsequent use of the IBDQ in trials, has shown it to be a valid measure of HRQOL in adult patients with IBD. This

Table 51.2 Disease-specific IBD health-related quality of life measures (adult and pediatric)

Name	Format	Scales	Comments
Adult Inflammatory Bowel Disease Questionnaire (IBDQ)	32-item Likert scale Interview format	Bowel symptoms, systemic symptoms, social function, emotional function	Well standardized; designed for clinical trials; developed on "sick" patients—GI referrals and inpatients
Modified IBDQ	36-item Likert scale Self-administered	Bowel symptoms, systemic symptoms, social function, emotional function, functional impairment	Derived from IBDQ; developed on "well" patients—local chapter of NFIC
Cleveland Clinic Questionnaire	47-item Likert scale Interview format	Functional/economic, social/recreational, affect/life in general, medical/symptoms	Correlates with SIP; developed on UC/CD surgical/non-surgical groups; quality-of-life index distinguishes groups
Rating Form of IBD Patient Concerns (RFPIC)	25-item visual analog scale Self-administered	Impact of disease, sexual intimacy, complications, body stigma	Correlates with SIP and SCL-90; developed on "well" patients—CCFA national sample
UC/CD Health Status Scales	9- or 10-item Likert scale Physician/patient scoring	Ulcerative colitis, Crohn disease	Standardized to healthcare use, function, psychological distress in CCFA national sample
Pediatric Computer-based animated questionnaire	35-item visual scale Children ages 5–11 years	30 generic questions, five disease specific (more detail not specified)	Only 16-patient pilot study reported to date Child does not have to read
PEDIBDQ	45-item Likert scale Children ages 8–18 years	Physical, emotional, and social	Reported in abstract form, with validation and reliability data
IMPACT	35-item Likert scale Self-administered Children ages 10–17 years	Bowel, emotional, functional, tests/treatments, systemic, body image (IMPACT-I, II); Well-being, emotional, social, body image (IMPACT III new domains)	Three versions (IMPACT-I, II, and III). Developed using several pediatric IBD cohorts; in use in clinical trials

Abbreviations used: *CCFA* Crohn and Colitis Foundation of America, *CD* Crohn disease, *CDAI* Crohn disease activity index, *GI* gastrointestinal, *NFIC* National Foundation for Ileitis and Colitis, *SCL-90* Symptom Checklist-90, *SIP* Sickness Impact Profile, *UC* ulcerative colitis
Adapted from Drossman [58]

measure has been shown to have strong correlation with patient, relative, and physician global ratings of HRQOL and discriminate between the groups of patients who did or did not require surgery [67]. Some researchers have expressed concern about the use of a single measure to describe the HRQOL for IBD, because of the frequently disparate nature of its component diseases, CD and UC [75]. For example, because CD can affect variable locations in the bowel, the range of symptoms can also vary greatly, with differences exacerbated by relapsing and remitting disease activity. This is compared with UC in which the bowel disease is limited to the colon. Given these differences, some researchers have suggested that a different or separate approach to HRQOL evaluation for these two diseases may be required. This issue was apparently not addressed in the development of the IBDQ [36, 67]. Given the increasing number of many available cross-culturally adapted versions of the IBDQ [76–83] and the development [84] and subsequent validation [85, 86] of the ten-item Short Inflammatory Bowel Disease Questionnaire (SIBDQ), it seems unlikely that other HRQOL measures for adult IBD patients will be developed, unless it is to target specific subgroups missed in the IBDQ item generation, such as patients with ileostomy.

Health-Related Quality-of-Life Assessment in Pediatric Inflammatory Bowel Disease

As is the case with pediatric quality-of-life assessment in general, consideration of quality-of-life issues in pediatric IBD has lagged behind that of the adult IBD cohort. The earliest semblances of quality-of-life inquiry were from a number of centers which reported the results of long-term follow-up or cross-sectional assessments of their pediatric IBD populations [2, 3, 87–93]. In many instances, rather than actually describing the quality of life, they were describing the functional status of the patients [87–89, 92, 93].

Goel et al. [87] and Lindquist et al. [89] did not use a formal measure to describe quality of life but rather, in their description of the current status [87] or clinical course [89] of the patients, included limitations on social activities, school attendance, or occupation as descriptors. Farmer and Michener [90, 91] developed a simple measure which provided three categories of quality of life: "Good—meaning ability to function in a nearly normal manner with minimal interference from the illness and its sequelae; Poor—indicated severe effect on life style, requiring medication and often frequent hospitalization; Fair—suboptimal but adequate functioning, i.e., chronic illness and partial disability." Patients were categorized based on interviews by trained personnel. The researchers acknowledged that their view of quality of life was a composite of several elements of the patient's life and that patients might experience varying degrees of quality of life over a long period of time. Patients were asked to consider the cumulative effect of the illness and treatment and to describe their current state of health. Farmer and Michener's long-term follow-up study of 522 patients (followed from 1955 to 1974) with onset of CD under age 21 found that approximately two-thirds of patients considered their functioning to be in the fair level, with only 6% rating their functioning as poor [90, 91]. Given the marked changes in management over the past five decades, it is unclear what relevance quality-of-life outcomes in such a cohort would have compared to a similar present-day cohort. More recently researchers have sought to assess quality of life in pediatric IBD using measures with domains which encompass a broader concept of quality of life [94–97]. MacPhee et al. [97] completed an assessment of 30 pediatric IBD patients using a number of generic psychological and quality-of-life questionnaires. Their study emphasized social supports and coping strategies. They used the Quality of Life for Adolescents and Parents questionnaire [98], a generic measure which gives a total satisfaction score with health status and similar scores for subscales.

Thomas et al. [94, 95] describe the early stages of development of a disease-specific quality-of-life questionnaire which they used to assess quality of life in their pediatric CD cohort. Focus group meetings were held with pediatric patients of ages from 8 to 17 years (two groups, 8–12 years and 12–17 years of age) to learn how their disease and its treatment affected their lives at school, at home, and with friends. An 88-item questionnaire was constructed based on the areas identified in the focus groups. The questionnaire contained six domains of HRQOL, including symptoms and treatment, social life, emotional state, family life, education, and future aspects. No data on validity, reliability, or sensibility were provided for this questionnaire [94, 95]. The questionnaire was used in one pilot study involving 16 children from one academic IBD program in England. Acknowledging the limitations of a small sample size, they found that CD appeared to most adversely affect the HRQOL of children as manifested through school absenteeism, fatigue limiting sports activities, and difficulties in taking holidays.

Moody et al. [96] studied quality of life in pediatric CD using a questionnaire they developed in conjunction with a British national lay committee of Crohn in Childhood Research Association (CICRA) members. Limited information is provided on the questionnaire's development, and its length and exact format are unclear from the published report [96]. Results from 64 valid questionnaires were received in a pilot study. The mean age of the children in this study was 14.1 ± 2.8 years (range 6–17 years). In this cohort 60% of the children reported prolonged absences from school, with a mean 3 ± 2.8 months' absence in the previous 12 months. Eighty percent of those who had taken examinations felt that their marks had suffered due to ill

health. Seventy percent of patients with CD were unable to participate in sports on a regular basis, 60% did not feel comfortable leaving their homes, and 50% did not feel they could play outside with their friends because of the illness. Forty percent of children also reported concerns about taking holidays and being able to have sleepovers at friends' homes. This study would suggest that CD has a major impact on the quality of life of pediatric patients. However, caution should be exercised in making these conclusions as there are several limitations of the published study. It is not clear if the questionnaire underwent any validity testing to ensure it was measuring what it intended to measure. Given the study design, in which a general mailing was sent to members of a society, there may be a strong response bias in favor of those whose quality of life is poor. As well, the authors do not tell us the number of questionnaires distributed, nor do they clarify the response rate.

Preliminary development of the Pediatric Inflammatory Bowel Disease Questionnaire (PEDIBDQ) for children and teens [99, 100] and a computer-based animated program to assess HRQOL for young children 5–11 years of age [101] have been reported in abstract or manuscript form. Further work has not been reported using these questionnaires, however. In the mid-1990s, researchers at the Hospital for Sick Children in Toronto, Canada, began work on a disease-specific measure, the IMPACT questionnaire [102], which today is the most commonly employed disease-specific measure for assessing HRQOL in the pediatric IBD population.

Ryan et al. [103] reported on the incorporation of HRQOL screening into clinical practice and its clinical utility in predicting disease outcome and healthcare utilization. One hundred twelve IBD youth ages 7–18 years completed the Pediatric Quality of Life Inventory, Version 4.0 (PedsQL 4.0), with retrospective chart reviews conducted to examine disease outcomes and healthcare utilization for 12 months after baseline quality of life assessment. They demonstrated that youth who reported lower HRQOL at baseline, on average, had increased healthcare utilization as measured by IBD-related hospital admissions, emergency department visits, use of psychological services, telephone calls to clinicians, GI clinic visits, and referral to pain management.

IMPACT

The Development of the Impact Questionnaire

There are three English iterations of the IMPACT questionnaire at present, and work is actively underway on translation of IMPACT-III into other languages. Work on IMPACT began in the mid-1990s because at that time there was no published disease-specific HRQOL instrument available for pediatric patients with IBD. Generic pediatric HRQOL questionnaires, such as the Child Health Questionnaire [33, 104], were felt to be insensitive to the disease-specific issues of IBD. Concerns about wording issues, including inappropriate omissions and inclusions for a pediatric target audience, led researchers at the Hospital for Sick Children in Toronto to seek a pediatric-derived instrument over the adult-derived IBDQ [48]. For example, one question in the IBDQ [67] pertains to limitation of sexual activity by IBD, an issue which was felt to be of limited relevance in a pediatric cohort, except perhaps for the older adolescent. Issues not covered by the IBDQ which were felt to be of likely relevance to a pediatric cohort included growth concerns and limitations on school and extracurricular activities.

Defining how a new HRQOL tool will be used is important in guiding the development process, as this helps ensure that the end product is addressing the underlying need. The IMPACT developers sought to create a questionnaire which would serve both as a descriptive and evaluative tool. As a descriptive tool, the measure would facilitate recognition in individual patients of disparity between apparent IBD activity and severity, organic disease-related phenomena, which the physician is accustomed to assessing, and emotional or functional disability. As an evaluative tool, it was to be incorporated as an outcome measure in clinical trials to assess change in HRQOL over time.

In the development of IMPACT, there was a focus on children aged 10–17 years. Younger patients were excluded because of concern that systematic exploration of quality of life among very young children would require significantly modified methods. Items to be included in the final questionnaire were generated chiefly from interviews of pediatric patients with IBD. Items universally of greatest importance for all IBD patients were included, as well as some items rated as very important by one subgroup of patients (CD or UC), even if not by others [102].

The original IMPACT [48], or IMPACT-I as it is currently known, consisted of 33 questions, and responses were given using a visual analog scale. Each question was scored out of seven, so that the final total score would be similar to what was seen with the adult IBDQ. Thus, the range of scores possible for IMPACT-I was 0–231. During the cross-cultural adaptation and translation process of IMPACT-I into the Dutch language, a modified version was developed [105]. This version, IMPACT-II, eliminated or modified four questions and added a new question, resulting in a 35-item questionnaire with simplified wording of the response options for the visual analog scale. IMPACT-II was available in both English [106] and Dutch [107] language versions. Some researchers preferred a Likert response scale, and IMPACT-III [108] was created, which is identical to IMPACT-II save for the five-point Likert response scales and anchors (Fig. 51.2). IMPACT-III is available in over 65 languages (as well as culturally adapted versions in English, French, and Spanish) (see Table 51.3). IMPACT-III is the questionnaire used for ongoing cross-cultural adaptation.

Fig. 51.2 Sample IMPACT-III question. As opposed to IMPACT versions I and II which used visual analog response scales, IMPACT-III uses a five-point Likert response scale

Table 51.3 Cross-cultural adaptations and translations of IMPACT-III[a]

Language
Arabic
Bengali
Bosnian
Bulgarian
Chinese (China, Malaysia, Taiwan)
Croatian (male and female versions)
Czech
Danish
Dutch (Belgium, Netherlands)
English (Australia and New Zealand, India, Ireland, Malaysia, North America, UK versions)
Estonian
Farsi
Finnish
French (Belgium, Canada, France, Switzerland versions)
German (Austria, Germany, Switzerland versions)
Greek
Gujarati
Hebrew
Hindi
Hungarian
Italian (Italy, Switzerland versions)
Japanese
Kannada
Korean
Latvian
Lithuanian
Marathi
Malay
Norwegian
Polish
Portuguese (Brazil, Portugal versions)
Romanian
Russian (Estonia, Israel, Latvia, Lithuania, Russia, Ukraine versions)
Serbian (Cyrillic, Latin versions)
Slovak
Slovenian
Spanish (Argentina, Chile, Mexico, Puerto Rico, Spain, US versions)
Swedish (Finland, Sweden versions)
Tamil (India, Malaysia versions)
Telugu
Turkish
Ukrainian

[a]As of March 2021

Through cohort studies, and more recently in randomized controlled trials [108–110], IMPACT has demonstrated itself to be a valid measure of disease-specific HRQOL in pediatric IBD patients 10 years of age and over. From this work, while disease activity and disease severity are two factors which have been identified as strongly correlated with HRQOL, regression modeling clearly shows that they can only explain a small part of the HRQOL "puzzle" [48, 106]. As well work to date has not shown any influence of disease type (CD or UC) in influencing the performance of IMPACT. With age there remains less clarity. The original validation did not show any significant differences in perceived HRQOL across the age group studied.

Research has shown that the perceived HRQOL as assessed by IMPACT is most influenced by the current health status rather than that suffered over the previous 12 months [48]. That the IMPACT questionnaire is greatly influenced by the patient's current health status is an important feature for its use in clinical trials. If IMPACT scores continued to be influenced more by the patient's health status over the preceding year than by their current disease status, short-term responsiveness to change in clinical status would be compromised.

To date the IMPACT questionnaire has been used to evaluate HRQOL in pediatric IBD patients in a number of research studies, involving a variety of study designs [106, 111–114]. These studies provide a preliminary picture of what the HRQOL is in this population, and increasingly the data obtained from such studies will allow clinicians and researchers to develop an improved understanding of the factors which both positively and negatively influence HRQOL in older children and teenagers with IBD.

Description of the Instrument (IMPACT-III)

The IMPACT-III questionnaire takes about 10–15 min to complete and contains 35 questions. Each question is scored on a five-point scale (Fig. 51.2). Individual questions within IMPACT are equally weighted. The scores are standardized to a 0–100 scale, with higher scores representing better quality of life.

The 35 questions originally encompassed six domains: bowel (7 concerns), body image (3 concerns), functional/social impairment (12 concerns), emotional impairment (7 concerns), tests/treatments (3 concerns), and systemic impairment (3 concerns) (Table 51.4). Perrin and colleagues relooked at the domain structure for IMPACT and through exploratory factor analysis proposed four factors with good to excellent reliability for IBD responses: general well-being and symptoms, emotional functioning,

Table 51.4 IMPACT-III: 35 questions sorted by four domains

Domain	Question
Well-being	Stomachaches
	Not being able to eat what you want because of disease
	Worried about having a flare-up How much energy Having to miss out on hobbies Diarrhea
	Having fun Being sick How did you feel How tired did you feel Able to play sports as much as you would like Able to go to school
Social functioning	Worries about health in future Being ashamed Is it harder to make friends Worried about blood with bowel movement Worries not to be able to go out on dates Teased or bullied because of the disease or treatment Worries about ever having an operation Afraid about not making to the bathroom in time Try and keep your disease a secret Difficulties to travel or go on holiday Able to talk to anyone about worries
Emotional functioning	How do you feel about taking medicines Worried about having a chronic condition
	The influence of the disease upon the family
	Thinking it is unfair to have this disease
	Being angry to have this disease
	Having rules imposed because of the disease
	How do you feel about investigations
Body image	How do you feel about height
	How do you feel about weight
	How do you feel about the way you look
	Being happy
*Not in a domain	Having to pass gas

social interactions, and body image (two questions were dropped which did not fit well with any domain, "feel about tests/treatments" and "how condition affects family") [115]. Similarly, as part of the cross-cultural adaptation and translation of the Croatian version of IMPACT-III, Abdovic et al. used factor analysis of their cohort data to propose a five-domain structure (dropping two items) [116]. However, a major limitation of these two studies is the lack of robust representation across the spectrum of disease activity among participants, such that a vast majority had inactive or mild disease. In response to these proposed domain structures, the IMPACT-III questions were reexamined with a large and robust sample consisting of data from two pediatric clinical trials (involving patients with CD and UC) as well as a cohort of children from the Crohn's & Colitis Foundation IBD Partners Kids & Teens study [117]. This combined cohort consisted of patients across the developmental age spectrum, and was balanced across gender, disease type, and disease activity. A new psychometrically validated four domain structure was created, of which many questions overlap with former domains. The new domains consist of the following: Well-being (12 concerns), Social (11 concerns), Emotional (7 concerns), and Body image (4 concerns). One question was not included in the domain structure as it did not fit well onto any domain, but given that it did not detract from overall questionnaire reliability this question remains as part of the IMPACT-III total score. This domain structure is now recommended for scoring the IMPACT-III questionnaire.

Readability statistics for the IMPACT-III are excellent with a Flesch–Kincaid Grade level of 4.8, a Flesch Reading ease of 74.3, and 1% passive sentences. This suggests a very appropriate level of wording given the target population of ages 10 and above.

Practical Issues for Use of IMPACT

Administration and Instructions to Respondents

The person administering IMPACT-III should verbally review the written instructions provided on the initial page of the questionnaire with the child completing the questionnaire. It is important that the responses are the child's, and parents should be specifically asked not to help their child with the answers. It is, therefore, helpful to have an assistant nearby to answer questions that the respondent might have, so that the parent(s) will not have to aid them. It should be made clear that if the child feels that the issue raised by a particular question is not a problem for them (i.e., questions mention blood in stool, but they have never had blood in stool), then the child should mark it as "best quality of life" response. This will help decrease the number of questions left blank.

Scoring

By convention, the higher the score, the better the quality of life. For IMPACT-III the "good" quality of life anchors are always presented on the left, with the "poor" quality of life anchors on the right. There are five Likert response options per question. For scoring purposes, from left to right, they can be numbered 100 through 0, decreasing in increments of 25. This scoring system was developed in order to normalize the total and domain scores out of a 0–100 range. This facilitates easier interpretation of scores across domains, groups of participants, and across studies using other HRQOL tools using the same standardized scoring system. To obtain a total

score, responses from all questions completed are summed and divided by the number of questions completed to compute a standardized score ranging from 0 to 100. Domain scores can be obtained by summing the responses for each question within a domain and similarly dividing by the number of questions completed within each domain (Table 51.4). Additional criteria and guidance are available around calculating scores when there are a high number of missed questions.

Interpretation of HRQOL scores is another important area to consider. In IBD, the HRQOL outcomes from either IBDQ or IMPACT have usually been reported as the mean total score for study participants at various study time points. Other ways of reporting HRQOL outcomes would be to focus on the mean scores of a domain (i.e., the well-being domain) for study participants at various study time points. The latter may be optimal when a specific intervention would be expected to have a predominant influence on a specific domain.

Deficiencies in Current Knowledge and Areas for Future Research

There is still much we have to learn and understand about HRQOL in pediatric IBD. Although we have a tool with which to assess disease-specific HRQOL in this population, a number of unanswered questions remain.

Identifying the Factors which Influence HRQOL

Disease type on its own, that is having UC or CD, does not appear to affect HRQOL [118, 119] differently. While some factors, such as disease activity and severity, are known to negatively influence HRQOL for both UC and CD [120–122], further research is needed to understand how this relationship may change as disease activity changes, or based on how disease activity is measured as some discrepancies have been reported. When disease activity is reduced or patients are in remission, disease state is less closely related to HRQOL outcomes [123]. Even for patients in remission, demographic, psychosocial, and other gastrointestinal symptoms can influence HRQOL. For patients with CD, experiencing residual pain despite having more controlled symptoms is related to lower HRQOL [124]. Varni et al. also found that stomach pain and constipation predicted HRQOL after controlling for other factors known to influence quality of life including age, sex, and ethnicity [125]. Thus, pain when discordant from disease state appears to play an important role in understanding patients emotional functioning, disability, and quality of life.

Furthermore, additional research is needed to elaborate on other key factors which may influence HRQOL. Many studies have found certain demographic factors to influence HRQOL. Having female gender [119, 121] and being older [119] consistently predict lower HRQOL across several studies. In terms of psychosocial influences, both patient depression and anxiety have been found to be related to HRQOL, while the influence of each may differ across disease type.

Hommel and colleagues have begun to explore non-disease-specific factors, such as behavioral dysfunction, which may influence HRQOL [126]. They describe two main types of behavioral dysfunction: internalizing symptoms (such as anxiety and depression) and externalizing symptoms (such as aggression and disruptive behavior). In their study they demonstrated that greater disease severity, externalizing symptoms, and internalizing symptoms were all independently associated with a lower HRQOL as assessed by the IMPACT questionnaire. As well, their findings suggested that internalizing symptoms had a mediating effect on the relationship between disease activity and HRQOL.

Engelmann and colleagues [127] conducted a cross-sectional study of 47 German adolescent IBD patients where they assessed disease activity, HRQOL (using IMPACT-III), and quality of life (using EQ5D, a measure of generic quality of life) and whether psychopathology was present using the Clinical Assessment Scale for Child and Adolescent Psychopathology (CASCAP). The CASCAP is a tool to assess psychopathology using data derived from patient and parent interviews. Fifty-five percent of patients fulfilled DSM-IV criteria for one or more psychiatric disorders, including adjustment disorders (25.6%), major depressive disorder (17.0%), anxiety disorder (6.4%), learning/developmental disorders (4.2%), and attention deficit/hyperactivity disorder (2.1%). Not surprisingly, patients with psychiatric comorbidity had significantly lower total IMPACT scores compared to those without this comorbidity. However, the effects of psychiatric comorbidity differed across categories of disease activity, where psychiatric comorbidity affected the HRQOL and quality of life scores only for patients with mild disease activity. A limitation of this study was the amalgamation of a range of psychiatric diagnoses together as one factor, where it may be that certain diagnoses have a greater or lesser influence on HRQOL/quality of life.

Capturing HRQOL assessments through one moment in time, as has been done in the majority of cross-sectional studies to date, is a significant limitation. Because HRQOL is likely influenced by multiple factors, both disease-specific and non-disease-specific, ensuring a sufficient sample size and following the study population over time will be important features of future study designs to address some of these limitations. Overcoming these limitations will be important in helping us to better understand the factors which influence HRQOL. By gaining an improved understanding of factors

which influence HRQOL, we can then work on developing specific interventions to target these factors, with the goal to improve HRQOL in these patients [128, 129].

Comparisons of HRQOL Between Patients with IBD, Patients with Other Chronic Pediatric Illnesses, and Healthy Peers

As IMPACT is increasingly used in clinical and research settings, an improved understanding of HRQOL in patients with pediatric IBD should result. Also important, however, is understanding how these patients fare when compared to children with other chronic illnesses as well as to healthy peers. To make these comparisons, generic HRQOL tools will need to be employed. Preliminary work looking at quality of life issues between patients with IBD and those with other chronic illnesses was carried out by Ingerski and colleagues [130]. They compared HRQOL across eight pediatric chronic conditions: obesity, eosinophilic gastrointestinal disorders, IBD, epilepsy, type 1 diabetes, sickle cell disease, post-renal transplantation, and cystic fibrosis [130]. Using the PedsQL generic HRQOL tool, these authors showed that it was youth with obesity and eosinophilic gastrointestinal disorders who had lower HRQOL than youth with other chronic illnesses. However, limitations of this work were the small number of patients in some of the chronic illness groups (e.g., 34 of 589 patients had IBD), and considerable variation was present across disease groups in terms of demographic and disease-specific sample characteristics [130]. Thus, further work needs to be done in this area but with a priori matching of participants across important demographic and disease-specific factors. Additionally, early work has also been done comparing HRQOL of pediatric IBD with healthy peers [131]. Not surprisingly they demonstrated in 55 children, ages 7–19 years, that older children with IBD had significantly lower HRQOL scores compared with age-standardized peers. Kunz and colleagues have carried out the largest study to date comparing HRQOL assessments of youth with IBD to published group data of chronically ill, acutely ill, and healthy comparison groups [120]. The 136 youth with IBD studied reported lower psychosocial functioning than the healthy comparison group, higher physical and social functioning than the chronically ill group, and lower school functioning than all published comparison groups. More work needs to be done to better characterize the degree and nature of any differences in HRQOL between pediatric IBD patients and those with other chronic illnesses and healthy peers. If consistent differences are noted, and in particular if impairments in HRQOL are demonstrated, then healthcare providers will have evidence to better advocate for research to identify interventions which will target these HRQOL impairments.

Assessing Disease-Specific HRQOL in Pediatric IBD Patients Not Captured by IMPACT Questionnaire

IMPACT is a tool to evaluate HRQOL in pediatric patients aged 10–17 years inclusive. The researchers who developed the questionnaire were concerned that issues of importance to younger patients with IBD may be different than the older cohort which was involved in the development of IMPACT. Also a self-administered questionnaire for these patients less than 10 years of age would be problematic given the developmental and comprehension concerns in the younger age range [11]. It is most likely that younger patients would require assistance in completing the questionnaire and/or a different method of delivery [11], such as computer-based questionnaire with video and/or audio components [101]. This is an area which requires further consideration, but it will be necessary to determine whether the relatively small population of patients with IBD who are less than 10 years of age can justify the development of a tool specifically for this age group.

During the development of IMPACT, patients with ostomies or those with disease limited to the rectum were not included. Therefore, the applicability of IMPACT to this cohort of patients has not been established. There may be HRQOL issues unique to this population not addressed by IMPACT. As well, IMPACT development involved participants who had been diagnosed with IBD for at least 6 months. The researchers wished to have a body of "lived experiences and concerns," and it is not clear whether the perception of issues influencing HRQOL is the same when the diagnosis is more recent. Despite this, many studies have included participants from the time of their diagnosis, not waiting for the 6 month time point from diagnosis to carry out the first HRQOL evaluation.

The Impact of Family on the Assessment of HRQOL in Pediatric IBD Patients

The role that family, both parents and siblings, plays in the HRQOL of pediatric IBD is just starting to be explored. There are multiple areas to be addressed. First is the whole issue of self-report and proxy-reported assessments of HRQOL. As discussed previously, in pediatrics there can be the added challenge of age or developmental status which may limit the ability to secure a self-report of HRQOL. The argument can be made regardless of whether a pediatric patient can self-report that having a parent's perspective on their child's HRQOL can add important information which impacts management decisions. A more comprehensive picture of youth HRQOL can be obtained through inclusion of the complementary perspectives of both child and parent-proxy reports

of HRQOL [120]. It is not yet clear, based on some of the disparate findings of the few studies which have looked at concordance between youth with IBD and parent-proxy HRQOL reports, exactly how strong the agreement is across domains. An initial study by Loonen et al. found that parent-proxy reports of social functioning were significantly lower than youth reports, but differences were not noted across other domains [105]. Ingerski et al. reported lower parent-proxy HRQOL scores across all domains of the PedsQL compared with youth self-report [130], except for the school functioning domain, where youth self-reported HRQOL was significantly lower than parent-proxy reported HRQOL. Using the KIDSCREEN-GROUP 2004, a self-report questionnaire consisting of five domains of general quality of life (physical activity, children's mood, family life, friends, and school performance), Mueller et al. compared scoring between 110 Swiss children with IBD and their parents [132]. In this study parents scored overall quality of life, as well as mood, family, and friends domains, lower than the children themselves, with better concordance noted for school performance and physical activity domains.

Gallo and colleagues from Argentina concurrently assessed HRQOL using IMPACT-III in 27 patients and one of their parents (82% mothers) [133]. As a specific parent-proxy report version of IMPACT-III has not been developed, the authors used a non-validated approach, asking the parents to interpret the questions from their child's perspective. With this method they showed moderate-to-high agreement between parent-proxy and patient ratings on most IMPACT-III domains, except for the emotional functioning domain where parents underreported (compared to the child's report) their child's HRQOL. Another consideration in the interpretation of parent-proxy ratings of their child's HRQOL is the quality of life of the parents themselves. Sattoe et al. suggest that assessing parents' quality of life may be more useful than asking parents for a parent-proxy report [134]. Researchers have shown that parent's own quality of life was significantly related to ratings of their child's quality of life [135–137]. More work needs to be done to understand these differences in proxy vs. self-reported HRQOL as well as factors that influence parents' perceptions of youth's HRQOL [130]. Regardless of differences noted, the inclusion of both patients' and parents' measures of quality of life can provide complementary perspectives, each of which should be respected [132].

A second area to be explored is the role that families play on an individual's perceived HRQOL. When family life is dysfunctional, there can be decreased emotional and behavioral functioning [138], while adaptive family relationships have been associated with positive psychological functioning [139]. Building on data among youth with end-stage renal disease and diabetes showing that there is a significant relationship between family functioning and HRQOL, researchers explored these issues in a cohort of adolescents with IBD, seeking to identify which domains of family functioning may be particularly problematic [140]. After statistically controlling for known impacts of disease severity and diagnosis, their data showed that teens from families with clinically elevated difficulties in problem solving, communication, and general family functioning reported lower HRQOL. This area needs to be studied further to ascertain whether a causal link exists between family functioning and HRQOL and, additionally, in the context of a prospective study, how this may vary over time.

Research has also highlighted the importance of examining maternal and paternal functioning separately, as there can be a differential impact on HRQOL outcomes [141]. As well, careful consideration of the potential interplay between the child and parent psychological status and the child's HRQOL has also been shown to be important [142]. Hommel and colleagues studied these issues, and their data suggested that adolescent depressive symptoms may serve as a mechanism by which parent distress is linked to poorer HRQOL in adolescents with IBD [142]. In a study of 99 adolescents with CD and their parents, Gray and colleagues further explored family level predictors of HRQOL by studying parenting stress as a potential mechanism through which disease activity affects HRQOL [143]. HRQOL was assessed using patient-completed IMPACT-III, while parents were given a measure of medically related parenting stress, the Pediatric Inventory for Parents. Disease activity was assessed from chart reviews. In this cohort drawn from three study sites, they demonstrated that parenting stress because of the occurrence of medical stressors partially mediated the disease severity–HRQOL relation. This study would indicate that as disease severity increases, parenting stress also increases, and patient HRQOL decreases. Additionally, several researchers have found that parental psychological distress [144, 145] and depressive symptoms [146] are also related to poorer HRQOL, which appears to be true even if patients are in remission. This demonstrates the importance of both patient and parent well-being in improving patient HRQOL. Discordance between parent-proxy and child scores, where parents estimate lower HRQOL than their child, may also result in increased likelihood for psychology referral in youth with IBD [147]. Better understanding of the relationship between family functioning and HRQOL may allow practitioners to better identify adolescents who are at higher risk for impaired HRQOL and to focus on families in need of support services or psychological intervention [140].

Cross-Cultural Comparisons of HRQOL in Pediatric IBD

A further gap in assessment of HRQOL in pediatric IBD is the lack of comparisons across different cultures and/or

languages. Other IBD outcome measures, such as the commonly employed disease activity measures, can be utilized irrespective of culture or language. They collect fundamental information which are not limited by ethnicity or language. This is not true for quality-of-life assessments. While we now have the generic and disease-specific tools to evaluate HRQOL across cultures and languages, there remains no reported comparison of HRQOL across cultures or languages. There have been an increasing number of published HRQOL reports from individual countries using cross-culturally adapted versions of IMPACT-III [116, 132], but none have specifically contrasted HRQOL across cohorts of pediatric IBD patients from different countries. Cultural differences with respect to disease perception and illness experience are becoming more apparent with the increasing immigrant population residing in Western countries [148]. The exclusion from a study of a group or population, based on culture or language, could lead to a systematic bias in studies of healthcare utilization or quality of life [149].

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Irritable Bowel Syndrome and Functional GI Disorders in Inflammatory Bowel Disease

52

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Irritable bowel syndrome (IBS) is a disorder characterized by altered bowel habits and abdominal pain in the absence of a detectable structural abnormality. There are no clear diagnostic markers for this illness and all definitions are based on clinical symptoms. Getting an accurate history from a child can sometimes be difficult and until recently IBS was not a common diagnosis made in children. Some pediatricians still view IBS as nothing more than a somatic manifestation of psychological stress [1]. Availability of better techniques to study bowel motility and sensory function along with advancements in functional brain imaging has improved our understanding of the pathophysiology of IBS. It is now thought that IBS symptoms result from the convergence of multiple factors, including a genetic predisposition, an infectious or inflammatory injury to the gastrointestinal (GI) tract leading to altered sensory perception by the brain, and an underlying bowel dysmotility. Functional abdominal pain and visceral hypersensitivity can coexist in patients with inflammatory bowel disease (IBD). Emerging data suggest that there may be an overlap in the symptoms and etiopathogenesis of IBS and IBD. In this chapter we will discuss how to make a symptom-based diagnosis of IBS and review the pathophysiology and management of IBS. We will also discuss the sensory perception and enteric nervous system changes in patients with IBD and how these can predispose to the development of functional GI symptoms.

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Epidemiology

A large proportion of children with IBS are still categorized under a broad umbrella of functional abdominal pain disorders, and the prevalence of IBS in children is underrecognized. Subcategorizing children presenting with chronic abdominal pain into IBS, dyspepsia, and functional abdominal pain is important because it helps narrow down the differential diagnosis, reduces the number of unnecessary investigations, and helps better target the therapy. In a study of 478 children referred to a large gastroenterology clinic with functional abdominal pain, 26% of the subjects had symptoms of diarrhea-predominant IBS [2]. Another pediatric study of 171 subjects with chronic abdominal pain reported that 68% of subjects fulfilled the clinical criteria for the diagnosis of IBS [3]. Community-based studies from North America and China suggest that 8–17% of school children have IBS-like symptoms [4, 5].

Clinical Features

In a majority of patients, a good clinical history is sufficient to diagnose IBS and differentiate it from organic diseases that can mimic IBS symptoms (Table 52.1). To standardize the diagnosis of IBS, symptom-based criteria have been developed and amended by the Pediatric Rome Committee (Table 52.2) [6]. Specific alarm symptoms, which alert the clinicians to the increased likelihood of an underlying organic disease, can help in the management and planning of investigative workup. In a large study of 606 children, the following alarm symptoms were more likely in children with Crohn disease compared to those with pain-associated functional gastrointestinal disorders (FGIDs), including IBS, hematochezia, weight loss, and difficulty in gaining weight. Nocturnal abdominal pain and sleep disruption were not helpful in differentiating children with IBS from those with Crohn disease [7].

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Table 52.1 Diseases that can mimic IBS symptoms

Diarrhea-predominant IBS
GI infections
Inflammatory bowel disease
Celiac disease
Carbohydrate malabsorption (lactose, sucrose, fructose, sorbitol)
Lymphocytic and collagenous colitis
Food intolerance
Constipation-predominant IBS
Celiac disease
Hypothyroidism
Anal sphincter/pelvic floor abnormality
Tethered spinal cord
Colon motility disorder
Neoplastic disorders (rare in children)

Table 52.2 Rome IV criteria for the diagnoses of irritable bowel syndrome [6]

Must include all of the following:
1. Abdominal at least 4 days per month associated with one or more of the following:
(a) Related to defecation
(b) Change in frequency of stool
(c) Change in form (appearance) of the stool
2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

The criteria should be fulfilled for at least 2 months before diagnosis

Abdominal pain is a prerequisite for the diagnosis of IBS. The pain can vary in intensity and location but is usually restricted to the lower abdomen; it can be episodic or superimposed on a background of constant ache. It is usually relieved by the passage of stool or flatus and exacerbated by meals. Almost 50% of adults with IBS also have symptoms of dyspepsia, and overlap between other pain-associated FGIDs and IBS has been reported [8]. Urinary bladder irritability and pelvic pain have also been associated with IBS-like symptoms.

Most patients with diarrhea-predominant IBS pass liquid or semiformed stool at frequent intervals. It can be accompanied with the passage of mucus, but passage of blood is rare. A majority of patients will report difficulty falling asleep, rather than sleep disruption. In patients with constipation-predominant IBS, the constipation initially can be episodic but usually becomes continuous. With time symptoms become refractory to treatment with laxatives. Stool consistency can be hard and the stool may be narrow in caliber. It can be associated with the feeling of incomplete evacuation; the child can spend a long time sitting on the toilet straining unsuccessfully to have a bowel movement. This can lead to rectal mucosal prolapse and development of solitary rectal ulcer syndrome, associated with passage of blood in the stool and tenesmus [9]. Adults with dyssynergia, a disorder where the subject is unable to coordinate bearing down with pelvic floor relaxation during defecation, can have symptoms that mimic IBS [10]. Constipation associated with dyssynergia can improve with biofeedback training, and this should be considered in the differential diagnosis in adolescents with constipation and lower abdominal pain. Some patients have periods of constipation alternating with diarrhea. Abdominal bloating, belching, and flatulence are also common symptoms.

Pathophysiology

The pathophysiology of IBS is likely to be multifactorial, and alterations in GI sensory perception, central neuronal dysfunction, abnormal motility, stress, psychological abnormalities, and luminal factors have all been implicated. The submucosal nerve plexuses receive sensory input from the bowel lumen through the sensory receptors. The enteric nervous system communicates with the brain through neural pathways as well as by immune and endocrine systems. The pain signals are transmitted from the primary sensory afferent neurons with cell bodies in the dorsal root ganglia to the dorsal horn of the spinal cord. Spinal pathways run to the thalamus and relay messages to the limbic system and the sensory cortex. The combined functioning of the GI motor, sensory, and central nervous system activity is termed the brain–gut axis. Abnormalities along the brain–gut axis, such as altered peripheral sensory perception, hypersensitivity of sensory neurons in the dorsal horn, and increased activation of brain regions associated with visceral pain sensation, have been reported in IBS [11].

Visceral hyperalgesia (an exaggerated pain response to a sensory stimulus) has been reported in children with IBS [12, 13]. Visceral hyperalgesia could result from sensitization of primary sensory afferent fibers innervating the gut or the neurons receiving input from visceral afferents along the brain–gut axis (Fig. 52.1) [11]. Peripheral sensitization of nerves within the GI tract can result from noxious injury and the release of inflammatory mediators and nerve growth factor by the fibroblasts and mast cells in the bowel wall. The resulting increase in transcription of the neuropeptides, substance P, and calcitonin gene-related peptide initiates nerve activation and the release of yet more substance P and recruitment of previously silent nociceptors [11].

Recent advances in functional brain imaging have provided a novel insight into the pathophysiology of chronic pain states and how supraspinal mechanisms of brain reorga-

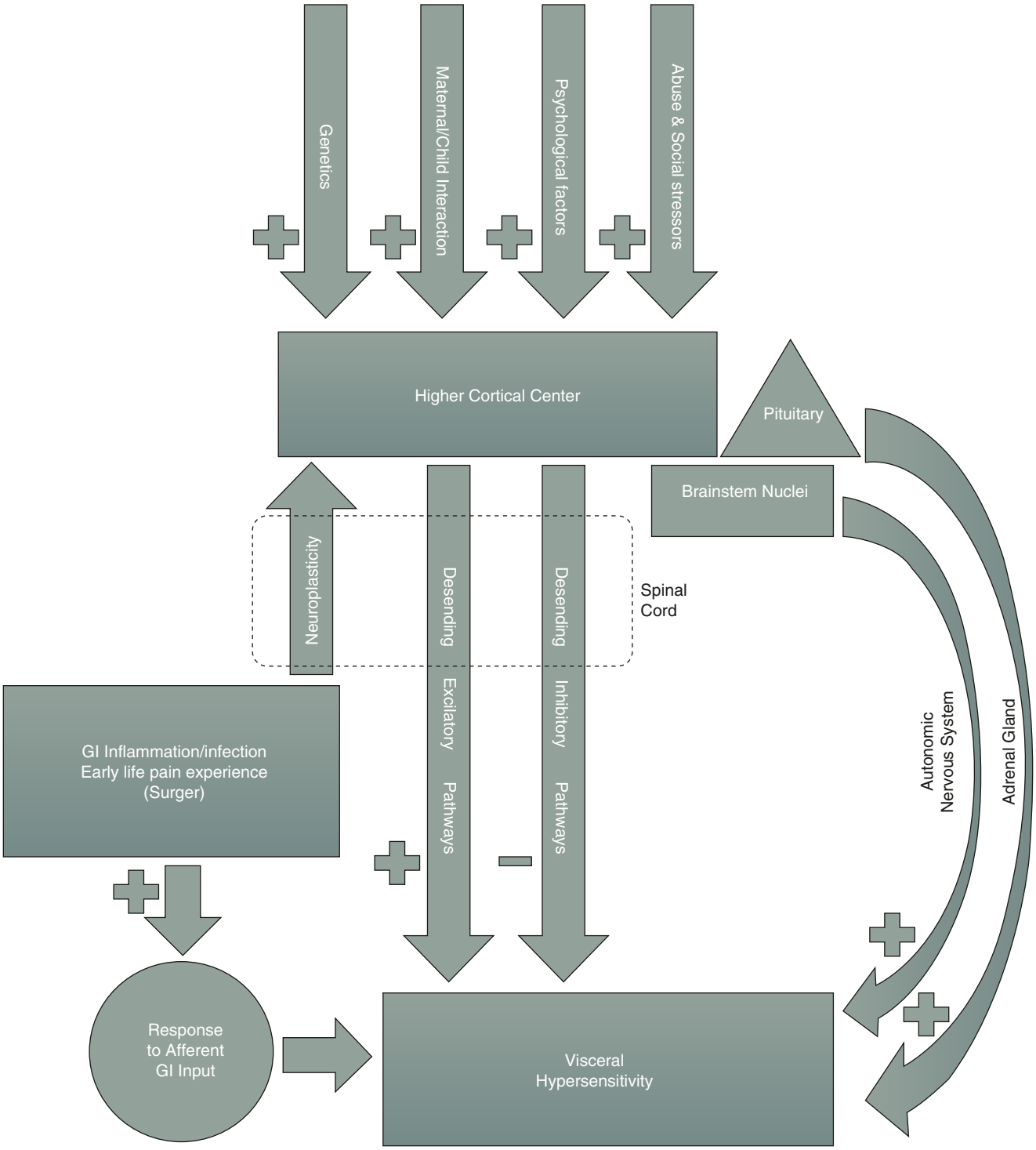

Fig. 52.1 Flowchart showing interaction between the sensory neuronal pathways and stress-related activation of the hypothalamus–pituitary adrenal axis. Stress-related activation of cortical and subcortical brain regions induces the release of increased quantities of corticotropin-releasing hormone (CRH) and adrenocorticotropin (ACTH) from the anterior pituitary. This in turn stimulates the release of glucocorticoids from the adrenal glands. In response to ANS activation, cells of the adrenal medulla produce catecholamines, such as adrenaline and noradrenaline. These have potential to modulate activity of the sensory neuronal pathways and cause visceral hypersensitivity. The cortical and subcortical brain centers can facilitate or inhibit the activation of second-order spinal neurons in response to visceral afferent stimulus

nization facilitate pain learning behavior and long-term maintenance of central sensitization. Tillisch and coworkers conducted a meta-analysis of 18 adult studies in which functional MRI or PET scans of the brain had been performed together with balloon distension of the rectum in patients with IBS and healthy controls [14]. Patients with IBS demonstrated a greater spatial extent of brain activity than controls, specifically in regions associated with pain modulation and emotional arousal. The authors concluded that published data support a role for central nervous system dysregulation in the pathogenesis of IBS [14]. A novel functional connectivity analysis approach to functional brain imaging studies allows one to measure temporal correlation of neurophysiological events and estimate how spatially distinct brain regions coactivate or work together in a specific brain states, therefore offering a practical tool for evaluating cortical modulatory effects on brain functioning during rectal distension stimulation in health and IBS. The human brain, intrinsically, is organized into distinct functional networks supporting various sensory, motor, emotional, and cognitive functions. Of particular relevance to the understanding of visceral hypersensitivity and altered brain–gut interaction in IBS is an intrinsic brain network, the salience network [15]. The salience network plays an important role in disparate attentional, cognitive, affective, and regulatory functions. In a recent study of adolescent patients with IBS, rectal balloon distension showed greater activation of neural structures associated with homeostatic afferent and emotional networks, especially the anterior cingulate and insular cortices. Compared to healthy controls, IBS subjects also showed excessive coupling of the salience network with the default mode network and executive control network [16]. Adult IBS patients show greater engagement of cognitive and emotional brain networks, including the salience network during contextual threat, suggesting that they may overestimate the likelihood and severity of future abdominal pain [17].

Low-Grade Inflammation

Following gastroenteritis 7–31% of adults develop persistent low-grade inflammation and IBS-like symptoms [18–21]. A study of a large outbreak of waterborne infection with *Campylobacter jejuni* and *E. coli* O157 in Walkerton, Ontario, yielded 228 cases of postinfectious IBS and 581 controls who had fully recovered. This study found a number of single nucleotide polymorphisms that distinguished postinfectious IBS patients from infected controls who had fully recovered [22]. The relevant genes were CDH1 coding for E-cadherin, a tight junction protein controlling gut permeability, Toll-like receptor (TLR) that mediates the cellular response to bacterial DNA, and IL-6 [22]. TLRs are normally downregulated to avoid inappropriate activation of the immune system by gut commensals [23]. Recently, increased expression of TLR-4 has been reported in females with IBS, predominately of mixed or diarrhea-predominant IBS [24]. Increased intraepithelial and lamina propria lymphocytic infiltration, together with an increase in enteroendocrine cells, has also been reported in bowel biopsies obtained from postinfectious IBS patients [21]. These changes can persist for up to 12 months and are associated with increased mucosal permeability [18, 21]. In children with IBS, immune cells' presence in the rectal mucosa was associated with a higher availability of 5-HT with higher 5-HT content and lower SERT mRNA compared to control subjects suggesting that mucosal inflammation may induce peripheral sensitization [25]. Bacterial gastroenteritis and Henoch-Schönlein purpura during early childhood can lead to development of IBS-like symptoms in later life [26, 27]. Bowel inflammation and pain in early childhood may lead to alteration in afferent signal processing due to neuroplasticity which can manifest in later life with functional pain during psychosocial stress.

Gut Microbiota

Studies using fluorescent in situ hybridization to detect bacterial 16s RNA suggest that there is an increase in bacteria within the mucus layer in patients with IBS [28]. Recently, great advances have been made in understanding the microbiota through the development of culture-independent technologies and, in particular, metagenomics. There are great diversity and interpersonal variation in the bacterial species and strains present in the gut microbiota. Although studies of fecal microbiota in IBS are limited, a recent pediatric study reported a significantly greater percentage of the class γ-proteobacteria especially *Haemophilus parainfluenzae* in patients with IBS. A *Ruminococcus*-like microbe was also more common in IBS subjects compared to controls in this study [29]. Several adult studies have reported reduced biodiversity of gut microbiota in patients with IBS [30]. Fermentable oligosaccharides, disaccharides, monosaccharide, and polyol (FODMAP) diet which lowers the intake of several fermentable carbohydrates has been shown to decrease GI symptoms in adults and children. In one pediatric study, the baseline gut microbiome composition and microbial metabolic capacity were associated with efficacy of FODMAP diet, suggesting that evaluation of gut microbiome may be helpful in predicating response to dietary intervention [31, 32].

Altered Motility

Abnormal rectal, colon, and small bowel motility has been implicated in IBS pathophysiology. Interpretation of colon motility studies in adults with IBS is hampered by a relatively primitive understanding of normal colon motility and its intrinsic variability. Abnormalities in colon motility and abnormalities in response to food and stress have been reported in patients with IBS [33] Abnormalities in small bowel motility, such as repetitive bursts of contractions or clusters, prominent high-amplitude waves in the terminal ileum, and an exaggerated jejunal motor response to a meal, have also been reported in adults with IBS [33, 34].

There is also a suggestion that patients with IBS handle small bowel gas differently, and there is slow transit of gas directly infused into the small bowel in adults with IBS [33]. Abdominal bloating and flatulence can also result from higher colonic fermentation in IBS [33, 35, 36]. Some patients without evidence of small bowel bacterial overgrowth can benefit from treatment with unabsorbable antibiotics [37], which raises the question of a qualitative change in bowel bacterial flora in IBS.

Biochemical Changes

Serotonin (5-hydroxytryptamine: 5-HT) is secreted in copious amounts by the gut enteroendocrine cells and serves as a critical messenger for GI fluid secretion and motility. It activates at least five different receptor types, and the 5-HT_3 and 5-HT_4 receptors are the most extensively studied in IBS [38]. The transporter of 5-HT (SERT) mediates the reuptake of 5-HT by the neurons and crypt epithelial cells and terminates its action.

Plasma 5-HT concentration is elevated in IBS patients [39], and the proportion of 5-HT secreting enteroendocrine cells is elevated in the GI tract in postinfectious patients with IBS [18]. Increased rectal mucosal 5-HT concentration has also been reported in children with IBS. The presence of low-grade inflammation was associated with higher 5-HT concentration in rectal mucosa in this study [25]. Symptom relief by serotonergic agents including 5-HT_3 antagonists and 5-HT_4 agonists provides additional support for a possible role of 5-HT in IBS pathophysiology [40].

Genetics

Familial aggregation and twin studies suggest that there may be a genetic predisposition to developing IBS [41, 42]. Twin studies have shown that the concordance rate for IBS is higher in monozygotic compared to dizygotic twins [43]. However, the presence of IBS in the respondent's parents made a much larger contribution to the risk of having IBS than did the presence of IBS in one's twin, suggesting social learning may be more important than the environmental factors in determining illness behavior [43]. Family members of patients with IBS are more likely to have the condition, compared to their spouse controls. To date, nearly 60 genes involved in different pathways, including serotonin, adrenergic, inflammation, and intestinal barrier function, have been studied to determine whether specific genetic variants may be associated with IBS [44]. Interleukin-10 is an anti-inflammatory cytokine, and fewer patients with IBS have the high IL-10 producing (G/G) genotype compared to healthy controls [41]. Four different studies have explored the association of SERT gene polymorphism in IBS [41]. SERT is important for terminating the GI activity of 5-HT. The wild-type l/l polymorphism results in normal function, whereas the presence of the short allele (s/l or s/s) results in impaired SERT function. As a group, SERT polymorphism was similar in healthy subjects and IBS patients, but some differences were observed in subgroups of IBS patients, and these differences could be population specific.

Psychological Factors

Community-based studies in adults have shown that IBS patients are indistinguishable from the rest of the population in terms of psychological comorbidities [45]. Higher psychological comorbidities have been reported in a subset of IBS patients who seek medical help [45]. Patients with psychosomatic disorders, such as depression have activation of the immune system and elevated CRP [46]. Adults who develop postinfectious IBS are more likely to develop depression [47], and depressive symptoms have also been linked to relapses of colitis [48] and disease activity [49] in patients with IBD. It is not clear if the depression is the result of chronic ill health or leads to the development of IBS. In children social learning of illness behavior can also contribute to the development of IBS; children of mothers with IBS are more likely to seek medical help for functional GI symptoms [50]. Children with IBS who have significant psychological comorbidities run a more protracted illness course and are less likely to respond to treatment [51].

Visceral Hypersensitivity and IBD

Bowel injury and inflammation can induce functional and structural changes in the enteric neurons and muscles. Increased numbers of ganglion cells, axonal degeneration, and a reduced number of interstitial cells of Cajal have been reported in IBD [21]. In Crohn disease there is increase in substance P and its receptors in the GI tract [21]. The bowel

innervation shifts from a predominantly cholinergic to a substance P predominant innervation in ulcerative colitis (UC) [21]. Increased expression of nerve fibers expressing transient receptor potential vanilloid type 1 (TRPV1) receptor in IBD and IBS has been reported [52] as well as in quiescent IBD patients with IBS-like symptoms [53]. The expression of TRPV1 is a feature of afferent pain fiber and upregulated by inflammation [53]. These changes can cause alteration in bowel sensory perception. Patients with active UC show a decreased threshold for painful and non-painful rectal distension stimulus [54]. The hypersensitivity can be widespread, and a lower pain threshold to esophageal distension has been reported in adults with UC [55]. In contrast, patients with isolated ileal Crohn disease have an increased pain threshold following rectal distension [56]. It appears that the development of visceral hypersensitivity in IBD may depend on the disease activity, type of inflammation, and region of the GI tract involved.

There is a considerable overlap between IBS and IBD symptoms. Adults who develop IBD may have a prodrome of IBS-like symptoms that can be as long as 7 years [57]. Some of these patients could have a delayed diagnosis of IBD, but some may have GI inflammation not severe enough to make a diagnosis of IBD but sufficient to cause IBS-like symptoms. Up to 57% of adults with Crohn disease and 33% with UC have symptoms, like pain and bloating, when in clinical, laboratory, and endoscopic disease remission [58]. Since a few inflammatory cells located strategically near the enteric nerves or myenteric ganglion cells can alter bowel function in IBS, similar changes could be responsible for the functional symptoms in patients with Crohn disease, which cause transmural inflammation [59–61].

Evaluation of placebo response in Crohn disease provides indirect evidence to the existence of functional GI disorders in these patients. Placebo therapy can alter the natural course of Crohn disease. In a meta-analysis of 23 adult studies using Crohn Disease Activity Index (CDAI) to measure Crohn disease activity, the pooled median remission rate with placebo was 19% (range 0–50%) [62]. Significant predictors of a placebo response were duration of participation in the study and number of clinic visits. The placebo effect increased with the increasing study duration (Fig. 52.2), suggesting that frequent contact with medical professionals relieved symptoms in some patients. A high CDAI and CRP at recruitment showed a negative correlation with the placebo response, suggesting that patients with a low or normal CRP and a comparatively mild clinical disease activity were more likely to respond to a placebo. Therefore, the obvious question is whether some of these patients with Crohn disease had functional GI symptoms to begin with and were therefore more likely to respond to a placebo.

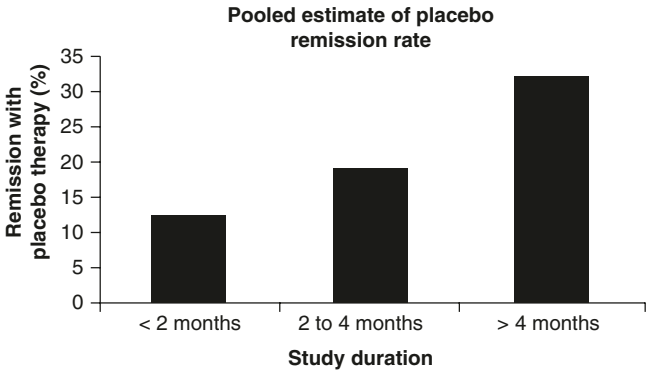

Fig. 52.2 Data from meta-analysis of 23 studies that used CDAI to measure disease activity in Crohn disease. The pooled estimate of remission with placebo therapy increased with study duration

Diagnosis

The diagnosis of IBS is based on clinical symptoms and signs (Fig. 52.3), and investigative workup, including endoscopic evaluation, may be necessary in a small percentage of children especially in the presence of alarm features. Abdominal pain is a common symptom in children with celiac disease but the prevalence of IBS is unknown. Adult studies suggest that 5–17% of celiac disease patients have IBS-like symptoms, and in one study of 1032 adults with celiac disease, 37% were diagnosed with IBS prior to the diagnosis of celiac disease [63]. More than 90% of these adults have improvement in IBS-like symptoms after starting gluten-free diet. Lactose intolerance has been reported in 15–25% of adults with IBS. However, it is yet to be determined if lactose exclusion results in resolution of IBS symptoms. In one large pediatric study, anemia, hematochezia, and weight loss were most predictive of Crohn disease in children presenting with chronic abdominal pain, with a cumulative sensitivity of 94% and specificity of 62% [7]. When evaluating children with lower abdominal pain and altered bowel symptoms one needs to consider the risk of harm associated with invasive test, such as colonoscopy, and this must be balanced against the risk of a missed diagnosis. Fecal calprotectin has a high negative predictive value (100%) in populations with low prevalence for organic disease, i.e., primary care screening of patients for IBD. One has to remember that the low positive predictive value of the test necessitates need for further investigations in patients with elevated fecal calprotectin levels. A meta-analysis has shown the clinical utility of fecal calprotectin to distinguish organic GI diseases, such as IBD from functional GI diseases, leading to less patients who have a functional GI disorder undergoing unnecessary endoscopy [64].

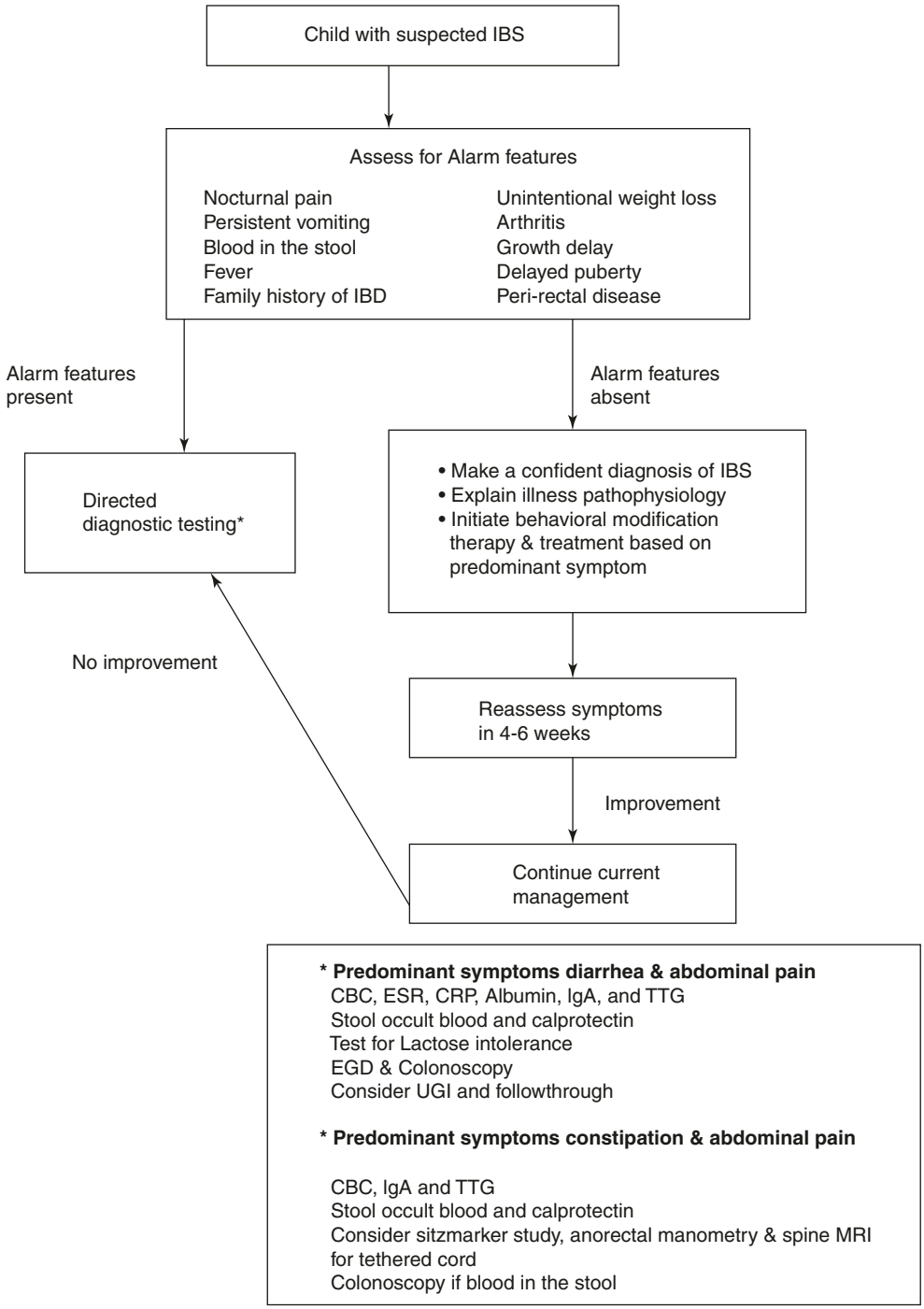

Fig. 52.3 Algorithm for management of children presenting with symptoms consistent with the diagnosis of IBS

Treatment

When evaluating children with IBS, it is important to allocate sufficient time for the consult to allow the child and family to share their concerns. One must acknowledge the presence of pain, adopt an empathic and non-judgmental point of view, and educate and reassure the child and the parents by explaining the source of symptoms in the absence of an identifiable cause [65]. It should also be made clear that the improvement will be slow, and the focus should be on normalization of psychosocial functioning, rather than trying to identify the cause for the symptoms.

Cognitive behavioral therapy (CBT), family intervention, and guided imagery, a form of relaxed and focused concentration, have been successfully used to treat functional abdominal pain in children and are also effective in IBS [64].

Adult studies have shown that attention management techniques, such as hypnosis and mindfulness meditation, are useful to treat IBS symptoms. Patients with prolonged illness and complex psychological comorbidities, which interfere with participation in a treatment plan, may require early referral to a multidisciplinary team, which includes a pain psychologist and a gastroenterologist [51]. CBT is based on the belief that our thoughts, behaviors, and feelings interact, and CBT aims to reduce or eliminate physical symptoms through cognitive and behavioral changes. It guides the patient to modify or change cognitive distortions and negative thinking and enables the patient to substitute these with more realistic thoughts, such as that the pain is likely to subside and does not represent a terminal illness. Several randomized controlled trials to test the effectiveness of pain interventions in children with functional abdominal pain using a self-management approach that includes component of CBT have yielded encouraging results. However, methodological difficulties and different criteria used to classify patients can make interpretation difficult. Cognitive behavioral and relaxation therapy are emerging as the first-line treatment for children with functional abdominal pain and are also useful to treat children with IBS.

Dietary triggers, such as caffeine, fatty meals, and carbonated soft drinks, should be eliminated. A lactose-free diet can help patients with IBS symptoms associated with lactose intolerance. Increasing dietary intake of fiber can help patients with constipation-predominant IBS, but metabolism of the bulking agents by gut bacteria can produce gas, which can worsen symptoms of bloating and flatulence. A meta-analysis in adults with IBS suggested that soluble fiber sources, such as psyllium, ispaghula, and calcium polycarbophil, may be more effective in improving global IBS symptoms compared to insoluble fiber [66, 67]. An innovative approach for treatment of IBS in adults comprises a reduction in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) in the diet [68, 69]. These short-chain carbohydrates have common functional properties in that they are poorly absorbed, osmotically active, and rapidly fermented by bacteria. A recent multicenter randomized controlled study in adults reported that FODMAP diet was not superior to traditional IBS dietary advice in adult patients [70]. In a small randomized placebo-controlled trial in children with IBS, a quarter of the study cohort reported improvement in abdominal pain and frequency of bowel movements only with FODMAP diet and another third reported improvement with FODMAP and typical American childhood diet. However, the symptom response was evaluated over a relatively short period of 2 days [31]. Dietary advice is an important component of symptom management in patients with IBS; however, FODMAP diet and traditional dietary advice may have similar beneficial effect on symptoms, and some experts have raised concerns about safety of FODMAP diet used over prolonged period of time.

Polyethylene glycol 3350 and milk of magnesia can be used as a stool softener in patients with constipation. Lubiprostone, a type 2 chloride channel agonist, is effective in treating constipation and constipation-predominant IBS in adults [71]. Pediatric trials documenting efficacy in pediatric age group are lacking. Menthol, the active ingredient in peppermint, inhibits smooth muscle contractions by blocking calcium channels. Enteric-coated peppermint oil capsules can help relieve abdominal pain [72]. Peppermint oil can, however, cause rectal burning, esophageal pain, and allergic reactions [72]. There are no controlled studies in children showing the efficacy of anticholinergics in IBS and adult trials have also produced conflicting results. In general, the anticholinergic effect in adults with IBS is comparable to a placebo [72]. The authors do not prescribe antispasmodics, but if a patient is already using them and finds them useful, then the authors do not discontinue the medication. Loperamide can be useful to reduce the stool frequency in diarrhea-predominant IBS patients.

Tricyclic antidepressants (TCAs) are useful in treating IBS symptoms in adults [72]. TCAs act primarily through noradrenergic and serotonergic pathways and have antimuscarinic and antihistaminic properties as well. TCAs facilitate descending inhibitory pain pathways and alter GI physiology to improve IBS symptoms. Amitriptyline has sedative properties that can be used to improve sleep quality when given at bedtime. The usual dose of amitriptyline is 0.2 mg/kg once at bedtime, but higher dose can be tried if there is no improvement in 2–3 weeks. A randomized controlled trial in 83 children with pain-associated FGIDs, including IBS, reported no significant difference between placebo and amitriptyline group after 4 weeks of amitriptyline therapy [73]. The amitriptyline dose in this trial was fixed, and the treatment duration was relatively short and may have affected the outcome. TCAs can cause cardiac dysrhythmia in patients with prolonged QT syndrome; therefore, an electrocardiogram prior to starting the therapy is advisable.

In recent years several organisms, such as *Lactobacillus* GG, *L. plantarum*, *L. acidophilus*, *L. casei*, the probiotic cocktail VSL#3, and *Bifidobacterium animalis*, have been used to treat IBS symptoms, such as bloating, flatulence, and constipation. However, only a few products have been shown to be effective in relieving pain and global symptoms in IBS [74–78]. One organism *B. infantis* was reported to be superior to both a *Lactobacillus* and placebo in relieving abdominal pain, bloating, and difficult defecation and also improved composite score in IBS patients [78, 79]. A meta-analysis concluded that *Lactobacillus rhamnosus* GG moderately increases treatment success in children with abdominal pain-

related FGIDs, particularly children with IBS [80]. The probiotic cocktail VSL#3 was reported to be superior to placebo in relieving abdominal pain and bloating and improve global symptom score in children with IBS [81]. The emerging data seem to suggest that probiotics may have a role in the treatment arsenal of pediatric IBS.

Neuromodulation has recently been shown to be an effective treatment modality for IBS. Dysregulated brain–gut axis signaling, which leads to visceral hyperalgesia, is part of the complex pathogenesis of IBS [82]. Central nervous system pathways play a vital role in the increased sensation of pain in response to physiologic stimuli, with numerous brain imaging studies documenting the structural and functional connectivity abnormalities in both adult and pediatric patients with IBS [82–84]. Functional MRI performed during rectal distension on adolescents with IBS and adolescent controls showed that greater activation in neural structures of the homeostatic afferent and emotional arousal networks in the IBS patients, supporting the role of altered salience network functioning as a neuropathological mechanism of IBS symptoms [16]. While deep brain and spinal cord stimulation, which have been shown to improve abdominal pain and altered bowel habits in adult IBS patients [85] are invasive, peripheral neurostimulation is a non-invasive approach to deliver modulation of the central pain pathways via stimulation of peripheral cranial neurovascular bundles in the external ear. The safety and efficacy of peripheral neuromodulation with an auricular device delivering percutaneous electrical nerve field stimulation, which is thought to stimulate branches of several cranial nerves (V, VII, IX, X) that project to the brainstem, compared to a sham device, have been demonstrated, namely, with significantly reduced worst abdominal pain and composite pain scores both short and long term, while improving global well-being and functioning [86].

"Irritable" Pouch Syndrome

Total proctocolectomy with ileal pouch–anal anastomosis is performed in patients with fulminant colitis or ulcerative colitis refractory to medical management. The most common long-term complication of ileal pouch–anal anastomosis is pouchitis [87] and presents with increased stool frequency, urgency, abdominal cramping, and bleeding (see Chap. 44) [87]. Patients with ileal pouch–anal anastomosis who have symptoms but no identifiable structural abnormalities are thought to have irritable pouch syndrome. It resembles other pain-associated FGIDs characterized by visceral hypersensitivity in the presence of normal rectal biomechanics. In one adult study of 61 symptomatic patients with ileal pouch–anal anastomosis, 42% had no macroscopic or microscopic inflammation of the pouch [87]. Almost half of the patients with symptoms but no pouch disease responded to treatment with antidiarrheal, anticholinergic, and antidepressants, similar to what has been used in treating patients with IBS [88].

Summary

The onset of IBS symptoms most likely represents the convergence of genetic and psychosocial factors, perhaps triggered by some external stimulus, such as a dramatic life event or an enteric infection or inflammatory condition. Dysmotility, hypersensitivity, and disturbed brain perception may be the consequence of these events rather than the primary abnormality. Persistent low-grade bowel inflammation may be responsible for IBS symptoms following a bacterial GI infection.

In some patients IBS symptoms may predate the development of IBD, and a subset of IBD patients can have "functional" GI symptoms. Altered bowel sensory and motor function due to inflammation-induced changes in the bowel neuromuscular apparatus may be responsible for "functional" GI symptoms in IBD. In due course we may realize that immune dysregulation plays a central role in the pathogenesis of both IBS and IBD and they are the two ends of a spectrum of GI inflammatory disorders.

Most patients with IBS have mild disease and require education, reassurance, and lifestyle changes. A smaller proportion with moderate to severe symptoms can benefit from CBT and treatment with pharmacological agents.

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Inflammatory Bowel Disease in Pregnancy

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Abigail J. Meyers and Sunanda Kane

Introduction

While the incidence of ulcerative colitis has remained stable, the incidence of Crohn disease (CD) has increased over the past few decades [1]. It is not clear whether this is due to improved diagnostic techniques, environmental or genetic influences, or other factors not yet identified. However, the consequence of this trend is a growing population of patients in their formative and childbearing years.

Having intercourse, age of sexual debut, and pregnancy rates do not differ among adolescents with and without disability based on a study by Suris et al. [2]. Disability, defined "as a long-term reduction in ability to conduct social role activities, such as school or play, because of a chronic physical or mental condition," [3] does not interfere with sexuality of an adolescent [4]. Thus, adolescent patients with inflammatory bowel disease (IBD) may be sexually active and are at risk for pregnancy. This chapter will review how pregnancy affects the adolescent with IBD both in terms of disease and management options and how IBD and its therapies may affect a pregnancy.

Contraception

The management of contraception in those female patients with IBD who do not wish to become pregnant differs from that in normal female patients. A recent study by Gawron et al. found that a quarter of women with IBD were not using any form of birth control even though they were at risk for an unintended pregnancy [5]. The most important goal still remains the selection of the most reliable method of birth control. Literature continues to have limitation in the effects of birth control on IBD symptoms.

Barrier methods of contraception are acceptable but are not as effective as alternatives. The use of intrauterine devices (IUDS) is considered a Category 1, or without restriction for use in IBD. However, it is not usually recommended, as any complaint of abdominal/pelvic pain could potentially delay the correct diagnosis of active IBD versus pelvic inflammatory disease [6]. There is additional risk of sexually transmitted illnesses in the younger population due to sexual behaviors, such as increased numbers of partners. There is a single case report of a patient who experienced an exacerbation of Crohn disease after insertion of a levonorgestrel intrauterine system [7]. However, no strict contraindication exists to preclude their use in the appropriate patient.

The data regarding the safety of oral contraceptives (OCs) in IBD are conflicting suggesting that the benefit overall outweighs risk but needs to take into consideration disease status, postoperative anatomy and smoking status [8]. Early studies suggested an increased risk (odds ratios ranging from 1.2 to 6) for the development of Crohn disease and ulcerative colitis with OC use. Several of these studies did not, however, account for tobacco use. Reports from Europe, where contraceptives contain a higher estrogen content, continue to show modest increases in risk for the development of Crohn disease after adjusting for cigarette use (odds ratios 1.2–2.0) [9]. A meta-analysis by Cornish et al. suggests that the overall OR is significantly higher for the incidence of Crohn disease with an odds ratio of 1.46 (1.26–1.70) [10].

Additional data suggest that OC use may exacerbate disease activity. Two small prospective studies have found an increased risk of disease recurrence after induction of remission in Crohn disease with OC use [9, 11]. Timmer found a hazard ratio of 3 (1.5–5.9) for increased disease activity following medical induction of remission. Alternatively, Gawron et al. have demonstrated that OCP use can help with cyclical symptoms of IBD and only a small proportion of women report symptomatic worsening [12].

Other considerations for OC use include increased risk of venous thromboembolism (VTE) and impaired absorption. Women with IBD are at a threefold higher risk for VTE than

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the general population [13]. It may be prudent to consider delaying OC use until disease has achieved more optimal control. Women with significant bowel resection do not have absorption concerns with OCs [14].

At this time, no standard guidelines exist for OC use, as there are many preparations available. The variable amounts of progesterone and estrogen are the factors that determine the side effect profile. The choice of which OC preparation to use has to be individualized, taking into consideration other factors, including patient history, parity, and personal preferences. It does appear prudent to try a formulation that contains the lowest amount of estrogen possible or the progesterone only formulations, given the additional risk factors of smoking and predilection toward thromboembolic events in patients with IBD. Hormonal contraception in the transdermal formulation may be considered because it avoids the addition of another oral pill for the adolescent patient as well as its delivery despite possible decrease in absorption during active flares in a patient with IBD.

Fertility

Adolescents with chronic conditions are just as likely to have sexual intercourse as their peers [3]. Even though adolescents may not be trying to get pregnant, the rising age of marriage and decreasing age of first intercourse combined with the inconsistent use of contraception has led to the continued trends of teenage motherhood [15].

Overall, the fertility rates for female patients with ulcerative colitis are essentially the same as those of the normal population [16]. Active Crohn disease, however, can reduce fertility in several ways, depending upon the location of inflammation [17]. Active inflammation in the colon and terminal ileal disease have been shown to decrease fertility. Active ileal inflammation can cause inflammation or scarring of the fallopian tubes and ovaries because of their proximity to the terminal ileum in the lower abdomen. Female patients with perianal disease may have secondary dyspareunia and decreased libido, contributing to lower fertility rates. The systemic effects of Crohn disease, including fever, pain, diarrhea, and suboptimal malnutrition, have also been implicated in decreased fertility. Female patients who have had any surgical resection are at risk for adhesions, which can also impair tubal function. Newer data have suggested that despite a decreased fertility rate, surgery does not affect success of in vitro fertilization in women with IBD compared to the general infertility population [18].

None of the medications used to treat IBD has an adverse effect on female fertility, but it is important to remember that sulfasalazine therapy reduces sperm motility and count in males [19]. These effects are not dose related and do not respond to supplemental folic acid. A sperm analysis study has failed to show significant differences on count or morphology in men with exposure to 6-mercaptopurine (6-MP) compared to established WHO criteria [20]. In addition, further epidemiologic work has failed to demonstrate an effect on birth outcomes in children born to fathers on 6-MP, despite an early study that suggested this association [21, 22].

Effect of IBD on Pregnancy

If a woman is doing well and in remission, there is no evidence to suggest that her risk of a flare is greater than that of a non-pregnant patient. While there is no minimum required time period for a patient to be in remission prior to a planned conception, at least 3 months is recommended. If active disease is present, it is likely to continue through pregnancy and will place the pregnancy at greater risk for a complication [23].

Female patients with inactive IBD at the time of conception appear no more likely to experience spontaneous abortion, stillbirth, or children born with a congenital abnormality [24]. Most studies suggest that babies born to female patients with IBD, regardless of disease activity, are of smaller birth weight [25] and more likely to be born preterm and small for gestational age [26].

The presence of IBD does not appear to have an impact on maternal complications related to pregnancy, including hypertension or proteinuria [27]. Broms et al. demonstrated that women with IBD were more likely to experience venous thrombosis and hemorrhage in the setting of active disease [28].

Effect of Pregnancy on IBD

The activity of IBD at conception remains the primary predictor of the course of pregnancy. For female patients with quiescent UC at the time of conception, the rate of relapse is approximately the same in pregnant versus non-pregnant patients [29]. This is in contrast to the presence of active disease at the time of conception, which is associated with continued or worsening disease activity in approximately 70% of female patients. Comparable observations are seen in CD [23]. The older literature suggested a trend for disease to flare in the first trimester, but this was documented prior to the accepted practice of maintenance therapy, continued even during pregnancy. Some patients will have symptomatic disease only when pregnant, with quiescence between pregnancies and exacerbations during subsequent pregnancies. The clinical course or outcome of previous pregnancies cannot predict either the clinical course of IBD or the outcome of pregnancy.

There are data suggesting that a history of childbearing changes the natural history of Crohn disease [30]. Female patients having been pregnant had fewer resections or longer intervals between resections as compared to female patients who had not had children but otherwise similar disease. One theory proposed is the inhibition of macrophage function by relaxin. Relaxin is a hormone produced exclusively during pregnancy which may result in less fibrosis and stricture formation by this inhibition of macrophages. In addition, a more recent population-based study of pregnancies in Copenhagen has suggested that pregnancy can change the natural history of IBD; women were less likely to experience a flare of their disease following pregnancy compared with those women who had not experienced a pregnancy [31].

Management of IBD During Pregnancy

Clinical Assessment

The main priority is to establish and maintain remission before the patient conceives. One of the problems in CD is the accurate definition of disease activity. In CD, a patient may feel fine even though she has an elevated C-reactive protein or an abnormal colonoscopy and/or X-ray. Many pregnant patients will have intermittent abdominal discomfort related to changes in bowel habits or gastroesophageal reflux that commonly occurs during pregnancy. In addition, abdominal pain in the pregnant IBD patient could be related to cholelithiasis, pancreatitis, toxemia, or a problem with the pregnancy itself. Clinically, these processes can be distinguished from a flare of IBD by a careful history, examination, and laboratory evaluation.

It is important to remember that during pregnancy, hemoglobin and albumin levels decrease by 1 g/dL, sedimentation rate increases two- to threefold, and there is a 1.5-fold rise in serum alkaline phosphatase. It is also important to keep in mind that a growing uterus changes normal anatomy, with the terminal ileum and appendix higher in the right upper quadrant.

In terms of radiographic testing, ultrasound exams are safe, as is magnetic resonance imaging [32] without gadolinium. Clearly, it is best to avoid exposure of the fetus to radiation from abdominal X-rays, especially early in the pregnancy. However, the absolute risk to the fetus of abdominal radiography is minimal, and clinical necessity should guide the decision making [33, 34].

There is no evidence that, if indicated, a sigmoidoscopy or colonoscopy will induce premature labor [35]. Most patients with IBD can be evaluated with sigmoidoscopy without full colonoscopy. However, if full colonoscopy is necessary to establish diagnosis or severity of disease, sedation with propofol with close fetal monitoring is suggested [35, 36].

Medical Therapies

The key principle to management is to remember that the greatest risk to pregnancy is more likely active disease than active therapy. Since there are limited definitive data available on the safety of IBD medications in pregnancy, the focus therefore should be on establishing remission before conception and maintaining remission during pregnancy. The two fundamental issues considering medical therapy in the pregnant IBD patient are regarding the outcome of the pregnancy: whether the mother is taking medications for her IBD compared to those who are not and whether the medications used to treat the pregnant patient are safe and effective.

Most investigators have shown that medical therapy, when analyzed as an independent variable, has no effect on pregnancy outcome [3, 16]. Those patients who have been reported to have adverse birth outcomes tend to occur more often in the setting of active disease. Table 53.1 outlines the relative safety profiles of those medications used in IBD.

Antidiarrheals

Loperamide use has not been associated with an increased rate of first trimester fetal malformations, spontaneous abortion, low birth weight, or premature delivery [37] and is considered low risk. One has to keep in mind, however, that increased stool frequency may be a sign of increased activity and loperamide use should be monitored. Diphenoxylate with atropine is teratogenic in animals, and fetal malformations have been observed in infants exposed during the first trimester [38]. Antispasmodics and anticholinergics have been associated with non-life-threatening fetal malformations and are best avoided during pregnancy [39].

Aminosalicylates

Sulfasalazine has been used for over 50 years in the treatment of ulcerative colitis. Sulfasalazine crosses the placenta with fetal serum levels equivalent to maternal levels [40]. Multiple studies have shown that despite this phenomenon,

Table 53.1 Safety of IBD medications during pregnancy

Low risk when indicated	Contraindicated
Oral, topical mesalamine	Methotrexate
Sulfasalazine	Thalidomide
Corticosteroids	Diphenoxylate
Total parenteral nutrition	
Loperamide	
Azathioprine/6-MP	
Biologics	
Tofacitinib[a]	
Metronidazole	
Ciprofloxacin[b]	

[a] Conflicting and limited data
[b] Not safe in third trimester

there appears to be no increased incidence of abnormal birth outcomes [41]. Sulfasalazine has been shown to inhibit folate acid metabolism, which can cause neural tube defects in the fetus [42]. While the risk of fetal abnormalities has not been shown to increase with sulfasalazine and its derivatives, pregnant female patients taking sulfasalazine should still supplement their diet with 2 mg of folate daily.

5-Aminosalicylic acid (5-ASA) and its metabolite acetyl-5-aminosalicyclic acid are found in both maternal and fetal plasma in female patients taking mesalamine; however, a meta-analysis of published studies has demonstrated its lack of effect on the incidence of adverse birth outcomes [43]. The use of topical 5-ASA agents during pregnancy has not been associated with any increase in adverse birth outcomes related to its use during pregnancy.

Antibiotics

The most frequently used antibiotics in IBD include predominantly metronidazole and ciprofloxacin. Animal studies have not shown any evidence of teratogenicity or increased fetal loss with metronidazole. Short courses of metronidazole during the first trimester of pregnancy for *Trichomonas vaginalis* have been shown to be well tolerated and low risk [44, 45]. In a study of 228 female patients exposed to metronidazole during pregnancy followed prospectively through their pregnancy, 86% of female patients were exposed during the first trimester [44]. The malformation rate was 1.6% in the treatment group and 1.4% in the control group. Female patients with IBD require the use of metronidazole for longer periods of time, and there are limited data regarding prolonged use of this medication.

In animal studies, no teratogenicity has been seen with ciprofloxacin, although musculoskeletal abnormalities have been identified in immature animals [46]. Moskovitz et al. found that in 27 patients who were receiving 1 g/day, even in the first trimester, its use appeared to be safe (18 patients) [47]. Another study investigated the effects of fluoroquinolones in the first trimester and did not show an increased risk of congenital malformations, prematurity, or low birth weight [48].

While these data are comforting, this information applies to the non-IBD population, where antibiotics are used short term. These agents are more commonly used for longer durations in IBD, and the use of these two antibiotics during pregnancy should currently be restricted to short-term courses.

Corticosteroids

As shown in studies for rheumatological conditions as well as for IBD, corticosteroids during pregnancy have largely been regarded as low risk [49]. Corticosteroids cross the placental barrier, but the fetal–maternal serum concentration of the steroids varies between different corticosteroid preparations. Prednisolone and prednisone are more efficiently metabolized by the placenta than dexamethasone or betamethasone, and fetal levels of this steroid are approximately eight- to tenfold lower than that of the maternal circulation [50]. Since corticosteroids are conjugated more rapidly to biologically less active sulfates in the fetus than the adult, a suppressive fetal blood concentration is not often reached with therapeutic doses used during pregnancy.

Among female patients with IBD, corticosteroids have not been found to be harmful to the fetus [22]. Mogadam et al. studied the effects of steroid use in 185 out of 531 pregnancies in female patients with IBD and did not find a statistically significant increased incidence of prematurity, spontaneous abortions, stillbirth, or development defects in the ulcerative colitis subgroup (4.6% in the treated group vs. 2.2% in the untreated group; $P > 0.10$) [49]. In the Crohn disease subgroup, patients did significantly worse in the treated group compared to the untreated group (13.5 vs. 1.9%, $P < 0.1$). Patients with CD may have more severe disease and require more medical intervention to control the activity of the disease, and it is possible that the severity of the illness in CD itself may have caused these patients to not fare as well as the ulcerative colitis patients.

Budesonide is a modified corticosteroid with about 10% systemic absorption and can be used for the induction of remission for IBD [51–53]. Beaulieu et al. looked at 539 female Crohns patients with 60 pregnancies in 41 women and 8 of these women received budesonide during pregnancy. Seven women carried to full term and 1 woman delivered at 35 weeks. They had no congenital abnormalities, spontaneous abortions, or other fetal or maternal adverse effects and no increased incidence of gestational diabetes or preeclampsia [54].

Immunosuppressants

As more patients with IBD are treated with immunosuppressants, there is a growing need for information on their effects on the pregnant patient and growing fetus.

Immunomodulators

There is a large body of literature on the use of immunomodulators among pregnant transplant recipients and those patients with autoimmune diseases [54, 55]. It is generally believed by the most experienced IBD clinicians that immunomodulators, such as 6-MP, azathioprine, and even cyclosporine, can be used safely during pregnancy if the mother's health mandates therapy, based on the evidence from these other conditions.

Thiopurines are used for steroid-sparing and steroid-dependent IBD. Azathioprine (AZA) is a prodrug of 6-MP and does cross the placental barrier, but the immunomodulatory effects of azathioprine do not affect the fetus due to the lack of inosinate pyrophosphorylase in the fetus, an enzyme

which converts azathioprine into the active metabolites of 6-MP and *S*-methyl-4-nitro-5-thioimidazole [56]. Several human studies have suggested that AZA and 6-MP are low risk during pregnancy when used for IBD [57].

An older study with a small number of pregnancies suggested its safety [58]. Francella et al., in a retrospective cohort study, investigated the possible toxicity of 6-MP from a review of records of 485 patients who had received the drug [57]. Of the 462 female patients who were contacted, 155 had conceived at least one pregnancy after developing IBD. Pregnancies were analyzed based on whether the patients had taken 6-MP before or at the time of conception compared with those IBD patients who had their pregnancies before taking 6-MP. There was no statistically significant increase in spontaneous abortion rates or major congenital malformations among patients taking 6-MP compared to control subjects [RR 0.85 (95% CI, 0.47–1.55), $P = 0.59$]. The authors concluded that the use of 6-MP or AZA and its beneficial effect on maternal health outweighed any risk to the fetus and that it was not unreasonable to continue its use throughout pregnancy. Recently, results regarding pregnancy in a prospective French cohort of Crohn patients have become available. There were no observed differences in the outcome of pregnancy for patients treated with thiopurines compared to women with CD who used no medications during pregnancy [59, 60].

In IBD, methotrexate is used in the management of steroid-dependent or steroid-resistant Crohn disease as an alternative to azathioprine and 6-MP. Methotrexate is a known abortifacient, showing increased risk of spontaneous abortions in various studies, currently used therapeutically at high doses in tubal pregnancies [61]. Therefore, methotrexate is a category X medication. Patients who are started on methotrexate should be strongly advised to use reliable contraception. If termination of a pregnancy is not possible, high doses of folic acid therapy are recommended to prevent CNS abnormalities, including anencephaly, meningomyelocele, and hydrocephaly. The optimum management includes careful counseling and effective contraception prior to any initiation with methotrexate therapy [62].

Biologic Agents

As biologic agents become increasingly prevalent for the treatment of IBD, more data are emerging in the pregnant population marking the overall safety of continuing certain biologic therapies throughout the duration of pregnancy to keep disease well controlled. A recent meta-analysis included 48 studies comprising 6963 patients and biologic therapy in IBD pregnancies was associated with comparable rates of early pregnancy loss, preterm birth, still birth, low birth weight, and congenital malformations as the general population and meta-regression did not reveal an association of disease activity on adverse outcomes [63]. Special consideration to vaccines for the infant when born includes delaying live virus vaccinations by 6 months with in utero biologic exposure [64]. MMR and varicella are live vaccines but given at 1 year and are appropriate for the infant exposed to biologic therapy in utero.

Anti-tumor Necrosis Factors (TNFs)

The early safety literature with infliximab includes one study by Katz et al. suggesting that infliximab exposure for CD or rheumatoid arthritis (RA) during pregnancy does not lead to a statistically significant increase in adverse outcomes compared to that of the general population, using the National Center for Health Statistics database between 1976 and 1996 for comparison [65]. Of 96 female patients who were studied, live births (67, 95% CI: 56.3–76.0 vs. 67%), miscarriages (17, 95% CI: 8.2–23.2 vs. 15%), and therapeutic terminations (16, 95% CI: 11.5–28.0 vs. 19%) were not statistically different from that of the general population. In this review, 8 of 14 miscarriages in female patients who were exposed to infliximab occurred at or before 10 weeks. It is thought that these miscarriages early in pregnancy were related more to disease activity than infliximab use. Maternal IgG is transported across the placenta as early as the late first trimester [66], but efficiency of transport is poor, so total fetal IgG levels are low until the late second or early third trimester, suggesting that it is not the infliximab exposure that would be contributing to this early miscarriage rate observation. A case–control study from France of pregnant women treated with infliximab versus those not failed to show any increased risk in pregnancy or neonatal outcomes [67]. A recent study from France of 1457 IBD pregnancies exposed to anti-TNF demonstrated no increased risk after 24 weeks gestation for complication in pregnancy; however, there was an increased risk for flare [68].

Because adalimumab is also a full antibody, it too crosses the placenta after week 20 of pregnancy. Drug can be detected in cord blood of the newborn up to 6 months following in utero exposure [69].

Certolizumab pegol does not cross the placenta as it is a pegylated Fab fragment [70]. However, at this time there is no recommendation to switch a patient from one agent to another if she is in remission solely because of these properties [71].

The European Crohn's and Colitis Organisation performed a meta-analysis in 2016 concluding that anti-TNF therapy does not increase adverse pregnancy outcomes when compared to the general population [72]. Similarly, the Rotterdam experience demonstrated safety of stopping anti-TNF therapy in the second trimester for those patients in remission, but those who demonstrate active disease to continue their anti-TNF therapy given that uncontrolled IBD is associated with poor pregnancy outcomes [73, 74]. Children born to mothers using anti-TNF therapy have been studied

up to 1 year of life without concerns of increased risks [68, 72]. It is recommended to continue anti-TNF therapy throughout pregnancy to decrease risk of IBD flare. If in remission, anti-TNF could be discontinued during the second trimester, especially with infliximab.

Anti-integrins

Vedolizumab crosses the placenta but data suggest that it is low risk during pregnancy and carries a B safety rating [75, 76]. A retrospective review was done of 46 pregnancies reported from six vedolizumab clinical trials; 24 female participants received vedolizumab with 11 of these women having live births with 9 at full term. Four of the women had spontaneous abortions but half of these women had moderate to severe disease activity demonstrating again that disease status plays a larger role in outcomes [77]. A recent systematic review of four studies looking at pregnancy outcomes in female patients with IBD on vedolizumab demonstrated an increased incidence of preterm births (OR 1.97, 95% CI, 1.10–3.54) but no difference in number of live births or congenital malformations [78]. This was demonstrated in a subgroup analysis of a Nielsen's large meta-analysis that preterm birth was higher in women with vedolizumab use than anti-TNF users [63].

Interleukins 12 and 23

Pregnancy safety data with use of ustekinumab is limited in the IBD literature. Recently, Volger et al. demonstrated data from spontaneous reporting, clinical studies and registries of 478 pregnancies with exposure to ustekinumab during pregnancy or within 3 months prior to conception. About 72% of these pregnancies resulted in live births with a rate of congenital anomalies being 3.9%. The rate of spontaneous abortion was 18.4%. Given these outcomes were consistent with the general population, ustekinumab exposure during pregnancy appears safe [79]. Recommendation is to continue medication through pregnancy to maintain remission and plan last dose 6–10 weeks before delivery and continuing therapy postpartum [80–82].

Small Molecules (Janus Kinase Inhibitor)

Tofacitinib data are limited but given that it is a small molecule, it may cross the placental barrier. Previously preconception contraception counseling was recommended given the limited safety data. Reviewing the safety databases retrospectively for UC, RA, psoriatic arthritis, and psoriasis demonstrated 158 pregnancies reported with maternal and paternal exposure of 74 and 84, respectively, without any reports of fetal death [79]. There were 19 reported spontaneous abortions and 93 healthy newborns. However, contraception was required for enrollment in the clinical trials so there is further limitation in follow-up and under reporting as women were discontinued in the trial upon becoming pregnant. Recent updates to the OCTAVE trials reported 34 pregnancies with exposure to tofacitinib and 15 maternal first trimester exposures demonstrated 60% healthy newborns, 13.3% medical terminations, 13.3% spontaneous abortions, and 13.3% lost to follow-up [80]. Due to the limited data, contraception is recommended and further monitoring will be performed in clinical studies.

Breastfeeding

The advantages of breastfeeding are well known, but the effects of IBD medications on breastfeeding still remain unclear. The breastfeeding initiation rates among adolescent mothers are approximately 35–40% [83] and are significantly less than the national rate, which is 60%. In a study by Kane et al., only 44% (54/122) of female patients with IBD had breastfed their infants, the majority of whom had UC [84]. A more recent study done in Canada showed the opposite; women with IBD nursed more frequently than the background population [85]. In neither study was there an increased risk for disease activity associated with the act of nursing itself; disease activity was related to cessation of therapies to treat disease.

Table 53.2 summarizes the safety data regarding medications and their use during breastfeeding.

Sulfasalazine and other forms of 5-ASA are excreted into the breast milk with milk concentrations that are about 40–50% of the maternal serum levels with outcomes suggesting its safety during breastfeeding [86]. There is one case report of diarrhea in a nursing infant of a mother who used mesalamine suppositories 6 weeks after childbirth with four additional challenges of breastfeeding following suppository administration leading to similar results [87].

In the case of immunomodulators, a small retrospective study from Austria looked at long-term safety outcomes of children breastfed with mothers taking thiopurine comparing to mothers without thiopurine use and all children had appropriate mental and physical development without increased hospitalizations or infections [88]. A prospective study done by Christensen [89] demonstrated milk concentrations were highest within the first 4 h of maternal ingestion and only equated to 0.0075 mg/kg bodyweight. Thus, it seems reason-

Table 53.2 Safety of IBD medications during breastfeeding

Safe to use when indicated	Contraindicated
Oral mesalamine	Methotrexate
Topical mesalamine	Ciprofloxacin
Sulfasalazine	Metronidazole
Corticosteroids	Loperamide
Azathioprine/6MP	
Biologics	

able to suggest that drug exposure is minimal and to minimize it further that a mother could nurse right before taking her dose.

Approximately 5–25% of the maternal serum concentration of corticosteroids reaches breast milk, and the amount received by the infant is considered minimal [50]. The commonly used corticosteroids, prednisone and prednisolone, result in low breast milk concentrations with doses of <20 mg of corticosteroids deemed to be safe to use during nursing [90]. Some suggest that breastfeeding is safer if delayed for 4 h after ingestion of steroids [91].

It is not mandated that women using biologic agents need to stop nursing. A prospective study was performed investigating detectability of biologics in breast milk and if breastfeeding during treatment was associated with increased infections or functional delays in the infant [92]. Infliximab, adalimumab, certolizumab, and ustekinumab were detected in breast milk. Infection and development were not different between infants from mothers receiving biologic, immunomodulatory, or combination therapy than those infants from unexposed mothers.

Other medications, such as metronidazole, ciprofloxacin, and methotrexate, should be discontinued in nursing mothers given their high concentrations in breast milk.

Mode of Delivery

The mode of delivery should most often be an obstetrical decision and not solely based on the presence of IBD. Adolescents have lower Cesarean section rates than adult women [93]. The indications for Cesarean section for obstetrical reasons are not different in female patients with IBD. The presence of UC does not have a significant impact on the method of delivery, nor it is an indication for a section per se. However, active perianal disease in Crohn disease may worsen after a vaginal delivery. One retrospective study of female patients with CD found that 18% of those without previous perianal disease developed such disease after delivery, usually involving an extensive episiotomy [94]. A retrospective chart review from 2014 found that there was no difference in risk of symptomatic flares of perianal disease with a vaginal delivery versus a C-section [95]. In addition, a recent study failed to demonstrate any influence the mode of delivery on the natural history of disease [96]. General guidelines include a planned C-section for any woman with known perianal or rectal CD or if the birth appears to be more complicated than initially presumed.

There has been debate whether female patients who have had ileal pouch–anal anastomosis (IPAA) should deliver vaginally or whether Cesarean section should be planned. In one study of 43 pregnancies in female patients' status post-IPAA, pregnancy was well tolerated, with a complication rate lower than in female patients who had an ileostomy [97]. Although more Cesarean sections were performed in female patients with IPAA, the explanation was likely due to the uncertainty about the pouch function. An extended follow-up of female patients with an IPAA who delivered vaginally showed no adverse long-term effects on pouch function. The type of delivery in patients with an IPAA should be dictated by obstetrical considerations. Other surgeons feel that the risk to permanent pouch failure is higher with a vaginal delivery and recommend any patient with surgery for UC undergo Cesarean section.

Surgery and Pregnancy

In the pregnant IBD patient, elective surgical procedures are uncommon, but those that are performed in the second trimester do not appear to carry a significant increase in perinatal morality in female patients without IBD [98].

The indications for surgery during pregnancy are identical to that of non-pregnant patients. These include obstruction, perforation, abscess, and hemorrhage. The approach of continuing medical therapy may only further increase the risk to both mother and fetus. In the ill pregnant IBD patient, the greater risk to the child is continued maternal illness rather than surgical intervention [99]. In general, doing what is best for the mother results in what is ultimately best for the fetus.

In patients with Crohn disease, Hill and colleagues described three pregnant patients with intraperitoneal sepsis, requiring surgery [100]. All three female patients recovered and delivered healthy infants. Most reports suggest proceeding to surgery when indicated. A variety of procedures have been performed, including proctocolectomy, subtotal colectomy with ileostomy, hemicolectomy, or segmental resection, and combined subtotal colectomy and Cesarean section. Two general points should be made: (1) primary anastomosis carries a greater risk of postoperative complication rate, and thus a temporary ileostomy is generally preferred, and (2) if the fetus is significantly mature, then Cesarean section along with bowel resection is indicated.

In female patients who have a total proctocolectomy with IPAA prior to pregnancy, there is controversy regarding postoperative fertility and sexual function. An early study suggests that these are maintained [101], but most recent studies [102, 103] suggest a significant decrease in fertility following this type of surgery. The good news, however, is that there are new data to suggest that in vitro fertilization in these patients is successful [104]. During actual pregnancy, however, female patients with IPAA did note an increase in stool frequency, incontinence, and pad usage, with symptoms resolving after delivery.

Pregnancy has not been shown to complicate stoma function. Female patients may experience some prolapse due to abdominal pressure, but no increased risk to the pregnancy is encountered.

Transition of Care

The time to transition of care from a pediatric gastroenterologist to an adult gastroenterologist should be an individualized decision. Factors, such as autonomy level, activity of disease, and transitioning in other phases of life, all should be taken into account. When the adolescent patient becomes pregnant, there may be consideration of transitioning care to the adult provider, depending on the pediatric and adult gastroenterologist's experience and comfort level in dealing with pregnancy [105].

Summary Points

- Adolescents with IBD are at risk of pregnancy.
- Fertility is affected in postsurgical UC and in active CD.
- There is no increase in adverse outcomes with quiescent IBD.
- Active disease at conception increases the risk for adverse outcomes.
- The majority of medications for IBD are safe in pregnancy and breastfeeding—active disease is more deleterious than active therapy.

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Pediatric Inflammatory Bowel Disease Care in Low- and Middle-Income Countries

54

Almuthe Christine Hauer

Introduction

The inflammatory bowel diseases (IBDs) have been regarded traditionally as diseases of westernized nations. However, the epidemiology of IBD is changing worldwide, as was shown in the largest systematic review to date including 147 population-based studies. Herein, Ng et al. revealed a worldwide increase in IBD incidence since 1990, including newly industrialized countries in Africa, Asia, and South America, with annual increases of up to 17.8% for Crohn disease (CD) and 14.9% for ulcerative colitis [1]. A similar trend was shown for pediatric-onset (<19 years at diagnosis) IBD when analyzing 144 population-based studies from 38 countries. Annual incidences were as high as 11.4/100,000 person-years in Asia, the Middle East, and Oceania compared to 15.2/100,000 in North America, and in time-trend analyses, almost 70% of CD studies reported an increasing incidence [2]. These data indicate that pediatric IBD (PIBD), too, has become a global disease, thus highlighting the need not only for research into its prevention but also for innovations in healthcare to manage this complex and costly disease.

Even in high-income countries (HICs), the quality of PIBD management may differ with significant diagnostic delays in remote German regions due to a lack of referral centers [3] or widespread variation in treatment and disease monitoring in North America [4]. Still, these observations contrast sharply with many low- and middle-income countries (LMICs) where, in addition to a general lack of resources, structured health insurance systems, and well-equipped centers, there are neither formally trained pediatric gastroenterologists nor training programs available [5]. Therefore, almost invariably general practitioners or pediatricians without special training will care for children with IBD who enter a healthcare system where diagnostic facilities are limited, as are the treatment options. Importantly, current guidelines usually target an audience with a subspecialist level of training, often assisted by cutting-edge diagnostic and treatment facilities.

In this chapter, recent guidelines on PIBD diagnostics and treatment published by ECCO (European Crohn's and Colitis Organization) and ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology, and Nutrition) are analyzed for their potential to be adjusted to everyday practicalities and real-life scenarios focusing on the so-called middle-income countries (MICs) with limited resources, but a somewhat structured healthcare system and documented increase in PIBD. Such MICs or "countries in transition" are defined on the basis of an "inequality-adjusted human development index" (IHDI) of <0.75 (the highest IHDI worldwide 0.889, Norway), which also takes into account the distribution of average achievements in health among the countries' populations, thus capturing losses in human development due to inequality. In 2020, an IDHI of <0.75 was applicable for countries such as Armenia, Bulgaria, Colombia, Indonesia, and Jordan [6].

Diagnostic Evaluation

Accurate diagnosis of PIBD should be based on a combination of history, physical examination, laboratory examination including basic and more specific serological and intestinal markers, as well as invasive examinations including esophagogastroduodenoscopy (EGD) and ileocolonoscopy (IC) with histopathology (Table 54.1). Importantly, children with chronic diarrheal symptoms should have an infection that could mimic PIBD ruled out [9]. In many LMICs, there is a high prevalence of intestinal infections and the absence of a sole diagnostic gold standard could lead to delays in diagnosis and accurate assessment of the disease [10, 11].

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Table 54.1 Diagnostics: examples of modifications

Published recommendations (ECCO/ESPGHAN guidelines, position papers)	LMIC-specific modifications, alternatives, and considerations
Clinical evaluation and laboratory tests	
Clinical evaluation (including growth monitoring and PIBD activity indices)	• Translation of Disease Activity Indices into patients' languages • Creation of mobile applications
Complete blood cell count including red blood count and platelet indices	• Further evaluation (iron, vitamin B12, folate) according to anemia subtype
CRP, ESR, albumin	• CRP and correlation with (transmural) inflammation in Crohn disease (CD) • Combining CRP, ESR and fecal markers to improve specificity, if not too costly
Testing of TPMT activity recommended prior to therapy with 6-Thioguanine	• Testing of TPMT activity phenotypically more cost-effective than genetically • Close monitoring of WBC and liver enzymes (early at onset of 6-TG therapy)
Testing for latent tuberculosis (TB) infection/intestinal TB by • Mantoux Tuberculin Skin Test (TST) or • Interferon-Gamma Releasing Assay	• Anti-TB therapy to be considered prior to (CD) treatment (endemic areas)
Exclusion of enteric infections (including *Clostridium difficile*)	• Stool microscopy for *Entamoeba histolytica* • Check for unusual infective agents and parasites (endemic areas) • Anti-amoeba therapy prior to IBD treatment in endemic areas
Fecal Calprotectin as surrogate markers of mucosal healing or inflammation (also in post-operative setting)	• Consecutively elevated FCal levels to select patients for endoscopy
Imaging	
Magnetic resonance enterography (MRE) imaging as modality of choice in pediatric CD (for small bowel evaluation), at diagnosis and for follow-up	• Intestinal ultrasound (IUS) most valuable alternative for small bowel evaluation (CT enterography similarly accurate, but radiation a disadvantage)
Endoscopy	
Esophagogastroduodenoscopy (EGD) and ileocolonoscopy (IC), performed: • By a pediatric gastroenterologist • After age-appropriate bowel preparation • Under general anesthesia/deep sedation • In a setting suited for children • With personnel trained in PIBD	EGD and IC performed: • By an adult gastroenterologist • In collaboration with a pediatrician • Recording of endoscopy in video format for further analysis (smartphones) Selection criteria for sedation according to ASA classification system • If no anesthesiologist is available, moderate and deep sedation considered to be performed by endoscopist (if trained in advanced pediatric life support)
Pediatric + adult gastro- and colonoscopes	• Use of adult gastroscopes for EGD and IC in children with BW > 10 kg
Histopathology	
Standardized histologic examination of endoscopic biopsies essential to initial PIBD work-up and follow-up	• Histologic examination recommended: Reduction of histopathologists' workload mandatory • Treatment of biopsies (immediate fixation by immersion in buffered formalin or equivalent prior to transport; [7])
Worldwide definition of PIBD phenotypes according to "Paris Classification" of endoscopic and histopathological findings	• Focus on histopathologic differentiation of IBD, in particular CD and ITB
Routine sampling of a minimum of 7–8 biopsies from upper gastrointestinal tract at initial evaluation (with two or more biopsies from each site)	• Routine sampling of 2–3 biopsies in total (1 duodenal, 1–2 gastric, unless there are macroscopic changes in the esophagus)
Routine sampling of a minimum of two biopsies from the terminal ileum, cecum, transverse colon, sigmoid colon, and rectum	• Routine sampling of 4 biopsies in total (1 terminal ileum, 1 ascending and descending colon, 1 from rectum)
Implementation of digital whole-slide imaging for visualization of the entire tissue on one slide with many digital products already available [8]	• With digitization of pathology laboratories still lacking: • Specific training of histopathologists regarding IBD diagnosis • Promotion of direct cooperation between LMIC and HIC institutions with exchange programs

Clinical Evaluation and PIBD Activity Indices

Systematic evaluation is not only mandatory in the initial PIBD diagnostic work-up but also essential for adequate disease monitoring. With the high growth failure prevalence, adequate growth assessment must therefore be performed at each visit, with a review of patients' growth charts [3, 12, 13]. Because locally developed growth charts are not always easily obtained, WHO (World Health Organization) growth charts and references could be used instead. For monitoring of disease activity, PIBD disease activity indices are of further interest. As stated elsewhere, the Pediatric Ulcerative

Colitis Activity Index (PUCAI) allows a symptom-based assessment that helps predicting clinical remission and correlates well with colonoscopic scores [14–16]. For pediatric CD, several indices are available. For example, the weighted Pediatric CD Activity Index (wPCDAI) combines symptoms, findings on physical examination, and basic laboratory test results, which are widely available. Translating these disease activity indices to LMICs' languages could expand their use as monitoring tools.

Serological Tests

Widely available, easy-to-use, and non-invasive objective markers are not only needed to monitor IBD activity but can also prevent unnecessary repeated endoscopic evaluations [17]. The heterogeneity of LMICs, both ethnically and economically, the test availability, and their costs represent major challenges in generalizing recommendations.

A complete blood cell count is a widely available tool, and while leukocytosis might be present in acute inflammation, leukopenia could be a side effect of immunosuppressants. In PIBD, both hemoglobin level and platelet counts were shown to add a diagnostic value in symptomatic children, with pooled AUC (area under the curve) of 76% and 79%, respectively [17]. Because IBD can be accompanied by thrombocytosis, the platelet count may help differentiate between IBD and infectious processes, as thrombocytosis is a relatively uncommon finding in infectious diarrhea [18]. Mean platelet volume (MPV), a readily available test may be another useful marker because it is influenced by the degree and type of mucosal inflammation, and when compared with white blood cell count, ESR (erythrocyte sedimentation rate), or CRP (C-reactive protein), it has a similar accuracy regarding IBD activity with lower levels in patients with active ulcerative colitis [19]. Additionally, the neutrophil–platelet ratio was found promising for assessing disease activity in ulcerative colitis [20], while in patients with CD, better evidence was found for the neutrophil–lymphocyte ratio [21].

CRP, when available at a reasonable cost is one of the most widely used inflammatory markers in IBD. An increase in CRP level correlates with acute inflammation, both intestinal and extraintestinal. In a study of 91 children with chronic gastrointestinal symptoms, CRP was elevated in 60% of patients with ulcerative colitis (UC) and in 100% of patients with CD [22]. CRP has a relatively short half-life, returning to baseline values quite rapidly once the inflammatory stimulus has resolved. It may therefore be a better measure of remission and response to therapy than other inflammatory markers in patients with IBD [23]. Furthermore, an elevated CRP in an asymptomatic CD patient may suggest transmural damage in a silent Crohn disease [24].

ESR serves as another surrogate measure of inflammation since acute inflammation is associated with increased levels of plasma proteins and higher plasma viscosity resulting in ESR prolongation. ESR can therefore be used as a non-specific inflammatory marker [25] and it is readily available at a reasonable cost. Alper et al. reported that almost two-thirds of children with IBD had an elevated ESR at diagnosis, which was even higher in patients with CD compared with UC (72% and 23%, respectively). They also showed that ESR correlated well both with endoscopic and histologic activities in pediatric Crohn disease colitis [26].

Albumin, a negative acute phase reactant is downregulated during acute inflammation. Its level at diagnosis has been shown to serve as a prognostic factor in patients with UC [27]. In contrast, in CD, a serum albumin level >3.8 g/dL was associated with better control of the disease [28].

Testing of thiopurine methyltransferase (TPMT) activity (genotype or phenotype) may help identify patients at risk of profound myelosuppression and is recommended prior to treatment with 6-thioguanine, when available. However, cytopenia can still occur despite normal TPMT activity. In addition to availability and cost-effectiveness in LMIC, it was shown that ethnicity may determine the rates of TPMT deficiency and new genes are being recognized which affect the drug response and metabolism. This test might therefore be individualized according to the specific population, as is testing for new mutations. For example, NUDT15 gene mutation leads to reduced tolerance of 6-MP in patients of South Asian descent [29–33].

Microbiological Investigations

In LMICs, tuberculosis (TB) is often endemic with a much higher frequency than IBD and routine BCG (Bacillus Calmette Guerin), vaccination is practiced. Also, the risk of latent TB or TB reactivation is present, and therefore, intestinal TB that mimics CD must be excluded. This should be based on a combination of history taking, physical examination, review of immunization and nutritional status, chest X-ray, Mantoux tuberculin skin test, and/or an Interferon-gamma releasing assay, according to the local prevalence and national recommendations [34–36]. For LMICs, World Gastroenterology Organization Global Guidelines consider a trial of anti-TB therapy for 2–3 months in CD management to determine the response in endemic areas [37]. Finally, TB testing prior to any anti-TNF therapy is mandatory.

Because immunosuppression can have harmful effects on patients with acquired immunodeficiency syndrome (AIDS), HIV testing must also be part of the initial diagnostic workup. It is however noteworthy that concomitant use of highly active antiretroviral therapy (HAART) and biologics now allows the control of viral replication and induces and

maintains remission in HIV-positive patients with IBD [38, 39]. Because a low CD4+ count might exert protection in patients with IBD and concomitant HIV infection, as a low CD4+ cell count was shown to be associated with a stable disease course and fewer relapses [40], it might be worthwhile to perform this test in the specific scenario just mentioned.

Prior to endoscopy, several other infections must be excluded, according to test availability and local practice [41]. In endemic areas, stool testing for *Entamoeba histolytica* and more extensive investigations for unusual infective agents and parasites should be performed [9]. In the diagnosis of amoebiasis easily performed stool microscopy cannot be replaced even by PCR and it remains the only way to prove hematophagous trophozoites thus indicating whether the disease-causing stage has been reached [42]. While the Centers for Disease Control recommend a minimum of 3 stool samples collected over a period of 10 days to improve the diagnostic sensitivity to 85–95%, World Gastroenterology Organization Global Guidelines consider a course of anti-amoeba therapy to be administered in UC and CD management in endemic areas and when there is limited access to diagnosis [42, 43].

Screening for *Clostridium difficile* infection is not only recommended at initial diagnostic workup for PIBD but also recommended in all patients with a suspected new exacerbation of IBD and before treatment modification according to test availability and local practice [9, 34, 41].

Fecal Calprotectin

Fecal calprotectin (Fcal) is a non-invasive diagnostic tool to detect mucosal inflammation, although not specific for IBD [9, 41]. However, its high sensitivity has proven to be cost-effective in distinguishing IBD from non-IBD in children, although in healthy infants, higher concentrations are found than in older children [44]. According to World Gastroenterology Organization Global Guidelines, Fcal could be helpful in the selection of further investigation, including endoscopy in developing countries with medium resources available, but it is not mentioned for LMICs [37]. While there is no ideal cut-off value to reflect mucosal inflammation and predict disease outcome, a Fcal value <100 mg/g usually reflects remission [41, 45]. Fcal is therefore a useful surrogate marker of mucosal healing, and its monitoring together with PUCAI allows an adequate assessment of disease activity in pediatric UC, without the need for endoscopy [46]. Repeated Fcal measurements may be used to longitudinally track changes in a patient's condition. In patients with UC, an endoscopic evaluation should be considered when Fcal is high, due to its good correlation with clinical disease activity, and endoscopic and histological indices [45]. Despite its broad use in many countries worldwide, the cost of Fcal is still relatively high, and in many LMICs not fully covered by national insurance programs. Research is still needed on cut-off values in the pediatric population and more importantly in developing countries, because of the varying range of normal values in healthy children by age.

Imaging

Objective evaluation of IBD extent and activity usually includes imaging; however, some techniques are not always available in LMICs. For example, to correctly differentiate CD and UC at diagnosis, small bowel evaluation should be always performed [9]. Indeed, several atypical phenotypes of UC, CD, and IBDU have been reported in children, and the involvement of the small bowel is useful to correctly define CD, evaluate the degree and the extent of the inflammation, and define the presence of disease-related complications [47, 48]. Moreover, in those patients whose ileum could not be intubated, imaging may help to reach a correct diagnosis and monitor disease [9]. The choice of which test to perform depends on local availability and expertise, and includes preferably magnetic resonance enterography (MRE), intestinal ultrasound (IUS), or capsule endoscopy, but when unavailable possibly computed tomography enterography (CTE) and small bowel follow-through (SBFT).

MRE is the preferred imaging modality at diagnosis and during follow-up as it allows to evaluate both the changes of the bowel wall and thus the degree of transmural inflammation, as well as perianal CD and extraintestinal complications (fistulae, abscesses) with no radiation exposure. In many LMICs, MR scanners are currently not widely accessible, especially in the smaller and more peripheral centers [49]. Moreover, the radiologist's expertise is another limitation of this technique, as no simple score systems for use in routine clinical practice have been developed so far. While SBFT is an alternative method to evaluate small bowel disease activity and extent, it is limited by the high-radiation exposure and the lack of assessment of peri-intestinal abnormalities [41]. Therefore, IUS which allows a dynamic real-time bowel assessment is a valuable alternative to MRE [50], even if its performance is strictly related to the operator's extensive training and experience. Published data report good performance of IUS for the diagnosis of CD (79.7% sensitivity, 96.7% specificity) and for the evaluation of already known disease (89% sensitivity, 94.3% specificity; [51]). Bowel wall thickness (≥3 mm) is the best IUS parameter for defining an active bowel disease with the highest sensitivity for ileal, right, and left colon lesions. Increased bowel wall vascularity or mesenteric hypertrophy are further signs of bowel inflammation that may be detected by IUS, as

are fistulae, abscesses, and stricture [51]. Based on those data, considering the wide availability, the low costs, and non-invasiveness for patients, IUS is the primary imaging modality in case of suspicion of PIBD or for disease monitoring. With regard to monitoring CD, cross-sectional imaging by IUS can be used [41], along with laboratory markers (CRP) and clinical evaluation. If available, small intestinal contrast ultrasonography (SICUS) is also an alternative to MRE, due to its good cost-efficacy and because it is also well-tolerated by patients [52]. Since capsule endoscopy, MRE and IUS were shown to be comparable in CD [53], monitoring can be performed by any of these as well as SBFT and CTE, based upon local availability and expertise. However, due to high-radiation exposure, SBFT and CTE should not be repeated routinely for patient monitoring.

Endoscopic Evaluation

Esophagogastroduodenoscopy (EGD) and ileocolonoscopy (IC) are costly and time-consuming but mandatory for the diagnosis of IBD and essential for disease monitoring. In PIBD, endoscopic evaluation is recommended to be performed by a pediatric gastroenterologist after an age-appropriate bowel preparation, under general anesthesia (GA) or deep sedation in a setting suited for children [9]. According to World Gastroenterology Organization, Global Guidelines even in LMICs adults with suspected IBD should have a flexible full-length colonoscopy including ileoscopy accompanied by biopsies, if available [37]. However, when it comes to PIBD, there is a striking difference between LMICs and HICs in the number of formally trained pediatric gastroenterologists [5]. While in some developed world regions there will be one pediatric endoscopist for every 100,000–200,000 inhabitants, in Bangladesh there are only 2 or 3 pediatric endoscopists for a population of around 150 million [54, 55]. In LMICs, late diagnosis, avoidable complications, and even death may occur in complex gastrointestinal cases because of limited health staff and specialists in pediatric gastroenterology [5]. As an alternative, pediatric endoscopy services might be performed by adult gastroenterologists in collaboration with pediatricians, which was reported by some LMICs to be proven safe and effective [56–58].

According to the NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) guidelines for training in pediatric gastroenterology choosing the right type of anesthesia is a competency requirement [59]. Standardized pre-sedation risk assessment using the ASA-Physical Status Classification System should be performed in order to determine the appropriate level of sedation for EGD [60]. However, the choice of anesthesia not only depends on patient and procedure-related factors but also the limited availability of anesthesiologists. Anesthesiologist-administered sedation is preferred in children with ASA class III–V, while children in ASA class I and II can be examined safely by non-anesthesiologists [61]. All endoscopists performing pediatric procedures should be certified for pediatric advanced life support and familiar with resuscitation protocols including airway management [62].

ESGE (European Society for Gastrointestinal Endoscopy) and ESPGHAN guidelines suggest that the choice of the type of instrument should depend on the child's weight and age [63]. However, a standard adult gastroscope can be used for EGD in children with a body weight ≥10 kg and a standard adult gastroscope for colonoscopy, if a pediatric colonoscope is not available. For children 2.5–10 kg, a pediatric or adult gastroscope can be used for colonoscopy, and for infants <2.5 kg, a pediatric gastroscope should be used.

Endoscopic evaluation is recommended before major treatment changes, to diagnose complications (stenosis, dysplasia), and to exclude other diagnoses (ischemia or CMV infection). The standard CD endoscopic index of severity (CDEIS) and/or the simplified index, Simple Endoscopic Score for CD (SES-CD), which are validated endoscopic indices for the assessment of CD activity in children, are recommended [64, 65]. Complete mucosal healing (MH) is defined as an SES-CD or CDEIS of 0, while endoscopic remission is defined as SES-CD or CDEIS ≤2. For assessment of UC activity in children two easy-to-use scoring systems, the Mayo endoscopic score and UC Endoscopic Index of Severity (UCEIS) are recommended [64, 66]. ESPGHAN Porto IBD Group stated that a complete MH is defined as a Mayo or UCEIS of 0, while endoscopic remission is defined as Mayo or UCEIS ≤1.

According to the ECCO-ESGAR (European Society of Gastrointestinal and Abdominal Radiology) guideline for diagnostic assessment in IBD, small bowel involvement should be evaluated in all newly diagnosed patients with CD, with a small bowel capsule endoscopy (SBCE) as an option and/or small bowel endoscopy by means of capsule endoscopy (CE) or enteroscopy [41]. Capsule endoscopy has the advantage of detecting even residual inflammation despite normal serum and stool inflammatory markers, as well as MH, and has therefore rapidly expanded worldwide. However, it is expensive and is not yet available in most developing countries [67, 68], which is also the case for enteroscopy.

The cancer surveillance program recommended in pediatric UC after 10 years from disease onset should best be performed in remission in order to discriminate between dysplasia and inflammation and carried out by an experienced pediatric or adult gastrointestinal endoscopist [64, 66]. An independent gastrointestinal specialist pathologist is needed to confirm the presence of low-grade or high-grade dysplasia [41, 64] and surveillance intervals should be individualized according to a risk stratification (e.g., family history of colorectal cancer).

Histopathology

Standardized histologic examination of endoscopic biopsies is an essential component of initial diagnostic workup for IBD and follow-up. In children, further "PIBD-Classes" have been developed that standardize the differentiation into five categories [69, 70]. Also, the dynamic features of PIBD phenotype with changes in disease location and behavior over time should be captured adequately in order to ensure the therapeutic goal of "mucosal healing." To define such phenotypes in a standardized manner, the evidence-based "Paris Classification" of endoscopic and histopathological findings should be used worldwide, since this also offers long-term predictive properties (ileal location at CD diagnosis indicating a long-term worse outcome; [71]). However, recent surveys from LMICs have shown significant shortages of pathology services, which are both of insufficient scope, with a disproportionately low ratio of pathologists per patient population enumerating 1,555,000 patients per pathologist in Sub-Saharan Africa, as well as inadequate quality as compared with HICs [72]: Global Guidelines include therefore a "cascade for IBD diagnosis" depending on available resources. However, flexible full-length endoscopies with biopsies and histological interpretation are now generally recommended even in LMICs [37] with pathologists' workload and costs of material to be kept down as much as possible including standardized reduction in number obtained biopsies (Table 54.1).

Since Crohn disease-associated granulomas were found in a significant proportion of children only in the upper GI tract biopsies, EGD should be performed in all children at the initial evaluation with two or more biopsies obtained from each site, irrespective of the upper GI tract manifestations and endoscopic appearance [15].

For reliable diagnosis of UC and CD, ileocolonoscopy with a minimum of two biopsies from the inflamed regions should be obtained [41]. The revised Porto Group criteria recommend obtaining biopsies from the terminal ileum, cecum, transverse colon, sigmoid colon, and rectum [9]. Identifying histologic changes in areas that appear normal on endoscopy in order to stage the extent of disease is particularly important with regard to CD diagnosis, as is the assessment for non-caseating granulomas.

Differentiating CD from intestinal tuberculosis (ITB) is mandatory in the developing world, where TB may be endemic and where the IBD incidence is on the rise. In these regions, large or confluent/caseating granulomas would be indicative for ITB and caseating necrosis on biopsy is even regarded as the exclusive feature further emphasizing the importance of histology in LMICs [8]. Histopathologic findings such as crypt architecture distortion are features of chronic colitis and would be atypical in acute infectious colitis [37].

Digitizing slides, even up to 40,000–200,000 slides per month is feasible, albeit only in HICs. While this system is not yet widely used in clinical setting, digitization with digital whole-slide imaging (WSI) makes a specimen more reproducible thus allowing capture and visualization of the entire tissue on a slide [73]. WSI solutions allow for potential migration of the entire workflow from the manual to the digital and could eventually reduce barriers between hospitals, regions, and countries, thus facilitating pathology consultations and referrals. However, costs of adequate scanning systems are still much higher than of microscopes. While providing virtual pathology services at remote sites might eventually facilitate international consultations, it is important for now to focus on training histopathologists in LMICs, particularly regarding IBD diagnosis, and to enforce direct cooperation between LMIC and HIC institutions.

Pharmacological Therapy

Inflammatory bowel disease treatment is individualized with a broad variety of medical and surgical options, as well as nutritional therapy, particularly in PIBD (Table 54.2). In LMICs many of the recommended non-biologic IBD medications like corticosteroids, mesalamine, methotrexate, and 6-thioguanine are available and international guidelines as to their indications and use can be adhered to. However, several medications like budesonide, 6-mercaptopurine, and tacrolimus, and preparations as enemas are not. In addition, neither genetic testing for drug tolerability (TPMT genetics) nor therapeutic drug monitoring (TDM) can be performed. When initiating thiopurines weekly monitoring of blood counts in the first month of treatment, and from then on at regular intervals is therefore necessary to identify patients at risk of profound myelosuppression. Similarly, liver and pancreatic enzymes need to be obtained. To guide therapy in patients with a suboptimal response, potentially interesting is the use of applications that are predictive for a low 6-TG level or patients' non-adherence [74].

PIBD treatment with biologics is still a challenge in the vast majority of LMICs. Vedolizumab and ustekinumab are largely unavailable and although adalimumab (ADA) is more often available than infliximab (IFX), both medications are too expensive for health systems to bear their costs. Negotiations between treating physicians and health authorities remain largely ineffective leaving patients and families alone in their search for funding by private means through charities or pharmaceutical companies. The introduction of effective biosimilars with a potential to substantially reduce costs [75] is necessary on a large scale. A comparison of the cost-effectiveness of IFX and ADA is similarly important in this context and was one of the topics addressed in a systematic analysis of 11 randomized clinical trials in adult patients

Table 54.2 Pharmacological, nutritional, and surgical therapy: examples of modifications

Published recommendations (ECCO/ESPGHAN guidelines, position papers)	LMIC-specific modifications, alternatives, and considerations
Measuring thiopurine metabolites in patients with incomplete response on stable thiopurine dosage	• Check patients' adherence with therapy
Change in treatment in patients with active disease despite adequate 6-TG level after at least 12 weeks of thiopurine treatment	
Anti-TNF: Top-down strategy	• Implementation of equally effective biosimilars with substantial cost reduction
	• Research of cost-effectiveness SC vs. IV biologics in PIBD
Therapeutic drug monitoring for anti-TNF treated patients at end of induction and during loss of response	• Empiric anti-TNF dose increase/interval decrease, add immunomodulator
Options following anti-TNF failure: ileocecal resection for limited Crohn disease (CD) Colectomy in Ulcerative Colitis (UC)	Ileocecal resection for patients with limited CD (laparoscopic approach preferred, if available)
	• Cyclosporine IV in refractory CD and UC
Exclusive Enteral Nutrition (EEN) as first-line therapy in active luminal CD	Unavailability of EEN: (a) Other effective induction therapies: corticosteroids, combinations of antibiotics, CD exclusion diet, combined with Partial Enteral Nutrition (PEN) (b) Negotiations with official scientific bodies (National Societies for PGHN, supported by ESPGHAN/sister societies) with governmental bodies/ insurances • Search for other financial means (grants, foundations, supply by industry)
PEN for maintenance of remission in CD	• Immunomodulators
Nutritional assessment at follow-up food fortification and/ or supplemental formula in selected cases	• Specifically trained physicians or nurses to replace dieticians/NTs • Continuous training in PIBD nutritional aspects of nurses by physicians
In Acute Severe Colitis (ASC), daily monitoring of body weight, caloric intake, hydration status including review by dietician/nutritional therapist (NT)	
Monitoring of micronutrients, e.g., vitamins D, B12, folate	• Micronutrient supplementation on clinical grounds, if no laboratory tests • Vitamin D supplementation as a routine
Surgery	
Ulcerative colitis	
• Elective surgery: Restorative proctocolectomy (+ IPAA + covering loop-ileostomy), performed by experienced surgeon (at least 10 pouches/year) • ASC: Three-stage procedure (subtotal colectomy with ileostomy first) • Minimally invasive laparoscopic approach	• Travel of experienced surgeon from another center (national/HIC) needed
• Suspicion of pouchitis: pouchoscopy with mucosal biopsies at first suspected episode of pouchitis	• If colonoscope unavailable, use of gastroscope possible instead • If endoscopy unavailable: (a) Digital examination (b) Exclusion of intestinal infections (c) Repeated measurements of FCal
First-line therapy for pouchitis: 14-day course of ciprofloxacin and/or metronidazole Persistent cases: Combined metronidazole + ciprofloxacin or oral/topical budesonide Cuffitis: Topical mesalamine	
Crohn disease	
Prevention of postoperative recurrence: anti-TNF significantly better compared to conventional therapies, even in unselected patients with CD Infliximab and adalimumab equally effective in preventing endoscopic postoperative recurrence	If anti-TNF therapy unavailable, in children with limited (≤0 cm) non-stricturing ileocecal CD with failure of conventional therapy or with growth delay, resection should be considered a reasonable alternative

with CD [76]. While a comparable efficacy of both drugs was shown, it is understandable that a drug administered subcutaneously is less expensive since less personnel and infrastructure support is needed. In addition, traveling to appointments is less often required potentially adding to patients' adherence. However, the extent to which treatment costs are offset by improved outcomes and fewer hospitalizations and surgeries, needs further systematic evaluation. So far, studies comparing IBD biologics including their cost-effectiveness, have been solely in adults [77].

When anti-TNF-agents are used, TDM is recommended [78], but this is unavailable in LMICs. Therefore, in case of a lack of initial response or loss of response (LOR), an empiric dose increase/interval decrease is recommended, with the addition of an immunomodulator, if not already used as combination therapy. Dose-escalation, interval shortening, or both were shown to improve treatment efficacy [79]. In fact, two randomized controlled trials did not show that empirical escalation of infliximab is inferior to TDM-based escalation in patients with CD [80, 81]. The addition of an immunomodulator in patients who have lost response due to development of anti-drug-antibodies is an established strategy for regaining response while salvaging the anti-TNF therapy [82]. However, when a patient is not responding or losing response to one anti-TNF agent after treatment optimization, a switch within class (infliximab to adalimumab or vice versa) is recommended [78], because it has been shown that patients who are intolerant or experience immunogenic failure have a high rate of response when switching "in class" [83, 84]. In the absence of other biologic classes, there are a few options following anti-TNF failure, which might be considered in LMICs. Enteral therapy may be effective in some cases, while for more severe cases, ileo-cecal resection for limited CD can offer excellent short-term and long-term results. This may be true even in the treatment of naïve patients [85] as shown in a pediatric study with clinical remission rates of 79% at 1 year and 56% at 2.5 years post resection, along with a significant effect on linear growth [86]. Regarding the efficacy of cyclosporine for induction of remission in CD one study demonstrated benefit in terms of colectomy-free survival in patients with refractory Crohn disease colitis [87]. In patients with UC and in the absence of biologics, colectomy should be considered, or alternatively a trial of remission induction with cyclosporine as a bridge to maintenance thiopurine therapy. Cyclosporine and infliximab demonstrated similar short-term efficacy for corticosteroid-refractory and acute severe UC in four randomized controlled trials [88, 89].

In patients with acute severe ulcerative colitis (ASC), if available up-front intensified induction with infliximab should be considered (10 mg/kg at weeks 0, 1, 4 and every 4 weeks thereafter) until complete response is achieved. Once achieved, a cautious de-escalation to standard dosing can be considered under close monitoring [90].

Nutritional Therapy

ESPGHAN guidelines cover a wide variety of nutritional topics related to PIBD [45, 66, 78]. Apart from the recommendation of exclusive enteral nutrition (EEN) and special diets for a variety of indications, other aspects including clinical assessment of the nutritional status, treatment of selective mineral and vitamin deficiencies, or use of partial enteral nutrition (PEN) to support the nutritional status of children with IBD deserve attention. In fact, although many specific formulas and diets are not available in LMICs, adjustments of many recommendations related to nutrition in PIBD seem feasible.

Although EEN is the recommended first-line therapy in active luminal CD [78], in LMICs EEN may not be accessible to all patients or covered by health insurance. In such cases, other effective induction therapies may be used, such as corticosteroids (CS), combination of antibiotics, or a CD exclusion diet (CDED) in combination with PEN. Based on meta-analyses, CS are equally effective as EEN [91, 92] but aside from their well-known side effects, they have lower rates of mucosal healing [93, 94]. There are data showing effects of azithromycin plus metronidazole [95], as well as good tolerability and efficacy of CDED in induction of remission of mild-to-moderate luminal CD in children [96]. In both cases, replication studies are needed before stronger recommendations can be made.

If PEN is unavailable for nutritional support in PIBD, nutritional modifications and fortification of food under the supervision of trained dieticians are an alternative and PEN can even be omitted as a maintenance therapy if adequate medication like immunomodulator is available instead. If CDED plus PEN is used, the specific protocol should be followed as published [96] and strict supervision by trained personnel is necessary to prevent deviations from the diet. At the same time, comprehensive efforts are necessary to make EEN and PEN available for all pediatric patients with CD and covered by health insurance companies. This should be achieved by negotiations between official scientific and clinical bodies (National Societies for PGHN) with governmental bodies and insurers. In the meantime, other financial resources like grants, foundations, or industry should be utilized, ideally on the initiative of local PIBD experts and in PIBD centers.

According to the ESPGHAN position paper on Nutrition in PIBD, a regular nutritional assessment should also be an integral part of follow-up and food fortification and/or supplemental formula are recommended in select cases [97]. In ASC, body weight, caloric intake, and hydration status should be monitored daily, including review by a dietician as needed [45]. However, in LMICs, there are often neither dieticians nor nutritional therapists (NT) available. Although a specifically trained physician or nurse can partly fulfill this role, dedicated dieticians or NTs are indispensable to any PIBD center. At the same time, PIBD specialists should regularly train dieticians/NTs and IBD nurses regarding all aspects of EEN/PEN.

Monitoring of micronutrients like vitamin D, folic acid, and B12 status is recommended at least in selected PIBD patients [97], as is DXA in high-risk patients with prolonged

malnutrition, delayed puberty, and/or steroid dependency [66]. However, in some LMICs, less common laboratory tests to measure vitamin or trace element levels, or DXA imaging may be lacking and/or are not covered by health insurance. Again, negotiations with responsible authorities are needed to achieve implementation and financial coverage of these important laboratory and imaging methods, which cannot be replaced by other less costly investigations.

Surgery

Despite recent significant advances in medical management, surgery continues to play a major role in the management of PIBD. As previously stated, in many LMICs, experience with PIBD is limited due to a lack of resources and infrastructure, and the absence of trained specialists in pediatric gastroenterology, as well as pediatric surgery.

A surgeon in LMICs is most likely to encounter PIBD during the course of an exploratory laparotomy for suspected appendicitis. Owing to an often observed background of malnutrition in many instances, primary anastomosis and strictureplasty are associated with significant risks. Parenteral nutrition is often unavailable and post-operative management of complex surgical interventions is therefore extremely challenging. Because of religious requirements, there is often a strong resistance to a stoma in Muslim cultures, although a religious ruling to accommodate such conditions exist [98]. The stigma of a stoma might compromise marriage and reduce the chances of starting a family. Surgeons often find themselves in a difficult position when it comes to surgical options and outcomes are difficult to quantify when compromises have to be made. In addition, continuity of medical care often falls to the individual surgeon and patients are dependent on the enthusiasm and expertise of an individual practitioner [99].

In UC, total colectomy is curative and restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) and a covering loop-ileostomy is the recommended elective surgery [45]. Three-stage procedure (subtotal colectomy with ileostomy first) is recommended for patients with complicated disease like acute severe colitis or severe malnutrition. However, the final choice of the surgical approach should be individualized. In a multicenter retrospective ESPGHAN study, surgeon's experience of <10 pouch surgeries/year (regardless of whether pediatric or adult surgeon) was the only factor associated with increased rate of (chronic) pouchitis [100]. However, in a survey of UK pediatric surgical centers, the median experience with IPAA was 0.9 cases/year of consultant practice and the majority had arrangements for joint operating with adult surgeons [101]. In LMICs, children with UC who require this type of surgery or a three-stage procedure should be operated in a pediatric care environment and in all instances collaboration of pediatric and adult surgeons is imperative. Creation of a national network and at least one IBD Referral Center/country, or in the closest country nearby, as well as visiting programs could be beneficial. Experienced surgeons from HICs could assist and advise surgeons from LMICs during surgeries (live video communication, "Tele-Porto," see ESPGHAN homepage), thus building twinned centers (exchange programs between LMIC and HIC centers). Given the risk of postoperative complications, especially with limited experience plans should be in place for follow-up consultation and alternative management in case of subsequent complication.

The ECCO-ESPGHAN guidelines recommend pouchoscopy at the first suspected episode of pouchitis [45]. If there is no available colonoscope to perform pouchoscopy with biopsies, according to recent adult guidelines, a gastroscope might be used and valuable information could be added by a digital examination [102]. There is consistent evidence that FCal is also a useful surrogate marker in the postoperative setting, as it shows a good correlation with the presence of pouchitis, confirmed by endoscopy. Serial measurements of FCal in asymptomatic patients can predict the short-term development of pouchitis, thus leading to early medical intervention [103]. In refractory pouchitis, not responding to the recommended antibiotic therapy (ciprofloxacin and/or metronidazole) and if no anti-TNF agents are available, thiopurines could be used. Topical mesalamine is recommended only for treating cuffitis.

Surgery for CD is not curative and limited resection is the key principle thus preserving bowel length. Surgical resection in children with CD is usually reserved for those who are refractory to anti-TNF therapy, have stricturing [B2] disease with prestenotic dilatation, or penetrating [B3] disease [104]. In the recent LIR!C trial which compared laparoscopic ileocecal resection and infliximab treatment in non-complicated patients with CD, the long-term outcome of patients in the surgical arm was excellent, with only 26% of 69 patients requiring anti-TNF therapy and none requiring a second resection [105]. Laparoscopic ileocecal resection was a cost-effective treatment and provided quality-of-life outcomes similar to treatment with IFX [106]. Another adult study compared early surgery in this category of patients with biologic treatment. Costs were significantly lower for early surgery vs. biologic treatment. Also, the quality-adjusted life years value was significantly better for early surgery vs. biologics (6.24 ± 0.01 and 5.81 ± 0.01, respectively). All these data support the strategy of early surgery (higher efficacy and less cost) compared with biologic therapy [107]. Hence, laparoscopic resection of both stricturing and actively diseased terminal ileum [<40 cm] can be offered as a sound therapeutic option in an interdisciplinary context, with a benefit and risk profile comparable to medical therapy [108]. Pediatric data are scarce and no RCTs are available,

but favorable clinical remission rates after resection have been shown, as mentioned previously [85]. Since for most patients surgery is not curative and postoperative recurrence (POR) is common, postoperative endoscopic evaluation at 6–9 months after bowel resection is recommended [64] to guide treatment adaptation. However, in LMICs, colonoscopy may be not easily available and Fcal and IUS can be considered as non-invasive alternatives to detect postoperative recurrence, especially after small bowel resection [41]. In patients who underwent surgical resection, and if anti-TNF-agents are not available, shortly after surgery thiopurine over 5-ASA maintenance is recommended to reduce postoperative recurrence risk. Metronidazole and enteral nutrition can be considered as alternatives, and 5-ASA may be considered for colonic disease. However, in patients with high risk of recurrence, any effort to provide anti-TNF agents should be made as strong evidence in adults with ileocolonic resections and primary anastomoses shows that they are the most effective strategy for the prevention of endoscopic recurrence [78]. A meta-analysis of studies including the comparison of anti-TNF (IFX, ADA) to non-biological comparators (azathioprine, mesalamine, and placebo) showed that anti-TNF-agents were significantly better in preventing clinical, endoscopic, and severe endoscopic and histological POR compared with conventional therapies, even in unselected CD patients. IFX and ADA proved to be equally effective in preventing endoscopic POR [109]. Even if the evidence is weak in support of the use of 5-ASA/sulfasalazine and antibiotics, they could represent an option in LMICs. Use of metronidazole is supported by a recent study, in which a metronidazole course over 3 months was associated with significantly lower endoscopic recurrence versus the control group [110]. Most pediatric CD patients in real-world settings will receive maintenance therapy administered within 4 weeks from surgery [78]. Anti-TNF naïve patients may use a thiopurine. However, endoscopic recurrence on thiopurine monotherapy should trigger a step-up to anti-TNF therapy, and IFX and ADA are probably equally effective in reducing POR [78]. However, since in many LMICs, no anti-TNF biosimilars are available, the options are limited. Relapse prevention with methotrexate might be an option, but there are no specific data available in this regard.

Conclusion

Pediatric IBD has become a global disease but its adequate management in LMICs remains a substantial challenge probably for years to come. Enhancing possibilities of formal training in pediatric gastroenterology including endoscopy, histopathology, and surgery is crucial, as is the continuous search for optimizing low-cost diagnostics and therapies. ESPGHAN has therefore initiated PIBD Masterclasses to be held regularly in LMICs and at a low cost. Voluntary peer-to-peer remote consultations for difficult PIBD cases by experts of the ESPGHAN "Porto Group" were also implemented, and are meant as a "physician-to-physician telemedicine service." Finally, an ESPGHAN Position paper on PIBD care in limited resource countries is underway and will address in detail the topics outlined in this chapter.

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Immunizations in the Child with Inflammatory Bowel Disease

55

Athos Bousvaros and Ying Lu

Introduction

The vast majority of children and young adults with inflammatory bowel disease (IBD) will undergo treatment with immunosuppressive medications at some point during their lives. Such treatment may be short lived (e.g., a brief course of corticosteroids during a colitis flare) or prolonged (e.g., combination therapy with immunomodulators and infliximab for moderate to severe Crohn disease) [1]. Treatment with immunomodulators or biologics increases the risk of opportunistic infections, such as herpes zoster [2, 3], Epstein-Barr virus [4], or cytomegalovirus [5]. Some of these illnesses (especially influenza, pneumonia, and varicella) are potentially preventable by the judicious use of vaccines. While the ideal time to immunize patients with IBD is prior to the onset of any immunosuppression, for many patients delaying treatment to "catch up on immunizations" is not possible. Papers in both adults and children have emphasized the safety of inactivated vaccines in immunocompromised IBD patients [6–8]. Most such papers also suggest withholding live vaccines in this population, despite a paucity of data on this topic [7]. The Infectious Diseases Society of America has also prepared a guideline on vaccination of the immunocompromised host which provides in-depth recommendations, as well as areas highly in need of future research [9].

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Underimmunization

The immunization rate for routine primary vaccines varies greatly among children with IBD around the world, ranging from 24% in France [10] to 90% in Canada [11] and Australia [12]. However, vaccination rates tend to be especially low for varicella (18–39%) [13, 14], pneumococcus (4–32%) [10, 12, 13, 15], meningococcus (24%) [13], human papillomavirus (HPV) (6–42%) [13, 14], and influenza (8–30%) [10, 12, 13, 16]. Factors contributing to low influenza vaccination rate include concerns that the vaccine will be ineffective, fear that patients will experience an adverse effect of the vaccine, concerns that the vaccine may cause a flare of their disease, and that the vaccine was not offered to patient [10, 16, 17].

In a survey of 178 pediatric gastroenterologists, only 28% believed that primary care providers (PCPs) were solely responsible for immunizations. The vast majority (94%) of pediatric gastroenterologists routinely assessed immunization status. Specifically, 63.5% assess at time of diagnosis, 30% at "well" visits, and 44% before starting immunosuppressive therapy. Vaccines most commonly assessed were influenza, hepatitis B, and varicella. Physicians were more likely to review immunizations if they implemented a reminder mechanism. The most common barriers to vaccination included inability to offer vaccinations in the immediate area, lack of coordination of care with PCP, and poor access to immunization records [18]. In a survey of adult patients with IBD, 50% acknowledged that preventing infectious diseases was important for patients, but this did not result in getting immunized. Main reasons for not getting vaccinated included lack of information from physician (47.5%), lack of awareness (35%), perceived lack of benefit (33%), and concerns about adverse events (26%). Patients thought the most reliable source of information about vaccinations was their gastroenterologist (58%) compared to general practitioner (35%) [19]. These concerns have been addressed by several pediatric studies that demonstrate inactivated vaccines are generally safe and effective in children with IBD [8, 19–23]. Therefore, methods to increase vaccination rates include

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educating patients, providing the vaccine in the gastroenterology clinic [24], coordinating care among the gastroenterologist, PCP and patient, utilizing a reminder system (by having a checklist or inclusion in electronic record template) [18], utilizing nurses, and prescribing vaccines to be administered at a local pharmacy if vaccines cannot be administered at the medical office [25]. If patients are not seen regularly, an automatic reminder can be sent through the patient portal to get vaccinated [26].

The authors of this chapter recommend that the pediatric subspecialists share responsibility with the PCP in making sure their immune compromised patients are protected against vaccine-preventable diseases, such as influenza. Children with IBD often have more frequent visits to their specialist than general pediatrician and look to the specialist to assess benefits and risks of various interventions (including immunization). The GI specialist therefore has an important role in educating patients about vaccines and in making sure that the appropriate vaccines are administered (either by the pediatrician or specialist) at the appropriate times.

Who and When to Immunize?

The Centers for Disease Control and Prevention published an updated immunization schedule, summarized in Table 55.1. It is generally recommended by experts in the field that inactivated vaccines be given as per the recommended schedule to patients with IBD [27]. There is a theoretical risk of viral dissemination with live vaccines in patients who are receiving "significant immunosuppression." Fortunately, IBD is uncommon in the child under 5 years, so the majority of live vaccines [including Measles/Mumps/Rubella (MMR), varicella] will be completed before the onset of the disease and before the onset of immunosuppressive therapy.

Patients receiving aminosalicylates as monotherapy are not considered immunosuppressed. These patients may receive all immunizations as recommended in Table 55.1. Patients considered "significantly immunosuppressed" include those who are severely malnourished or receiving high-dose steroids (≥20 mg/day or ≥2 mg/kg/day for at least

Table 55.1 Summary of immunization recommendations from Centers for Disease Control and Prevention [60]

Immunization	Type	Route of administration	Patient age at time of recommended administration
Hepatitis B	Inactivated	Parenteral	0–18 months (three doses)
Diphtheria and tetanus toxoids and acellular pertussis	Inactivated	Parenteral	2–6 months (three doses) 15–18 months (one dose) 4–6 years (one dose)
Tetanus and diphtheria toxoids and acellular pertussis	Inactivated	Parenteral	11–12 years (one dose)
Haemophilus influenza type b	Inactivated	Parenteral	2–6 months (three doses) 12–15 months (one dose)
Pneumococcal	Inactivated	Parenteral	2–6 months (PCV13 vaccine, three doses) 12–15 months (PCV13 vaccine, one dose) 2–18 years (in immunocompromised patients, PCV13 and/or PPSV23 depending on prior pneumococcal vaccinations, revaccinate with one dose of PPSV23 5 years after first dose of PPSV23)
Inactivated poliovirus	Inactivated	Parenteral	2–18 months (three doses) 4–6 years (one dose)
Hepatitis A	Inactivated	Parenteral	1–2 years (two doses)
Human papillomavirus	Inactivated	Parenteral	11–12 years (two doses if initial dose given at 9–14 years old; three doses if initial dose given at 15 years or older)
Meningococcal	Inactivated	Parenteral	11–12 years (one dose) 16 years (one dose)
Influenza injection	Inactivated	Parenteral	6 months, then annually Younger than 9 years, two doses if not previously received two doses of tri- or quadrivalent influenza vaccine
Influenza intranasal	Live attenuated	Intranasal	2 years, then annually
Rotavirus	Live attenuated	Oral	2–6 months (two or three doses depending on brand)
Measles Mumps Rubella	Live attenuated	Parenteral	12–15 months (one dose) 4–6 years (one dose)
Varicella	Live attenuated	Parenteral	12–15 months (one dose) 4–6 years (one dose)

14 days), thiopurines, methotrexate, cyclosporine, tacrolimus, anti-tumor necrosis factor therapy, ustekinumab, tofacitinib, vedolizumab, and natalizumab. For this group of patients, live vaccines are generally not recommended [6, 7, 27]. Therefore, it is ideal to immunize prior to starting immunosuppressive therapy, especially with live vaccines. If the patient is clinically stable enough to start immunosuppressive therapy at a later time, then it is ideal to wait at least 4 weeks after varicella vaccination, and at least 6 weeks after MMR vaccination, to initiate therapy. If the patient will be taken off immunomodulators or biologics, it is recommended to wait at least 3 months prior to administering live vaccines, and for corticosteroids, at least 1 month [6, 7].

Inactivated Vaccines in Children with IBD

In general, a useful rule is that inactivated vaccines can be administered safely to IBD patients, irrespective of the degree of immunosuppression. In a recent meta-analysis, 39–100% of children with IBD demonstrated adequate immunogenicity post-vaccination in general. Immune response to vaccines was not significantly decreased in pediatric IBD patients receiving immunosuppressive therapy compared to those on non-immunosuppressive therapy or healthy controls [23]. The majority of patients in general achieved post-vaccination seroprotective levels. However, among all vaccines, influenza B induced the weakest immunogenicity. Patients did not experience vaccine-associated serious adverse side effects or IBD flares [23, 27].

The trivalent influenza vaccine is both safe and immunogenic in children and young adults. This vaccine is usually administered in the fall and protects against three strains of influenza. The trivalent influenza vaccine has generated protection against two strains of influenza A and one strain of influenza B. (In recent years, the quadrivalent influenza vaccine was developed which included a second strain of influenza B.) Three prospective studies have demonstrated that the trivalent influenza vaccine is usually well tolerated in children with IBD, including those receiving immunosuppressive therapy. However, immunogenicity may be reduced, especially in patients receiving biologic therapy. Mamula et al. performed a prospective study using the 2002–2004 vaccine, in which 51 children with IBD and 29 healthy children were immunized. Compared to the healthy controls, children with IBD receiving combination therapy (with immunomodulators and biologics) were less likely to respond to two of the three strains in the influenza vaccine [28]. In contrast, Lu et al. demonstrated a good response to the 2007–2008 influenza vaccine, and a high prevalence of seroprotection to both influenza A strains in the vaccine. The less immunogenic influenza B strain, however, resulted in a decreased rate of seroprotection in patients receiving anti-TNF therapy [29]. DeBruyn and colleagues again demonstrated excellent safety and immunogenicity to the two A strains in the vaccine but decreased immune response to the B strain [30]. It should be noted that strain B is also less immunogenic even in healthy children [31]. A subsequent study by deBruyn of 137 children with IBD receiving maintenance infliximab therapy demonstrated that timing of vaccination relative to infliximab infusion (immunization at time of infliximab versus midway between infusions) did not impact serological protection [32]. None of these studies demonstrated any increase in adverse events or increase in IBD flares. In summary, data from influenza vaccine studies in pediatric IBD support the recommendation that children with IBD receive annual influenza immunizations. Even patients on immunosuppressive therapies respond well to the two A strains in the vaccine, though antibody titers to the B strain may be reduced.

Hepatitis B vaccination has also been assessed in children with IBD. Patients with latent hepatitis B who are treated with anti-tumor necrosis factor inhibitors are at risk for viral reactivation leading to severe viral hepatitis or even liver failure [33, 34]. In studies where pediatric IBD patients were tested for immunity against hepatitis B, 49–63% were found to have the antibodies [35, 36]. Urganci et al. administered the hepatitis B vaccine series to children with IBD who were not previously vaccinated. Seroconversion was achieved in 70% of IBD patients compared to 90% of healthy controls ($p = 0.02$). Of children who did not achieve seroconversion, a subsequent booster dose resulted in an adequate response in 50% (7/14) of IBD patients and 60% (3/5, p = NS) of controls. There were no vaccine-associated adverse events [20]. Moses and colleagues conducted a prospective study of hepatitis B status in their pediatric IBD population on infliximab therapy and documented that 13% had never been immunized against hepatitis B, and that approximately half of patients who were previously immunized did not have protective levels of anti-HBs. The investigators then administered a booster vaccine to 34 of these patients without protective titers and noted a 76% response rate. Children and young adults receiving infliximab more frequently (approximately every 5.9 weeks) were less likely to respond to the booster dose of hepatitis B [35]. In the adult IBD scientific literature, Gisbert and colleagues found that therapy with anti-TNF was associated with a suboptimal vaccine response, but not with immunomodulators [36]. In another study, Gisbert et al. demonstrated that the rate of seroconversion for patients who received the vaccine series on an accelerated double-dose schedule (months 0, 1, 2) was higher than the single dose at the standard schedule (months 0, 1, 6) (75% vs. 41%, $p < 0.001$) [37].

Of children with IBD tested for hepatitis A antibody testing, 21–51% were found to have immunity [14, 20]. Studies evaluating the immunogenicity of hepatitis A vaccine sug-

gest that both children and adult patients with IBD mount an excellent response (97–100%) after receiving two doses [20, 21, 38]. However, the rate of seroconversion was lower in adult patients on anti-TNF therapy compared to those who were not on anti-TNF therapy (92.4% vs. 99.1%, $p = 0.001$), and in patients treated with ≥2 immunosuppressants compared to those on <2 immunosuppressants (92.6% vs. 98.4%, $p = 0.03$). There was no difference in rate of seroconversion between patients on TNF inhibitor monotherapy and those on TNF inhibitor combined with another immunosuppressant [38]. The vaccine was safe and did not exacerbate IBD [20, 21].

The theme of suboptimal immunogenicity associated with TNF inhibitor therapy extends to pneumococcal vaccine as well. One pediatric study of patients with IBD aged 5–18 years with no history of pneumococcal immunization were administered one dose of pneumococcal conjugate vaccine (PCV13). Immunogenicity was similar between patients with IBD and healthy controls (90.4% vs. 96.5%, p = NS). However, the geometric mean titer was higher in patients who were not on immunosuppressive therapy compared to those who were treated with TNF inhibitors or immunomodulators [39]. These findings are similar to a recent adult IBD study by Pittet and colleagues, where the seroprotection rate of PCV13 vaccine increased from 43.9% at baseline to 90.4% post-vaccination ($p < 0.001$). However, patients treated with TNF inhibitor therapy attained slightly lower seroprotection rates than counterparts on other types of immunosuppressive therapy (thiopurine, methotrexate, oral corticosteroids) or non-immunosuppressive therapy. The vaccine was safe for all treatment groups [40]. Several studies within the adult IBD literature agree that the immune response to 23-valent pneumococcal polysaccharide vaccine (PPSV23) is decreased in patients receiving TNF inhibitor therapy (either as monotherapy or in combination with immunomodulators, 45–63%) compared to patients not receiving immunosuppressive therapy (78–89%) and to healthy controls (85%). Immunomodulator monotherapy was not associated with a hindered immune response (79%) [41–43]. The vaccine was well-tolerated without serious adverse events [39, 42, 43].

In contrast, the immunogenicity of HPV vaccine does not appear to be diminished by immunosuppressive therapy. Jacobson and colleagues administered three doses of Gardasil to girls and young women age 9–26 years while being treated with immunomodulator or TNF inhibitor therapy for IBD. All patients developed an excellent immune response with 96–100% seropositivity to HPV types 6, 11, 16, and 18. The geometric mean titers for each serotype were similar to those of healthy historical female controls from Merck. The IBD patients did not have experience serious adverse events or worsened disease activity related to the vaccine [22]. Similarly, immunosuppressive therapy does not hinder the immune response to *Haemophilus influenza* type b vaccine. A small study by Dotan and colleagues concluded that thiopurine monotherapy generally does not impair the cellular or humoral response to the vaccine in adults with IBD [44].

This theme of adequate immunogenicity is again reflected in two prospective studies that administered the diphtheria [23] and pertussis [45] booster vaccine in adolescents with IBD who had no history of booster immunization after age 6 years or a history of infection. Subjects achieved a similar seroprotection rate for diphtheria irrespective of whether they were treated with or without immunosuppressive therapy (93.8% vs. 92.9%, p = NS). Similarly, there was no difference in response rates for pertussis booster among patients with IBD receiving no immunosuppressive therapy, those on thiopurine monotherapy, those on combination thiopurine and TNF inhibitor therapy, and healthy controls [45]. There were no vaccine-associated serious adverse events for either booster [23, 45].

Immunizing the Child with IBD: Practical Aspects

When a child is newly diagnosed with IBD, the ideal time to immunize is before the start of any immunosuppressive therapy. However, as many children with IBD are acutely ill, treatment can often not be withheld. Thus, the clinician is often caught between "a rock and a hard place": should the patient be immunized and treatment postponed, or should therapy be instituted with plans to vaccinate at a later time? Making these decisions involves a careful assessment of the risk/benefit ratio and an informed discussion with the parents. If possible, one can consider using exclusive enteral nutrition to induce remission and buy time to catch up on immunizations before starting immunosuppressive therapy.

For patients with mild to moderate ulcerative colitis who are undergoing corticosteroid induction, but in whom maintenance therapy with aminosalicylates is planned, immunizations can usually be postponed until after an initial course of corticosteroids. Once corticosteroids are weaned, and aminosalicylate therapy is started, both inactivated and live vaccines can be given. There is no consensus on how long corticosteroids need to be stopped before immunizations are given, but expert opinion suggests that 4 weeks after discontinuation of steroids is probably safe [6, 9].

More problematic is the child with moderate to severe Crohn disease or ulcerative colitis who may require corticosteroid treatment and subsequent immunosuppression with thiopurines, antibody to tumor necrosis factor, or calcineurin inhibitor. In these children, obtaining immunization records from the primary care pediatrician and assessing whether the recommended immunization series have been administered is important. If children received their recommended MMR

and varicella immunizations in childhood, they are probably at low risk of contracting these illnesses. Pediatric patients with IBD who had titers drawn were found to have immunity to 66% to measles, 61% to mumps, and 79% to rubella [14]. Obtaining individual serum titers to measles and varicella virus may also be helpful in documenting immunity. A positive antibody to measles virus is relatively good evidence of ongoing seroprotection, but the antibody to varicella vaccine is less reliable.

One area of ongoing controversy is whether varicella vaccine can be safely administered to some children on immunomodulators. The American Committee on Immunization Practices does allow for the administration of zoster vaccine (which is more potent than varicella vaccine) to adults on low-dose 6-MP (≤1.5 mg/kg/day), azathioprine (≤3 mg/kg/day), or methotrexate (≤0.4 mg/kg/week) [46]. Of children diagnosed with IBD, the percentage who have immunity to varicella varies widely, from 9% in the UK to 71% in Canada, with older age being associated with seroprotection [14, 47]. Moreover, Harris and colleagues in the UK retrospectively collected data over a decade (2009–2018) and found that pediatric patients with IBD who were immunized with varicella needed less post-exposure prophylaxis (0% vs. 28%, $p = 0.0006$) and had fewer varicella-related hospital admissions (4% vs. 22%, $p = 0.01$) compared to those who were not immunized [47]. Our group published a case series of six children with IBD on 6-MP or infliximab therapy who had received varicella vaccine (either inadvertently by their primary care physician, or deliberately after discussion of risks and benefits), and all experienced no adverse effects. Five of the six children developed an immune response [48]. Ansari et al. vaccinated ten pediatric patients with IBD with a negative or unknown varicella titer prior to starting immunosuppressive therapy. Post-vaccination antibody levels were obtained in eight of these ten patients, and all eight responded [49]. Thus, in the rare situation where there is a high prevalence of wild-type varicella, the benefits of protection against the wild-type virus might outweigh the risk of the immunization. Clearly, more data are needed in this very understudied area.

Another question that frequently comes up in these patients is whether family members can receive routine live vaccines. Once again, there is a paucity of data. Expert opinion suggests that family members can receive live vaccines (including measles, varicella, or zoster vaccine) except the oral polio and intranasal influenza vaccine, even if there is an immunosuppressed patient with IBD in the house. However, if a vaccine-associated rash develops in the affected family member, they should avoid close contact with the patient until lesions clear [9, 50]. Unfortunately, a study by Waszczuk and colleagues on this "cocoon immunization strategy" to protect immunocompromised patients by vaccinating close contacts found that only 40% of children of adult patients with IBD were immunized with at least one recommended vaccine. The most common reasons parents gave for not vaccinating their children were belief that immunizations were unnecessary (52%) and concern about side effects (25%) [51].

Women with IBD of childbearing age are often receiving immunomodulators and biologics to keep their disease in remission throughout pregnancy. Infliximab, if given in the third trimester, can pass transplacentally and enter the fetus's bloodstream. Therefore, there is potential for infants born to women with IBD to have a reduced response to inactivated vaccines, and to be at risk for complications of live vaccines. However, in a small study, immunoglobulin levels (IgG, IgM, and IgA) and antibodies to tetanus toxoid and *Haemophilus influenza* type b (Hib) were drawn in infants at least 6 months old of age and born to mothers who received at least one dose of infliximab or adalimumab during the third trimester. The study found that all infants had adequate immunoglobulin levels except half had a low IgM level. The vast majority (92%) mounted an adequate response to both tetanus and Hib vaccines [52]. A study by Beaulieu and colleagues demonstrated similar findings. Infants of mothers with IBD treated or not treated with biologic therapy during pregnancy had similar seroprotection rates between the two exposure groups for Hib (71% vs. 50%, $p = 0.41$) and tetanus toxoid (80% vs. 75%, $p = 0.66$). The median infliximab level in cord blood was similar between infants who did or did not mount seroprotective levels to Hib ($p = 0.3$) or tetanus toxoid ($p = 0.93$) [53].

For patients in whom influenza or varicella infection is suspected or confirmed, immunosuppressive therapy should be held until the patient is clinically improving or the infection resolves. Patients with IBD, regardless of their medication status, should be treated with antiviral medications (including oseltamivir) when clinically indicated. If patients being treated with immunosuppressive therapy lack immunity against varicella and experience a significant exposure to varicella, then VariZIG or acyclovir should be given. VariZIG should be administered as soon as possible and within 96 h of exposure. If >96 h have elapsed since exposure, or VariZIG is unavailable, then some experts suggest giving acyclovir within 7–10 days of the initial exposure. If immunocompromised patients acquire varicella infection, then intravenous acyclovir is recommended [54].

COVID-19 Infection and Vaccine Development: Relevance to Inflammatory Bowel Disease

At the time this chapter is being written, we are in the midst of a pandemic with a coronavirus variant called COVID-19 (COrona VIrus Disease-2019). As of January 2021, approx-

imately 85 million cases of COVID-19 have been reported worldwide, with 1.8 million deaths. The United States is the epicenter of the pandemic, with approximately 20 million cases reported, and over 345,000 deaths [55]. COVID-19 is a positive-sense single-stranded RNA virus, transmitted primarily through droplets. The most important protein in the COVID-19 virus is called the spike (S) protein, which is divided into two main subunits. The S1 subunit regulates receptor binding to cells through angiotensin-converting enzyme 2, and the S2 subunit promotes membrane fusion [56]. Common clinical symptoms of COVID-19 infection include cough, fever, myalgia, shortness of breath, and loss of taste or smell. The COVID-19 virus is highly contagious, and in a subset of individuals can result in severe pneumonia or death. Individuals thought to be at high risk include the elderly, obese patients, individuals with diabetes, and patients on high levels of immune suppression. Studies thus far of the IBD population suggest that corticosteroid therapy may increase the risk of severe COVID-19 infection, while patients on anti-TNF agents do not appear to be at increased risk for severe disease [57]. Fortunately, pediatric patients seem to have a lower risk of disease than older adults.

The pandemic has resulted in an unprecedented and highly ambitious scientific program to develop vaccines, so the pandemic may be curtailed. As of January 2021, a number of vaccines have already been developed, and been tested in phase 3 trials. At this point in time, two vaccines have been given emergency use authorization (EUA) by the Food and Drug Administration to be administered in the United States: one developed by Moderna and the National Institute of Allergy and Infectious Disease, and the other developed by BioNTech and Pfizer. Both these vaccines target the RNA region that generates the spike protein. At the current time, these vaccines are only being administered to healthcare professionals and very high-risk individuals, but we anticipate that this will change significantly by the time this chapter is published. For both of these vaccines, two immunizations are necessary. The BioNTech-Pfizer vaccine is administered as a two-dose series, 3 weeks apart, and according to the EUA, can be administered to individuals over 16 years of age. In contrast, the Moderna vaccine is administered as two doses 1 month apart, and under the EUA can be given to individuals over 18 years of age. Based on phase 3 trials, the vaccines have over 90% efficacy in the general population, though the efficacy in the elderly may be slightly decreased (around 85%). Adverse effects include injection site pain, fatigue, headaches, muscle aches, chills, and fever [58, 59]. Given that these vaccines are inactivated, we anticipate that they will be administered to patients who are receiving immune suppressive therapy in the future. However, at the time this chapter is being written the authors do not have any data on the safety or efficacy in patients with IBD. The recommendation at the current time is to follow current CDC guidelines for prevention of COVID-19 infection, including appropriate social distancing, good hand hygiene, and mask wearing; see www.cdc.gov for additional information on COVID-19.

Summary

Immunizations that can be given safely and should be given to children with IBD as part of the recommended immunization schedule include diphtheria and tetanus boosters, influenza, pneumococcal, meningococcal, human papillomavirus, hepatitis A, and hepatitis B. In general, the less immunosuppression a patient is receiving, the more likely they are to mount an effective immune response. Live vaccines, including measles virus and intranasal influenza vaccine, should not be given to IBD patients being treated with immunosuppressive therapy. Varicella live attenuated vaccine has been given without complication to some patients on mild immunosuppression but is generally not recommended. Therefore, providers should ideally inquire about immunization status at time of diagnosis and vaccinate if necessary prior to starting immunosuppressive therapy, especially in the case of live vaccines. Both primary care physicians and patients need additional education on the safety and efficacy of inactivated vaccines.

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Colitis-Associated Cancers

56

David Faleck and David Kelsen

Clinical Presentation of Colitis-Associated Cancers

The signs and symptoms of a primary colitis-associated cancer frequently overlap with those of active inflammatory bowel disease. For patients with ulcerative colitis and Crohn disease who have ongoing symptoms of IBD, change in bowel function is a frequent occurrence. Diarrhea and rectal bleeding may be attributed to active IBD, and abdominal pain and bowel obstruction may be interpreted as sequelae of IBD. More ominous signs such as anorexia and weight loss may also be ascribed to active IBD. Patients with Crohn disease involving the small bowel may undergo surgery for stricturing disease, and it may not be recognized until during the operation, or even until pathology is reviewed that there was malignant transformation of the bowel. For patients with less active IBD, which may have been quiescent for years, new symptoms may also be ascribed initially to a flare and managed medically. Thus, a delay in diagnosis appears to compound a more aggressive biology (see Systemic Therapy for Advanced Colitis-Associated Cancer, below), which results in a large percentage of CAC being diagnosed at more advanced stages [1]. The overlap in signs and symptoms of the underlying inflammatory bowel disease with those of developing cancer in an IBD patient leads to an emphasis on prevention and early detection.

Pathogenesis and Genomic Alterations in Colitis-Associated Bowel Cancers

Currently, colitis-associated cancers are felt to be due to direct or indirect effects of chronic inflammation. As opposed to CAC, the key genomic-driving factors in the development of the much more common sporadic colorectal cancers (CRC) have been known since the late 1990s [2, 3]. Rather than arising from dysplasia in a chronically inflamed IBD gut mucosa, mutations in the Wnt or Mismatch Repair pathways lead to the development of adenomatous polyps. The pathways of sporadic CRC and its precursor adenomatous polyp mirror those occurring in familial cancer syndromes (Familial Adenomatous Polyposis (FAP) and Lynch Syndrome, responsible for ~3–5% of CRCs), which are the result of an inherited (or for ~30% of FAP patients, spontaneously acquired) germ-line cancer susceptibility gene.

Eighty to eighty-five percent of sporadic colorectal cancer develops in the setting of abnormalities in the Wnt pathway. In this process, loss of *APC* (a tumor suppressor gene) function due to point mutation occurs as an initiating or "gatekeeper" event for subsequent molecular alterations that culminate in the development of an adenoma. This is the key genetic abnormality in FAP, which leads to widespread development of innumerable adenomas. Loss of TP53 (also a tumor suppressor gene) function occurs later in the sequence, typically at the transition of an adenoma to carcinoma. Activating Kras mutations (an oncogene) are a frequent subsequent event. In sporadic CRC, the incidence of Kras and other mutations differs between right sided vs. left side colorectal cancers.

The remaining 15% of sporadic CRCs arise through a mutator pathway that involves loss of function of DNA base mismatch repair (MMR) genes, e.g., *hMLH1* and *hMSH2* (germ-line mutations of mismatch repair genes are responsible for Lynch Syndrome which is identified in ~3% of CRC). In this pathway, loss of MMR gene function results in a phenotype termed *microsatellite instability* (*MSI*). Sporadic CRCs that demonstrate MSI are often diploid (as opposed to the aneuploid state of chromosomal instability Wnt pathway-related tumors), tend to occur in the proximal colon, and frequently display histological features such as a medullary or solid growth pattern, a signet-ring cell histology, a plethora of tumor-infiltrating lymphocytes, and an adjacent inflammatory reaction often referred to as a "Crohn-like reaction." Another distinguishing feature of MSI-positive sporadic

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CRCs is the better survival of patients with those tumors compared to those without MSI. The hyper-mutated state of dMMRP/MSI high cancers also has therapeutic implications: these cancers are responsive to immune modulation therapy using agents targeting PD1 or CTLA4 [4] (Fig. 56.1).

While colitis-associated cancers share several features in common with sporadic CRC, there are also important differences. Similarities include that both arise from a precursor dysplastic lesion. However, in the case of sporadic CRC, the dysplastic precursor is a discrete, polypoid growth called an

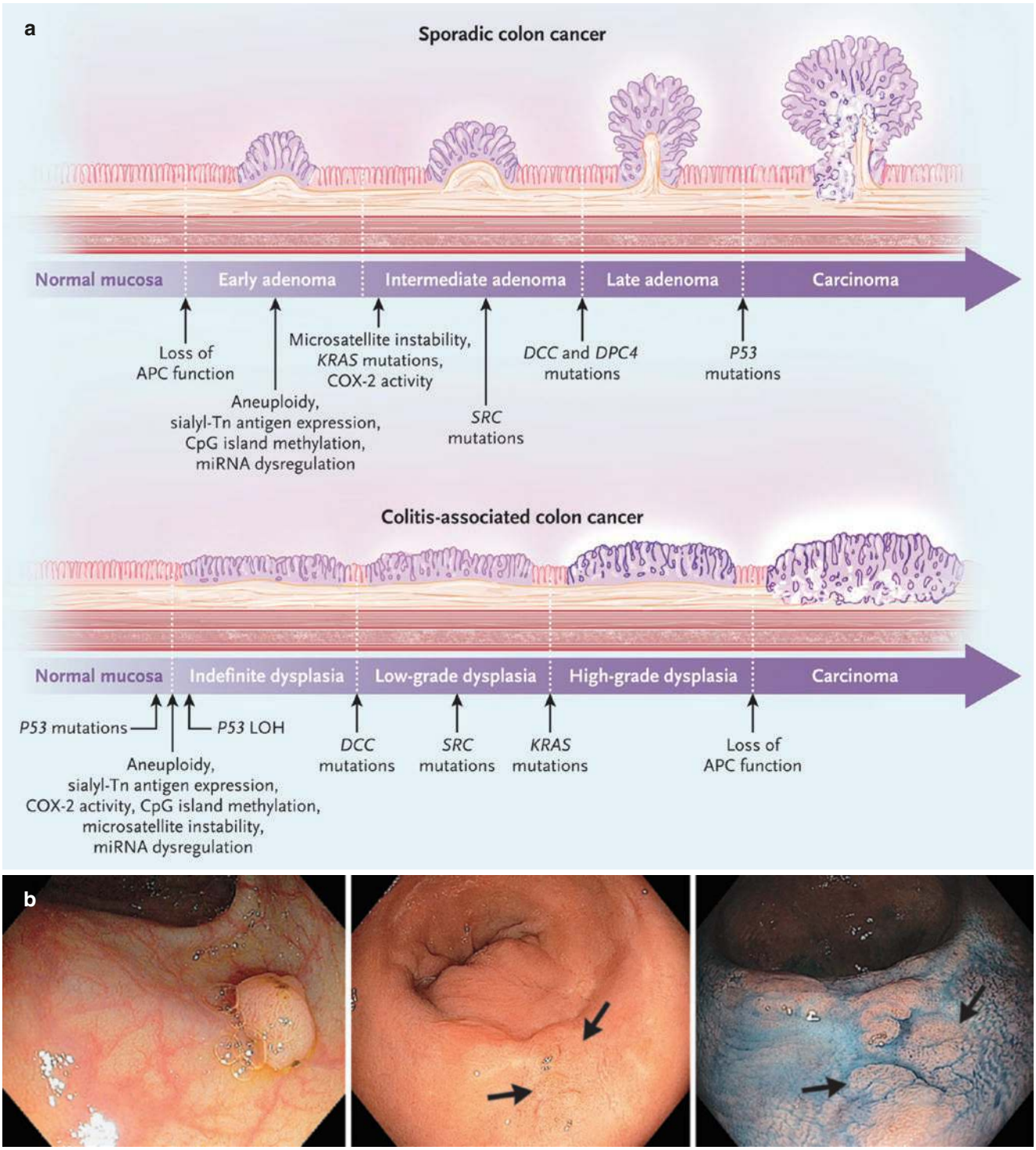

Fig. 56.1 Genomic alterations in the initiation and progression to cancer in sporadic colon cancer compared to colitis-associated colon cancer. (**a**) is a schema comaring the genomic steps in the development of "sporadic (not CAC, not inherited germline) colon cancer; (**b**) shows a polypoid lesion (From Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. N Engl J Med. 2015 [5])

adenoma, which typically progresses through greater degrees of dysplasia and increasing villous histology and eventually leads to cancer. In IBD, while dysplastic areas may appear polypoid, they are frequently flat or only slightly raised. The substantial differences in the overall spectrum of genomic alterations between CAC and Sporadic CRC are described below [6, 7].

Clinical differences between sporadic CRC and CAC include a younger median age at the time of diagnosis for CAC patients than sporadic CRC patients. Dysplasia and occasionally even CAC may be multifocal, suggesting a precancerous "field change" of the colonic mucosa compared to the colons of patients with sporadic (non-familial syndromes) adenomas and colon cancer, where synchronous cancers are rare [8]. The risk for both synchronous and metachronous neoplasia leads to different surgical approaches: colitis-associated neoplasms are often treated with more extensive resections, including subtotal colectomy or total proctocolectomy, particularly for patients with ulcerative colitis, whereas sporadic cancers are treated with more limited resections for cancer. Finally, recent data suggest worse outcomes for patients with later-stage CAC, with shorter survival for advanced-stage CAC patients when compared to same stage CRC patients [1].

Spectrum of Genomic Alterations in Colitis-Associated Cancer

Although sporadic CRC and CAC share several types of molecular changes, the frequency of these molecular alterations differs (Fig. 56.2) [6, 7]. As shown, *APC* mutations are more common in sporadic colon cancer; this molecular alteration is much less frequent in CAC and as shown above, they occur later in the progression to cancer. There is also a difference in frequency of APC mutations between UC and Crohn Disease-associated cancers: recent data from next-generation sequencing analysis of colitis-associated cancers suggest that *APC* mutations may be more common in Crohn-associated cancers than in cases associated with UC (Fig. 56.3) [6].

TP53 alterations are nearly universal in colitis-associated cancers, and may be the initiating event. The majority of these *TP53* alterations are missense mutations occurring in the DNA-binding domain of p53. Many of these missense mutations may also possess gain-of-function capacities, including enhancement of invasive properties, attenuation of apoptosis, and increased genomic instability [9, 10]. The early presence of mutant p53 in the inflamed colon of IBD patients may be a driver of the subsequent progression to

Gene	CAC (n = 47)	TCGA-CRC (n = 212)	FM-CRC (n = 3117)	CAC *v* TCGA-CRC	CAC *v* FM-CRC
	Percent altered			*P*-value	
TP53	89%	52%	75%	**<.001**	**.02**
APC	21%	76%	76%	**<.001**	**<.001**
KRAS	40%	42%	53%	.7	.07
SMAD4	17%	14%	16%	.8	1
MYC	26%	4%	9%	**<.001**	**<.01**
GNAS	13%	11%	6%	.6	.06
IDH1	11%	1%	0.60%	**<.01**	**<.001**

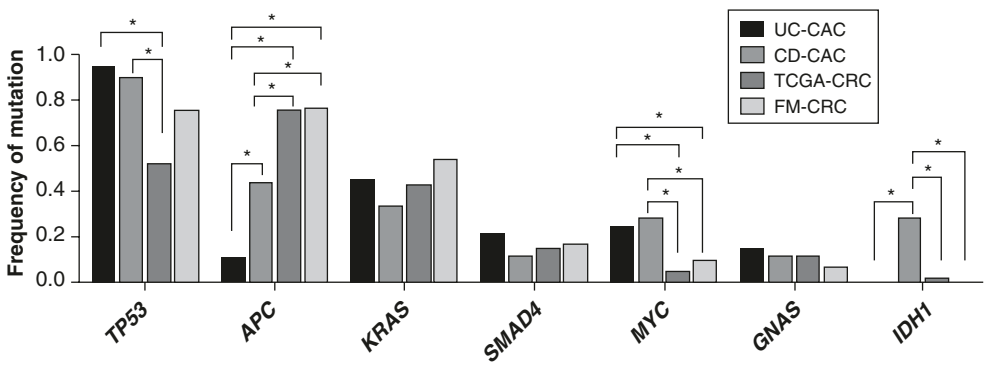

Fig. 56.2 Comparative analysis of the frequency of alterations in recurrently altered genes in CAC and in sporadic CRC. Top: Table showing the frequency of alterations in the indicated genes in the CAC cases overall (UC associated plus CD associated) vs. the frequency of alterations in the same genes as found in TCGA-CRC and in the FM-CRC, and associated *p* values based on Fisher's exact test. Bottom: Bar graph showing the relative frequency of GAs in the indicated genes in CAC associated with UC (UC-CAC), CAC associated with CD (CD-CAC), TCGA-CRC, and FM-CRC. Differences in the frequency of alterations that were statistically significant, based on Fisher's exact test, are indicated with a star. (From Yaeger et al. Gastroenterology 2016)

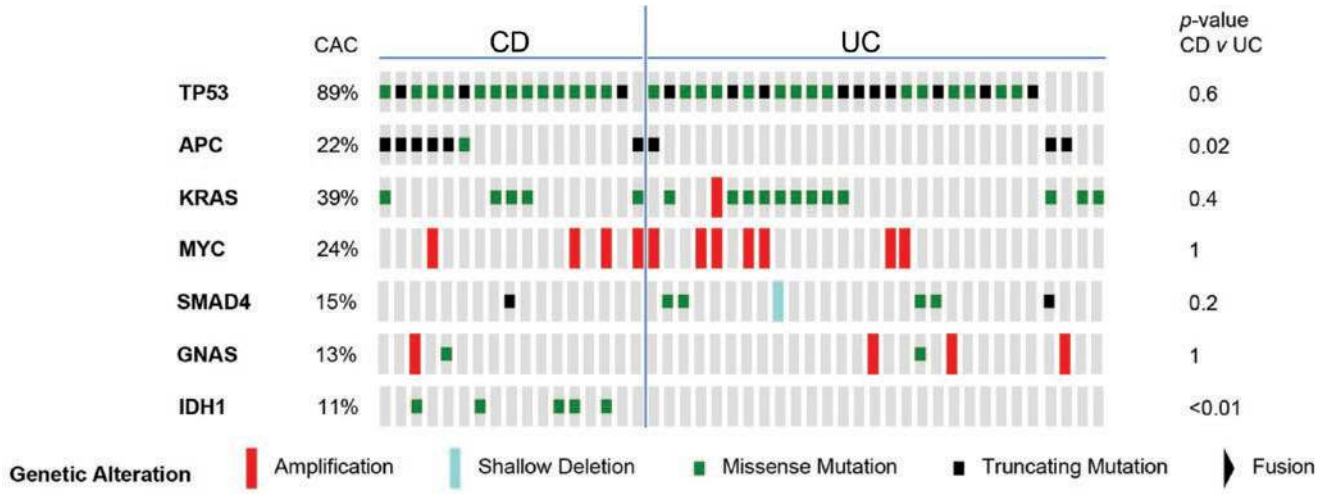

Fig. 56.3 Spectrum of Selected Genomic Alterations (analyzed by Next Generation Sequencing) of Colitis-Associated Cancers comparing underlying IBD by Crohn Disease and Ulcerative Colitis. Note that APC mutations, while less frequent than in sporadic Colorectal cancer, are found at a higher rate in Crohn Disease CAC. IDH1 mutations are also seen more commonly in Crohn Disease CAC

carcinoma by invigorating inflammation in the immediate microenvironment of the cells with mutant p53 [10]. Using a murine model, where exposure to dextran sodium sulfate (DSS) induces an acute colitis, Cooks et al. studied the role of mutant *TP53* versus loss of *TP53* on the development of adenomas and progression to carcinoma [10]. The mice with mutant *TP53* developed more frequent inflammation-associated colon cancer and developed carcinoma much earlier than mice with knockout of one *TP53* allele, suggesting that mutant p53 may not only make the mice more susceptible to chronic inflammation but also accelerate the development of carcinoma on an inflammatory background. *TP53* mutations can be detected in mucosa that is histologically non-dysplastic or indefinite for dysplasia [11].

Besides the incidence of APC and TP53 mutations, there are other substantial differences in the spectrum of genomic alterations between CAC and sporadic CRC. *IDH1* mutations at the R132 hotspot occur in about 10–15% of colitis-associated CRC, particularly in cases associated with CD [6, 12]. IDH1 R132 mutations are exceedingly rare in sporadic colorectal cancer and occur in no more than 1% of cases [13]. The R132 mutation in *IDH1* results in a mutant isocitrate dehydrogenase enzyme that cannot participate in the oxidative carboxylation of isocitrate, leading to dysregulated cellular metabolism, interfering with the generation of the key-reducing agent (NADPH), and producing the oncometabolite 2-hydroxygluatarate, which is associated with an altered epigenetic state with the CpG island methylator phenotype (CIMP) [14]. Other recurrent genetic alterations identified in CAC include *MYC* amplification, which occurs in both sporadic CRC and CAC but is significantly more common in CAC, and alterations in fibroblast-growth factor signaling, including FGFR1/FGFR1 amplification and translocations and ligand amplifications [6]. A recent report has found a difference in extracellular matrix remodeling in peritumoral stroma comparing CAC with CRC, both in a preclinical model and in human CAC [15]. The role of the bowel microbiome and altered bile acid composition as factors inducing the genomic changes associated with colitis-associated cancers are areas of active investigation.

Epidemiology and Incidence

Crohn and Rosenberg first described rectal cancer as a complication of UC more than 80 years ago [16]. It quickly became apparent that IBD, both ulcerative colitis and Crohn disease, are associated with an increased risk of bowel cancers; colorectal cancer in both UC and Crohn disease, and small-bowel cancers in Crohn disease. The magnitude of the risk has been the subject of study over the last several decades. While clearly elevated compared to the general population, the incidence of bowel cancer in patients with IBD is probably lower than previously thought. Nonetheless, it should be recognized that CACs are among the most serious complications of IBD and pose an important cause of morbidity and mortality in these patients [17].

Early estimates of the incidence of CAC were based largely on series developed from individual institutions, usually large referral centers, and likely overestimated the lifetime risk of CAC. In a meta-analysis of the risk of CRC in ulcerative colitis reported in 2001, in which 116 studies were included, Eaden and colleagues found the overall prevalence of CRC to be 3.7% and an overall incidence rate of 3 cases per 1000 person years duration [18]. The risk increased with each decade of active disease and corresponded to a cumula-

tive incidence of CRC of 2% at 10 years, 8% at 20 years, and 18% at 30 years disease duration. Based on this meta-analysis and earlier studies, typical estimates of CRC incidence ranged between 0.5% and 1% per year after 10 years of colitis.

More recent studies raise the possibility that prior reports overestimated the incidence and risk of CAC [19]. Data from France [20], Denmark and Sweden [21], Canada [22], and Olmsted County, Minnesota [23] have suggested a CAC incidence (mostly in UC patients) of between 1 in 500 and one in 600 per year, far lower than the 1 in 300 rate calculated in Eaden's meta-analysis. These have corresponded to relative risk calculations ranging from 1.1 to 2.7 times the general population. Meta-analyses based on these and other more recent population-based cohorts found cumulative incidence of CAC in ulcerative colitis of 1% at 10 years, 2% at 20 years, and 5% at >20 years disease duration [24]. The risks appear higher for patients with long durations of IBD, especially IBD beginning in pediatric patients [25], and those with more extensive colitis.

The risk of CAC in Crohn disease involving the colon appears similar, with a meta-analysis of Crohn colitis finding a risk of 2.9% at 10 years, 5.6% at 20 years, and 8.3% at 30 years of disease [26]. Patients with Crohn disease that is isolated to the small bowel do not appear to be at increased risk of colorectal cancer [27]. Lightner et al. recently reported a comparison of endoscopically assessed rate of progression from dysplasia to adenocarcinoma, in Crohn Disease vs. Ulcerative Colitis. They found that although dysplastic events were more common in UC, the rate of progression to adenocarcinoma was not significantly different [28]. These data support current surveillance guidelines which do not distinguish between UC and Crohn colitis regarding when to start surveillance nor interval of endoscopic surveillance.

While variation in study populations may account for some of the observed decline in CAC rates over time, improvement in endoscopic surveillance techniques (see below), and better control of inflammation with new anti-inflammatory agents as well as possibly a modest benefit from chemoprevention (see below) may play a role as well. Although the risk is lower than thought in the 1990s and early 2000s, the overall data support an increased risk for CAC in both ulcerative colitis and Crohn disease, supporting the use of surveillance and early detection programs.

Conditions Increasing the Risk of Colitis-Associated Cancers

As noted above, several clinical variables have been suggested to affect the risk of developing CAC. These variables include age at IBD diagnosis, duration of active IBD, anatomic extent of bowel inflammation, degree of inflammatory activity on endoscopy and histology, concomitant primary-sclerosing cholangitis (PSC), and a family history of colorectal cancer. Table 56.1 classifies these different risk modifiers.

Table 56.1 Risk modifiers of colorectal cancer in ulcerative colitis

Accepted risk modifiers	
Duration of colitis	*Long duration of colitis increases risk*
Age of onset	*Early age of onset increases risk, possibly independent of duration*
Extent of disease within the bowel	*Greater extent increases risk*
Degree of Inflammation	*Increased cumulative inflammation increases risk*
PSC	*Presence of PSC increases risk*
Family history of carcinoma	*Family history of CRC increases risk*
Possible risk modifiers	
Sulfasalazine/5-ASA	*Use may reduce risk*
Biologics/Small Molecules	*Control of inflammation may reduce risk*
Folic acid	*Supplementation may reduce risk*
Ursodeoxycholic acid	*Use may reduce risk in UC patients with PSC*
Unlikely risk modifier	
Glucocorticoid use	
6-MP/AZA use	

PSC primary-sclerosing cholangitis, *CRC* colorectal cancer, *UC* ulcerative colitis, *AZA* azathioprine

Duration of Colitis

As noted above, the total duration of colitis is associated with an increased risk of colorectal cancer in both ulcerative colitis and Crohn disease [26]. Surveillance guidelines, thus, recommend initiation of surveillance in patients with active colitis for 8 years [29–31]. However, up to 20% of patients will develop CRC sooner than 8 years after diagnosis [32], though whether this is due to diagnostic delays, long-standing subclinical disease, or accelerated carcinogenesis is not well understood. As such, the development of effective non-invasive biomarker assays for early detection of CAC is a high priority to enable more efficacious screening from the time of diagnosis of IBD.

Age of Onset of Inflammatory Bowel Disease

Important to pediatricians, age of colitis onset, perhaps as a variable independent of disease duration, has been implicated to modify the risk of CAC [33]. An early report found that at 35 years of follow-up, 43% of subjects with documented UC prior to age 15 had developed CRC [34]. Several more recent studies have confirmed elevated rates, if not the

magnitude, of this early study. In a Swedish national cohort study [35], patients with pediatric-onset (<18 years) IBD had a HR of 19.5 for long-term increased risk of CAC compared to matched non-IBD patients, though the risk of cancer before age 18 remained exceedingly low. Similarly, in a population-based study from Denmark and Finland, patients with pediatric-onset IBD were found to have elevated incidence of colorectal cancer relative to non-IBD controls (SIR 15.3) [36]. Although the precise magnitude of lifetime CAC risk for younger patients who develop UC or CD is still not fully determined, CAC itself is very rarely diagnosed in patients in their late adolescence but has been identified in patients in their 20s or 30s. Importantly for pediatricians, early control of inflammation may serve to lessen the cumulative inflammatory burden (see below), which offers the opportunity for long-term risk reduction in the development of CAC for individuals with pediatric-onset IBD.

Anatomic Extent of Colitis

The length of involved colon also correlates with cancer risk: the greater the surface area of colitis, the greater the cancer risk. A risk gradient by colitis extent has been observed in several studies, with isolated proctitis conferring minimally increased risk, and extensive colitis conferring a risk up to 4.5 times control, with left-sided colitis conferring a moderately increased risk [19, 21]. As histologic inflammation appears to be a key driver of neoplasia (see next section), the microscopic extent of disease should be used to define areas at risk [37].

Histologic Inflammation

Several studies have demonstrated that degree and cumulative burden of histologic inflammation are important predictors of CRC risk. Data from the St Mark's surveillance program in the UK first demonstrated that histologic severity of inflammation correlated with colorectal neoplasia or cancer risk [38], and these data have been since replicated in other cohorts [39]. More recently, the concept of cumulative inflammatory burden has been described by the St Mark's group [40] and validated externally [41], which quantitates the actuarial degree of histologic inflammation over time per individual across surveillance colonoscopies. Cumulative inflammatory burden was found to be an important, independent predictor of CRC risk and supports a theoretical role of inflammatory control as chemoprevention.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease in which there is progressive inflammatory fibrosis of the biliary tree. It is an infrequent complication of IBD, affecting 2–8% of patients with ulcerative colitis. Conversely, among patients with PSC, 62–72% have underlying IBD [42], prompting the recommendation to screen for IBD at the time of PSC diagnosis [43]. Patients with PSC have been observed to have a markedly increased risk of CRC [21, 42] and CRC-related death (e.g., HR 8.3 in a recent population-based study [21]) and so are recommended for annual colonoscopies. Recent data support an increased incidence of CAC in children with concomitant IBD and PSC as well [25]. The explanation for this marked increased risk appears to be multi-factorial. Colitis activity in PSC is often mild or even subclinical, and so patients with PSC may have a longer duration of inflammation than suspected clinically, raising their risk for CRC. Additionally, accelerated carcinogenesis has been proposed due to altered bile acid metabolism, gut dysbiosis, and distinct genotypes [44].

Family History of Colorectal Cancer

Family history of CRC has long been recognized as a risk factor for the development of sporadic colorectal cancer. In patients with IBD, a family history of colorectal cancer may add to the personal risk of development of CRC as well. Nuako and colleagues at the Mayo Clinic were the first to clearly demonstrate this increased risk, calculating an odds ratio of 2.3 (95% CI 1.1–5.1) in their case–control study [45]. In a population-based study from Scandinavia, Askling and colleagues found a similar elevated risk of 2.5 (95% CI 1.4–4.4) [46]. It is suspected that patients with a positive family history for colorectal cancer may have two independent driving factors increasing their personal risk of colorectal cancer: inflammation from IBD and an inherited cancer susceptibility gene. The genomic alterations associated with CAC are different than those associated with germ-line (inherited or spontaneous) mutations; future analysis of germ-line and somatic tumor specimens will allow a more precise estimate of each factor's contribution of in the development of colorectal cancer in patients with IBD. Recent genomic alterations analysis regarding the spectrum of genomic alterations in colitis-associated cancer versus sporadic colorectal cancer, discussed above, excluded from the analysis patients with a known germ-line cancer susceptibility gene mutation.

Prevention of Colitis-Associated Cancers

Pharmacotherapy and Chemoprevention

As with sporadic and familial colorectal cancer, investigators are actively seeking medications that might decrease the risk of developing CRC in IBD. The introduction of more effective drug therapy for moderate and severe IBD, by decreasing chronic inflammation, may in itself decrease the risk of dysplasia and cancer but conclusive proof for this remains elusive. A variety of preventative agents have been studied in IBD, primarily in retrospective studies, with mixed results.

Sulfasalazine/5-Aminosalicylates

Sulfasalazine and their derivative 5-aminosalicylic acid (5-ASA) products are the most commonly used medications for management of IBD and have been investigated for their chemopreventive effects. Studies assessing their role in reducing CAC have been limited to case control and cohort analyses given the logistical challenges in conducting a randomized, blinded clinical trial, and have yielded conflicting results [47–49]. Several systematic reviews and meta-analyses pooling these heterogenous data have demonstrated significant chemopreventive benefit with approximately 50% reduction in CAC incidence, in spite of not dysplasia, which raises questions about the biologic plausibility [50, 51]. Nonetheless, as a generally well-tolerated agent with favorable safety profile, the use of these agents should be encouraged in all patients with mild-moderate UC who achieve remission with these agents.

Thiopurines

Before the more recent widespread use of biologics for IBD, the purine analogs azathioprine and mercaptopurine were commonly used maintenance therapies in IBD and still are an important component of the IBD armamentarium. While these agents have been linked to an increased risk of certain malignancies, including lymphoma and non-melanoma skin cancer [52, 53], their relationship with CRC is less clear. Several studies and meta-analyses have assessed their impact on development of dysplasia and CAC and have failed to demonstrate a consistent benefit [54–56], and given their risk profiles, these agents are not recommended for the purposes of chemoprevention alone.

Biologics/Small Molecule Agents

Biologic agents including anti-TNF therapy (e.g., infliximab, adalimumab, certolizumab, golimumab), anti-integrins (e.g., vedolizumab), and newer anti-interleukin agents (e.g., ustekinumab), as well as the small-molecule JAK inhibitors (e.g., tofacitinib) have changed the landscape of IBD therapy and have driven the goals of therapy to increasingly rigorous endpoints including endoscopic and histologic healing [56, 57]. However, while control of inflammation may account for some of the apparent decreasing incidence of CAC discussed above [21], the impact of these agents, both individually and collectively, on the risk for CAC has not been well studied. Despite more than 20 years of anti-TNF use, scarce data have assessed the relationship with CAC [55]. Some evidence of a protective effect emerged from a recent database-based study that found significantly lower rates of CRC in both UC (OR 0.78) and CD (OR 0.69) for patients treated with anti-TNF agents [58]. At present, the use of these agents should be guided by therapeutic targets in IBD, which includes achieving mucosal healing, but there are insufficient data to recommend one class of agents over another for prevention of dysplasia or cancer.

Folic Acid

Folic acid has been studied for chemoprevention in sporadic colorectal cancer with mixed results [59, 60], and several non-controlled studies have assessed its role in prevention of CAC. Two studies by Lashner [61, 62] specifically looking at this outcome, were statistically negative but had favorable point estimates, and a meta-analysis of these along with eight other studies that assess folic acid chemoprevention as a secondary outcome found an overall significant benefit in chemoprevention of CRC with a pooled HR of 0.58 [63]. While more robust data are needed to support this intervention, given the low cost and the low risk of adverse events with folic acid supplementation, this can be considered for at risk patients.

Ursodeoxycholic Acid

Ursodeoxycholic acid, an exogenous bile acid used in the treatment of PSC, has also been studied. In UC-PSC patients, an impressive chemopreventive effect has been demonstrated, with a 40% difference in neoplasia noted between the ursodeoxycholic acid-treated group (32%) and the

untreated group (72%) [64]. This was additionally demonstrated in a randomized clinical trial of ursodeoxycholic acid in which a 74% reduction in dysplasia or CRC was noted [65]. Newer data, however, from the same group that studied it in the earlier trial, demonstrated that high-dose ursodeoxycholic acid at 28–30 mg/kg per day actually gave rise to *more* colorectal neoplasia [66]. As the benefits of ursodeoxycholic acid on PSC are questionable at best, it is uncertain whether low-dose administration should be given as a chemopreventive agent in patients with concomitant IBD and PSC.

Screening, Surveillance, and Risk-Reducing Surgery

Screening and Surveillance

For screening and surveillance to be effective, they should reduce CRC mortality in IBD patients. Pending the development of effective chemoprevention regimens and/or effective early detection biomarkers to identify patients in whom dysplasia or very early CAC is developing, endoscopic screening and surveillance are the primary modalities used for prevention of CAC. Endoscopic modalities may be effective either through the prevention of CRC by the removal of precursor lesions, or through early detection of CRC at a more curable stage. No prospective, randomized trials have been performed to unequivocally demonstrate a mortality benefit to surveillance colonoscopy, but multiple non-randomized studies support this contention. A recent Cochrane review evaluated multiple cohort studies and found a significantly lower rate CAC-associated death in the surveillance group (8.5%) compared to the non-surveillance group (22.3%) (OR 0.36 (95% CI: 0.19–0.69), $p = 0.002$) [67]. Additionally, this review found a significantly higher rate of early-stage CAC detection in the surveillance group (15.5%) compared to the non-surveillance group (7.7%) (OR 5.40 (95% CI: 1.51–19.30), $p = 0.009$).

Screening for dysplasia in IBD is generally recommended after 8 years of colitis that extends proximal to the rectum in UC [29] and involves more than one third of the colon in CD [30]. Surveillance for dysplasia is continued every 1–3 years according to current US guidelines [29, 30, 68] (though can be extended up to 5 years in low-risk patients per current European guidelines [31]), adjusted according to patient risk factors and results of prior colonoscopies. For patients with concomitant PSC, screening is recommended from the time of diagnosis, and surveillance is performed annually.

In the past, the finding of dysplasia on an endoscopic biopsy led to consideration of total proctocolectomy [69, 70].Older studies suggested that the presence of LGD or especially HGD was a high-risk marker that should prompt consideration of colectomy [71]. (Figure 56.4 shows the histology of low-grade dysplasia, high-grade dysplasia, and colitis-associated adenocarcinoma). These series suggested a high rate of progression (>50%) from even LGD to advanced neoplasia [72], and a substantial rate of finding an undiagnosed synchronous cancer (e.g., ~20% [73–75]) for colectomies done for a pre-operative diagnosis of LGD. However, with advances in endoscopic technology for dysplasia detection and endoscopic techniques for dysplasia resection, there has been a paradigm shift in the management of IBD-associated dysplasia over the last two decades. This shift was best captured in the SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patient) guidelines published in 2015 that elevated the role of endoscopy to the forefront in detection and management of IBD-associated dysplasia [68].

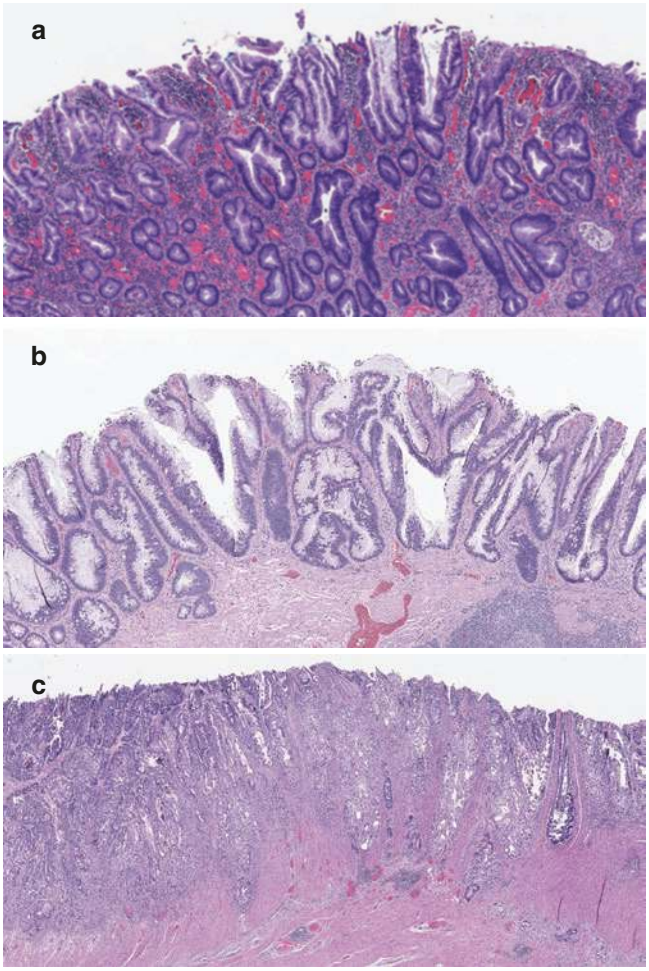

Fig. 56.4 Histology photomicrographs (three micro photographs are attached): Histology of (**a**) low-grade dysplasia, (**b**) high-grade dysplasia, and (**c**) colitis-associated adenocarcinoma of the colon. (Courtesy of Dr. Jaclyn Hechtman, MD, Department of Pathology, Memorial Sloan Kettering Cancer Center)

Endoscopic Detection

Most dysplasia was previously believed to be flat or invisible [76], thus, necessitating total colectomy when an area of dysplasia was detected [71]. To enhance detection of dysplasia in the era of fiberoptic colonoscopy, random surveillance biopsies were introduced in the early 1990s based on a modeling study suggesting that 33 non-targeted biopsies could enhance detection of colonic dysplasia [77]. Thereafter, performance of four quadrant random biopsies every 10 cm (or in each of 8 colonic segments) was adopted for IBD surveillance exams and recommended in numerous guidelines [78–80]. However, with the advent of improved imaging techniques including high-definition white light endoscopy, dye-based chromoendoscopy, and virtual chromoendoscopy, more recent studies have found that the vast majority of dysplasia is, in fact, visible [81–83]. This recognition has called the utility of random biopsies into question [78, 84], with data compiled by the SCENIC guidelines finding that only 1/1000 random biopsies reveal dysplasia and that only 1–1.5% of patients undergoing surveillance would not have dysplasia detected in the absence of random biopsies [68]. More recent guidelines reflect the diminishing value placed on random biopsies and suggest that these can be omitted in the setting of chromoendoscopy [31] or possibly even with high-definition white light [29]. Nonetheless, some recent data do suggest a role for random biopsies in the highest risk patients, such as those with concomitant PSC, a history of dysplasia, or active inflammation [85, 86], and so these continue to be performed at the discretion of the endoscopist.

High-definition white light has been found to be superior to standard white light in the detection of neoplasia in the setting of IBD [87] and is now widely recommended wherever available [68]. Two imaging enhancement techniques, dye-based chromoendoscopy and virtual chromoendoscopy, have also shown promise in enhancing detection of dysplasia and are incorporated into many surveillance recommendations. Dye-based chromoendoscopy, the application of methylene blue or indigo carmine dye spray to provide a contrast between dysplastic and non-dysplastic colonic tissue, has been shown to enhance detection relative to standard-definition white light [68]. Its additive benefit above high-definition white light, however, remains a matter of debate; several recent randomized trials showed enhanced detection with chromoendoscopy [88], while others showed no benefit [89] and a recent meta-analysis found no benefits in pooled randomized trials [90]. This persistent uncertainty, as well as the added cost and procedure time with its use, have limited the uptake of dye-based chromoendoscopy in the general gastroenterology community. Nonetheless, chromoendoscopy is performed by many IBD specialists, can be readily learned by practicing gastroenterologists [91], and is recommended in the highest risk patients and in particular scenarios, e.g., evaluation of the so-called "invisible" dysplasia (dysplasia detected on random biopsies).

Virtual chromoendoscopy employs light-filtering technology such as narrow-band imaging (NBI) built into modern colonoscopes and has been proposed as a more efficient and less costly alternative to dye-based chromoendoscopy for enhanced detection of dysplasia. Early studies of this technology found that it was no better than standard-definition or high-definition colonoscopy and so the SCENIC guidelines recommended against its use [92, 93]. However, more recent studies of NBI in IBD have shown, which may be equivalent to dye-based chromoendoscopy in detection of dysplasia and is quicker and cheaper to perform [94, 95], leading to recent guidelines suggesting that it can be used as an alternative to dye-based chromoendoscopy for IBD surveillance [29]. Especially with incremental improvements with new, second-generation NBI which uses brighter image enhancement and has been found to increase adenoma detection in the general screening population [96], virtual chromoendoscopy can serve as an important adjunct to routine surveillance colonoscopies and may offer benefits of ease of use, lower cost, and increased familiarity over dye-based chromoendoscopy.

Endoscopic Resection

A second-key factor in the paradigm shift in the management of IBD-associated dysplasia was the pivot from using dysplasia as a *marker* for future colon cancer and, thus, a signal for colectomy, to recognizing dysplasia as a *precursor* lesion that could be effectively resected, thereby preventing the development of colon cancer. In 1999, two groups reported that after polypectomy for polypoid LGD in the setting of IBD, there were no subsequent colorectal cancers observed over a follow-up period of 3–4 years [97, 98]. Multiple subsequent studies confirmed a low rate of progression to CAC after complete endoscopic resection of polypoid lesions, with a meta-analysis finding a pooled annual CAC incidence of 0.5% after resection of polypoid dysplasia [99]. This heralded the shift towards endoscopic resection of dysplasia in IBD, which was augmented by enhanced ability to detect dysplasia (as discussed above), improved universal nomenclature for describing dysplastic lesions [68, 100] (e.g., Paris Classification), and the evolution of enhanced resection techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [101]. This shift was highlighted in the SCENIC guidelines, in which endoscopic surveillance, rather than colectomy, was recommended as the preferred approach after complete endoscopic resection of polypoid dysplasia [68].

In contrast to the clear recommendations after removal of polypoid dysplasia, the natural history and ability to com-

pletely resect non-polypoid dysplasia remained a matter of some debate, with SCENIC providing a more qualified "suggestion" for endoscopic surveillance after resection, rather than "recommendation." Nonetheless, there is an effort to move away from even this classification of polypoid dysplasia versus non-polypoid dysplasia in favor of a distinction between endoscopically resectable and non-endoscopically resectable dysplasia [102]. New techniques such as ESD, an advanced resection technique pioneered in Japan and now entering into more common practice in the US [103], continue to push the envelope of "endoscopic resectability." Several studies have examined the short-term success of advanced endoscopic techniques such as ESD for removal of flat dysplasia and found that despite the added challenges of fibrotic tissue, ESD is technically feasible with good immediate success in expert hands, with en bloc lesion resection rates of 80–100% and clear pathologic margins (R0) resection of 76–80%, comparable to that in the non-IBD population [104–109]. However, the long-term efficacy in preventing CAC and the rates of metachronous neoplasia after resection of these high-risk lesions are less clear but appear to be high and require very close surveillance if an endoscopic approach is selected [110].

In sum, endoscopic techniques for detection and resection of IBD-associated neoplasia have made tremendous advances over the last several decades and have prompted a paradigm shift from primary surgical to primary endoscopic management of dysplasia in the setting of IBD (Fig. 56.5). Importantly, this should be coupled with effective pharmacotherapy to maximize healing of underlying colitis in order to facilitate effective detection and mitigate against the risk of further dysplasia. Nonetheless, there are still numerous indi-

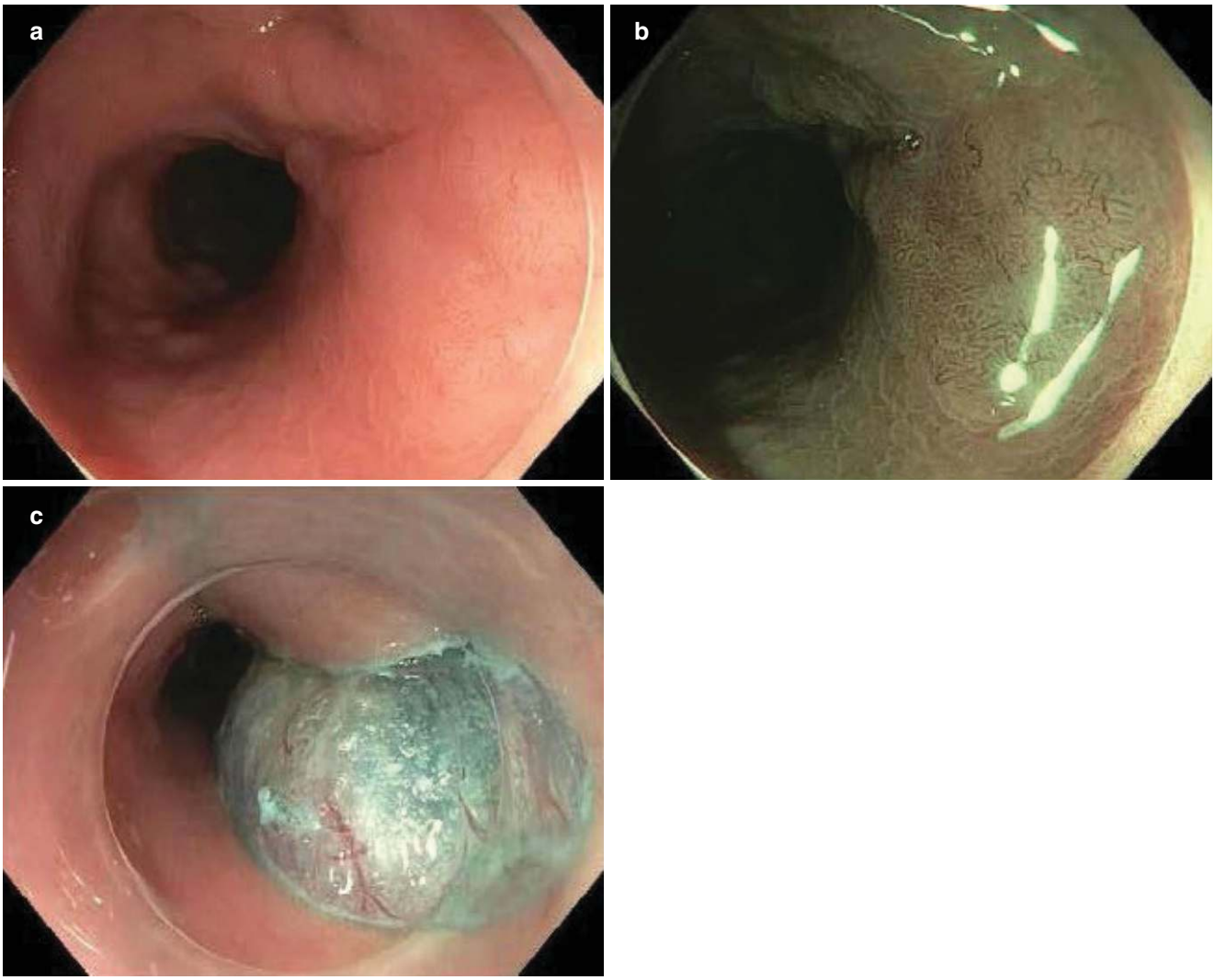

Fig. 56.5 Flat dysplasia in IBD seen with (**a**) high-definition white light endoscopy and (**b**) narrow-band imaging. (**c**) Flat lesion after endoscopic submucosal dissection. Pathology revealed low and focal high-grade dysplasia with clear margins. (Courtesy of Dr. Makoto Nishimura, MD, Memorial Sloan Kettering Cancer Center)

cations for surgical management in the modern era. The detection of invasive adenocarcinoma of the colon in the setting of IBD is a clear indication for surgical management, generally with total proctocolectomy. In other high-risk individuals, such as patients with endoscopically unresectable dysplasia, persistent invisible dysplasia, or multifocal flat or high-grade dysplasia, risk-reducing surgery may be recommended to decrease the risk of CAC [111].

Risk-Reducing Surgery

Prophylactic resection of the organ at increased risk for the development of cancer in high-risk populations is an accepted approach for several malignancies. For women who have been identified as carriers of germ-line mutations in cancer susceptibility genes such as BRCA 1 or 2, with a high lifetime risk for breast or ovarian cancer, prophylactic bilateral mastectomy and bilateral salpingo-oophorectomy have been demonstrated to decrease the risk of development of breast and ovarian cancer [112]. Patients with inherited or spontaneous germ-line mutations of the APC gene are at high risk for colorectal cancer; prophylactic proctocolectomy with the option for ileoanal anastomosis decreases the risk for colorectal cancer [113]. A similar approach has been used for IBD patients felt to be at high risk for the development of CAC, i.e., those with endoscopically unresectable dysplasia, or those with high-risk dysplasia, and these patients are generally recommended for definitive surgical management. Nonetheless, the spectrum of patients with multifocal or advanced neoplasia that are managed endoscopically versus surgically continues to evolve as discussed above and remains a priority area for further investigation.

Biomarkers

Identifying biomarkers, including genomic changes associated with dysplasia and early-stage CAC, which can be found in, e.g., blood or stool, are a high priority. The objective is to develop a robust bioassay which will identify dysplasia or CAC in asymptomatic (for cancer) patients with either Crohn disease or ulcerative colitis. Among potential biomarkers currently being studied, there are blood-based (plasma) assays for circulating tumor DNA and exosome protein cargo, and stool biomarkers. If a sensitive and specific assay was available, patients with a positive biomarker would then undergo endoscopic evaluation to localize the site of dysplasia or carcinoma. Several methodologies, including those mentioned above, are under study, but none has yet been proven to be adequately sensitive and specific to non-invasively identify dysplasia and carcinoma.

Systemic Therapy for Advanced Colitis-Associated Cancers

Currently, although the emerging genomic data outlined above have demonstrated a difference in the spectrum of genomic alterations between CAC and sporadic colorectal cancer, as well as differences between CAC comparing ulcerative colitis versus Crohn disease, cancers arising in inflammatory bowel disease are staged using the same systems as for sporadic colorectal cancer. In the United States, the AJCC Cancer Staging Manual, eighth edition presents the staging system for colorectal cancer [114]. This and other data clearly show that the earlier the stage of a colon or rectal cancer, the better the outcome if the disease is resectable with curative intent.

While it was previously felt that stage-for-stage there was no difference in outcome for patients with CAC developing in the setting of Crohn disease or ulcerative colitis, this may not be true for more advanced cancers. Cure rates after resection of early-stage CAC (stage I and II) are similar to those of cure rates after resection of early-stage CRC. Recent data, however, suggest that for patients with Stage IV (metastatic disease) cancers, outcomes using the same systemic therapies are worse for CAC patients compared to CRC patients.

Because CAC is uncommon, currently the same systemic therapy regimens used to treat sporadic CRC are employed in patients with CAC (cytotoxic chemotherapy with or without VEGF or EGFR targeted antibodies). It should be noted that studies comparing outcomes for advanced CAC versus CRC patients receiving systemic therapy are retrospective, involve small numbers of patients and frequently from a single institution. With this in mind, and for example, investigators from Memorial Sloan Kettering Cancer Center recently reported the results of a retrospective, matched control cohort analysis comparing outcome, measured as objective tumor response, and progression-free and overall survival, in a group of 18 CAC patients and 18 CRC patients. Genomic alterations analysis was performed in all patients [1]. Standard-of-care chemotherapy regimens were used and were balanced between the two groups. While the response rates were similar (CAC 35.7% vs. CRC 57.1%, $p = 0.45$), the median duration of response for CAC was significantly shorter (1.4 months vs. CRC 11.8 months, $p = 0.006$). There was no difference in dose density of first-line therapy between cohorts, suggesting that shorter response duration for CAC was due to more rapid development of chemotherapy resistance. Median overall survival was significantly shorter for CAC patients (13 vs. 27.6 months), $p = 0.034$. The median duration of survival of 27.6 months for CRC patients is quite consistent with what is currently expected for patients with stage IV sporadic CRC. As expected, there was a difference in the spectrum of genomic alterations

between CAC and CRC cohorts. However, alterations associated with a poor prognosis (e.g., B-Raf) were no more frequent in the CAC cohort. Similar results have been reported in two other series. These data suggest that while currently the same chemotherapy regimens are used for both CAC and CRC, better understanding of the possible rapid development of resistance in CAC and the development of regimens targeting the genomic alteration seen more commonly in CAC are important in developing better therapies for advanced-stage CAC patients.

Small-Bowel Adenocarcinoma in Crohn Disease Patients

Small-bowel adenocarcinomas are much less common than colorectal cancer in both the general population as well as in patients with IBD. In 2020, ~5300 new cases are anticipated in the USA; only a small percentage is associated with IBD [115]. While the duodenum is overall the most common portion of the small bowel for adenocarcinoma (approximately 50%), in Crohn-associated small-bowel cancers, the distal ileum is a more common primary site, followed by the jejunum. Patients with Crohn disease are at significantly increased risk of small-bowel adenocarcinoma and small-bowel adenocarcinoma-related death, with increased incidence estimates of ninefold compared to the general population in a recent population-based cohort from Scandinavia [116], to over 60-fold in prior studies [117]. Small-bowel adenocarcinoma has its own staging classification in the AJCC eighth edition.

While an asymptomatic small-bowel primary adenocarcinoma might be found during surveillance imaging, symptoms such as obstruction or bleeding more commonly precede the diagnosis. However, frequently these symptoms are attributed to underlying Crohn disease, and adenocarcinoma is rarely suspected. Therefore, an abrupt change in symptoms or in imaging appearance in previously stable Crohn disease patient should prompt suspicion of the development of a small-bowel cancer. Differentiating a benign stricture from the rare development of small-bowel adenocarcinoma may not be possible prior to an operation.

For patients in whom pre-operative testing has confirmed small-bowel adenocarcinoma arising in IBD, staging procedures include those routinely performed for other bowel cancers. These include CT scans of the chest, abdomen, and pelvis. FDG-PET CT scan may be used to evaluate for metastatic disease; however, increased FDG avidity within the small bowel may be due to inflammation. The extent of both adenocarcinoma and underlying Crohn disease determines the extent of surgical resection for operable cancers. Additionally, in a patient in whom adenocarcinoma of the small intestine is diagnosed, especially distal ileal cancer, underlying inflammatory bowel disease should be considered.

Other Malignancies

While the increased risk of colorectal and small-bowel adenocarcinoma in the setting of long-standing IBD are well known, several other types of malignancy appear to be increased in patients with IBD. These can be generally categorized into disease-related malignancies and immunosuppressive medication-related malignancies, though there is frequent overlap between the two. Disease-related malignancies include not only intestinal adenocarcinomas, as discussed above, but also anal carcinoma, cholangiocarcinoma, intestinal lymphomas, and possibly prostate cancer. Anal carcinoma occurs at higher rates and at younger ages in patients with IBD [118] and can be related to chronic perianal fistulae, often adenocarcinomas [119], or HPV-related squamous cell cancers, which may occur more readily in the setting of chronic immunosuppression [118]. The diagnosis of anal cancer can be challenging due to concomitant perianal disease that presents with overlapping symptoms, and the disease is often diagnosed late and carries a poor prognosis [120]. Cholangiocarcinoma risk is markedly elevated in the setting of concomitant PSC [121] and significantly increases all-cause mortality [122], especially in young patients (<40 years) with PSC-IBD [123]. Intestinal lymphomas appear to occur at increased frequency in patients with IBD and may be a sequela of both chronic intestinal inflammation as well as chronic immunosuppression, though the absolute risk of intestinal lymphoma remains low [124, 125]. Several recent studies also note an increased risk of prostate cancer in men with IBD, though whether this is due to disease-related factors (e.g., chronic pelvic inflammation or systemic immunosuppression) versus an ascertainment bias (e.g., due to more frequent health contact or rectal examinations) is not yet clear [126, 127].

Immunosuppression-related malignancies that occur in patients with IBD include extra-intestinal lymphomas, skin cancers, cervical cancer, and urinary tract cancers. Anti-TNF therapies and thiopurines have both been implicated in an increased risk for lymphoma [52, 128] including the rare but highly fatal hepatosplenic T-cell lymphoma that has been observed in young men often on combination therapy with both of these agents [129]. Skin cancers can occur as a result of immunosuppressive therapy, with thiopurines conferring an increased risk of non-melanoma skin cancer [53, 130] and anti-TNF therapy possibly increasing the risk of melanoma [131, 132]. Cervical cancer rates are increased in women with IBD, possibly related to the impact of immunosuppres-

sive medications on HPV activation and activity [133, 134]. Finally, urinary tract cancers are more common in the IBD population, in particular in older men who smoke or who have a history of thiopurine exposure [135, 136].

Summary

While the incidence of colitis-associated cancers is lower than reported in previous decades, CAC remains an important risk for patients with ulcerative colitis and Crohn disease. CAC in pediatric patients is fortunately very rare, but individuals with childhood onset IBD remain at substantial lifetime risk for CAC. Currently, identifying patients at elevated risk, aggressive control of modifiable risk factors such as chronic inflammation, and endoscopic surveillance for detection and resection of dysplasia and early detection of colitis-associated cancers remains the standard of care. Small intestinal cancer occurs at an increased rate in patients with Crohn enteritis, but the absolute risk remains small. The genomic events leading to dysplasia and cancer are better understood, but key driver events need to be more clearly identified. Eventually, targeting these driver events may lead to more effective prevention strategies. Finally, the development of highly specific and adequately sensitive blood or stool-based biomarkers to detect dysplasia and CAC at its earliest stage in patients with IBD remains an unmet medical need.

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Quality Improvement in Inflammatory Bowel Disease

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Introduction

In recent decades, research has generated an enormous growth of medical science, technology, and therapeutics. Knowledge from basic research, translational research, randomized clinical trials, and outcomes research has enabled experts in many fields to develop and disseminate evidence-based clinical practice guidelines with recommendations for medical practitioners. Yet health services research suggests that health care could perform a great deal better than it does today. For example, an audit of medical records of 4000 adults in 12 cities in the USA showed that only 55% of recommended preventive, acute, and chronic care was being received [1]. Similar deficits have been observed in ambulatory pediatrics [2]. A study of 3000 hospitals found that only five of ten recommended care measures were provided to a large majority of patients [3]. A report of the Institute of Medicine, Crossing the Quality Chasm, calls for improvements in six dimensions of healthcare performance: Safety, Timeliness, Efficiency, Effectiveness, Equity, and Patient centeredness (STEEEP) [4]. The National Scorecard on U.S. Health System Performance, an assessment of healthcare outcomes, quality, access, equity, and efficiency, found that the U.S. achieves an average score of only 66%. If the U.S. improved performance in key areas, it could save an estimated 100,000–150,000 lives and 50–100 billion dollars annually [5].

Improving the care of patients requires more knowledge; achievement of improvements requires the application of the principles of continuous quality improvement [6, 7]. Quality improvement in health care is the application of knowledge to make changes that result in better care and outcomes.

One of the barriers to quality improvement is unnecessary variation in care. Unnecessary variation, which erodes quality and reliability and adds to costs, is derived in part from habitual differences in practice style that are not grounded in knowledge or reason [8]. Variation makes it impossible to determine if a change in practice results in change in care because small improvements are frequently obscured by the background noise of variation. Quality improvement efforts

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can reduce unnecessary variation; reducing variation is a necessary prerequisite to improve quality. To attain continuous quality improvement in health care, it is necessary to repeatedly measure the processes and outcomes of care and design, implement interventions to improve the processes of care, and re-measure to determine the effect of the interventions [9]. In this chapter, we present an introduction to quality improvement and how it has been applied to pediatric inflammatory bowel disease, with brief discussions of variation in care, the Chronic Illness Care Model, the need for quality improvement, the Improvement Model, the improvement collaborative, the ImproveCareNow Network, next steps/future directions, maintaining improvement, and administrative and funding considerations.

Variation in Care

Inflammatory bowel disease (IBD) is the most common serious chronic gastrointestinal disease afflicting children and adolescents in North America, yet there is currently considerable variation in the way gastroenterologists diagnose and treat IBD [10, 11]. Variation in care can be due to underuse, overuse, or misuse of diagnostic and therapeutic interventions. An example of underuse is failure to obtain small bowel imaging or neglecting to identify and treat growth failure; an example of overuse is unnecessary prolonged prednisone treatment [12]; and an example of misuse is prescribing infliximab to a patient with tuberculosis [13]. While some variations are due to patient needs or preferences, many variations are due to a lack of adherence by practitioners to best practices. Other variations are due to lack of data to guide practice leading to different practice strategies based on anecdotal experience or other non-evidence-based reasons [10]. Standardization of care occurs when physicians agree to provide care in a uniform manner of care appropriate for each patient. This can be evidence based, or in the absence of evidence, can be based on expert opinion or consensus. Standardization of care reduces unnecessary variation and, when combined with systematic studies of planned variations (including randomized studies), can lead to increased knowledge and improved outcomes.

Figure 57.1a is a theoretical example of a wide variation in the number of diagnostic tests performed prior to initiating treatment (labeled Before). When a larger number of tests than average are performed, it could indicate overuse of some tests, while a smaller number than average could indicate underuse. In this example, after a successful quality improvement project leading to less unnecessary variation in care, there is less overuse and less underuse than before,

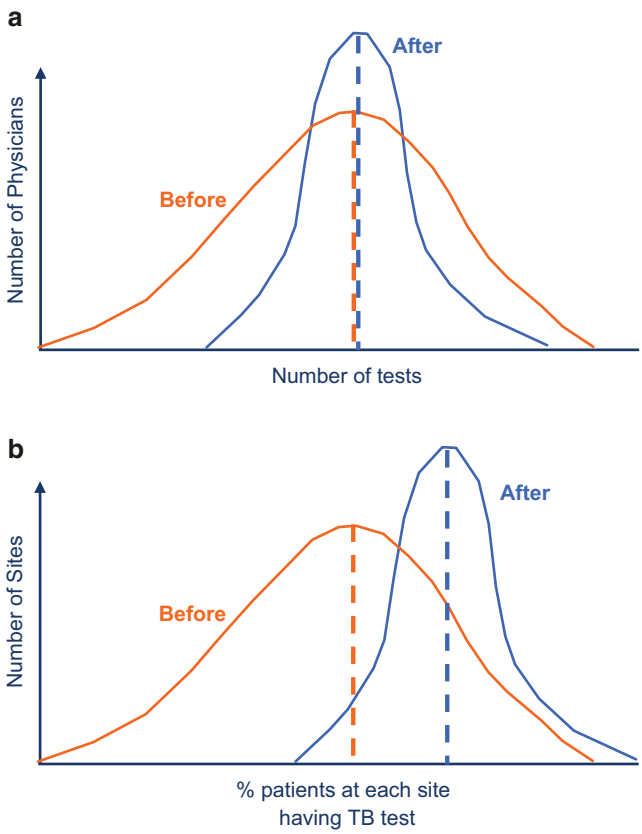

Fig. 57.1 Variation in care. (**a**) Improving quality by decreasing variation. (**b**) Improving quality by shifting distribution

although the average number of tests is the same. Figure 57.1b is a theoretical example of a wide variation and a low percentage of patients at most sites having a skin test for tuberculosis before initiating infliximab therapy (labeled Before). After a successful improvement project, there is less variation and a higher rate of skin testing.

Variation in care has been demonstrated in pediatric IBD [10, 11, 14]. In one study, pediatric gastroenterologists enrolled patients with Crohn disease who were starting treatment with a thiopurine (6-mercaptopurine or azathioprine) or infliximab [11]. Data from 250 patients at 80 sites were examined for variation in diagnostic and therapeutic interventions. Diagnostic studies in which care was uniform-included complete blood count, performed in 100% of patients, erythrocyte sedimentation rate and colonoscopy in 96%, and upper endoscopy in 89%. However, imaging of the small bowel had not been performed in 19%, and a stool test for pathogens had not been performed in 29%. Thiopurine methyltransferase (TPMT) had been measured in 61% of patients before treatment with a thiopurine; in 85%, TPMT was normal. Nonetheless, even when TPMT was normal,

40% of patients received an initial dose of thiopurine that was lower than recommended. Testing for tuberculosis before initiating treatment with infliximab was not documented in 30%. In addition, 36% of severely underweight patients were not receiving a multivitamin supplement, supplemental formula, or tube feeding [14]. The same study also demonstrated widespread inter-center variation in the treatment of newly diagnosed children with Crohn disease, even after adjusting for possible differences in case mix between institutions [14]. Variation in the use of immunomodulators and infliximab in patients with Crohn disease has also been reported [10, 15]. This considerable variation in diagnostic and therapeutic care in pediatric IBD, reflects the presence of underuse, overuse and potentially misuse of interventions that may lead to unintended differences in healthcare costs and outcomes.

Documentation of variation in care has been important in efforts to standardize and improve care in other fields of medicine [3]. For example, the Epidemiologic Study of Cystic Fibrosis demonstrated large variations in practice patterns regarding the prescription of various therapies as well as the fact that a significant proportion of CF patients are not monitored as recommended by the Cystic Fibrosis Foundation (CFF) [16, 17]. In this study, only 58% of patients had quarterly visits to their CF Care Center, 76% had biannual spirometry, 79% had annual airway cultures and 68% had annual chest radiographs [18]. CF Registry reports are now presented in such a way as to reveal practice variation among practice sites, partly in order to motivate an evaluation of this variation and to promote standardization where indicated.

The Chronic Illness Care Model

The Chronic Illness Care Model provides a useful framework for developing changes to the system of IBD care [19–21]. Wagner and colleagues conducted an exhaustive literature review and program assessment to identify the key components of systems of healthcare delivery that result in improved outcomes for patients with chronic illness. Wagner's model includes the following components: family and patient self-management support; decision support; delivery system design; clinical information systems; community resources; and the healthcare organization (Fig. 57.2). Family and patient self-management support includes the methods used by the clinic to increase families' participation in care. Decision support includes the use of care protocols that are integrated into practice systems. The delivery system design component includes the use of planned encounters,

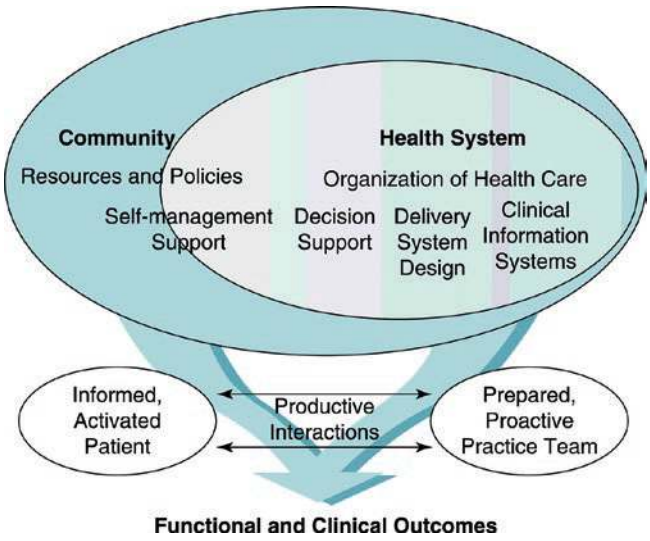

Fig. 57.2 The Chronic Illness Care Model. (Adapted from EH Wagner, *Joint Commission Journal on Quality Improvement* 2001;27:65, by permission)

clarity in the roles and responsibilities of team members with appropriate training, and the use of regular meetings of the care team to review performance. The clinical information system refers to the ability of caregivers to access data and use registries for care and to provide regular feedback to the team, and also information technology to facilitate scheduling and patient tracking. A prepared proactive practice team interacts with an informed activated patient to improve functional and clinical outcomes.

Improvement science is broadly defined as the science of implementing and testing change. There are many different ways in which improvement science is applied in practice. Each involves the common theme of methodically implementing and testing small changes, and then adopting or rejecting the changes based on the findings of testing [22]. Improvement interventions can range from prospective randomized controlled trials to observational studies [23]. The application of improvement science has led to major advances in quality in the automobile, microchip, and other industries [24–26] which raises the question whether it works in health care or not. Quality improvement interventions utilizing the Chronic Care Illness Model in asthma, congestive heart failure, depression, and diabetes have improved clinical outcomes, processes of care, and quality of life [27]. Studies of controlled trials of interventions that contain at least one element of the Chronic Care Model have demonstrated significant improvements in care [28]. In a cohort study to determine the effect of a specialist nurse on the outcome of 340 patients with IBD, intervention resulted in a 38% reduction in hospital

visits, a 19% reduction in hospital length of stay, a 10% increase in patients in remission, and improvement in patient satisfaction [29]. A multi-center randomized controlled trial of a quality improvement project in IBD showed similar results [30]. In the United Kingdom, development of a pediatric IBD service has improved provision of services and access to care for patients [31]. In Australia, the implementation of a dedicated IBD service was associated with a reduction in the use of steroids and opiates as well as a reduction in hospitalizations for IBD [32].

The Need for Quality Improvement in IBD

Have Crohn disease outcomes improved during the last four decades? In a report published in 2004, a structured systematic literature review was performed to evaluate measurable outcomes in Crohn disease. Evaluation of mortality, cancer, disease recurrence, extra-intestinal manifestations, and medication use failed to show consistent evidence for improvement in inflammatory bowel disease outcome during the previous four decades [33]. However; more recent studies have shown decreased mortality in IBD [34], decreased colectomy rate in ulcerative colitis [35], and decreased surgical rates in pediatric Crohn disease within 3 years of diagnosis [36]. Despite advances in research and therapy, the application of knowledge to the improvement of health outcomes and quality of life has lagged. Hospitalization rates for IBD, particularly Crohn disease, increased from 1988 to 2011, contributing to a substantial rise in inflation-adjusted economic burden [37, 38]. Further, even in the era of biologics, the proportion of patients with inflammatory bowel disease not entering remission remains high [39]. Are we optimizing biologic therapies? Are patients with IBD receiving optimal care? A study found that adults with IBD referred for a second opinion often were not receiving optimal medical therapy [40]. There was prolonged use of corticosteroids, failure to use steroid-sparing agents, suboptimal dosing of mesalamine and immunomodulatory medications, inadequate measures to prevent metabolic bone disease, and inadequate screening for colorectal cancer.

A study of the pediatric patients' diagnostic evaluation diagnosed with IBD also identified substantial gaps in small bowel imaging, though this was found to improve over the 5-year course of study [41]. Other evidence indicates a shift toward magnetic resonance imaging and away from ionizing radiation in pediatric IBD [42]. Many pediatric patients diagnosed with Crohn disease had not been tested for intestinal pathogens, had not had imaging of the small intestine, were not receiving a multivitamin supplement, had not been tested for TPMT prior to treatment with a thiopurine, had not been tested for tuberculosis prior to treatment with infliximab, and were receiving suboptimal dosage of medications [11].

Another important aspect of pediatric IBD care needing a quality improvement focus is transition to adult GI care, with the goal of proving comprehensive and uninterrupted care for the adolescent and young adult. The term "transition" refers to the longitudinal process of obtaining the knowledge and skills necessary to care for oneself and one's chronic disease in an adult setting, whereas "transfer" refers to the eventual physical move from pediatric to adult care. Across multiple chronic diseases, it has been demonstrated that poorly managed transitions can result in inappropriate utilization of healthcare resources and adverse health outcomes [43, 44]. The variable (and often complete lack of) transition care processes as well as inconsistent measures of transition readiness in many institutions across the United States continue to put young adults at risk for adverse health outcomes at transition [45–47].

Quality improvement in adult gastroenterology has previously focused on endoscopic procedures [48–56]. More recently, there has been an emphasis on reducing venous thromboembolic events in hospitalized IBD patients [57, 58]. However, the American Gastroenterological Association (AGA) Task Force on Quality in Practice issued a report recommending the formation of an AGA Quality Center to assure uniform documentable excellence in quality of clinical care and GI practice, to support the aims for quality health care set forth by the Institute of Medicine, to identify key quality of care indicators in the treatment of digestive diseases and how they will be measured, to develop programs and tools to assist in implementing evidence-based guidelines and measuring and reporting adherence to quality indicators, and to develop patient education materials to ensure that patients have appropriate expectations regarding high-quality, patient-centered, evidence-based care [59]. In 2011, the AGA developed a set of IBD process measures, approved by the American Medical Association's Physician Consortium for Performance Improvement that focus on transitioning patients to corticosteroid-sparing therapy and preventive care. The AGA subsequently developed a series of quality improvement measures called the Physician Quality Reporting System (PQRS) [60]. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) has also developed a set of process measures. In conjunction with measure development, the AGA has also developed the Digestive Health Outcome Registry (DHOR) to help practices develop benchmarking, outcomes measurement, and population management capabilities for patients with IBD [61].

The Improvement Model

The Improvement Model is the foundation of a system for innovation and a framework for developing, testing, and implementing incremental change [62]. The model is based on three questions (Fig. 57.3): What are we trying to accomplish? How will we know that a change is an improvement? What change can we make that will result in improvement? Any approach to improvement must be based on building and applying knowledge. Within the overall framework, the Plan-Do-Study-Act (PDSA) Cycle is a structured application of the scientific method that provides a means to learn rapidly in complex organizational settings. The Plan phase consists of stating the objective of the test, making predictions, and developing a plan to carry out the test. The Do phase consists of carrying out the test, documenting problems and unexpected observations, and beginning an analysis of the data. The Study phase consists of completing the analysis of the data, comparing the test data to predictions, and summarizing what was learned. The Act phase consists of deciding upon and carrying out the changes to be made, and considering what will be the objective of the next cycle. The Improvement Model means applying the principles of using data; developing, testing, and implementing changes; and working collaboratively to bring about improvement in the outcomes of health care (Fig. 57.4). The improvement model can be applied to any aspect of health care.

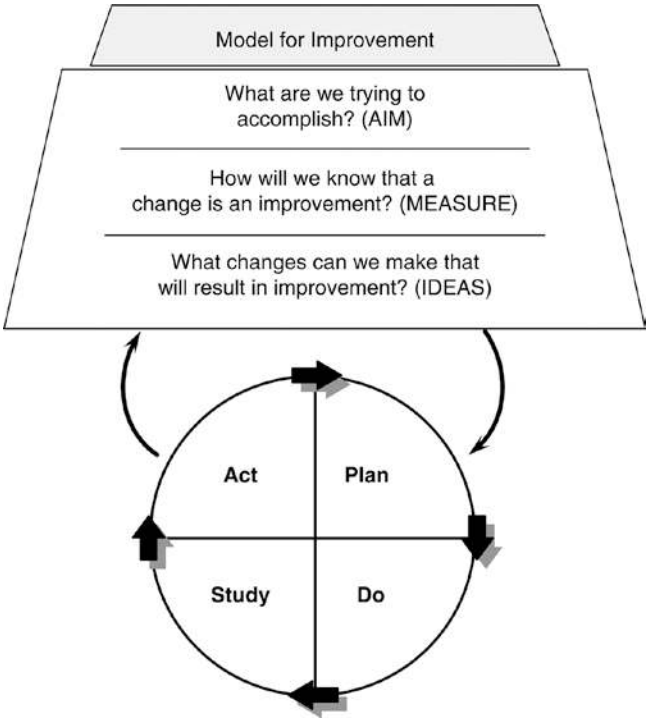

Fig. 57.3 The Improvement Model. (Adapted from Langley, Nolan, Nolan, Norman and Provost [37], page 10, by permission of Jossey Bass)

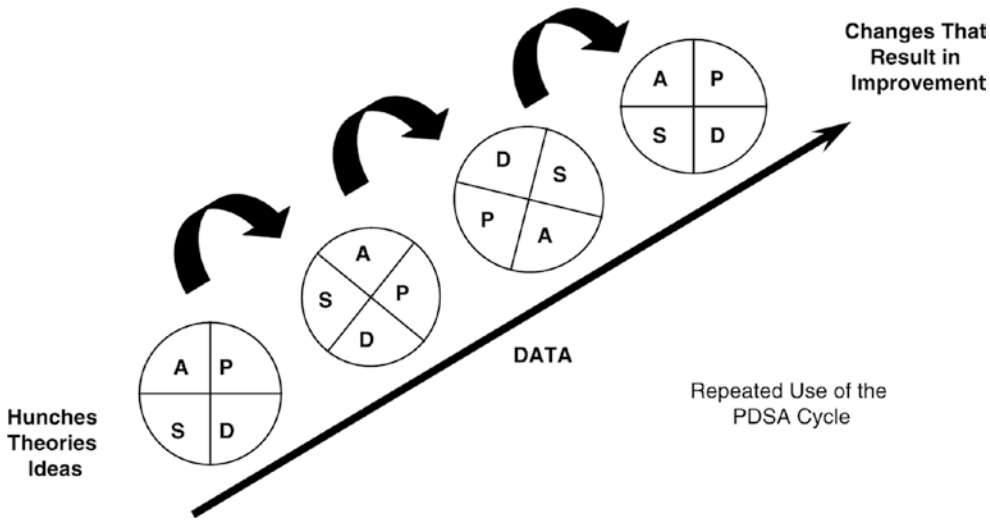

Fig. 57.4 Repeated use of the Plan-Do-Study-Act cycle. (Adapted from Langley, Nolan, Nolan, Norman and Provost [37], page 9, by permission of Jossey Bass)

Improvement Collaborative

An improvement collaborative is a sequential process in which a group of multidisciplinary teams from different practice sites work intensively together using the principals of improvement science to improve the delivery of care and the quality of life of patients [63, 64]. Improvements consist of redesigning delivery systems to ensure that patients receive recommended care and are not subject to underuse, overuse, or misuse. An improvement collaborative includes three main phases: (1) a design and development phase, in which the aim and measures for the project are developed (see Table 57.1), and changes to be tested are identified and summarized using formal methods for the design of new processes and systems; (2) an implementation phase in which practice sites work together to test and adapt changes in care delivery; and (3) a dissemination phase, where, as changes in the processes of care delivery are tested and reliably achieve desired goals, they are disseminated to other and eventually all pediatric gastroenterology practice sites. Participating sites collect data about their patients' care, share data about the outcomes of care with all of the other sites, identify sites that are performing better, examine reasons for the better performance, set benchmarks for outcomes, and share ideas to enable the other sites to improve their outcomes. Participating sites gather together for conferences to share data and ideas, and then return to their sites to perform PDSA improvement projects there, gathering and sharing new data in an incremental process (Fig. 57.5).

Table 57.1 Measurable outcomes of treatment of pediatric IBD

Disease activity
Remission rate
Interval between relapses
Complication rates (e.g., fistula)
Nutritional status
Growth, final adult height
Days missed from school
Emergency department visits
Hospitalization rate
Hospital length of stay
Surgery
Patient and family satisfaction
Patient quality of life
Adverse drug events (e.g., infusion reactions)
Therapeutic drug monitoring
Surgical complication rate
Objective biomarkers of disease activity: calprotectin, lactoferrin, hemoglobin, erythrocyte sedimentation rate, c-reactive protein, albumin
Procedural assessments: endoscopy, imaging

An IBD improvement collaborative is intended to encourage practices to adopt a more organized approach to IBD care. It is based on models of behavior change and diffusion of innovations in medical practice including involvement of opinion leaders in the medical community, recognition of a performance gap, involving physicians and staff in developing a strategy to make changes to close the gap, compatibility of the intervention with current practice, and reinforcement of positive change [65]. It is designed to identify and address barriers in the way care is delivered in IBD clinics.

This type of systems' intervention is especially important in pediatric IBD clinics because many pediatric IBD practice sites operate within large tertiary medical centers with relatively rigid infrastructures requiring significant and determined effort to change; IBD care is characterized by a complex mixture of preventive and chronic therapeutic interventions; distance and other factors make frequent return visits difficult for many patients, so accidental omission of services and other missed opportunities for care are difficult to recognize and are harder to correct; and the responsibility

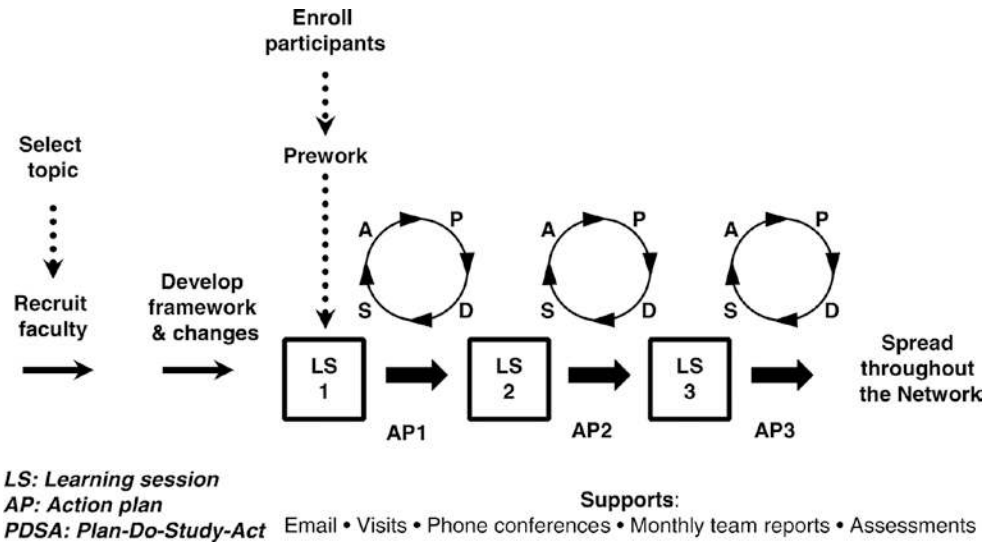

Fig. 57.5 A schematic drawing of the sequence of events in an Improvement Collaborative. (Adapted from a presentation of the Institute for Healthcare Improvement)

for care is shared by multidisciplinary teams and multiple physicians with diverse responsibilities who may overestimate the consistency with which they deliver specific services [66].

The ImproveCareNow Network

The first improvement collaborative in IBD, called ImproveCareNow, was established in early 2007; its global aim is to build a sustainable network of all pediatric gastroenterologists in the US to improve the care and outcomes of children with Crohn disease and ulcerative colitis [67]. In its first 5 years, it grew from 8 to 34 centers, with approximately 300 pediatric gastroenterologists and 10,000 pediatric IBD patients. By 2020, the ImproveCareNow Network grew to 110 centers across 38 states in the US and internationally, including England, Belgium, and Qatar, which include approximately 970 pediatric gastroenterologists and 35,000 patients (www.improvecarenow.org). The six primary drivers of the ImproveCareNow Network are (1) a prepared proactive practice team; (2) accurate diagnosis and disease classification; (3) appropriate drug selection and dosage; (4) adequate nutritional intake; (5) adequate growth monitoring; and (6) informed, activated, and engaged patients and families.

ImproveCareNow developed and implemented five major interventions: (1) enrollment and data quality; (2) consistent reliable care; (3) population management; (4) pre-visit planning; and (5) self-management support. The centers aimed to identify and enroll all of their IBD patient population, collect data from all visits using a standardized template for data elements, and provide complete and accurate data in a timely fashion. ImproveCareNow developed a Model IBD Care Guideline for Consistent Reliable Care, based on an integration of evidence and consensus, and key clinical measures, and process and outcome measures, to monitor the performance at each center and the collaborative as a whole [68]. In addition, algorithms for nutrition and growth were developed.

A population management tool was developed and used to ensure that patients were being seen regularly, and to identify patients who were not receiving model IBD care and who could benefit from for a proactive change in their management. A pre-visit planning checklist was developed and implemented at centers to review important clinical data, to identify and highlight variables that fall outside of protocol guidelines (e.g., drug dosages and results of previous laboratory tests), identify and arrange for needed resources at the time of visit (e.g., pre-ordering laboratory tests; scheduling a dietician), and assist the clinician in preparing an agenda of important issues requiring attention at the visit. In 2011, a systematic program was undertaken to develop tools for patient and family self-management support, including providing patient education, eliciting patient and family priorities for visits, confirming patient understanding of new information, setting and monitoring patient goals collaboratively, and improving adherence.

One of the primary strengths of the ImproveCareNow network is a focus on learning from data. Each participating center receives monthly reports with tables and longitudinal graphs of their performance on the key clinical and data quality measures, and a twice-monthly population management reports. These electronic reports provide both aggregate and individual patient- and visit-level data that can be used to monitor populations of patients and identify subgroups of patients in need of attention or intervention. The reports are used to identify sub-populations of patients with medical issues in need of attention, for example, patients who are on systemic steroids or patients with suboptimal nutritional status. They also are used to identify patients who have outgrown the doses of their medications. The reports can also facilitate failure mode and affect analyses to study problems and gain insights to inform improvement efforts. The reports also include run charts and control charts to help identify special-cause variation when a significant change from baseline has occurred. Centers also have the ability to compare their performance to that of other centers and of the entire network [69].

The data that inform these reports are collected from each patient at each outpatient visit. ImproveCareNow has developed processes by which automated data transfer can be done from electronic medical record systems to populate the data registry. This has reduced the burden of data collection and errors associated with duplicate data entry for many of the participating network sites. For sites without the capability of electronic data transfer, manual data entry is performed. There are numerous quality checks to minimize errors in manual data entry. Data collection includes all the data necessary for calculating the short pediatric Crohn disease activity index (sPCDAI) and the pediatric ulcerative colitis activity index (PUCAI) [70–72].

The ImproveCareNow Network has implemented a process for generating automated pre-visit planning forms that can be automatically generated on demand for each patient (Fig. 57.6). These forms are one-page summary sheets that are pre-populated with patient-specific historical data pulled from the registry. These forms served to streamline the pre-visit planning process for each practice. The automation was part of a larger emphasis on improving the digital architecture of the ImproveCareNow network registry [69].

IBD PRE-VISIT ASSESSMENT

Patient Name:	**Birth Date:**	**Primary Provider:**
Patient Num:	**Current Age: 17.2**	**Secondary Provider:**

Diagnosis: Crohn Disease –8/2011	Last Visit:	Last PPD & Date:
Phenotype: Stricturing	Wt (kg):	
Lower: Ileocolonic	Ht (cm):	Last CXR:
Upper Proximal: No	BSA:	
Upper Distal: No	Date of last hospitalization:	Last Gold Test & Date:
Perianal Phenotype: No		

>> **Visits:**	12/26/2016	02/20/2017	03/27/2017	05/01/2017	06/05/2017	06/26/2017	08/07/2017	10/09/2017	Age of Result
sPCDAI	*15*	*25*	*15*	*45*	*25*	*10*	*10*	*0*	
PGA	*Mild*	*Moderate*	*Moderate*	*Moderate*	*Mild*	*Mild*	*Moderate*	*Mild*	
Nutritional Status	*Satisfactory*	*At risk*	*At risk*	*At risk*	*Satisfactory*	*Satisfactory*	*Satisfactory*	*Satisfactory*	
Growth Status	*Satisfactory*	*At risk*	*Satisfactory*	*At risk*	*Satisfactory*	*Satisfactory*	*Satisfactory*	*Satisfactory*	
Albumin	*2.8*	*2.7*	*2.8*	*2.8*	*2.9*	*2.8*	*3.0*	*3.3*	*11 mo* ⓘ
CRP		*5.80*	*3.70*	*4.70*	*2.60*	*3.40*	*5.60*	*2.30*	*11 mo* ⓘ
ESR		*81.0*	*77.0*	*62.0*	*59.0*	*61.0*	*60.0*	*27.0*	*11 mo* ⓘ
Hematocrit		*33.6*	*33.3*	*33.3*	*33.5*	*32.5*	*33.6*	*42.3*	*11 mo* ⓘ

*Result date may differ from visit date ⓘ Lab ordering guidelines: 5-ASA:q6mo 6mp/ASA/MTX:q3-4mo Biologics:q2-3mo

Care Stratification

CS Score	CSS Group	Current Disease Activity	12 Month Disease Activity	BMI Z-Score	Ht Velocity	Hosp Adm within 3 months	Currently on Cortico	Cortico last 12 months	Psychosocial Risk Factors
2	0-3 (Low)	1 (Mild)	1 (Mild/Moderate/Severe)	0 (BMIZscore >=-1 or Missing)	0 (HtVelocityZscore >=-1 or Missing or N/A)	0 (No or Unknown)	0 (No or Unknown)	0 (No or Unknown)	No

>> **Treatments**	Dose (mg)	mg/kg (last wt)	Guideline	ⓘ Attention Needed
Immunomodulators				
Thiopurines TPMT date / result	Normal/high (8/21/2011)		Consideration: If active dz, consider 6TGN levels q 90	ⓘ 6-TGN date is missing. Check whether result exists. If not, consider ordering.
Methotrexate	20.0	11.3(mg/m2)	12.5 - 15 mg/m2 up to a maximum of 25mg PO/SQ/IM; Maintenance for adult 15-25mg	ⓘ Dose/BSA is below minimum of recommended range. Consider increasing dose to between 12.5 and 14.1mg/m2. A dose above 14.1 mg/m2 will result in a total weekly dose greater than 25mg per week.
Biologics				
Stelara	90.0	1.3		

Fig. 57.6 Automated pre-visit planning form for one patient pre-populated with data drawn from the ImproveCareNow registry specific to the individual patient. The form includes summary information about the patient's disease phenotype as well as longitudinal data from the last several visits including weight, height, and laboratory information

The first ImproveCareNow report of outcomes was based on a 3-year follow-up of 6 of the initial centers with 1188 patients [73]. Changes in care delivery were associated with an increase in the proportion of visits with complete disease classification, measurement of thiopurine methyltransferase (TPMT) prior to initiation of thiopurines, and patients receiving an initial thiopurine dose appropriate to their TPMT status. There were significant increases in the proportion of Crohn disease (55–68%) and ulcerative colitis (61–72%) patients with quiescent disease (between 2007 and 2015). There was also a significant increase in the proportion of Crohn disease patients not taking prednisone (86–90%). These findings suggest that improvements in the outcomes of patients with Crohn disease and ulcerative colitis were associated with improvements in the process of chronic illness care. Variation in

the success of implementing changes suggests the importance of overcoming organizational factors related to quality improvement success. As ImproveCareNow grew and sustained its improvements, the Network was recognized as an exemplar of pediatric collaborative improvement networks [74]. After 7 years, the ImproveCareNow Network outcomes had improved further and the clinical remission rate for children with IBD increased to 77% [75, 76], and by 2020, it was 82% (www.improvecarenow.org, Fig. 57.7a, sustained remission noted in Fig. 57.7b). To further improve outcomes, ImproveCareNow is creating a learning health network in which patients and parents play an integral role in participation and governance of the network and work together with network clinicians and researchers [63].

The adult IBD community has also developed a quality improvement collaborative through the Crohn's and Colitis Foundation, IBD Qorus™, which includes over 50 sites. In 2020, they embarked on a new initiative called Treat to Target to encourage more frequent monitoring to ensure treatment strategies that align a remission-based therapeutic goal with the patient's personal goals regarding quality of life. Thus far, two care pathways have been developed to aid in the recognition and treatment of anemia and nutrition.

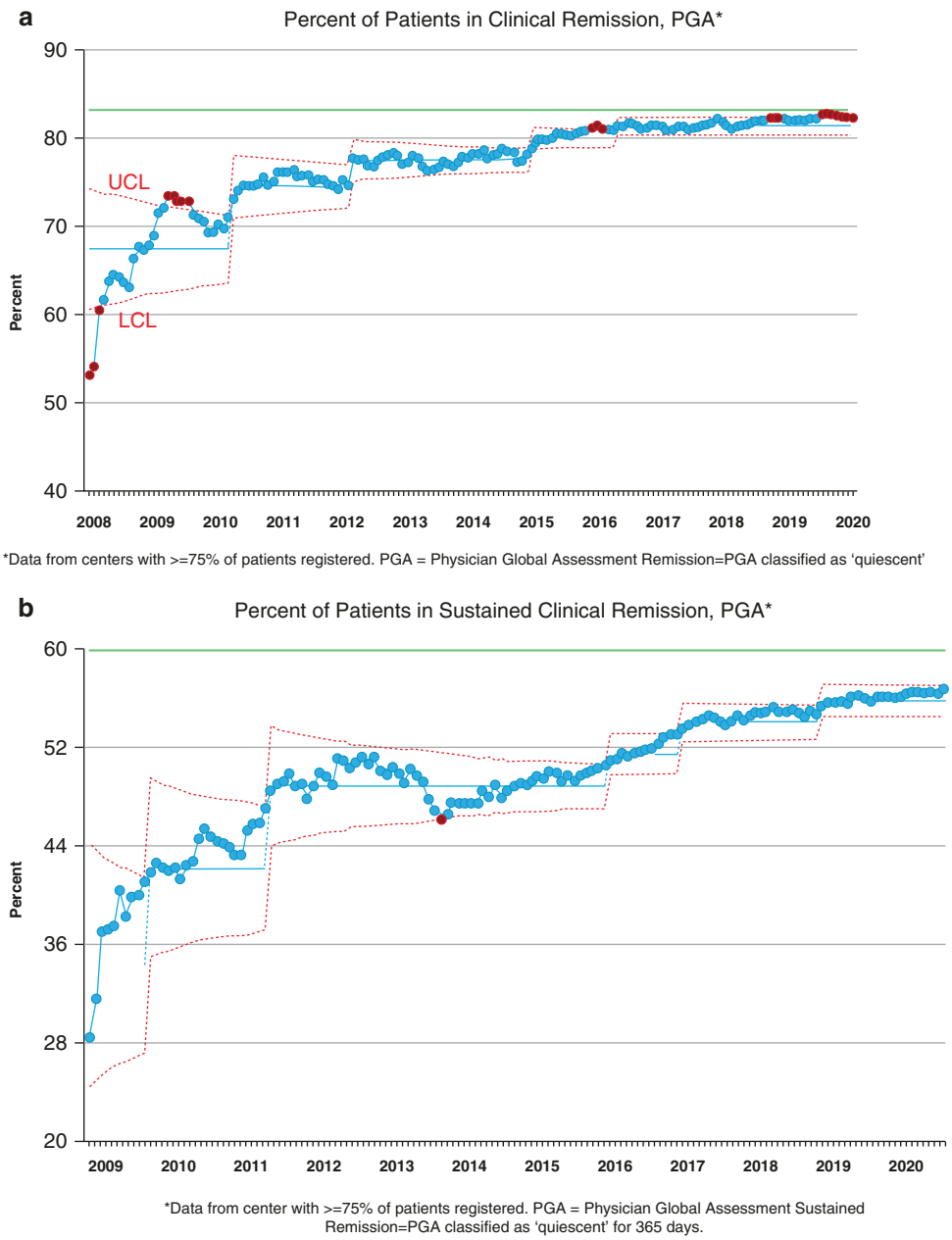

Fig. 57.7 (**a**) Improvement in remission rate, based on Physician Global Assessment, of a cohort of patients with Crohn disease in the ImproveCareNow Network from 2008 to 2020. Monthly results for all centers combined are presented as a control chart (Shewhart chart). The center line represents the mean proportion; the dashed upper and lower control limits (UCL and LCL, respectively) reflect the inherent variation in the data and were calculated as ±3 standard deviations of the centerline proportion. The shift in center line indicates a special-cause variation in remission rate. (**b**) Improvement in sustained remission rate from 2009 to 2020

Learning Health Network

A Learning Health Network, as originally conceived by the Institute of Medicine (now the National Academy of Sciences) is a community of clinicians, researchers, other professionals, and patients and families; working together with a focus on improving outcomes; using safe, effective evidence-based care; and providing better care at lower cost [77]. In a Learning Health Network, research is a natural outgrowth of clinical care; new knowledge is generated easier, faster, better, and cheaper. Innovative technology may also be employed so data are available in real time and can be used for clinical, research, and improvement purposes. The key drivers of a successful learning health network—an enhanced registry, improvement science, a robust research infrastructure, and a community of engaged stakeholders—are exemplified by the ImproveCareNow Network [74]. Data obtained at the time of a clinical encounter are analyzed by the enhanced registry and presented for clinical use as previsit planning and population management reports [69]. An enhanced registry can also generate a quality performance report that identifies gaps in care, enabling the center improvement teams to identify and focus on specific aspects of its care delivery system applying improvement science methods to improve processes and outcomes. Education and training of each center's improvement team in improvement science are essential to achieve improved care and outcomes. The repository of data is also a gold mine for research enabling retrospective and prospective observational cohort studies of natural history, real-world evidence of clinical care and outcomes, and pragmatic clinical trials. A Learning Health Network can also facilitate the development of new drugs by studies of real-world and long-term effectiveness of drugs; optimizing medication use by clinicians and patients; engaging clinicians and patients to prioritize and design studies; data queries to identify potentially eligible research subjects to facilitate study design and recruitment; conducting prospective drug efficacy studies; and conducting postmarket surveillance to monitor for serious adverse events. A registry that is 21 Code of Federal Regulations (CFR) Part 11 compliant and produces Study Data Tabulation Model (SDTM) and Analysis Data Model (AdAM) reports can further contribute to drug development by meeting standards of regulatory agencies. The National Academy of Sciences suggests extensive participation of patients and families in leadership, governance, education, communication, and other operations, which is necessary to optimize the success of a learning health network [78]. A Learning Health Network also provides opportunities for academic and professional advancement, leadership, and career development by enabling research, networking, building collaborations, and providing opportunities for committee involvement and leadership.

Leveraging the power of learning health systems and networks provides opportunities for higher level and more complex interventions to be tested and implemented. For example, the ImproveCareNow Network has developed a series of Learning Labs (i.e., a group of sites focusing on a specific topic or goal such as population management, previsit planning, clinical standardization/personalized care, COVID-19 response, and transition to adult care). The movement of clinical practice toward a treat-to-target approach has prompted a Learning Lab (consisting of over 25 centers) to address therapeutic drug monitoring via a care pathway. As part of the design process, a workgroup of clinicians, researchers, patients, and parents reviewed published literature and performed an environmental scan of current practice. This information was then used to develop and implement interventions and measures to address the clinical standardization of therapeutic drug monitoring for anti-TNF alpha therapies, a project still in process.

Maintaining Improvement

In any quality improvement effort, once an improvement is achieved, it must be maintained. Different challenges exist for sustaining an improvement. These range from challenges maintaining consistent error-free data collection, and reminding clinicians to continue reviewing data regularly to updating treatment protocols to remain consistent with the evolving literature. New clinicians require onboarding, and as patients transition from pediatric to adult care, new patient representatives need to be recruited.

Ongoing data monitoring enables centers to detect deterioration in processes or detrimental changes in outcomes. Such data can then allow data analyses to facilitate identifying areas or processes in need of modification in order to return to the prior level of improvement. An example of maintaining improvement includes ensuring that once a center's remission rate improves, they are able to maintain that high level of remission. Some challenges to maintaining a high remission rate include staffing changes; changes in treatment paradigms; availability of new medications; insurance or policy restrictions on access to medications; and the occurrence of pandemics or natural disasters.

Maintaining an updated registry with ongoing monitoring can allow a center to become aware if there is a change in either process measures such as timely data entry, or outcomes such as hospitalization rates or remission rates. Regular population management meetings with review of center-level registry data help the clinicians and staff to detect changes in data. If a particular measurement, such as proportion of patients with adequate nutrition status, has a stable pattern over time, called *common-cause variation*, then if there is a deviation from that rate, it is identified as

special-cause variation. Detecting special-cause variation provides an opportunity for the team to investigate the circumstances and identify potential reasons for the change.

In order to maintain improvement efforts in clinical practice, such monitoring of data must become an integral part of clinical care. Embedding processes of monitoring data into routine care enables clinicians to keep track of their population of patients and proactively address issues in care as they arise.

Improvement Science in the Business of Health Care

Improvement science and methods can play an important role in the leadership, business, and finances of healthcare systems. QI skills are in effect a problem-solving mindset. Health system leaders value system thinkers who are in a continuous improvement mode to facilitate efficiencies across the system. This mindset allows segmentation of complex clinical and operational issues into aims that can be achieved by application of the model for improvement. The approach of system leaders who use improvement science as a business strategy includes (a) purpose driving the mission and vision of organizations; (b) viewing the organization as a system; (c) a process or system of obtaining information to improve; (d) planning based on the data obtained and integrated with business strategy; (e) managing individual and team improvement activities by carrying out PDSA cycles to implement improvement; and (f) incorporating the perspectives of key stakeholders, such as customers and employees, as well as managers of operational and business units [62].

Improvement science and methods can be leveraged across the health system in both clinical and non-clinical domains. In addition to the clinically focused activities described above, examples in the non-clinical setting include the patient experience, business operations, and system-wide dashboards of key measures of system success.

The Triple Aim of Health Care was conceptualized in 2008 by the Institute for Healthcare Improvement as the simultaneous pursuit of three aims: improving the experience of care, improving the health of populations, and reducing per capita costs of health care [79]. Value in healthcare is quality per unit of cost; higher quality (better outcomes and patient experiences) and lower cost mean higher value. Improvement science methods can be applied to both improving outcomes and reducing unnecessary resource utilization in system and microsystem operations and workflow, as well as in management of population health strategies and complex diseases. Current fee-for-service and volume-based reimbursement models for clinical care delivery lead to excess cost from services that are not necessary. The emerging models of value-based care focus on disease prevention, care coordination, and case management as well as paying providers for improved outcomes and patient experiences within a defined population. The concept of an IBD Medical Home, as championed by Regueiro et al., has shown significant reduction in Emergency Department utilization, as well as increased adherence and improved quality of care [80–83].

Conclusion

While the fundamental purpose of research is to gain knowledge, the goal of quality improvement is to improve care and outcomes. Ultimately knowledge gained through research can be applied to clinical care, and quality improvement can advance care through complementary methods, so both research and quality improvement are necessary to improve outcomes [84, 85]. The road map of translational research begins with basic biomedical science and advances to clinical efficacy knowledge, to clinical effectiveness knowledge and finally to improved healthcare quality and value [86]. Measurement and accountability of healthcare quality and cost, implementation of interventions and healthcare system redesign, and scaling and spread of effective interventions are necessary to transform the healthcare system.

There has been a growing interest in quality of care, particularly in the era of health care reform and its emphasis on performance, accountability, and value in health care [87]. Multiple stakeholders have emerged with strong interests in defining what quality is, how it should be measured, and how the results should be used. These include patients and patient advocacy groups; providers and their professional societies; Medicare, Medicaid, and commercial payers; foundations; certifying boards and credentialing bodies; not-for-profit organizations, notably the National Quality Forum, as well as the National Committee for Quality Assurance; and business consortia such as The Leapfrog Group, an organization which fosters public reporting of healthcare quality and outcomes (hospital quality ratings). The Patient Protection and Affordable Care Act emphasizes quality measurement and requires Medicare to develop mechanisms for Accountable Care Organizations, a delivery model that rewards groups of providers with payments if they can contain costs, improve quality, and assume financial risk for their outcomes. In summary, issues related to quality of care have permeated all areas of healthcare delivery, including training, credentialing, clinical care, access to care, outcomes, documentation, cost, and reimbursement [88]. As the quality landscape continues to change, so too will its impact on the practicing clinician [89].

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Fostering Self-Management and Patient Activation

58

David Alain Wohl and Justin Vandergrift

Introduction

As chronic medical conditions, such as inflammatory bowel disease (IBD), predominate as a reason for seeking medical care, both patients and their healthcare providers have increasingly recognized the importance of their forging a long-term partnership in which both take actions to achieve clinical goals. In this model, the provider provides guidance, advice and feedback, while the patient engages in behaviors aimed at achieving and maintaining health, and there is a degree of shared responsibility for outcomes. The patient side of this bargain is often described as *self-management*.

Below, we outline what self-management is, highlight evidence that self-management can improve clinical outcomes, and provide guidance on how healthcare providers can cultivate strong self-management of children living with IBD—all from the perspective of parents of young patients with Crohn disease.

Defining Self-Management

Although often equated with adherence to medication and clinic visits, self-management entails a number of complex, evolving, and life-long activities, of which adherence is but one part. Therefore, successful self-management of chronic disease is not pegged to any one action but is characterized by the cultivation of a number of behaviors and strategies that lead to a better quality of life and increased likelihood for improved disease-related outcomes.

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Fig. 58.1 Tasks (outer circle) and skills (inner circle) that support disease self-management [1, 2]

A concise and useful conceptualization of self-management includes *tasks* that need to be undertaken and the set of *skills* that are required to help achieve them (Fig. 58.1) [1]. Clinicians can help patients identify unfulfilled tasks and work to help develop the skills that may be lacking.

Self-Management Tasks

The model calls for three major tasks: *medical management, role management, and emotional management*. *Medical management* addresses some of the most obvious elements of taking care of one's self including adhering to medication or a specific diet or nutritional intervention. *Role management* involves the patient making minor or

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major lifestyle and activity adjustments in response to disease, for example, having specific accommodations at school or avoiding certain sports for those with colostomies. In *emotional management*, the many fears, anxieties, and frustrations that accompany a chronic illness are acknowledged and addressed as part of handling life with the disease.

For each task there are obvious leverage points that clinicians can use to make the patient aware of the problem and work together to arrive at a solution. Importantly, though, efforts to successfully develop these self-management tasks will require cognizance of a patient's perceptions and priorities. For example, in the case of a child living with IBD for whom avoiding abdominal cramps is a primary focus, the medical, role, and emotional management has to be conducted largely within the stated context of reducing pain and discomfort—even if the clinician's priority is to ensure control of inflammation and promote proper growth. Therefore, clinician recommendations regarding the need to take daily oral medication (medical), eliminating trigger foods (role), and referral to a clinical psychologist (emotional) are, in the case above, all couched as being part of the plan to keep the pain away.

Self-Management Skills

These key tasks can be achieved through developing a set of six skills that *Loring and Holman* recently added and which provide a greater sense of the work involved in self-management [2]. These skills include *problem solving, decision-making, resource utilization, patient–provider partnership, action-planning*, and *self-tailoring*. As described below, each skill can call on innate resources of the patient and family and/or be fostered and supported through intervention.

Problem-Solving is a core self-management skill. Obstacles to well-being and quality of life are inevitable, and being able to tackle them is critical to manage chronic illness. To do this, patients need to be capable of defining the problem, developing potential solutions, implementing these solutions, and evaluating the results. Advice and support from family, providers, and community may be necessary. For example, an 11-year old with indeterminate colitis dreads going to the clinic to get his anti-TNF infusion. He finds it boring, and "not fun," and he hates feeling sedated by the pre-medication. His parents discuss the problem with the physician and she considers infusion without pre-medication. His parents suggest that they download favorite TV shows for him to watch during the infusion and then go out to his favorite pizza shop afterward.

Decision-Making can follow problem-solving and is enhanced by education and training. When a 15-year old with Crohn disease receiving weekly methotrexate injections developed a fever of 101 °F on the day of his shot, based on instructions they had received at the clinic, he and his parents decide to hold the injection and contact the on-call clinician the next day.

Resource Utilization is becoming an increasingly important element of disease management. Paradoxically, as more information becomes available and accessible to patients regarding their condition, particularly online, there is less clarity as to which sources provide the most relevant and valuable advice. In pediatric IBD, the Crohn's & Colitis Foundation website (www.crohnscolitisfoundation.org) is a trove of reliable information in written and video format. ImproveCareNow (ICN), a large network of pediatric IBD programs dedicated to quality improvement, supports blogs and patient/parent discussion forums (www.improvecarenow.org). The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) also has a site for families to learn more about digestive diseases including IBD (www.gikids.org). Teaching patients and families to access these and other reliable resources has become integral to successful self-management.

Patient–Provider Partnering can be considered the keystone skill for managing a chronic disease—one on which all other self-management skills rely—but is also the most complex. The doctor–patient relationship model has traditionally been 'vertical,' with the healthcare provider issuing orders that the patient was expected to dutifully follow. While this model may be more applicable to the management of acute medical problems (e.g., appendicitis), it is ill-suited for longer term care. In recent years, patients have advocated for a more 'horizontal' or level relationship with their healthcare providers—clinics and hospitals, vying for healthcare dollars, have obliged. Strong partnerships between children with IBD, their families, and the clinician lead to greater trust, adherence, and engagement.

Action-Planning can be thought of as a next step to problem-solving and decision-making and entails skills for making a behavior change and sticking to it. A college freshman at an out-of-state school has been using nightly tube feeds to help keep her Crohn disease in remission since she was 12 years old. Now living in a single room dorm, she often feels like not 'dropping the tube,' especially on weekends, and is missing feeds. During her clinic visit, she is able to discuss the problem with the clinician and nutritionist and together they develop an action plan to take weekends off from the tube and use oral supplements these days instead. The patient feels she can do this, and implements the plan.

Self-Tailoring calls for a practical approach to use the self-management skills. Not every self-management skill is needed at all times and there must be some adaptation of response to fit the current demand. However, this tailoring is conducted by the patient/family. Therefore, the high school

senior learning how to re-order his own medications from a specialty pharmacy calls on problem-solving and action-planning skills to keep his refills from running out.

Self-Management for Kids

Together, these skills and the core tasks are intended to provide a path toward minimizing the deleterious effects of a chronic illness, while maximizing opportunities to maintain well-being and quality of life. It should be recognized that this self-management framework was developed following work with adult patients. For children, particularly those who are younger, much of the self-management heavy lifting is done by parents. The 'self' in self-management, therefore, is not 'myself' but is 'my child living with IBD,' and perhaps 'my other family members affected by my child's illness.' This is an important distinction and the literature speaks even less to this self-management by proxy model than it does to traditional self-management.

That said, the principles of self-management can be applied to and adopted by the parent of a child living with IBD. Naturally, over time, there is a shift from parent management to self-management by the patient. This transition process can be smooth, or not, as discussed in Chap. 61 and below.

For the healthcare provider, supporting and motivating health promoting behaviors for a parent or caregiver is going to look different than it will for a child.

Does Self-Management Really Matter?

Intuitively, good self-management could be expected to produce better health outcomes. While this is a reasonable assumption, medicine is replete with examples where good sense did not translate into good results. An evidence-based approach to the incorporation of self-management into medical care in general has been challenged by its complexity and a lack of uniformity in its definition. Most of the work in this area has focused on medication adherence, which via self-report, pill count, and pharmacy refill can be more readily estimated and quantified.

For children living with IBD, risks for suboptimal medication adherence that have been identified include predictable treatment-specific factors such as patient perceptions regarding the side effects and the complexity of the regimen [3, 4], as well as pill size and taste [4, 5]. Among the patient-level factors linked to suboptimal IBD medication adherence, it will come as no surprise to the parent of a teenager that none are as potent as adolescence [5, 6]. During this period of childhood development, there is a desire for autonomy, a strong interest in peer relationships, and more challenging school and social demands—all developmentally appropriate but potential barriers to adherence for all but those with the most well-developed self-management skills. Additionally, perceptions that the IBD medication is not necessary or not working can lead to missed doses [3, 6]. Family-level barriers to adherence include conflict and dysfunction, while high parent involvement in IBD care facilitates adherence and models self-management skills [5, 7–9]. Lastly, provider-level factors also can influence medication adherence in children. Satisfaction with the provider, provider trust, continuity of care with same provider, and verbal support by the provider are each associated with higher adherence in children across different disease states [10].

Overall, these studies describe a spectrum of a behavior (adherence) influenced by multiple factors across different levels. These associations are instructive insomuch as they can guide interventions, most of which have had modest effects on medication-taking.

Even less is known about what works best to foster strong true self-management behaviors more broadly. A recent meta-analysis looked at published randomized controlled trials of self-management interventions for IBD in adults [11]. Only six studies met the researchers' criteria for inclusion. The studies had disparate populations, sample sizes, primary outcomes, and interventions. One, a psychologist-delivered intervention, had all of the self-management skills proposed by Lorig and Holman, while most included two skills (*decision-making* and *patient–provider partnering*). Overall, there was an emphasis of the interventions on disease management with less attention paid to dealing with symptoms, education, and lifestyle accommodations. There was a generally favorable effect on disease activity in four of the six studies, and positive quality of life impact in three. This analysis provides a signal for the benefits of self-management in IBD, while making plain the severe limitations of the research that has been conducted thus far. Again, much less is understood about this approach in children with chronic diseases such as IBD.

How to Cultivate Self-Management

Given the potential benefits of self-management in pediatric IBD, the question that arises is how to foster these skills. As mentioned above, for some, self-management comes naturally. These patients and families are engaged in the care being provided, are proactive, adherent, and work closely with the medical team. For others, self-management skills have to be cultivated. Unfortunately, most clinics are not well-equipped to evaluate and support self-management

among their patients. Training and education takes time which is generally not reimbursed.

However, there are opportunities to promote self-management that are low-intensity and inexpensive. Foremost is development of a trusting patient–provider relationship, or ideally a trusting patient–*clinic* relationship. As mentioned above, a lack of connection between child (or parent) and provider can have consequences including poor adherence to medication and care. Additionally, electronic record systems (EMRs) are providing patients more direct access to their records and to their providers. Many support electronic communication portals for reporting of issues between visits—a boon to those, like us, who 'lean in' hard to self-management for our children. Increasingly, there are technological innovations that facilitate self-management including applications that send reminders to take medication or track stool frequency, and devices that measure physical activity.

Lastly, an aspect of self-management that has not been explicitly mentioned by those who have conceptualized it is community connectivity. Like *resource-utilization*, community connectivity involves tapping into a source of information and support, but here the resource is obtained on a human-to-human level and is reciprocal. In the existing model of self-management described above, skills are present or, ideally, developed by patients and professionals. Increasingly, patients are learning from other patients how to best manage their disease. This can occur face-to-face during support groups or educational forums, or virtually on the internet.

In pediatric IBD, ImproveCareNow has created a network of clinics with the mission of raising the quality of medical care and services. An intentional byproduct has been the creation of a community of parents of children with IBD. These 'parent-leaders' work with their clinics to achieve better self-management and ultimately better outcomes for families at their centers by rapidly sharing and distributing advances and knowledge to other families. The connectivity of patients, families, and providers through technology adds an entirely new and novel tool to bolster self-management awareness and skills.

Parent and Patient Activation

Through interactions with patients and their families, clinicians can find those who are willing to go the extra step to learn, educate, and participate. Often these 'activated' patients and families are eager to help the clinic to understand what life with IBD is really like between the clinic visits and these insights can create solutions for self-management issues which can be shared and applied to other patients.

The core of this activation is the understanding that patients and families are experts in the care of IBD. Their experiences are tangible, personal, and value-rich because their child's disease is forefront to daily activities. Often a family will develop a simple solution at home that solves common problems faced by many patients. These 'silent solutions' can dramatically change outcomes for hundreds of families but will remain silent if the clinic does not engage the patient and their family.

Clinicians can discover such pearls where they may least expect it. A simple question asking the patient *if* they are taking their medication often gets a simple answer. Probes for *how* and *when* they take medication, what they do to not forget a dose, or how they overcome side effects, delivers richer information and will encourage greater interaction between the family and provider.

Clinic parent-leaders are parents of children with IBD who are willing to work with families at the clinic to distribute advances and knowledge. The parent-leader might organize events with other parents to share ideas about treatment or answer questions from newly diagnosed parents. Other examples include quarterly newsletters prepared by the parent-leader and distributed to other clinic IBD families; at some centers mentoring programs have been established where newly diagnosed families or those facing invasive interventions such as initiation of nasogastric tube feeds, or major events such as surgery, speak with a 'veteran' family that has been through the experience.

Co-production

Following patient activation is co-production. Co-production is best summed as an environment where clinicians and patients share decision-making and work in harmony to create a better healthcare experience. At its core, co-production requires trust between patients (parents) and providers. The benefit of co-production is a better system of treatment for all patients.

According to Ruth Dineen, Founder and Co-Director of Co-Production Wales, "*co-production is an approach to public services which enables citizens and professionals to share power and work together in equal partnership, creating opportunities for people to access support when they need it and to contribute to social change*" [12]. She outlines four key features of co-production:

- Values all participants as equals and assets
- Develops and supports peer networks
- Reciprocity so that benefits accrue to all involved
- Outcomes focus such that the outcome of interest is that which matters most to the individuals, rather than process

Co-production only occurs when clinicians value parents and patients as partners and experts in their disease. This trust is essential in developing a bi-directional communication where clinicians provide advice to patients and patients provide feedback to clinicians. Co-production will bloom where communication flow is open, honest and non-judgmental.

Below are four examples of co-production from IBD clinics that work with a parent leader. Each problem and solution was created through a foundation of open communication, valuing of opinions, and with the goal of producing better outcomes for other families at the clinic.

Pill Cases

During a routine call with a parent-leader, a nurse practitioner described the difficulties another family was having while their child was tapering off prednisone. Careful not to share identifying details, the nurse practitioner related how the child's family incorrectly followed the taper sequence three times and was putting him at risk for complications.

The parent-leader came up with a simple solution to solve the issue. If the taper sequence was pre-loaded into pill cases, then patients would have less difficulty in following the schedule. The parent-leader raised funds and bought pill cases for the entire clinic. This clinic has an on-site pharmacy. Now when a prednisone taper is prescribed, the medication is pre-loaded into pill cases before the family leaves the clinic. This simple solution costs less than $2 per patient, is easy to implement, and can change the outcomes for countless patients.

This solution presented itself because of trust between the clinic and their parent-leader. No confidential information was shared, just a simple exchange of ideas and solutions.

Shot Anxiety

A parent-leader in another clinic identified a simple solution to help children who receive injections at home. This parent saw that 'shot time' was often met with anxiety and was creating a difficult family life for many patients. Through research, this parent identified a device which uses sensory confusion to make shot administration easier. She purchased the device (less than $25) and used it at home with great success. Adherence improved, anxiety was lessened, and both the child and her family were less tensed around injection time.

During a clinic visit the parent-leader mentioned their success with the device to the physician. Later, she helped the clinic obtain grant funding to purchase additional devices so that all patients at the clinic who received injections at home could benefit.

Spanish Language Educational Videos

One parent-leader met a Spanish speaking family sitting in the IBD waiting room, while waiting for their own appointment and noticed that the hospital provided an interpreter for them during the visit. However, at the end of the visit, the after visit summary and disease information given to them was in English, not Spanish. The parent-leader saw the family throw all printed materials into the trash can as they left the clinic.

In response, this parent proposed that the clinic shows short educational videos in English and Spanish. These videos featured children asking providers common questions about IBD, covering treatment and how will it interfere with their daily life. In one version, a Spanish-speaking physician answered the young patient's questions. During the filming, the parent-leader noticed the interest of the patient's father peaked. After filming the child, the father and mother asked if they would participate in the video. The result is a rich video where the parents asked questions at the forefront of their child's care (https://youtu.be/fton8Vx95K4?t=6m31s). The questions asked were perfect and familiar to many IBD families. This example, in particular, demonstrates that most people will help and educate others if provided the opportunity to do so.

The Need for Reliable Education

As described above in the description of the *resource utilization* skill, parents and patients need quality information to better manage IBD. This need for reliable data and guidance is at its peak during three phases of treatment: diagnosis, before procedures and surgery, and during medication changes. Although the internet can be a useful tool for finding information, it is recommended that clinicians steer patients towards sites which contain unbiased and useful information as early in the relationship as possible.

The Crohn's & Colitis Foundation, ImproveCareNow, and NASPGHAN (http://www.naspghan.org/ and www.gikids.org) all have websites that are content-rich and unbiased. Information is presented in written and video formats.

Self-education can be supplemented with interactive events. Several major IBD clinics, including the Center for Pediatric IBD at Children's Hospital of Philadelphia, hold annual education sessions for patients and their families https://www.chop.edu/health-resources/ibd-education-day-2022-videos. Educational events can even be facilitated by a

parent-leader. Parents have also established resource libraries for patients, quarterly newsletters, and monthly educational seminars or 'Q&A' nights. Each of these is designed with the aim of steepening the learning curve for patients and families so that with knowledge they will be more confident in their treatment decisions and self-management.

Conclusions

Self-management of a chronic illness like IBD can seem as easy as following medical advice and taking medication as directed. However, the successful navigation of a life-long condition that can be quiescent and then flare is anything but simple. Each child living with IBD, and each of their families, need to develop strategies that will optimize well-being and minimize the risk of adverse outcomes.

These strategies allow the patient to take on tasks that encompass therapeutics, lifestyle adjustment, and coping while leveraging a set of necessary skills. Clinicians can facilitate such self-management by becoming familiar with their patients and understanding where they are on the spectrum of self-management. Opportunities for intervention must be identified and then acted on.

Patient/parent activation can be a powerful self-management tool that enhances empowerment and engagement in care, while also providing lessons that can be shared and applied to help others. Considering parents and patients as partners, who can co-produce solutions, will allow clinicians to better care for their patients, and address commonly encountered problems.

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Advocacy for Pediatric Patients with IBD

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Introduction

Advocacy encompasses individual, community, and state and federal efforts to speak up for positive change. Pediatricians perform advocacy at the individual and community level every day for their patients. The physician–patient partnership is well equipped to optimize patient outcomes, not only by ordering tests and prescribing treatment, but by learning about the needs of the patient and family and supporting those needs. In some offices, a team of people including physicians, social workers, psychologists, nurses, dietitians, and administrative staff work together to address patient needs while in others, the physician takes on many of these roles. In this chapter, we will address ways in which the physician and medical team can support patients living with inflammatory bowel diseases (IBD) and their families in navigating barriers to their best outcomes. Chapter sections will cover advocating in school, obtaining health insurance, navigating insurance company denials, acquiring social security disability, and attaining leave for family and caretakers.

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Advocacy Directed at Schools

Children with IBD often experience challenges in school functioning, including attendance, academic progress, and participation in school and extracurricular activities. Children with chronic illness miss school more often than their healthy peers. Students with IBD miss school due to medical appointments, hospitalizations, scheduled infusions for biologic medication administration, or for simply feeling unwell. Patients also experience symptoms in school that can interfere with their ability to learn. As a result, school performance may suffer [1, 2].

The conditions and environment of school may also present challenges to children with IBD. In one qualitative and explorative analysis, approximately 15% of parents reported that schooling was substantially compromised by their child having IBD [3]. Families also reported dissatisfaction with school facilities (i.e., bathrooms) to accommodate needs of their children [3]. Patients were frustrated by a lack of understanding of their disease by their teachers [3]. Additionally, grade point average suffered in a separate adjusted analysis [4]. To mitigate the challenges faced by pediatric patients with IBD, pediatric gastroenterologists can help facilitate school accommodations.

Legislation exists to provide a framework and legal construct for physicians to advocate for their patients in school. Enacted to promote the inclusion and integration of people with disabilities into the mainstream, Section 504 of the Rehabilitation Act of 1973 bans disability discrimination [5]. The main definition for one with a disability who is protected under Section 504 is a "person who has a physical or mental impairment that substantially limits one or more major life activities." IBD is considered a physical disability because it interferes with life activities, namely, bowel, digestive, and immune functioning. Under Section 504, students with disabilities have the right to reasonable accommodations.

Section 504 covers students in kindergarten through post-secondary education. All schools that accept federal funding are required to adhere to Section 504 and provide reasonable

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accommodations to those with disabilities. Despite not a financing statute, Section 504 does provide for enforcement of the mandate; a school that is found by the Office of Civil Rights to be out of compliance with Section 504 may lose its federal funding. A 504 plan is used in schools to help students with chronic illness and other disabilities to obtain individualized accommodations so that their academic success is not impacted by their health. A 504 plan helps teachers to know what the needs of the student are and how they can best address them. Under this statute, the student with IBD, their parent or guardian, and the school administration formulate a plan to accommodate the student's additional needs due to their underlying condition.

A 504 plan can be initiated by the parent or school and is a modifiable document that is required to be reviewed annually. For patients with IBD, 504 plan accommodations may include but are not limited to: unlimited restroom privileges, stop-the-clock testing, excused school absences for medical reasons, home tutoring during times of need, and allowance of snacks and water in the classroom. Parents and providers can work with the school to advocate for what the child specifically needs. A 504 plan is not only for those with active disease; it is also meant to be in place for patients with inactive disease. Planning for active disease preemptively makes that time easier to navigate than if the plan was not already in place. Pediatric gastroenterologists are poised to know the needs of the student and should be an integral part of the plan's development. The Crohn's and Colitis Foundation outlines key components to consider when devising a 504 plan for the student. They also provide a template to guide plan development, which can then be tailored to the individual student [6].

Students with IBD may also be supported through the Individual with Disabilities Education Act (IDEA) [7]. This federal legislation states that all are entitled to free and appropriate public education. Individuals in kindergarten through twelfth grade who live with a disability that affects their full participation in school (without assistance) are covered by the IDEA act. Schools are required to identify these students and develop an individualized education plan (IEP) to outline support for the student. A committee is convened to design each student's plan, and schools are financially reimbursed by the federal government for services provided in the IEP. Examples of impairments that affect school participation and are covered by the IDEA are autism, traumatic brain injury, and/or visual or learning impairments. While the act does not cover physical disabilities like IBD, for students with both IBD and neurological or developmental disabilities, their IBD accommodations would be covered in their IEP and they would not require a separate 504 plan. The IEP should include all accommodations the child may need in school because of their IBD and should outline plans for when the child has active disease, regardless of their disease status at the time of plan formulation.

Patients with IBD benefit when their pediatric gastroenterologist participates in school advocacy. Families may not be aware that their child can receive services in school which ensure that their academic success is not impacted by their health. We can serve our patients best when we partner with them to optimize their education. Resources are available to encourage families to be their best advocates. With the support of their pediatric gastroenterologists, students with IBD can look forward to their best performance and participation in school.

Advocacy Directed at Insurance Companies

Obtaining Health Insurance and the Options Your Patients Have

Treating IBD can be costly [8]. One study estimated on an annual basis, IBD patients incurred a threefold higher cost of care and double out-of-pocket costs than non-IBD patients [8]. Over nearly a 20-year period, the annual health care expenditures nearly doubled for IBD patients, with pharmacy expenses being the largest cost driver [9]. It is essential for patients to have some form of health insurance in order to cover the expenses of care and treatments.

The majority of Americans receive their health insurance via their employer. It can be the least expensive option for families since employers pay for part of their insurance. Some employers will offer health coverage on the first day of work, while others require a period worked before the employee is eligible for benefits. In 2010, the passage of the Affordable Care Act expanded coverage for young adults to stay on their parents' insurance until the age of 26.

If your patient does not have health insurance because their family is unemployed, between jobs, or let their previous insurance lapse, what are their options? What assistance and advice can your office help provide them? Outside of employee-sponsored health insurance plans, patients may be eligible to obtain health insurance via multiple options such as Medicaid, Children's Health Insurance Program (CHIP), Children with Special Health Care Needs (CSHCN) funding, Health Insurance Marketplace, or financial assistance through the individual hospital (see Table 59.1). Patients may also receive financial assistance for medications through pharmaceutical companies. For more information on various health coverage options, please refer to www.usa.gov/finding-health-insurance.

Although the federal government contributes funding, Medicaid is administered and operated by states. Patients are eligible for Medicaid if they are a United States citizen, have

Table 59.1 Health insurance and pharmaceutical assistance options

Options to obtaining health insurance
• Medicaid
• Children's Health Insurance Program (CHIP)
• Children with Special Health Care Needs (CSHCN)
• Health Insurance Marketplace
• Financial assistance through the individual hospital
Financial assistance for medications
• Pharmaceutical Co-pay assistance programs
• Pharmaceutical assistance programs cover medication costs

a social security number, are a resident in the state they are applying for coverage, and meet individual state financial requirements. If your patient's family makes too much money to qualify for Medicaid, they may be eligible for low-cost or free health insurance via CHIP. Patients can determine if they are eligible for Medicaid or CHIP by visiting their state Medicaid website or by answering a few questions at https://www.healthcare.gov/lower-costs/. Patients can apply for Medicaid and CHIP via their state Medicaid agency. Applications are typically done online, in-person, or over the phone.

The Health Insurance Marketplace was created by the Affordable Care Act, which allows people to purchase health insurance that best meets their needs. Applicants must apply during the limited enrollment period that takes place every year from November 1st through December 15th. There is a special enrollment period if a family has experienced a new life event. Qualifying new life events include changes in household (got married, had a baby, adopted a child, got divorced and lost health insurance, or loss of insurance because a family member passed away), change in residence (moving to a new home in a new zip code or county), or sudden loss of health insurance. To determine if your patient is eligible go to https://www.healthcare.gov/coverage-outside-open-enrollment/special-enrollment-period/.

Depending on the state your patient lives in, they may be eligible for coverage of their health care through Children with Special Health Care Needs (CSHCN). Authorized by Title V of the Social Security Act, CSHCN receives funding via the federal Maternal and Child Health Services Block Grant. Through CSHCN, services for diagnosis and treatment may be covered for children and youth with medically eligible conditions. However, with the broad and flexible scope of Title V legislation, each state may implement their CSHCN services differently. Additionally, medical eligibility for CSHCN coverage may vary between states. In Ohio, for example, CSHCN funds are administered through a state program called Children with Medical Handicaps (CMH). IBD is an eligible diagnosis under CMH, and as long as the patient is under the age of 21 and meets financial guidelines, this program will cover the costs of office visits, imaging, lab work, procedures/anesthesia, hospitalizations, and even treatment/medications. To determine if your patient is eligible for CSHCN coverage, contact your state's health department. You can also find your state's Toll-free Maternal and Child Health Information Line by visiting https://mchb.hrsa.gov/maternal-child-health-topics/children-and-youth-special-health-needs.

If your patient does not qualify for any of the programs listed above, or if they have private health insurance and are struggling to pay medical bills, another option would be to seek financial assistance through the individual hospital. Most hospitals have patient account representatives that can screen patients and help them apply for financial assistance through their institution. Financial assistance offered can vary between each hospital but may help cover a portion of your patient's owed medical expenses.

Medication costs continue to increase [9] with high out-of-pocket costs for families [8]. Co-pay assistance programs by pharmaceutical companies can cover a significant amount of out-of-pocket costs per year for patients with private insurance. Each pharmaceutical company offers their unique plan and some limit copays to $5 per treatment. While co-pay assistance programs will cover the cost of the medication, it will not cover the cost of the facility fees to infuse the medication. Patients can sign up for some co-pay assistance programs online, but some will require both the provider and patient signature.

If your patient does not have insurance, an additional option to cover medication costs are through patient assistance programs offered by individual pharmaceutical companies. Patient assistance programs can provide patients with the medication for free, but similar to co-pay assistance programs, it does not cover the cost of the facility fees to infuse the medication. Most patient assistance programs also require a paper application with both the patient and provider signature. Additionally, patient assistance programs have financial guidelines to determine eligibility. Patients will then need to provide a proof of income, which usually requires their most recent federal tax return. Most patient assistance programs need to have the patient's financial information renewed annually in order to maintain coverage.

Navigating Insurance Company Denials and Prior Authorizations

Navigating prior authorizations and denials are exceedingly common and time consuming for medical offices. If an insurance company denies coverage for a medication, patients usually have no idea how to appeal the decision and do not have the proper medical documentation and medical litera-

ture justification to appeal the decision. It becomes the responsibility of the provider's office to file the appeal. Nationally, approximately 39–59% of health insurance appeals are reversed [10]. Thus, appealing a denial is not a waste of time or resources, and it is beneficial to the patient. It can also be challenging for a patient to appeal a denial without the physician advocating for them.

Increasingly, health insurance companies are requiring that physician offices obtain prior authorization before they will grant coverage of the medication. Prior authorizations are in place to help keep healthcare costs down. Insurance companies want to verify that it is medically necessary, the use of the medication follows up-to-date recommendations, and the drug is the most economical option to treat that condition. While prior authorizations are supposed to create checks on the system and make sure that it is cost effective, they also lead to treatment delays and place additional administrative burden on providers and their offices. Many states have passed laws that regulate the prior authorization process by limiting the length of time insurers have to complete the prior authorization review. This whole process does interrupt the shared decision-making process between a patient and their provider. During the office visit, different medications are discussed to treat their condition, along with risks and benefits, and a decision is made between the patient and the provider. Ultimately, insurance approval is required and made without the input of the patient or the provider.

Prior authorizations may be denied if proper documentation was not submitted to the insurance company. If that is the case, the prior authorization is resubmitted with all of the proper medical information such as diagnosis, medication, dose, TB status, and other therapies tried and failed. The Affordable Care Act established common-sense consumer protections, and this requires insurance companies to inform the patient why a claim was denied and how to appeal the decision. It also guarantees the right to an internal appeal. Prior authorizations are usually denied because of three reasons: (1) the insurance company requires a patient to try an insurance preferred medication prior, (2) the insurance company deems the therapy experimental, or (3) administrative denial.

Appealing a denial on behalf of your patient to the insurance company can be confusing, though it is important that you update the patient on the process and the status of the appeal. The provider's office should submit the necessary documentation that pertains to the relevant exception that you are seeking (see Fig. 59.1). Depending on the patients insurance, it may require a peer to peer or a letter of medical

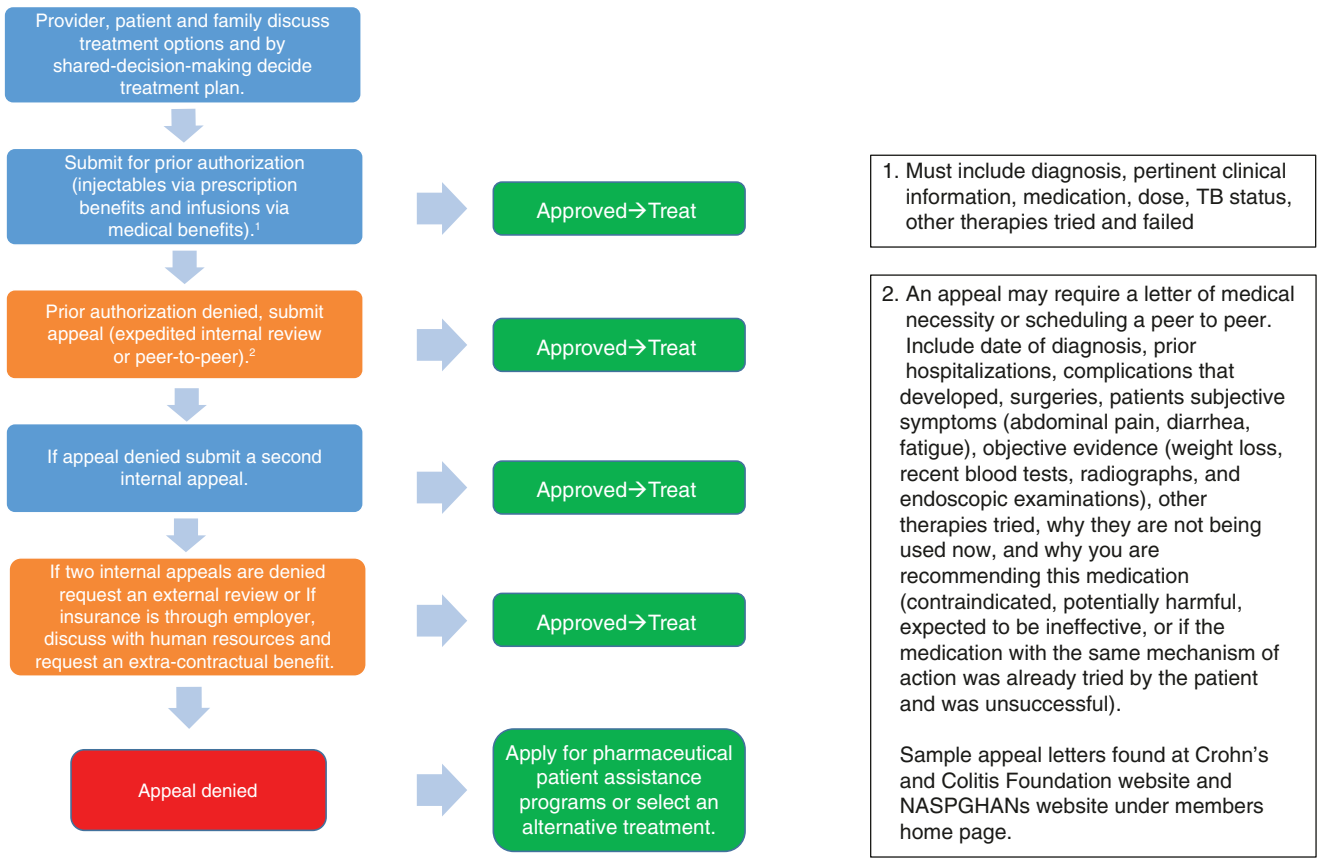

Fig. 59.1 Prior authorization and appeal process algorithm

necessity that includes the patient's illness in detail. The history should include the approximate date of diagnosis and the effects on the patient's life (including a history of prior hospitalizations, complications that developed, and surgeries). The patient's subjective symptoms (e.g., abdominal pain, diarrhea, fatigue) are important, but objective medical evidence is vital (i.e., weight loss, recent blood tests, radiographs, and endoscopic examinations) demonstrating ongoing intestinal inflammation. They include which conventional medications have been utilized and why they are not being used now (e.g., lack of efficacy, adverse effects) and highlight why a given condition requires a specific medication and explain why the insurance company recommended medications are contraindicated, potentially harmful, expected to be ineffective, or if the medication with the same mechanism of action was already tried by the patient and was unsuccessful. General appeal letters for medications, dose adjustments, and tests/procedures can be found on the Crohn's and Colitis Foundation website and NASPGHANs website under the member's home page and clinical practice. http://www.crohnscolitisfoundation.org/science-and-professionals/programs-materials/appeal-letters/ and https://naspghan.org/.

Experimental/investigational appeals can be challenging because these therapies are usually newer, more expensive, and off-label because it is only approved for adults and not yet approved for pediatrics. It is important to highlight the patients' medical course and medications that have failed them in order to highlight the patient's specific need for the novel therapy requested. It is recommended that the physician attaches published, peer-reviewed literature and supportive information that reassures the novel treatments' safety and efficacy to the appeal. Insurers tend to appreciate randomized longitudinal trials in which patients are followed for a significant period and involve placebos or a control group.

When writing a letter of appeal to an insurance company, it is very important to not let the insurer equate "off label use" with "investigational" use. When the FDA approves a medication for use, they typically approve it for one very narrow indication. An "indication" implies a specific disease, condition, or age group. For example, the FDA may approve a medication for patients with ulcerative colitis over 18 years of age. However, that does not mean that the medication should be restricted to that population. According to the American Academy of Pediatrics, "the term off label does not imply an improper, illegal, contraindicated or investigational use. Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient" [11].

A third type of denial by insurers is an administrative denial. This type of denial occurs when there is a coverage request for a treatment that is expressly excluded from coverage. In an administrative denial, a coverage request will be denied without regard for medical necessity. However, it is possible to force an insurer to conduct a medical necessity review.

If the initial internal appeal is denied, a second appeal will need to be submit. If two internal appeals are denied, the Affordable Care Act established the right to take your appeal to an external review, which consists of an independent third party that reviews the insurer's decision. In addition, under the Affordable Care Act, every state has a Consumer Assistance Program (CAP) to help consumers with insurance appeals. The CAP in your state may be in your state's Insurance Department, or it may be a separate entity. The CAP is funded largely by federal grant funds.

At last, if your patient obtains its medical insurance through their employer, you may recommend that the patient discusses the issue with their human resource department. Employees can ask their employer to grant an extra-contractual benefit, which provides coverage for something that otherwise would not be covered.

Unfortunately, if all internal and external appeals are denied, then patients can apply for patient assistance programs through the individual pharmaceutical company or select an alternative treatment covered by their insurance company.

In summary, navigating health coverage options and working with insurance companies can be extremely frustrating and time consuming for you, as well as your office staff. It is important that you become a strong advocate for your patient because ultimately it is in the best interest for your patient and their health. It is also crucial that you keep the patient and their family up to date throughout the process, especially if coverage is denied. Laws over the years have been created to protect patient rights and improve the appeals process. It is important that as physicians, we advocate for our patients in the office setting and in state and federal government.

Social Security Disability Benefits

Many people do not realize that children may be eligible for Supplemental Security Income (SSI), one of two forms of Social Security disability benefits. There is often confusion about SSI and Social Security Disability (SSDI) because you apply for both programs with the Social Security Administration (SSA). While both SSDI and SSI provide financial assistance to individuals living with disabilities, SSDI benefits are determined based on both the individual's disability and personal/family work history. When determining eligibility for SSDI benefits, the individual/family needs

to have worked long enough to be insured under the social security system. SSI does not require a work history and gives money to individuals, including infants and children, who have medical impairments and meet both citizenship and financial guidelines. Typically, the financial guidelines are for those with low income and few resources. For more information about eligibility guidelines for SSI and SSDI, please refer to ssa.gov/benefits/.

For a child to be eligible for disability benefits, they must have a medically proven physical or mental condition(s) that causes severe functional limitations and must have lasted, or is expected to last, at least 12 months. IBD is a condition listed in the SSA's impairment listing manual. However, there are specific diagnostic criteria that must be met in order for a patient to qualify for disability benefits. If a patient does not meet the diagnostic criteria, they may still qualify if they can show that their condition makes it impossible to work, attend school, or engage in basic activities of daily living. Additionally, multiple impairments that by themselves do not qualify may satisfy the condition of marked, severe limitation when combined. If your IBD patient has another condition(s) also causing impairment on their life, there is a higher chance that they may qualify for disability benefits due to having multiple limitations.

Patients can apply for disability benefits online, over the phone, or by contacting their local Social Security office. While patients will need to request official medical records to submit to the SSA, you can assist your patients in this process by writing a letter of support. This letter should explain the child's condition, brief overview of medical history, current physical or mental limitations, and instructions on how the SSA can request the child's medical records at your institution. It is helpful to inform your patients that once their application is submitted, it can take between 90 and 120 days before they will be notified of a decision. It is also important to let your patients know to be prepared to appeal an initial determination. A majority of individuals who apply for disability benefits are denied after their initial attempt. Appeals can be successful when the application is reconsidered. Helping your patients understands the application and appeal process can make the process of applying for benefits clearer and less stressful.

In addition, an integral part of living with any chronic illness is helping maintain self-identity and promoting patient empowerment. Health care providers must foster an environment that avoids an internalized notion of a "disabled" self-concept. The burden and process of securing entitlements that require the proof of "disability" may be counterproductive to the message we strive to convey—that the child is a whole person, who is more than the disease. Health care providers, who can facilitate the SSI application in an efficient and seamless manner, will help preserve this message.

Family and Medical Leave for Caregivers

Caregivers of children with IBD often risk losing their jobs when they take time-off to care for their children. Providers may be able to spare them this crisis by helping them to maintain employment security under the Family and Medical Leave Act (FMLA). FMLA is a federal law that requires covered employers to provide an eligible employee up to a total of 12 workweeks of unpaid leave during a 12-month period for a serious health condition, or to care for a family member (spouse, child, or parent) with a serious health condition. FMLA is enforced by the U.S. Department of Labor Employment Standards Administration, Wage and Hour Division. While FMLA is a federal protection, some states have their own laws covering employee sick leave. However, in states with family and medical leave laws, employers must adhere to the family and medical leave statutes that provide the most protections to workers. In states without family and medical leave laws, FMLA guidelines must be followed by default.

Employers that are required to follow FMLA guidelines are those in local, state, or federal government agencies, those in public or private elementary or secondary schools, and those in the private sector with 50 or more employees in 20 or more workweeks in the current or preceding calendar year. Employees that are eligible for FMLA must have worked for the same employer at least 12 months, for at least 1250 h during the previous 12 months, and be employed at a location where at least 50 individuals are employed by the employer within a 75-mile area. It is important to note that FMLA does not require paid leave and an employer may permit an employee to use all available vacation, sick, or paid time-off time during such leave. Additionally, the 12 weeks of leave need not be consecutive. For example, a parent of a child who is on infliximab treatments can take a day of leave every few weeks to get the infusions and their job will be protected under FMLA. Employers must post a notice to their employees explaining the rights and responsibilities under FMLA, or they may be fined.

A child has a "serious health condition" under FMLA if he or she is incapable of self-care due to a mental or physical disability that limits one or more of the "major life activities." Just as is the case under the Americans with Disabilities Act, "major bodily functions," including digestive function, are included within "major life activities," so this would apply to children with active IBD. A "serious health condition" is also defined as a condition that continues over an extended period of time, requires repeated visits to a health care provider, and may involve occasional episodes of incapacity. Even if symptoms are inactive, children with IBD have the potential to require this care due to the cyclical nature of this chronic disease. Primary caregivers of children

with IBD should ask for FMLA leave at the beginning of every year, whether or not they use it, so that they are protected if the child's disease becomes active or they need to take off work to care for their child on an intermittent basis.

Caregivers of children with IBD may apply for continuous and/or intermittent leave under FMLA. Continuous leave is typically requested if the child is hospitalized for a long period of time or needs to undergo a surgical procedure. In this case, the caregiver is asking for a consecutive period of time-off so that they can provide care for their child in the hospital or at home until the child recovers. Intermittent leave is typically requested for the child's required routine follow-up, which includes office visits, trips to get labs done, and/or appointments for infusions. Intermittent leave is also beneficial to have for unexpected time-off, such as times when the caregiver may need to take off work to care for their child's episodic flare-up or take their child to the emergency department or urgent care.

When requesting FMLA leaves, the employee must request it in writing with their employer at least 30 days in advance if the need for leave is foreseeable. If the need for leave is unforeseeable, employee requests must be made as soon as possible and must comply with an agency's normal call-in procedures. If a physician anticipates a child who will require increased parental care because of the worsening of the disease, this should be discussed with the family so that the caregivers may request FMLA leave before the crisis occurs. While FMLA does not require the use of any specific form or format, the US Department of Labor offers certification forms that make it easier for employers to understand the reason the employee is seeking leave. For caregivers of patients with IBD, this form is titled "Certification of Health Care Provider for Family's Member's Serious Health Condition." Appendix 1 includes an example of this form filled out for a patient diagnosed with IBD. However, employers may use their own FMLA forms as long as they provide the same basic notice information and require only the same basic certification information.

When filling out FMLA for a family, it is important to demonstrate the need for FMLA leave. You will first want to include a general description about IBD and the patient's date of diagnosis and recent or upcoming office visits and hospitalizations. It is important to make clear that IBD is a lifelong, chronic condition that will require routine care and medical supervision with a gastroenterologist. You will also want to add an estimated frequency that the caregiver may need to take off work to bring their child to follow-up treatments or appointments. Additionally, it is beneficial to note the unpredictable nature of IBD and explain how the caregiver may need to call off work in short notice for potential hospitalizations, episodic flare-ups, procedures, or to seek immediate medical attention. In doing so, it is helpful to emphasize the importance of the caregiver being present so that they can provide their child with psychological support, transportation, and assistance with basic activities of daily living. See Appendix 1 for an example of a filled out FMLA form for an IBD patient. Protecting job security can ensure financial stability and enable parents to focus on their child's acute needs and the impact on the family.

Summary

Children and families living with IBD inherently face many challenges. Awareness, support, and proactive intervention can garner crucial resources to thrive in school, financially, and as a family. Healthcare providers serve in the fundamental position of generating awareness and providing access to these resources. While some care centers will have multidisciplinary support, every clinician should incorporate an approach to address barriers for children with IBD. With attention to policies on 504 plans and IEPs, children can realize their full potential in school. With diligent navigation of health insurance options and patient assistance programs, the cost of care can be more affordable. With dedication and persistence, critical therapies can be accessed. With awareness and execution, caregivers can ensure intact employment and supplemental income. The provider who is an effective advocate will attend to the financial, educational, and social implications of IBD, and ensure a better quality of life for the child and their family.

Acknowledgments We would like to acknowledge the contributions of Jennifer Jaff and Suzanne Rosenthal who wrote the first two published versions of this chapter and Janis Arnold and Athos Bousvaros who wrote the third published version of this chapter.

Appendix 1

Certification of Health Care Provider for Family Member's Serious Health Condition (Family and Medical Leave Act)

U.S. Department of Labor
Wage and Hour Division

DO NOT SEND COMPLETED FORM TO THE DEPARTMENT OF LABOR; RETURN TO THE PATIENT.

OMB Control Number: 1235-0003
Expires: 8/31/2021

SECTION I: For Completion by the EMPLOYER

INSTRUCTIONS to the EMPLOYER: The Family and Medical Leave Act (FMLA) provides that an employer may require an employee seeking FMLA protections because of a need for leave to care for a covered family member with a serious health condition to submit a medical certification issued by the health care provider of the covered family member. Please complete Section I before giving this form to your employee. Your response is voluntary. While you are not required to use this form, you may not ask the employee to provide more information than allowed under the FMLA regulations, 29 C.F.R. §§ 825.306-825.308. Employers must generally maintain records and documents relating to medical certifications, recertifications, or medical histories of employees' family members, created for FMLA purposes as confidential medical records in separate files/records from the usual personnel files and in accordance with 29 C.F.R. § 1630.14(c)(1), if the Americans with Disabilities Act applies, and in accordance with 29 C.F.R. § 1635.9, if the Genetic Information Nondiscrimination Act applies.

Employer name and contact: _____

SECTION II: For Completion by the EMPLOYEE

INSTRUCTIONS to the EMPLOYEE: Please complete Section II before giving this form to your family member or his/her medical provider. The FMLA permits an employer to require that you submit a timely, complete, and sufficient medical certification to support a request for FMLA leave to care for a covered family member with a serious health condition. If requested by your employer, your response is required to obtain or retain the benefit of FMLA protections. 29 U.S.C. §§ 2613, 2614(c)(3). Failure to provide a complete and sufficient medical certification may result in a denial of your FMLA request. 29 C.F.R. § 825.313. Your employer must give you at least 15 calendar days to return this form to your employer. 29 C.F.R. § 825.305.

Your name: _____
First Middle Last

Name of family member for whom you will provide care: _____
First Middle Last

Relationship of family member to you: _____

If family member is your son or daughter, date of birth: _____

Describe care you will provide to your family member and estimate leave needed to provide care:

_____

_____

_____

_____ _____ _____
Employee Signature Date

SECTION III: For Completion by the HEALTH CARE PROVIDER

INSTRUCTIONS to the HEALTH CARE PROVIDER: The employee listed above has requested leave under the FMLA to care for your patient. Answer, fully and completely, all applicable parts below. Several questions seek a response as to the frequency or duration of a condition, treatment, etc. Your answer should be your best estimate based upon your medical knowledge, experience, and examination of the patient. Be as specific as you can; terms such as "lifetime," "unknown," or "indeterminate" may not be sufficient to determine FMLA coverage. Limit your responses to the condition for which the patient needs leave. Do not provide information about genetic tests, as defined in 29 C.F.R. § 1635.3(f), or genetic services, as defined in 29 C.F.R. § 1635.3(e). Page 3 provides space for additional information, should you need it. Please be sure to sign the form on the last page.

Provider's name and business address: _____

Type of practice / Medical specialty: _____

Telephone: (_____) _____ Fax:(_____) _____

PART A: MEDICAL FACTS

1. Approximate date condition commenced: _____

Probable duration of condition: Lifelong chronic duration

Was the patient admitted for an overnight stay in a hospital, hospice, or residential medical care facility?
___No ___Yes. If so, dates of admission: _____

Date(s) you treated the patient for condition: _____

Was medication, other than over-the-counter medication, prescribed? ___No ✓ Yes.

Will the patient need to have treatment visits at least twice per year due to the condition? ___No ✓ Yes

Was the patient referred to other health care provider(s) for evaluation or treatment (e.g., physical therapist)?
____ No ____Yes. If so, state the nature of such treatments and expected duration of treatment:

2. Is the medical condition pregnancy? ✓ No ___Yes. If so, expected delivery date: _____

3. Describe other relevant medical facts, if any, related to the condition for which the patient needs care (such medical facts may include symptoms, diagnosis, or any regimen of continuing treatment such as the use of specialized equipment):

Patient is diagnosed with a condition called Inflammatory Bowel Disease (IBD), which involves chronic inflammation of the digestive tract. IBD is lifelong and requires routine care medical supervision with a Gastroenterologist. IBD if often characterized by recurrent flares of symptoms, which can include severe abdominal pain, bloody diarrhea, fevers, and other medical complications if not monitored closely.

PART B: AMOUNT OF CARE NEEDED: When answering these questions, keep in mind that your patient's need for care by the employee seeking leave may include assistance with basic medical, hygienic, nutritional, safety or transportation needs, or the provision of physical or psychological care:

4. Will the patient be incapacitated for a single continuous period of time, including any time for treatment and recovery? ___No ___Yes.

   Estimate the beginning and ending dates for the period of incapacity: _____

   During this time, will the patient need care? __ No __ Yes.

   Explain the care needed by the patient and why such care is medically necessary:

5. Will the patient require follow-up treatments, including any time for recovery? ___No ✓ Yes.

   Estimate treatment schedule, if any, including the dates of any scheduled appointments and the time required for each appointment, including any recovery period:

   Patient will have infusions/routine clinic visits approximately once every (***) weeks, lasting for (***) hours in duration.

   Explain the care needed by the patient, and why such care is medically necessary: Infusions are needed to induce/maintain remission. Routine clinic visits are needed to monitor labs and prevent any future flares/complications.

6. Will the patient require care on an intermittent or reduced schedule basis, including any time for recovery? __ No ✓ Yes.

   Estimate the hours the patient needs care on an intermittent basis, if any:

   8 hour(s) per day; 1-2 days per week from _____ through _____

   Explain the care needed by the patient, and why such care is medically necessary: In addition to infusions and routine clinic visits, episodic flares, hospitalizations, urgent care/emergency department visits, and even procedures may be required for patients with IBD. If hospitalized, admissions can last anywhere from 3 days to 3 weeks.

7. Will the condition cause episodic flare-ups periodically preventing the patient from participating in normal daily activities? ____No ✓ Yes.

Based upon the patient's medical history and your knowledge of the medical condition, estimate the frequency of flare-ups and the duration of related incapacity that the patient may have over the next 6 months (e.g., 1 episode every 3 months lasting 1-2 days):

Frequency: 1-2 times per _____ week(s) 1 month(s)

Duration: _____ hours or 2-3 day(s) per episode

Does the patient need care during these flare-ups? ____ No ✓ Yes.

Explain the care needed by the patient, and why such care is medically necessary: Flares that occur with IBD can vary depending on their symptoms, duration, and frequency. Flares can often be managed at home with parent supervision, though there are times when a flare may require medical follow-up and/or immediate medical attention. Hospitalizations/ emergent procedures may even be needed if the flare is significant. In these instances, parent care is highly needed.

ADDITIONAL INFORMATION: IDENTIFY QUESTION NUMBER WITH YOUR ADDITIONAL ANSWER.

3, 5, 6, & 7) - Parent care, psychological support, transportation, and supervision is needed for ALL routine follow-up, medical evaluations/treatment, potential hospitalizations/procedures, and episodic flares. Parent care includes assistance with basic activities of daily living, such as helping with hygiene needs, mobility, eating/dietary monitoring, and maintaining continence.

Signature of Health Care Provider **Date**

PAPERWORK REDUCTION ACT NOTICE AND PUBLIC BURDEN STATEMENT

If submitted, it is mandatory for employers to retain a copy of this disclosure in their records for three years. 29 U.S.C. § 2616; 29 C.F.R. § 825.500. Persons are not required to respond to this collection of information unless it displays a currently valid OMB control number. The Department of Labor estimates that it will take an average of 20 minutes for respondents to complete this collection of information, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. If you have any comments regarding this burden estimate or any other aspect of this collection information, including suggestions for reducing this burden, send them to the Administrator, Wage and Hour Division, U.S. Department of Labor, Room S-3502, 200 Constitution Ave., NW, Washington, DC 20210.
DO NOT SEND COMPLETED FORM TO THE DEPARTMENT OF LABOR; RETURN TO THE PATIENT.

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Advocacy for Pediatric Patients with Inflammatory Bowel Disease

60

Janis Arnold and Athos Bousvaros

Introduction

Physicians who treat patients with chronic illnesses know that the practice of medicine has come to involve the practice of patient advocacy. Whether it be justifying a prescription for a non-formulary medication or trying to help a child obtain necessary accommodations from a school, physicians who treat children with IBD have to learn to be advocates. Although this is not something we are taught in medical school, it has become an integral facet of practicing collaborative medicine in the United States in the twenty-first century. Use of a medical team approach is most important to meet the advocacy needs of patients. The medical team may involve the physician, nurses, social workers, nutritionists, psychologists, and administrative staff.

In smaller centers, providers may find themselves taking on multiple roles. We will discuss the following five substantive areas in which advocacy for patients is necessary:

1. Navigating school administrative requirements to enable optimal academic plans for ill children with IBD to attend school.
2. Insurance company denials of a needed therapy, including mental health services.
3. Social Security disability assistance for children and adolescents.
4. Family and medical leave for caretakers of children with IBD.
5. Restroom Access Act.

We would like to dedicate this chapter to our former collaborator and close friend, Jennifer Jaff.

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Advocacy Directed at Schools

Children with IBD are often embarrassed to attend school because of their digestive symptoms. We once cared for a child who had not been in school for a year and one-half because his parents did not understand that they could request accommodations for him that would have allowed him to stay in school. They essentially hoped his symptoms would resolve, or that he would learn to adjust on his own. The family was unaware of where to go for help, or what legal recourse they had. When the school district sent them forms to fill out to begin the process of evaluating the child for accommodations, the family did not understand what purpose of the forms or the evaluation were, so the child stayed disengaged from school for nearly 18 months. Ultimately, intervention by an attorney with expertise in school advocacy resulted in resolution of the problem and the return of the child to school.

There are two related statutes that provide protection for students with IBD: the Individuals with Disabilities Education Act ("IDEA"), [1] and Section 504 of the Rehabilitation Act of 1973 ("Section 504"). [2] The IDEA applies to state and local education agencies, whereas Section 504 applies to educational institutions that are recipients of federal funds. The two statutes are related, but they are not identical.

Whereas the IDEA applies only to grade and secondary schools, Section 504 pertains to all levels of education—grade school to college to graduate schools that accept federal funding. The IDEA is geared toward students who need special education services related to a learning disability as opposed to students with a physical condition like IBD, whereas Section 504 is broader, and includes physical disabilities as well as learning disabilities (although special education services are available only under the IDEA). Patients with IBD usually do not have a lifelong learning dis-

[1] 20 U.S.C. § 1400, *et seq.*
[2] 29 U.S.C. § 794(a).

P. Mamula et al. (eds.), *Pediatric Inflammatory Bowel Disease*, https://doi.org/10.1007/978-3-031-14744-9_60

ability that requires placement in special education classes. However, they may require some accommodations due to school absence during periods of illness, or because their illness sometimes limits their participation. Thus, patients with IBD are more likely to be eligible for accommodations under section 504 than they are for accommodations under IDEA.

The IDEA provides that a child with a disability who needs special education is entitled to a free appropriate public education. The IDEA defines a child with a disability to include children with a number of specific types of disabilities, including visual and hearing impairments, speech and language impairments, autism, traumatic brain injury, and emotional disturbances. While inflammatory bowel disease is not explicitly stated in the IDEA, the law does include a proviso providing assistance to children with "other health impairments." However, children who qualify for assistance under IDEA must have a physical or mental disability that affects their ability to fully participate in school without some form of assistance, whereas children who qualify for accommodations under Section 504 need only to show that they have a medical condition that substantially impairs one or more major life activities, regardless of how they perform in school.

Under the IDEA, the first requirement imposed on the states is to "identify, locate and evaluate" children in need of special education services (called "child find"). Once children are located, the IDEA requires states to meet the needs of those children. The core of the IDEA is the "individualized education program" or "IEP." Under the IDEA, states are required to conduct an evaluation before special education benefits are granted. The evaluation determines whether the child is, in fact, a "child with a disability" and has special educational needs. The process should be initiated by the school, which should provide notice of the evaluation to the parents. The child may be tested and evaluated using a variety of tools; after this evaluation is completed, the actual IEP is formulated.

The IEP should be a separate written statement for each qualifying student that includes a statement of the child's level of educational performance; a statement of goals; a statement of the special education and related services to be provided; an explanation of the extent, if any, of the child's participation in mainstream programs; a statement of any individual modifications; the projected date for commencement of these services; and the duration of the services. In fashioning the IEP, the strengths of the child, the parents' concerns, and the results of the most recent evaluation of the child must be considered.

The IEP "team" includes the parents, at least one non-special education teacher, at least one special education teacher, a representative of the local agency who is qualified to assist in formulating IEPs, other experts brought in at the request of the parents or the State, and, if appropriate, the child. The IDEA provides safeguards to ensure parental involvement at all stages of the child's education, and parents may challenge any aspect of an IEP by requesting a hearing, and if they remain dissatisfied, they may file suit in federal court. Schools that provide services under the IDEA are also eligible for financial support through the state and federal government.

In contrast, Section 504 of the Rehabilitation Act was enacted to promote the inclusion and integration of people with disabilities into the mainstream. Section 504 provides that disabled children cannot be denied the benefits of any program that receives federal financial assistance, including public education. In general, a child is disabled if he or she has a "physical or mental impairment" that "substantially limits" one or more "major life activities" as those terms are used in the Americans with Disabilities Act. [3] Major life activities include bodily functions, such as the bowel, digestion, and immune functions.

Once the student's medical disability is established, the next step is to determine what accommodations (under Section 504) or special services (under the IDEA) must be provided. While section 504 is a more inclusive statute than IDEA, school districts providing services under 504 plans are not reimbursed for their expenses by the federal government. Because Section 504's definition of disability is broader than the IDEA's, many IBD patients will qualify under Section 504 but not under the IDEA. These are called "504-only students." For some patients, accommodations are minimal (e.g., providing medication during school hours, or being excused from physical education class), whereas for other students, accommodations are more extensive (including limiting home work loads and home tutoring). Under the IDEA, a child may be eligible for speech therapy, special education services, and even nursing care. Any assistance a student receives from a school must be provided for free.

Any child who needs accommodation under IDEA or section 504 must be the subject of an evaluation *before* taking any action with respect to placement. Once testing is concluded, schools use the results, as well as teacher recommendations, physical condition, social or cultural background, and adaptive behavior in designing the plan for the student. Parents must have notice and opportunity to examine the evaluation records, there must be a hearing at which the parents and/or other guardian can appear, and there must be a procedure for review of the decision.

There are at least two issues that face IBD patients that are not well addressed by the law. First, children who do well in school are presumed not to need help. The IDEA defines "child with a disability" to mean a child with health problems "who, by reason thereof, needs special education and related services." A student who does not need special educa-

[3] 42 U.S.C. § 12101, *et seq.*

tion because she is performing well academically is not a "child with a disability" under the IDEA. Therefore, only children with IBD who have neurologic or developmental conditions that impair learning are covered under the IDEA. However, this is not the case under Section 504, which provides reasonable accommodations to any student who is substantially impaired by a major life activity, regardless of the effect—or lack thereof—on the ability to learn.

Second, the IDEA does not provide explicit guidance for children with a chronic disease that remits and relapses. However, as of January 2009, Section 504 provides that an episodic illness that is disabling when active also is considered to be disabling when in remission. This presents a challenge for both the parents and the school, because even though Section 504 now recognizes chronic illness, it is difficult to write an IEP or Section 504 plan that is not intended to apply only intermittently. Because chronic illness is cyclical in nature, there will be times when a student needs home schooling or temporary access to typed handouts, and other times when the student has no need for help. The waxing and waning course of IBD and the unpredictability of the illness necessitate that the 504 plan for an IBD patient be flexible and change depending on whether the patient is ill or in remission.

Generally, it is the child's parents in conjunction with the members of the health care team that realize that educational accommodations may be needed for their chronically ill child. In patients with IBD, this need is often recognized during a period of prolonged illness (such as in a hospitalization for intravenous medication or surgery). At this point, parents and members of the health care team should list the child's needs in writing, and discuss with school officials to develop a written plan. A plan under either the IDEA or Section 504 may include accommodations such as seating chart placement, extended time for testing, adjustment of class schedules, use of aids such as tape recorders, permission to photocopy a classmate's handwritten notes, class and/or homework assistance, administration of medication, behavioral support, initiation of tutoring prior to the standard 14 consecutive days of absence, access to bathroom without the required hall passes, permission to have a water bottle in class, or multiple sets of textbooks. For chronically ill patients with IBD, parents and school officials should have this integrated academic plan for IBD students in place.[4]

The IBD Center at Boston's Children's Hospital had the opportunity to work with a high school student who experienced her first severe flare-up of her ulcerative colitis, which had been well controlled for many years. Her symptoms were initially unresponsive to various medications. She ultimately was placed on tacrolimus, which lead her to develop the side effects of hand tingling, joint pain, and hand tremors. Though her medication regimen decreased her GI symptoms enough to allow school re-entry, the side effects from the necessary medication left her unable to fully participate in the classroom requirements, including note taking. Consequently, this interfered with her ability to have the adequate review materials to study for tests. We collaborated with the patient's mother and the school to develop a 504 plan for the patient. Among other plan provisions, relevant accommodations included allowing her to identify a classmate in each course whose notes she had permission to photocopy. It also was detailed that the teacher would, when appropriate, provide the student with typed copies of the class notes and outlines. An additional item was written into her 504 plan which stated that, if she had to be absent unpredictably, the plan coordinator would be responsible for getting the student a copy of the classmates' notes and teacher outlines within 48 h of the missed school days. This protected the student's academic performance and reduced the anticipatory anxiety regarding not being able to keep up with the class notes—anxiety that could lead to exacerbation and prolonging of her disease's symptoms.

Although a Section 504 plan can be implemented during periods of illness, many families and patients find it helpful to coordinate and delineate these educational adaptations prior to what may be experienced as a medical crisis or complications, given our awareness that these disease processes are unpredictable and can change quickly. It is often difficult and burdensome to try to arrange these meetings and plan at times when families are simultaneously focusing on acute medical demands and the family reorganization that must accommodate them. Nonetheless, it is critical that normal school attendance, curriculum participation, and activity should be encouraged during the periods of remission (see Appendix 1).

While written advocacy through letters supporting a 504 plan is helpful, sometimes a direct phone call from the physician or team member to the principal or vice principal is even more effective. For example, we had a patient who could not complete tests in a timely manner because the stress of the test would cause her intestinal symptoms to flare. While written documentation was sent, and most teachers responded adequately to the written documentation, one teacher remained resistant to implementing "stop the clock testing." A call from the patient's physician to the school administration resulted in a more detailed discussion between the principal and the teacher, which enabled the student to receive appropriate accommodations.

[4]Ketlak D. Advocating for your chronically ill child within the school setting. Pediatric Crohn's and Colitis Association Website http://pcca.hypermart.net/advocating.html. 2002.

COVID-19 Considerations

The unprecedented COVID pandemic has changed the delivery of health care and the navigation of social settings as we know them everywhere. Among the immeasurable implications, the pandemic has also led to necessary restrictions in school settings to mitigate the risk of transmission of this virus. As a result, many of these restrictions have unintentionally, but immovably created barriers and limitations that would otherwise have been able to support students with IBD. For example, many schools have created one-way hallways to reduce traffic and increase physical distance; many of the students with IBD experiencing stool urgency have to walk much farther to get a restroom that may otherwise be very proximal to their location. Additionally, many communal school bathrooms must reduce capacity by taking altering stalls out of use, thereby reducing overall access. These measures to increase safety around COVID are the ones that have had less success of overriding on behalf of the demands associated with IBD. This requires individualized discussions with schools regarding infrastructure limits and student needs, to determine "reasonable" accommodations under the law, in the climate of COVID-19. Remote learning was also commonplace during the COVID-19 pandemic, but almost all school systems now have returned to in person learning. While many IBD patients are receiving immune suppressive therapy, the vast majority of patients are able to attend in person school.

Advocacy Directed at Insurance Companies

Inflammatory bowel disease is a costly illness; one 1992 study estimated the per capita annual costs of Crohn disease ("CD") to be approximately $6500 dollars, though a small number of patients account for the bulk of that cost. [5] Charges for a hospitalization may approach $30,000, especially when that hospitalization involves surgery.[6] In addition, the increasing utilization of highly expensive biologic therapies (including infliximab, adalimumab, and vedolizumab) means that annual costs of medications may be tens of thousands of dollars. For these reasons, coverage by third-party payors is essential for most patients.

Insurance company denials of prescribed therapies are exceedingly common. Often, pediatric prescriptions are automatically denied simply because the patient is under age 18, and the drug has been approved by the FDA for individuals over 18 years. When coverage for a therapy is denied by an insurance company, the patient in all likelihood will not be able to pay for it him or herself. Thus, appealing the decision may be necessary. Nationally, approximately 70% of health insurance appeals are granted. [7] That means, in most cases, appealing is not a waste of the patient's time. However, without the physician's help and advocacy, appeals are difficult, if not impossible.

Yet, not all physicians know what to say to an insurance company. For example, when one physician was sent a denial of coverage for a 30-day supply of ondansetron (Zofran), and the patient asked her to call her insurance company and appeal the denial, the physician's response was "what do you want me to say?" In this case, the patient was also a patient advocate, and could coach her doctor through the appeal by telling her to explain that everything else had been tried and failed, and that intractable nausea required this medication. But what happens to a patient whose physician does not know how to be an advocate?

There are at least two main categories of appeals: ***medical necessity appeals*** and ***experimental/investigational appeals*** due to the nature of the medicine, device, or other treatments. For medical necessity appeals, the physician and patient must highlight the particulars of the patient's medical condition, and why a given condition requires a specific medication. As an example of a ***medical necessity appeal***, a patient who develops nausea from generic sulfasalazine but tolerates enteric-coated brand name sulfasalazine may initially have the brand name drug denied. However, a brief letter from the physician describing the precise adverse event to the generic medication, and the need for the brand name drug will usually result in approval by the insurance company. Here, both forms of the medication have similar proven efficacy, but one form is medically necessary because it is better tolerated by the patient.

The second category, ***experimental/investigational appeals***,[8] typically occurs with a newer, more expensive therapy that is beginning to enter the armamentarium of accepted treatments, or perhaps a medication that is being used off-label, including medications that are approved for adults but not yet for the pediatric population. Typically, in this circumstance, the physician has access to published literature that supports a claim that a given medication or treatment will help their patient. However, the insurance company or other payor either is unaware of the published literature or does not feel the evidence in support of this new treatment is sufficient to provide reimbursement. For this reason, the

[5] Hay JW, Hay AR. Inflammatory bowel disease: costs-of-illness. J Clin Gastroenterol 1992; 14:309–17.

[6] Cohen RD, Larson LR, Roth JM, Becker RV, Mummert LL. The cost of hospitalization in Crohn's disease. Am J Gastroenterol 2000; 95:524–30.

[7] Block S. Don't take it lying down if your insurer refuses to pay. USA Today Sept 1, 2005. 2005; State of Connecticut's Office of the Health Care Advocate. Connecticut survey of managed care. Available online at http://www.ct.gov/oha/cwp/view.asp?a=2277&q=299978. 2002.

[8] Some insurers characterize these as medical necessity appeals. However, regardless of the label the insurer places on the denial, when an insurer denies coverage on the ground that a service has not been studied adequately, our advice regarding the content of the appeal is the same.

payor denies coverage and refuses to reimburse for therapy. This type of appeal (appeal of coverage denial) is the more difficult. The physician and patient must demonstrate that the patient has failed other conventional treatments, highlight the patient's specific need for the novel therapy requested, and provide published, peer-reviewed literature and supportive information that support the novel treatment's safety and efficacy.

When writing a letter of appeal to an insurance company, it is very important to not let the insurer equate "off-label use" with "investigational" use. When the FDA approves a medication for use, they typically approve it for one very narrow indication. An "indication" implies a specific disease, condition, or age group. For example, The FDA may approve a medication for patients with ulcerative colitis over 18 years of age. However, that does not mean the medication should be restricted to that population. According to the American Academy of Pediatrics, "the term off label does not imply an improper, illegal, contraindicated or investigational use. Therapeutic decision making must always rely on the best available evidence and the importance of the benefit for the individual patient" (AAP committee on Drugs, Off Label use of drugs in Children. Pediatrics 2014; 133:563–7).

When appealing the denial of coverage of a treatment that the insurer states is off-label, experimental or investigational, the essential tool for obtaining approval is the appeal letter/letter of medical necessity. In summary, the physician should first describe the patient's illness in detail. The history should include the approximate date of diagnosis, and the effects on the patient's life (including a history of prior hospitalizations and surgeries). Other more conventional medications that have been utilized should be described, and why are not being used now (e.g., lack of efficacy, adverse effects). Peer-reviewed literature supporting the medication the patient now needs should be attached to the appeal. Insurers tend to appreciate longitudinal trials in which patients are followed for a significant period of time, and which involve placebos. This may well be impossible in all cases; for example, if a patient or physician is seeking coverage for a medical device, there may not be a functional equivalent of a placebo that ethically could be used. However, the best literature will be peer-reviewed articles published in medical journals documenting randomized trials in which the treatment is compared to a control group of some kind. Other evidence, including open-label trial data or recent proceedings from medical meetings may also be useful, but will not carry the same weight.

According to one publication, the range of off-label medication use in pediatrics can range from 10% to as high as 80% (Gore et al., Curr Clin Pharmacol. 2017;12:18–25). Because testing medications through clinical trials in pediatrics can be challenging, there is often a lag time of several years between the approval of an effective medication in adults, and the subsequent pediatric approval. Therefore, when one faced with a sick patient and a limited number of options, off-label use is often a medical necessity. In addition to the documentation of the medical necessity of off-label use, given the lack of FDA-approved medications for inflammatory bowel disease, society position statements will also help bolster the case for off-label use to payers. According to the 2014 American Academy of Pediatrics statement on off-label medication use, "the term "off-label" does not imply an improper, illegal, contraindicated, or investigational use. Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient."

If feasible, the physician also should obtain a letter of support from experts in the field stating that the proposed treatment plan is appropriate. In one instance, a physician prescribed adalimumab for ulcerative colitis, and coverage initially was denied as "experimental, investigational or unproven." In this case, once the payor was provided with sufficient information regarding the patient's ulcerative colitis, the failure of other treatments, and the medical literature supporting the efficacy of adalimumab for this condition, they agreed to reimburse for the necessary treatment.

A third type of denial by insurers is an **administrative denial**. Administrative denials do not involve a medical necessity determination. This type of denial occurs when there is a coverage request for a treatment that is expressly excluded from coverage. For example, if an insurance policy expressly excludes abdominoplasty as a cosmetic surgery, a coverage request for abdominoplasty will be denied without regard for medical necessity. Even in this type of case, though, it is possible to force an insurer to conduct a medical necessity review, for example, if a patient requires a medically necessary stoma revision and hernia repair that cannot be performed without the abdominoplasty, the physician may be able to convince the insurance company to consider the medical necessity of the abdominoplasty as long as the insurer agrees that the stoma revision and hernia repair are medically necessary.

Regardless of the type of appeal, there are some general considerations. Insurers will not grant benefits solely based on a patient's subjective report of symptoms. The physician and patient in describing the indication for the appeal must provide "objective medical evidence" (i.e., evidence that can be measured scientifically). In addition to describing the patient's current symptoms (i.e., abdominal pain, diarrhea, fatigue), the physician should provide results of recent blood tests, radiographs, and endoscopic examinations that demonstrate ongoing intestinal inflammation. In addition, if a patient develops an adverse event (AE) to a conventional therapy, the AE should be described in detail (e.g., not simply "infusion reaction to infliximab" but "chest pain and hives with infliximab, which recurred on rechallenge"). While the provider should not ignore the patient's subjective

reports of symptoms, subjective evidence of ongoing disease activity may not be sufficient to prove medical necessity. A physician who writes a letter of medical necessity according to the above guidelines (summarized in Appendix 2) stands a good chance of getting the needed treatment covered. Appendix 3 includes a recent letter from our program requesting a peer-to-peer review on a child who repeatedly had ustekinumab (Stelara) denied by insurance, despite multiple phone calls from the office to the company and specialty pharmacy. This letter resulted in a successful appeal and provision of the medication.

Increasingly, insurance companies and payers are proposing that infusions of biologics be moved to inside the patient's home, rather than an infusion center. This is a smaller cost for insurance companies, but carries significant yet unquantifiable risk for the patients. Many parents may not understand risks and benefits, and we as providers may not know who precisely is administering the infusions. There are regulatory licensing issues that cannot be verified the In-Home Service Agency (IHSA), especially in regard to being licensed to provide this service to children. The IHSA staff would need to know how to get in touch with the on-call providers at a patient's provider office, and there can be significant documentation and thus continuity of communication disruption do after an infusion. It is not always clear if needed labs be drawn, which is important to consolidate into the infusion for patients with needle phobia, and if so, how the results are reported. It is difficult to know how about adverse events are shared with relevant teammembers, and what mechanisms are in place to determine if the patients feel safe and satisfied with the care/infusions that they are receiving. Pragmatic considerations include patient safety, pediatric-trained nurse availability, care coordination, patient-centeredness, shared liability, administrative support, clinical governance, and costs of care.

In pediatrics, documentation has been successful in illuminating these concerns and the implication to children. While clinical guidelines have been established by North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition[9] for assuring safe protocols and pathways for home infusions, significant advocacy can help maintain the administration of these in certified and qualified infusion centers affiliated with the provider, and staffed by trained infusion nurse and nurse practitioners (see Appendix 4).

Nutritional approaches for IBD have included total parenteral nutrition, specific dietary exclusions, partial enteral nutrition (EN), and avoidance of all dietary intake using Exclusive Enteral Nutrition (EEN). Avoidance of all dietary intakes using EEN has been shown to be superior to partial EN when the additional oral dietary intake is not controlled.[11] In small controlled studies, EEN has been shown to be superior to steroids in achieving mucosal healing, while being notably free from important adverse events. For providers and caregivers alike, there may be preference to avoid steroids, especially in children with already delayed pubertal growth or preexisting comorbid psychiatric disorders. However, the cost of EN and EEN can be costly, making it hard for families to afford.

Advocacy documentation that clearly outlines the substance and nutritional rehabilitation and growth parameters are helpful to obtain insurance coverage. When EEN is able to be justified as the primary source of all nutritional intakes, there is a great chance of coverage. Data from studies that show mucosal healing are important in these advocacy letters of medical necessity.

Another area in which letters of medical necessity may be necessary is in obtaining mental health referrals for patients with IBD. Given the stress of IBD and the social stigma associated with its symptoms (rectal bleeding and diarrhea), the risk for exacerbations of IBD during periods of stress, and the mood-altering effects of medications, patients with CD and ulcerative colitis ("UC") often derive significant benefit from psychological support. We are aware [9] the there are often significant associated psychological and social effects resulting from both short-term and long-term steroid use, including mood lability, mania, anxiety, and symptoms mirroring those of depression. Many children with IBD not only have to cope with the unpredictable impact of these emotional ramifications, but also the body image issues that are often secondary to side effects of the unavoidable and recurrent steroid administration necessary to keep the disease process controlled. Studies have demonstrated that a significant proportion of adolescents and young adults with IBD have symptoms of depression, which in turn contribute to decreased quality of life.[5,6,10] Most payors are receptive to the concept that treatment of a chronic illness in childhood requires psychological as well as medical support. On occasion, however, payors will deny mental health services on the grounds that coping with IBD does not warrant formal treatment by a psychologist or psychiatrist. Health care providers caring for children with IBD are acutely aware that anxiety and depression may impact both disease activity and compliance with the medical regimen. Thus, properly timed psy-

[9] Barfield, E. et al. Assuring Quality for Non-hospital-based Biologic Infusions in Pediatric Inflammatory Bowel Disease: A Clinical Report From the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Journal of Pediatric Gastroenterology and Nutrition: April 2018 - Volume 66 - Issue 4 - p 680–6.

[10] Szigethy E, Levy-Warren A, Whitton S, et al. Depressive Symptoms and Inflammatory Bowel Disease in Children and Adolescents: A Cross-Sectional Study. J Pediatr Gastroenterol Nutr 2004; 39:395–403; Engstrom I. Mental health and psychological functioning in children and adolescents with inflammatory bowel disease: a comparison with children having other chronic illnesses and with health children. Journal of Child Psychology and Psychiatry and Allied Disciplines 1992; 33:563–82.

chological or psychosocial intervention often is a crucial factor in overall the treatment success and likelihood of a prolonged remission.

Appealing a denial of psychological support is similar to appealing a denial of any other medically necessary therapy. A letter from the medical team should summarize relevant literature that describes the psychological needs in patients with IBD. The letter also can emphasize the complex relationship between a patient's GI condition, mental health, compliance, and quality of life. It should be emphasized that a patient who is psychologically sound is less likely to undergo recurrent testing and hospitalization for a symptom related to stress and anxiety, all of which [11] would be more costly for the insurance company. This usually is a sufficient reason for insurers to grant limited benefits. While a limited series of sessions is not ideal, these sessions at least allow the patient to gain entrance into the mental health system. At that point, a mental health provider can then determine further indications for ongoing treatment (see Appendix 5).

In one instance, a 14-year-old patient with Crohn Disease had a complicated course of her illness, having been hospitalized twice for unpredictable flares of her disease and a blood clot in the venous portion of her brain, both times leading to lengthy admissions followed by intensive outpatient follow-up. Her illness' sporadic and inconsistent response to her treatment plan led to periods of intense stress and pressure, thereby exacerbating symptoms of her disease. The family lived in a small town in a different state from the one in which her gastroenterologist practices, and the only local mental health providers available practiced from a more psychotherapeutic framework. Her insurance company would not cover services at the urban hospital's specialized medical coping clinic, which was out-of-network for mental health services, yet which provided the specific cognitive behavioral approach that the medical team and family felt would be the best fit for her targeted goals of learning relaxation strategies and coping with the present medical demands. The social worker and physician composed a letter to the insurance company outlining the patient's specific circumstances, the physical and psychological complications, and the importance of the patient obtaining mental health services that were based on a framework specific to her needs at that time. The letter detailed that the clinic specialized in treating children and teenagers with treatment specifically geared toward helping management of comorbid medical and emotional issues related to IBD. The appeal highlighted that the patient's access to particular cognitive-behavioral strategies could reduce the risk factors for a necessary and more costly medical or psychological hospitalization, and the unavailability of access these services through local providers covered under the plan. Her insurance company ultimately authorized coverage for ten treatment sessions, allowing her to learn biofeedback and other concrete mechanisms to help her best cope with the concurrent medical challenges, and provide a forum for ongoing formal assessment and treatment of depression or an anxiety disorder related to the disease process.

Although a good result was achieved in this case, what happens if denials continue to occur? At this point, it may be appropriate to have your patient enlist the assistance of an individual with expertise in conducting health insurance appeals, such as a patient advocate or an attorney. Under the Patient Protection and Affordable Care Act (ACA), all insurance plans must now offer what is called an external appeal. External appeals involve an independent review of the noncoverage decision. All decisions involving the exercise of medical judgment—and in some states, even administrative denials—are subject to external appeal. The independent reviewer, who will be a medical professional with the relevant expertise, has the authority to overturn the insurer's denial of coverage. Thus, do not give up if your first level appeal is denied. Many of the more complex cases—especially those deemed experimental/investigational by the insurer—will be won at the external appeal stage.

Also under the ACA, every state has a Consumer Assistance Program (CAP) to help consumers with insurance appeals. The CAP in your state may be in your state's Insurance Department, or it may be a separate entity. These CAPS are funded largely by federal grant funds.

Finally, under the ACA, as well as under pre-existing law, the insurer must offer to provide a free copy of the materials upon which they relied in denying coverage. In addition, upon request, they have to provide diagnosis and procedure codes so that you can ensure that the denial is not due to a billing error. If you have any question about the reason for the denial of coverage, you or your patient should request a copy of the insurer's file.

Many insurers maintain their clinical policy bulletins on the "provider" section of their website; if not, you are entitled to a copy by mail. If you have a denial based on the fact that the insurer does not believe the treatment you have prescribed is medically necessary or experimental/investigational, you should search the insurer's website for the clinical policy bulletin on point, which will explain exactly when the insurer believes the treatment is or is not medically necessary or experimental/investigational. Note the date on which the clinical policy bulletin was reviewed last, as well as the medical literature on which the insurer relied in formulating its coverage policy. This will suggest the points that you will need to address in your appeal.

[11] Van Limbergen, J et al. Toward enteral nutrition in the treatment of pediatric Crohn disease in Canada: A workshop to identify barriers and enablers. Can J Gastroenterol Hepatol. 2015 Oct; 29(7): 351–56.

If a physician and patient are both frustrated by repeated denials of a treatment thought to be medically necessary, consider three steps:

1. Have your patient discuss the difficulty with the human resources department at their employer, especially if they work for a large employer that self-insures. The employee can ask the employer to grant what is called an "extra-contractual benefit," providing coverage for something that otherwise would not be covered.
2. Request a copy of the insurance company's file, which is guaranteed by law. This information may be valuable in the future.
3. Consider referral to an attorney or patient advocate.

Health insurance appeals can be labor intensive. In addition to the patient's physician, a team of professionals (including nurses, social workers, therapists, and attorneys) may need to assist in preparing the appeal. However, in the United States in 2011, effective advocacy to explain medical needs to third-party payors has become an essential element of care of complex patients.

Of note, insurance appeals and letters indicating medical necessity are getting more complicated, seemingly obstructive and nuanced than ever. There are additional roadblocks that necessitate uninterrupted, coordinated clinician advocacy and data of what is at often avoidable medical stake for patients with risk and impact to safe wellbeing. The impact on physician and provider time is tremendous; pre-prepared data from multiple providers in a practice, outlining the safety implications to children may improve response from payers and insurance companies. Amplifying this to local legislators and state representatives may be indicated.

Social Security Disability

Many people do not realize that children may be eligible for Supplemental Security Income ("SSI"), one of two forms of Social Security disability benefits. [12] However, medically impaired children up to the age of 18 may receive benefits if the income and resources of the parents and child are within allowed limits, as long as the parent worked long enough to be insured under the Social Security system (typically, 40 quarters, or a total of 10 years, with 20 of those quarters occurring in the last 10 years). The child must not be doing any substantial work, and must have a medical condition that has lasted or is expected to last for at least 12 months. A child eligible for SSI will qualify for Medicaid.

Whether a child is considered disabled depends on whether he or she has a physical or mental condition that can be medically proven and which results in marked and severe functional limitations that last or are expected to last at least 12 months. A physical or mental condition that results in marked and severe functional limitations might be one that meets the applicable listing of impairments (see Appendix 6), or it might involve a combination of impairments (for example, Inflammatory Bowel Disease and Attention-Deficit Hyperactivity Disorder, or IBD and depression).

Although both the income and the benefit levels for SSI are low, the value of Medicaid is great for children with IBD. While some physicians do not accept Medicaid assignments, Medicaid coverage for children under the Early and Periodic Screening, Diagnostic and Treatment services ("EPSDT") is extraordinarily broad—broader than most commercial insurance, especially for children with mental health and even dental needs.

In order to assist a family to apply for SSI, the health care provider should consult the listings of impairments set forth in Appendix 6 and write a letter that addresses each element of the listing. The listing itself tells you what sorts of evidence the Social Security Administration ("SSA") will need. For all intents and purposes, this is the same as the "objective evidence" needed in commercial insurance appeals, the listings may require specific testing. For example, the listing for malnutrition associated with a gastrointestinal problem requires a measure of stool fat excretion, even though the current medical standard may be other diagnostics, such as blood tests. Therefore, while the physician is can include any diagnostic testing relevant to the patient's case, he/she should expressly include the diagnostic testing required by the SSA.

Although the SSA will ask you for your medical records, a letter of support that culls the records and explains the child's condition in the terms set forth in the listings of impairments may well be the key to obtaining these benefits. A physician who is asked to write a letter in support of an application for SSI should track the listings of impairments as closely as possible and attach the evidence that the listings mention. The physician or provider who facilitates this process, and who helps successfully obtains SSI benefits for a patient who needs such assistance, is playing a critical role in improving the likelihood of the success of the prescribed treatment plan.

In addition, an integral part of living with any chronic illness is to help in maintaining self-identity, so that self-esteem and feeling victimized by the disease demands does not disempower the patient. As health care providers, we want to attempt to help the patient preserve that sense of control and self-esteem, and thus avoid an internalized notion of a "disabled" self-concept. This is another reason to help make the

[12] The other form of Social Security disability is called Social Security Disability Income, or SSDI. This benefit is available only to patients who have worked and paid into the Social Security system for 40 credits, or 40 quarters (10 years). As such, this benefit is available only to adults.

process of securing entitlement from these state programs as efficient and seamless as possible. The burden of having to go to such lengths to prove disability can often take on a life of its own in the pursuit, and this would be counterproductive to the message we reinforce—the child as a whole person, who is more than the disease. Health care providers, who can facilitate the SSI application to prevent a lengthy proof process, can be doing their part to help preserve this message.

Family and Medical Leave for Caregivers

Caregivers of children with IBD risk losing their jobs when they take time off to care for their children. Providers may be able to spare them this crisis by educating them on the availability of, and helping them to obtain leave and maintain employment security under, the Family and Medical Leave Act ("FMLA"). [13] Covered employers must grant an eligible employee up to a total of 12 work weeks of unpaid leave during a 12-month period to care for an immediate family member (spouse, child, or parent) with a serious health condition. The FMLA applies only to an employee who has been working for the same employer for at least 12 months, for at least 1250 h during the previous 12 months, and at a location where at least 50 individuals are employed by the employer within a 75-mile area.

A child has a "serious health condition" if he or she is "incapable of self-care" due to a mental or physical disability that limits one or more of the "major life activities." Just as is the case under the Americans with Disabilities Act, processing of bodily waste is a "major life activity," so children with active IBD have a "serious health condition" under the FMLA.[9] Even if symptoms are inactive, children with an IBD diagnosis have the potential to require this care, due to the cyclical nature of chronic illness. The FMLA does not provide for paid leave. In addition, an employer may permit an employee to use all available accrued but unused vacation, sick, or PTO time during such leave. The use of other such leave does not extend the time off beyond 12 weeks.

One of the lesser-known aspects of the FMLA is that the 12 weeks of leave need not be consecutive. For example, a parent of a child who is in infliximab treatment can take a day or 2 of leave every few weeks under FMLA.

Primary caregivers of children with IBD should ask for FMLA leave at the beginning of every year, whether or not they use it, so that they are protected if the child's disease becomes active. In order to obtain FMLA leave, the employee must request it in writing, and the physician often must complete paperwork that employers give the employee and provide a medical certification establishing the need or potential need for FMLA leave. An FMLA medical certification can describe IBD as a serious health condition falling into various descriptive categories. Depending on the symptom severity, demonstrating need for FMLA leave may best be accomplished by the physician. The medical certification supporting the need for FMLA leave is in some ways similar to a letter of medical necessity one prepares for a health insurance appeal (see Appendix 7).

If a physician anticipates, a child will require increased parental care because of the worsening of illness, this should be discussed with the family. Parents who may need to take time off from work should request FMLA leave before the crisis occurs. Parents who do so will protect their jobs as long as they do not take more than the maximum twelve weeks of leave during the year. This job security can go far in helping ease caregiver's anxiety, allowing them to better focus on coping with the child's acute needs and the impact on the family.

Restroom Access Act

Patients with IBD may have a debilitating need to use the restroom urgently, while out in public places. This can be difficult, as not all establishments and business have restrooms designated for public use. In response, the advocacy needs around these unpredictable circumstances, many states have now passed Ally's Law, also known as the Restroom Access Act, to support this medical need.

Ally's Law requires that retail businesses with toilet facilities for employees allow customers with certain medical conditions to access these. The bill was named after a teenager in Illinois with Crohn Disease, who was denied access to a store restroom, and suffered embarrassing consequences. This bill first became law in Illinois in 2005. Ally's Law falls under the Americans with Disabilities Act of 1990.

It typically applies when (1) the retail establishment has two or more employees currently working and (2) the employee-only restroom is in a location that is both safe to the patient and not a security risk to the retail establishment. Some businesses may be exempt from the Restroom Access Act. Those with fewer than three employees, for example, are not obliged to let a customer use an employee toilet as it may leave the store open to damage or theft. The law does not require retail stores to alter their facilities for people with eligible conditions and establishments are also not easily liable if a customer sustains an injury, while using an employee restroom.

A store may require the patient to present a document signed by a medical professional attesting to their IBD. The Crohn's and Colitis Foundation has "I Can't Wait" wallet

[13] 29 U.S.C. § 2601, *et seq.* Many states have their own, more liberal version of family and medical leave. You should consult your State's Department of Labor for more information.

cards that can be provided to patients to carry in their personal belongings and show a store employee.

There has been exciting expansion of this Act. While there are visions of a federal act, currently the following states have passed a version of this: Colorado, Connecticut, Delaware, Illinois, Kentucky, Maine, Maryland, Massachusetts, Michigan, Minnesota, Ohio, Oregon, Tennessee, Texas, Washington, and Wisconsin.

In many cases, these states have passed the Act as a result of grassroots efforts by those with IBD and their supporters. If there is a state that has not passed this Law, anyone can be a champion for this legislation. The Crohn's and Colitis Foundation has a template model of legislation that can be downloaded and submitted to local lawmakers.[14]

Summary

Inflammatory bowel disease affects more than a patient's intestinal tract; it affects their quality of life, including otherwise routine functions of school and work. In addition, IBD affects families, not just individual patients. Therefore, physicians should become familiar with the ways they can help patients and their families overcome the varied hurdles facing children with IBD. In particular, providers should train themselves, or be trained, in how to appeal insurance company denials, assist in the development of a plan of accommodation for a school-aged child, support an application for Social Security benefits, and point out the availability of Family and Medical Leave to caregiver parents. Collaboration with other members of the medical team such as nurses and social workers to address these issues is essential, as is the ability to identify advocacy resources in the community, which may not be specific to IBD. By providing such services, the physician may alleviate some of the financial, educational, and social complications that can turn a flare of IBD into a more serious destabilizing family crisis. The provider who is an effective advocate will derive gratification from the knowledge that they have helped their patient have a better health-related quality of life. Advocacy has and can continue to change the landscape for the health care profession, research science, and patient resources related to IBD. Provider advocacy and public awareness have a reciprocal impact to create real progress and momentum.

Acknowledgement We would like to acknowledge the contributions of two individuals who are no longer with us, and their collaboration in this work. Jennifer Jaff, Esq (deceased), was the principal author of the first three editions of this chapter. She founded and ran Advocacy for Patients with Chronic Illness, Inc., a legal advocacy group that fought vigorously against insurance company denials, and obtained chronically ill patients access to needed therapies. Suzanne Rosenthal was a cornerstone of the legislative advocacy that appeared in prior editions, and informed our own work and commentary. She was one of the original founder of the Crohn's and Colitis Foundation (formerly of America), and a strong force on Capitol Hill to raise awareness of these diseases among legislators and the lay public.

[14] https://www.crohnscolitisfoundation.org/sites/default/files/2019-10/Restroom%20Access%20model%20legislation.docx.pdf

Appendix 1: Sample Letter for Patient's Student File Regarding Educational Accommodations Needed for an IBD Diagnosis

To Whom It May Concern:

This letter is being written on behalf of our patient, **XXXXX (DOB: XX/XX/XX)**, who recently was diagnosed with Crohn Disease, a chronic inflammatory bowel disease of the intestines. As chronic illness is cyclical in nature, XXX can face gastrointestinal symptoms in a recurrent pattern, with periods of symptom inactivity in between active flare-ups and complications. Cramps may be severe and may be worse when there is a need to use the toilet; symptoms may worsen in an unpredictable manner and conversely, may go into remission for varying lengths of time. During a flare-up, this illness will substantially impair the major life activities of bowel and digestive functions. The medical team is currently working to coordinate the long-term treatment plan as the team explores the impact of these symptoms on her body and her body's response to the medication regimen.

Even if a patient no longer requires an inpatient hospitalization, we could expect the patient still to experience ongoing symptoms until the medical team is able to arrange her maintenance treatment regimen. XXX has been seen for her first outpatient follow-up appointment since diagnosis, and the medical team continues to monitor her symptoms, which continue to intermittently interfere with her ability to attend school for a full day.

In the long term, however, with the understanding and support of her teachers and other school personnel, we expect XXX to participate in school activities. When the medical team better determines the best course of maintenance treatment for her, we have no reason to expect that it should routinely interfere with her academic plan or performance. In addition, XXX may be tardy or absent from school from time to time if her condition is flaring. The disease process can affect many aspects of a person's life; depending on the current symptoms, patients can find it difficult to cope as there is an interference with their physical and social functioning.

We feel it would be helpful for XXX's school re-entry to begin in a partial day format, as her body continues to adjust. In the immediate, short term, we believe it is in XXX's best interest that she be eligible for home tutorial services so that her academic studies are not compromised by this acute period of her condition. These services would also be recom-

mended to have in place, should flare-ups occur in the future, causing her to intermittently and unpredictably miss schoolwork.

We know that the emotional and physical pieces are interrelated in complex ways, and patients can experience flare-ups during times of emotional tensions and stress. This can relate to changes in the physiologic functioning of the gastrointestinal tract. While periods of intense stress and pressure can exacerbate symptoms, it is important to note that they do not cause the disease and are not responsible for the development of the illness.

Please understand the extenuating circumstances facing XXX, should the physical or emotional adjustment to the demands of her chronic illness intermittently impact her ability to carry out her academic responsibilities. Please contact XXX with further questions. Thank you for your time and understanding. We look forward to being able to collaborate with the school in any manner that will optimize her future academic and medical plans.

Appendix 2: Preparing an Effective Insurance Company Letter of Medical Necessity

- Patient's Name (and name of insured if not the patient).
- Patient's Insurance ID number, Social Security number, and date of birth.
- The treatment requested and denied.
- Your specialty and years of experience.
- Your experience with the particular device, medication, or treatment.
- The patient's diagnosis including both subjective and objective support for the diagnosis (patient's subjective complaints **plus** weight loss, recent barium study, endoscopy reports with pathology, etc.).
- What treatments have been tried over what period of time (go back to the date of diagnosis and describe all that has been tried and failed, explain the reason for the failure, i.e., failure to control disease, allergic reaction, adverse event such as pancreatitis).
- If device, medication, or other treatment is considered by the insurance company to be experimental, investigational, or unproven, summary of the medical literature, preferably including copies of the literature (both summary and copies of literature are enclosed).
- Why you believe this therapy or service is clinically indicated for this patient at this time.
- Describe your plan to assess treatment efficacy (whether your therapy will help this patient). For example, in a patient with CD involving the ascending colon, state you will follow the patient monthly, and monitor exam, hematocrit, C-reactive protein, and perform a colonoscopy after 6 months to assess mucosal healing.
- Summarize your medically necessary request again, and offer to talk to any health care professional from the insurance company if additional information is needed.

Appendix 3: Letter of Medical Necessity for Ustekinumab

Dear sirs:

I am writing this letter to request a formal outside peer-to-peer review from a pediatric gastroenterologist for the approval of ustekinumab for my patient _____ Using this medication is medically essential in order to treat her severe, refractory Crohn disease, which remains active despite multiple medications and two surgeries, the most recent being a diverting ileostomy.

To summarize her course, _____ developed her Crohn disease at the age of 9. Her disease involves her ileum, colon, and perianal region. She has been treated with mercaptopurine (disease remained active), infliximab (did well initially but developed antibodies in 2010), adalimumab (no response), certolizumab (no response), thalidomide (partial control of her disease but triggered ovarian failure), methotrexate (disease flared), and vedolizumab (no response). She underwent an ileal resection in 2009, and because of her refractory disease underwent a diverting ileostomy in March 2015.

Unfortunately, the patient's disease has recurred, both at her ileostomy and in her perianal region. We admitted her for intravenous corticosteroids, and administered ustekinumab, a monoclonal antibody that has proven efficacy in Crohn disease, based on randomized phase 2 and 3 clinical trials (papers attached). For some reason, while the initial doses of this medication were approved, we subsequently had a denial by a physician reviewer who has no expertise in pediatric gastroenterology.

_____'s insurance has been very supportive in the past, and understands of the severity of this child's illness and the need for treatment. Our medical options are limited, and a panel of experts in this division supports the use of ustekinumab. The patient has also received an outside second opinion by Dr. _____ (another Crohn expert in the region) who supports this approach. If _____ is not treated, her Crohn disease will progress, resulting in additional hospitalizations and surgeries.

I am a pediatric gastroenterologist who is considered a national authority in the treatment of pediatric Crohn disease (see attached CV). I would be happy to speak with anyone from the insurance or any physician reviewer to describe _____'s clinical situation.

Sincerely,

Athos Bousvaros MD, MPH

Appendix 4: Sample Letter to Support Maintenance of Infusion at Infusion Center

To Whom it May concern:

This letter is being written on behalf of XXX (DOB____) for whom a transition to in home infusions has been proposed to initiate a "non-medical switch" from an infusion center that specializes in the care of pediatric and young adult IBD to another provider. This is being done purely for cost saving purposes to benefit the third-party payor. While such moves may save costs in the short term, we strongly oppose the move for quality and safety reasons. We list the reasons below.

1. Our infusion centers have administered over 10,000 infusions to patients over the last decade, and our incidence of infusion reactions is much lower than that reported in the literature. This is due to careful attention to the infusion, patient and physician education, and among the lowest in the country.
2. When infusion reactions do occur, they can sometimes be life threatening. Some of our patients have developed severe reactions requiring epinephrine, saline boluses, intravenous steroids, and emergent assessment by trained physicians. If these types of reactions occur outside of an infusion center prepared to handle them, we are concerned they could result in severe adverse outcomes.
3. The infusion provider requested has not demonstrated they have expertise in the management of inflammatory bowel disease patients, or children with IBD. Such patients often have symptoms of either active IBD or possible infection when they present for their infusions. If the patient has such an issue, our trained infusion nurses and nurse practitioners are capable of providing thorough assessments, having in on call or house physicians provide consultation. In contrast, the home infusion company or provider that lacks experience will cancel the infusion, and/or refer the patient to the emergency department.
4. The situation above may result in interruption of care, with reduction of the frequency of infusions. Such interruption of care is known to be detrimental to patients, and associated with the development of antibodies to infliximab, loss of response to the therapy, and flares of Crohn's or colitis. This may in turn result in a preventable hospitalization or a change to another medications product that may be less effective or more expensive.
5. We have no oversight or input in the quality control of home care companies. We do not know whether the personnel are certified in adult life support, pediatric life support, or management of inflammatory bowel disease. We do not know how the medication is mixed or administered. There is limited collaboration or interaction with these companies. Based on the experience with parenteral nutrition, we do know that these companies often are prone to medical errors, administer incorrect doses of therapies, and that such interventions are associated with adverse patient outcomes.
6. In addition, it has also been documented that "non-medical switching" by insurance companies is associated with adverse patient outcomes in IBD.

Therefore, we strongly oppose the request for XXX on patient safety and quality grounds. If we are approached by a physician that works for the insurance company that makes such a request, we will take the following actions:

1. We will request of the insurance company physician making the request their name, company they work for, subspecialty (adult or pediatric), whether or not they are board certified in adult or pediatric gastroenterology.
2. We will send a copy of this letter to the patient's insurance company and to the insurance company physician.
3. We will inform the patient that the insurance company has requested a "non-medical switch," and that we oppose such a switch, because we have concerns about patient safety implications. We will notify the patient of the specific physician, and the company requesting the switch.
4. We will ask the patient and/or parent to go to the human resources department of the company they work for, and inform them that the insurance company is requesting a "non-medical switch" that is opposed by the patient's subspecialty physician.
5. We will make it clear that any adverse outcomes that result from this switch should be reported to us, to the insurance company, and to the Massachusetts Commission on insurance.
6. We will carefully track such "non-medical switches," and inform patients and the public about adverse events that occur because of these actions.

I am very willing to meet with medical directors of third-party payors to review our data and present our concerns in more detail. Thank you for your consideration.

Sincerely,

_____, MD

Appendix 5: Sample Letter for Appeal of Denial of Mental Health Benefits

To Whom It May Concern:

This letter is being written on behalf of our patient, **XXX (DOB:)**, whom we follow for her diagnosis of Crohn

Disease, a chronic inflammatory bowel disease of the colon and small intestine. We submit this letter in support of her being permitted to receive out-of-network mental health benefits at/through (agency name/private provider) as a clinical case exception. XXX has had a complicated course of her illness, having been hospitalized several times for unpredictable flares of her disease, both times leading to lengthy admissions followed by intensive outpatient follow-up. Her illness' response to our treatment plan has been sporadic and inconsistent, causing great stress on both her mind and body. We know that the emotional and physical pieces are interrelated in complex ways, and patients can experience flare-ups during times of emotional tensions and stress. This can relate to changes in the physiologic functioning of the gastrointestinal tract; we have seen this occur with XXX. Her medical complications have led to periods of intense stress and pressure, thereby exacerbating symptoms. XXX's specific circumstances are physically and psychologically complicated, and it is crucial to be able to integrate the medical and psychiatric services; this will be critical to providing the most comprehensive and cost-effective care.

(Agency name/private provider) specializes in diagnosing and treating children and teenagers with comorbid physical and psychiatric/psychological issues. (Agency) provides and coordinates integrated plans of treatment, including psychopharmacology, cognitive behavioral therapies, and family work specifically geared toward helping in managing these comorbid populations. Studies have shown that this type of integration of medical and psychiatric services can decrease both medical and psychiatric morbidity, and thus medical costs.

XXX's ability to access these services could be essential in reducing the risk factors for a necessary medical or psychological hospitalization. A hospitalization would be much more costly, both financially and in terms of the missed developmental learning opportunities in the social and academic realms.

It is in XXX's best interest to receive ongoing psychological care in a formal clinical model. However, we would request authorization for at least a two-session evaluation so that the formulation and treatment recommendations can be passed on to community psychiatric providers in their network. We feel strongly that the optimal coordinated care plan would include your insurance plan's willingness to authorize 12–14 treatment sessions so that XXX and her family can have access to the specialized skills of (agency/provider), thereby reducing the chances of an emergent, and perhaps more costly, hospitalization.

Please understand the extenuating circumstances impacting XXX. Thank you very much for your time and consideration in this urgent matter. Feel free to contact XXX with further questions. We look forward to hearing your response.

Appendix 6: Social Security Listing of Impairments for Children with IBD

Section 105.00, Digestive Impairments in Children

A. *Disorders of the digestive system* which result in disability usually do so because of interference with nutrition and growth, multiple recurrent inflammatory lesions, or other complications of the disease. Such lesions or complications usually respond to treatment. To constitute a listed impairment, these must be shown to have persisted or be expected to persist despite prescribed therapy for a continuous period of at least 12 months.
B. *Documentation of gastrointestinal impairments* should include pertinent operative findings, appropriate medically acceptable imaging studies, endoscopy, and biopsy reports. Where a liver biopsy has been performed in chronic liver disease, documentation should include the report of the biopsy. Medically acceptable imaging includes, but is not limited to, X-ray imaging, computerized axial tomography (CAT scan) or magnetic resonance imaging (MRI), with or without contrast material, myelography, and radionuclear bone scans. "Appropriate" means that the technique used is the proper one to support the evaluation and diagnosis of the impairment.
C. *Growth retardation and malnutrition*. When the primary disorder of the digestive tract has been documented, evaluate resultant malnutrition under the criteria described in 105.08. Evaluate resultant growth impairment under the criteria described in 100.03. Intestinal disorders, including surgical diversions and potentially correctable congenital lesions, do not represent a severe impairment if the individual is able to maintain adequate nutrition, growth, and development.
D. *Multiple congenital anomalies*. See related criteria, and consider as a combination of impairments.

105.07 ***Chronic inflammatory bowel disease (such as ulcerative colitis, regional enteritis), as documented in 105.00***. With one of the following:

A. Intestinal manifestations or complications, such as obstruction, abscess, or fistula formation, which has lasted or is expected to last 12 months; or
B. Malnutrition as described under the criteria in 105.08; or
C. Growth impairment as described under the criteria in 100.03.

105.08 ***Malnutrition, due to demonstrable gastrointestinal disease causing either a fall of 15 percentiles of weight which persists or the persistence of weight which is less than the third percentile (on standard growth charts)***. And one of the following:

A. Stool fat excretion per 24 hours:
   1. More than 15 percent in infants less than 6 months.
   2. More than 10 percent in infants 6–18 months.
   3. More than 6 percent in children more than 18 months; or
B. Persistent hematocrit of 30% or less despite prescribed therapy; or
C. Serum carotene of 40 mcg./100 ml. or less; or
D. Serum albumin of 3.0 g./100 ml. or less.

Appendix 7: Preparing an Effective Letter for Family Medical Leave Act provisions

- Caregiver/parent's name (employee).
- Patient's name.
- Patient's diagnosis, date of diagnosis, length of treatment—chronic illness requires lifelong medical attention of some level.
- If relevant, recent or upcoming overnight stay in a hospital including estimation of incapacity after discharge home.
- Explain incapacitation as inability to attend school or perform other regular daily activities during the times of hospitalization, recovery, or scheduled outpatient medical procedures.
- All occasions and specifics of ongoing and continued treatment by a health care provider as an outpatient, specifically outlining caregiver's responsibility for medication administration, monitoring and reporting of bowel habits at home, coordination with other sub-specialty providers, as applicable.
- Phrases indicating episodic, intermittent, unpredictable, cyclical nature of the IBD disease process, with the need for ongoing, periodic outpatient visits.
- Emphasis of importance of the caregiver being present at these visits for active and ongoing discussion with the medical team to be able to participate in progressive treatment plan decisions that impact the child.
- Explanation that child's intermittent incapacity may cause the caregiver to work intermittently or on less than a full schedule.
- Identification of any potential future treatment or collateral providers in the child's care, including medication infusion at a day hospital center, routine exploratory procedures, imaging studies.
- Anticipate the potential involvement of radiologists, laboratory technicians, infusion center staff, physical therapists, dieticians, mental health professionals, so that if a caregiver has to accompany a child to an appointment with one of these providers, without your presence, it can still be validated by the employer as qualifying for FMLA hours.
- Specification that child requires basic medical assistance for medical decision making, transportation to appointments, and psychological comfort to assist in the management of the impact of the treatment regimen, given the interruption to daily functioning, and the invasive nature of portions of the treatment plan.

Transition from Pediatric to Adult Care

61

Jonathan Moses and Sandra C. Kim

Introduction

Transition of care is emerging as an increasingly important area of care in patients with chronic conditions including inflammatory bowel diseases (IBD). Transition from pediatric to adult care is not simply a transfer of patient care from one provider to another. It is a dynamic process defined as the purposeful planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health-care systems [1]. Education, communication, and preparation promote self-management skills, confidence, and independence, which help ensure a successful transition. Effective transition requires a multidisciplinary and coordinated approach to ensure successful "graduation" which is marked by independence, effective self-management, and establishment of care with an adult gastroenterologist and adult medical care team. Several medical societies and groups have issued consensus statements regarding the need for coordinated and well-planned transition for adolescents and young adults with chronic medical conditions [2–5]. According to the American Academy of Pediatrics (AAP), the transition should address the following: (1) Ensure that all young people with special health-care needs have an identified health-care professional who attends to the unique challenges of transition and assumes responsibility for current health care, care coordination, and future health-care planning; (2) Identify the core knowledge and skills required to provide developmentally appropriate health-care transition services to young people with special health-care needs and make them part of training and certification requirements for primary care residents and physicians in practice; (3) Prepare and maintain an up-to-date medical summary that is portable and accessible; (4) Create a written health-care transition plan by age 14 together with the young adult and family. At a minimum, this plan should include what services need to be provided, who will provide them, and how they will be financed. This plan should be reviewed and updated annually and whenever there is a transfer of care; (5) Apply the same guidelines for primary and preventive care for all adolescents and young adults, including those with special health-care needs, recognizing that young people with special health-care needs may require more resources and services than other young people to optimize their health; (6) Ensure affordable, continuous health insurance coverage for all young people with special health-care needs throughout adolescence and adulthood [3]. A recent 2018 update to these guidelines from the AAP introduced the "Six Core Elements of Health Care Transition" to serve as a template for individual institutions in the transition of pediatric patients to adult care [6] In addition, the clinical report discusses further integration of the transition process into the health-care system by using quality improvement tools, along with the development of unique billing codes to allow for fair compensation of these services and effective tracking of transition-related interventions.

Similarly, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), the European Crohn's and Colitis Organisation (ECCO), and the Crohn's and Colitis Foundation have issued specific statements regarding the transition of care for adolescents with IBD [7–9]. NASPGHAN recommendations for the practitioner suggest the following: (1) The pediatric gastroenterologist should begin seeing adolescent IBD patients without their parents to build a relationship promoting independence; (2) Introduce the patient and family to the concept and benefits of transition; (3) Identify a skilled gastroenterologist who cares for young adults and recognizes the different set of expectations that young adults with childhood-onset IBD have versus those recently diagnosed

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with IBD; (4) Prepare a detailed medical letter and brief medical summary for the new adult gastroenterologist; (5) Recognition that the timing of transition requires flexibility due to individual special circumstances. These guidelines address a number of issues adolescents with IBD encounter, including the process of moving from parental oversight to independence and self-reliance and transferring care from the nurturing medical care approach commonly seen in pediatric care practices. Other factors that should be incorporated into the transition process include the need for both parents/guardians and pediatric health-care providers (including physicians, nurses, and many other health-care providers) to relinquish caregiver roles of young adults living with a chronic illness and to facilitate successful transfer of care to an adult subspecialist.

Despite these useful guidelines, there is still no "gold standard" or defined best practices for transition of care in IBD, highlighting the need for more research on this vulnerable population [10]. In this chapter, we will outline the recommendations for transition of care in IBD, unique features of the adolescent IBD population, barriers to transition of care, and approaches, skills, and tools that can facilitate a successful transition to adult IBD care.

Background

Although there is growing emphasis on the transition of care for adolescents with chronic medical conditions, there is a relative lack of data about which approaches and models work best in adolescents and young adults (AYA) with IBD [11] although there has been increasing interest in this area. Despite variability in processes between institutions, transition of care for young adults with IBD is important for several reasons. First, up to one-third of parents and one-fourth of teens are apprehensive about transition to an adult provider [12]. Second, youth with IBD have diminished health-related quality of life (HRQOL) [13] that can dramatically increase during adolescence when they are especially vulnerable to psychological stress [14]. HRQOL is a vital aspect of patient care, patient–physician communication, and shared decision-making, with data suggesting worse HRQOL correlates with more negative feelings by AYA with IBD toward the transition process [15]. Finally, a well-planned and coordinated transition to adult care has been shown to improve outcomes in patients with other chronic diseases, with newer data accumulating over the last several years specifically for patients with IBD [10, 14, 16–18]. Factors associated with successful health-care transition include starting the process early, having family members and health-care providers foster personal and medical independence, and confirming that the young adult verbalizes the desire to function in the adult medical world [19]. Recent data using self-determination theory demonstrated factors such as competence (feeling effective) and provider relatedness (support for autonomy from others) can predict transition readiness [20].

The ultimate goal is a prepared, proactive healthcare team and an informed, active patient—a concept particularly applicable to patients with IBD. Evidence supports the idea that pediatric and adult-oriented medical practices represent two different medical subcultures. If young adults and family members are not well prepared for participation in the adult health-care system, they will have trouble with this transition and may not receive the care they need [19]. There is recognition of a "vulnerable" period after transfer of care, and prior to establishing with an adult provider, which can result in poor outcomes for AYA patients, including transfer failure rate of up to 12%, higher utilization of the emergency department for medical care, and increased rate of hospital readmissions [21, 22].

Challenges and Barriers to Transition for Adolescent IBD Patients

Researchers have begun to identify specific barriers to transition in teens and young adults with IBD. These barriers include differences in pediatric-onset versus adult-onset IBD, differences between pediatric and adult care, psychosocial factors, treatment adherence and poorly developed self-management skills, attachment to pediatric providers, individual maturity, and readiness for transition. Recently, two different groups found that patient and parent/guardian attachment to pediatric providers was among the most significant barriers to transition [23, 24]. Not surprisingly, multiple studies have also found that patients with emotional and cognitive delay faced additional challenges in the transition process [23, 25].

Differences between pediatric- or adolescent-onset IBD and adult IBD can also have a significant impact on the transition process. Although pediatric- and adolescent-onset IBD is common, occurring in roughly 20–30% of all cases [26, 27], there are significant differences in pediatric and adolescent disease presentation and severity; most notably, pediatric/adolescent IBD is more aggressive and extensive [28–30]. Van Limbergen and colleagues found patients with pediatric-onset disease were almost twice as likely to have extensive ulcerative colitis (UC) compared to those with adult-onset disease. Similarly, among those children with Crohn disease, 40% had extensive disease compared to 3% of their adult counterparts. Surgery within 10 years of diagnosis was twice as common in pediatric-onset UC. Although there was less surgery in pediatric-onset CD, more than one-third required surgical intervention within 10 years of diagnosis [30].

Goodhand et al. demonstrated that compared to adults, teens have more severe disease. Adolescents were more likely to be on azathioprine (46% vs. 17%, $P < 0.0001$) or infliximab (20% vs. 8%, $P < 0.05$). Furthermore, teens were more likely to require hospitalization (46% vs. 14%, $P < 0.0001$). This is further complicated by the fact that teens were significantly more likely to miss medical appointments than adults (median appointments missed: adolescents 20% vs. adults 0%; $P < 0.0001$). The authors concluded that earlier-onset IBD is more complex, and, therefore, specific adolescent transitioning clinics should be established [28]. This highlights the need for additional research to better understand outcomes and the natural history of IBD in this unique group that spans both the pediatric and adult populations.

Treatment adherence and self-management are key skills that teens must master during the transition process but are often difficult for AYA [31–33]. Several studies have identified barriers to adherence in adolescents that include the following: forgetting to take medications [34], lack of time, feeling well, medication side effects [35], and therapeutic regimen complexity [36]. These barriers can be further exacerbated by the patients' underlying anxiety and depression [34]. In addition to adherence, teens must develop a wide range of self-management skills often lacking in teens with IBD prior to "graduation" from their pediatric provider. Fishman et al. surveyed teenagers aged 16–18 years and found that only 43% confidently knew their medication name and dose and even fewer knew about important side effects. In addition, AYA relied heavily on parents to schedule appointments (85%), request refills (75%), and contact providers between visits (74%) [31]. In a follow-up study, Fishman and colleagues surveyed 294 youth (10 years and older) and found that although 95% could name their medication, just over half knew the correct dose and less than one-third could report a single major side effect [37]. Although self-management skills and independence have been shown to increase with age, they do not necessarily correlate with disease duration, reinforcing the complex nature of teaching skills to teens with IBD [33, 38]. Newer tools measuring self-efficacy and resilience are being studied in an effort to identify assessment tools independent of the patient's chronological age that could potentially be more reliable in predicting successful transition to an adult provider [39].

Differences in approaches to pediatric and adult medical care can have a profound impact on the transition process as well. Hait and colleagues point out pediatric care tends to be multidisciplinary and family focused requiring parental direction and consent. On the other hand, a single physician often provides care in adult medicine; the relationship involves shared decision-making exclusively between the patient and provider rather than the entire family. The adult health-care clinic visit is patient focused, and the provider expects the patient to be autonomous and independent [40].

A survey of adult gastroenterologists in 2009 reported that 51% had received an inadequate medical history from pediatric providers, 55% of young adults with IBD demonstrated deficits in knowledge of their medical history, and 69% did not know their medication regimens [40]. The authors suggested educating the young adult IBD patient is essential but not a substitute for delivering an accurate medical history to the adult provider. In contrast to this survey of adult gastroenterologists, a French survey of 48 young patients with IBD (and their parents) who had transitioned from pediatric to adult care revealed that the majority (85% of patients and 74% of parents) felt they were ready for transition to adult care [12]. Only 22% of patients and 32% of parents were apprehensive of the process. Of the 57% who attended a joint medical visit with the pediatric and adult providers, all considered it beneficial for transmitting records and most (93% of patients and 100% of parents) considered it beneficial for building confidence in the new gastroenterologist, highlighting the benefit and need for more transition clinics. Priorities for a successful transition can also vary greatly between stakeholders, with discordance being demonstrated between patients, caregivers, and physicians, further complicating the process [41, 42].

Transition Steps

The appropriate age to begin teaching these skill sets will vary with each patient's level of maturity and interest. A recent survey of patients and caregivers by Maddux and colleagues reported the majority of respondents chose 16–17 years of ages as the best time to initiate the discussion on transition [42]. However, most societal recommendations endorse starting by age 12–14 years to give the patient and family adequate time for the process and allows each patient the opportunity to gradually assume more responsibility for taking care of their own unique problems. The skill sets involve accruing knowledge (education), developing self-management skills based on that knowledge (focus on independence), and understanding the mutual impact of inflammatory bowel disease and lifestyle decisions on future health and well-being. This process should be tailored to the individual patient based on their needs.

NASPGHAN, the National Alliance to Advance Adolescent Health, and others have made useful planning and readiness checklists to help facilitate the successful transition to adult care (GotTransition.org [43, 44]; NASPGHAN [45]).

Overview of the Transition Process

A number of tools, checklists, and planners to facilitate the transition process and transfer of care are described in Table 61.1. It is important to remember that the process should be tailored to the individual patient and family and may need to be adapted according to factors such as insurance, location, and post-high school plans.

Patients (Age 12–14)

At this age, the patients should be introduced and educated on the idea of transition and begin steps to prepare themselves toward this goal. There are two skill sets that should be attained for this age group.

Skill Set 1

Knowledge related to their illness: This first step is designed to help patients learn about their specific disease, either Crohn disease, UC, or IBD-unclassified (IBD-U). The patient should be able to articulate they have IBD, including both gastrointestinal and extraintestinal symptoms, and recognize when they are having a flare and what might be precipitating the flare (diet, stress, other medications, etc.) and when they should visit their physician. The child should be able to express the impact of his/her disease on daily functioning at school, socially, and at home. Providing handouts with these key points and specific age-appropriate websites can help patients develop resources for ongoing education and new information (e.g., https://www.crohnscolitisfoundation.org/justlikeme).

Skill Set 2

Knowledge related to medications: This step includes information about specific medications they are taking (name, dose, why they are taking the medication, timing of each dose, possible side effects) and establishing a plan to take medications on their own without being reminded. This step is also crucial as a first step in preventing the lapses in adherence to medication, which occurs quite frequently at this age and throughout adolescence [32]. Bell has also noted that adolescent risk taking, magical thinking, and denial can all contribute to poor treatment adherence [49]. Patient education and problem-solving skills training are key approaches to overcome these issues, as is having a positive relationship with health-care providers and family members [50, 51]. Because increased authority from parents and professionals, overprotection, and sick role in teens with chronic disease may lead to learned dependency [49], this is a good time to begin to promote independence by setting a date when the

Table 61.1 Transition resources and tools

Educational resources and transition guidelines for providers
"A case-based monograph focusing on IBD: Improving health supervision in pediatric and young adult patients with IBD" (NASPGHAN)
"Educate, communicate, anticipate: Practical recommendations for transitioning adolescents with IBD to adult health care" [44]
"Transition of the patient with inflammatory bowel disease from pediatric to adult care: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition" [7]
"Transitioning the adolescent inflammatory bowel disease patient: Guidelines for the adult and pediatric gastroenterologist" [8]
Transition readiness assessment and tools
For patients
Patient checklist for preparing to transition from a pediatric to adult care practitioner [46]
"Preparing to transition from a pediatric to adult care practitioner": http://www.gikids.org/files/documents/resources/IBD-TransitionTeenIBD.pdf
For providers
Healthcare provider checklist for transitioning a patient with IBD from pediatric to adult care [45]
"Transitioning a patient with IBD from pediatric to adult care": http://www.gikids.org/files/documents/resources/Checklist_ONLYHealthcareProdiver_TransitionfromPedtoAdult.pdf
TRxANSITION scale and STARx transition readiness questionnaire [47, 48]
Health passports, self-management tools, and symptom trackers
Good 2 Go Transition Program—MyHealth Passport: https://www.sickkids.ca/myhealthpassport/
Resources for adolescents and parents
Crohn's and Colitis Foundation Campus Connection: https://www.crohnscolitisfoundation.org/campus-connection
ImproveCareNow: https://improvecarenow.org
Just Like Me: https://www.crohnscolitisfoundation.org/justlikeme
IBD Transfer Toolkit, ImproveCareNow: https://www.improvecarenow.org/transition_to_adult_care
Doc4me app: http://www.doc4me-app.com/
Transition advocacy and support for patients, parents, and providers
"Got Transition/Center for Health Care Transition": http://gottransition.org/
The Society of Adolescent Health and Medicine: http://www.adolescenthealth.org/Home.aspx

patient will visit with their provider alone, starting by performing the physical exam without the parents/guardians in the room.

Parents/Family (Age 12–14)

Reiss and colleagues have found that parents often feel excluded when their child transitions to an adult provider, especially after they have dedicated many years of supporting and being involved in their children's health care [19]. Parents may also have concerns about "letting go," and family resistance can be a major barrier to successful transition. In order to prevent these negative feelings, parents should also be informed and educated regarding the eventual need for transition—the process of "letting go," so that their child can function independently as they leave home for work or college. The main role of the family at this time is to support the child through the disease symptoms and exacerbations and to provide a comfortable and protective atmosphere for this transitioning period. Since parents are actively involved in the daily care of their young adult children, they are the key personnel to reinforce the list of items needed at each visit for a successful transition. They should be notified that future clinic visits might include an established period of time for the young adult patient to meet with the health-care provider on their own. As part of the process, the parents can be provided the opportunity and a primary role in making their child independent through each step. They can proactively educate their son/daughter on crucial topic areas including insurance coverage, refilling medications, and scheduling appointments independently. Another important role for parents is to observe and confirm to the pediatric GI team that their child is making progress mastering the skills required for independence prior to the transfer of their care to adult providers.

Pediatric Team (Age 12–14)

The pediatric team often includes the pediatric gastroenterologist, nurse, psychologist, dietitian, and other pediatric subspecialists involved in managing the patient's care. The pediatric gastroenterologist, who is typically the primary provider, will establish the parameters for the support staff in promoting this transition period. Teaching of transition skills (those chosen as most important by each practice or institution) may be directed by a nurse, nurse practitioner, or the gastroenterologist, depending on staffing and availability. It is critically important for the physician to convey the importance of the process to the patient and family so that they understand, recognize, and accept the benefits of increasing the patient's self-management of their disease.

The pediatric gastroenterologist should address the concept of independent clinic visits for the patient with the family. This should start by including the parents for the initial portion of the visit, followed by the gastroenterologist performing the physical exam without parents/guardians in the examination room. Topics the pediatric gastroenterologist should consider addressing include information and guidance regarding drugs, alcohol, dating/sexuality, and health maintenance issues (i.e., diet, exercise). It is also important to address medication adherence, which can impact future health and can be a significant issue in young adults with IBD [52]. Furthermore, potential psychological issues should be screened and identified so that referrals can be placed with mental health professionals. This helps address anxiety disorder/depression which, when left untreated, can hinder the transition process and successful attainment of the necessary self-management skills [34].

Focus on Independence

Patients (Age 14–17)

Patients in this age group should acquire the following two major skill sets that focus on increasing their independence:

Skill Set 3

Knowledge related to procedures and tests: This would include laboratory tests, diagnostic imaging, and endoscopic procedures used in managing the patient with IBD. The goal is for patients to not only be comfortable with the different tests and procedures but also to recognize their importance and purpose in managing their disease long term.

Skill Set 4

Basic medical knowledge: This step emphasizes basic medical knowledge all patients should know, regardless of the presence or absence of a chronic illness. This includes knowing how to measure their weight, take their temperature, and read a thermometer. It also includes learning or knowing where to find telephone numbers and locations for their health-care provider, their clinic, and the hospital. They should be able to articulate their medical history and to identify names of community-based social support groups and organizations (e.g., Crohn's and Colitis Foundation) if they are available in their region. Patients should be able to articulate the medical risk of nonadherence, and they should understand the impact of illicit drugs and alcohol on their illness as well as the interactions with their ongoing medications. This may take a little time in the office demonstrating some of these skills, and it will require some work from the family to help set up their own system for reinforcing this

information. In addition, patients might be asked to prepare questions ahead of time for the doctor and nurse or dietician.

The patients should begin filling their own prescriptions, scheduling their own appointments, and keeping medical information and insurance information. The patient should also develop a method of tracking symptoms and issues related to their IBD. This makes their clinic visit with their physician effective and centered on the patient while helping the patient to demonstrate the ability to be more independent with their health care. During the visit, the patient can privately address questions they have regarding adolescent issues and discuss future plans upon the completion of high school. Patients should be educated, however, that the parent or guardian must legally be informed about the overall condition and high-risk behaviors more common in teens and young adults that could seriously affect their disease.

Parents (Age 14–17)

Since the main focus at this age is to promote independence, the family/parents/guardians should teach their child the intricacies of medical care as if they were out on their own. Examples include the following: maintaining a current medication list, filling and refilling prescriptions, and scheduling clinic appointments. They can provide guidance on organizing medical information in a dynamic fashion, which is crucial. Parents should also provide all information regarding insurance (insurance card, relevant contact numbers). Most importantly, the parents should continue to reinforce the skill sets that the patients need at this developmental stage outside routine clinic visits and to update the pediatric health-care team on their child's progress during the transitioning process.

Pediatric Team (Age 14–17)

The pediatric gastroenterologist as well as the pediatric health-care team should start and continue to focus on the patient instead of the parents or guardians when providing explanations and when obtaining the history. This includes making sure part of the visit occurs without parents in the room and allowing the patient to decide on the appropriate timing. This allows the physician to directly interact with the patient and is essential in the progression toward independence the young adult needs prior to transfer of care. The physician should explain to the patient what the parent or guardian must legally be informed about regarding their condition. During this process, the physician and patient should develop goals and timelines for specific skills required during the transitioning process (i.e., filling prescriptions and scheduling appointments). These visits should also include the opportunity to address sensitive topics including drug and alcohol usage, as well as the impact of disease and on sexuality and fertility. Future work and school timelines need to be considered during this transitioning process to optimize effective timing for the transfer of care as well as identifying future adult providers. Psychosocial monitoring including screens for anxiety, depression, and quality of life as well as transition readiness is recommended given the impact of ongoing psychosocial comorbidities on medication adherence and effective transfer of care.

Self-Management: Health and Lifestyles

Patients (Age 17–18)

This is the crucial period before the actual transfer of care to an adult provider. The two skill sets they need at this stage include the following:

Skill Set 5

General self-management skills: Skills attained in this set put the knowledge acquired in the other skill sets to practical use and help patients move toward independence. The patient should receive an outline or plan for managing their disease, especially as they may leave home for work or school. They should be familiar with their medications and their medical history, learn to call in their own prescriptions, make their own clinic appointments, begin to collect copies of their health records/medical summary for work/school, and learn about adult providers, based on the location of where they will be in the near future (adult gastroenterologists near their new home/school/work). They should carry a copy of their insurance card, either as physical hard copy or as a saved photo on their smartphone, and understand the concept of medical insurance as well as more specific details including eligibility requirements, co-pays, and other potential resources for coverage such as Social Security Disability Insurance (SSDI).

Skill Set 6

Health and lifestyle decisions: The acquisition of skills from this skill set includes the patient gaining a general understanding of the importance of health maintenance and the potential interplay of their disease and lifestyle decisions. General knowledge includes the beneficial effects of exercise and an appropriate diet as well as the adverse effects of drugs, alcohol, and smoking. They should know the specific impact of disease activity on fertility and sexuality and the consequences of nonadherence. Patients should understand that at age 18, they are considered autonomous adults in terms of their health care; they have the right to make their

own health choices, and their health information cannot be shared with others including parents or guardians without permission.

Parents (Age 17–18)

Several studies in other chronic diseases have shown that parents may feel relegated to the sidelines as their children transfer to adult care. If the transition process has been implemented from an earlier age, and the parents have been educated, this should not occur. Parents can have concerns about their sons' or daughters' limitations in self-advocacy or cognitive function, and thus, can be justifiably worried about their ability to cope. These issues should be addressed at this visit, so everyone involved (the parents, the pediatric team, and the patient) can find a solution to overcome any obstacles. Ultimately, at this age, the parents should show less and less responsibility for the patient's care as the patient assumes more responsibility. This is the time where the parents need to officially practice letting go. They should encourage their child to go to their follow-up visit alone or at least allow them to visit with the doctor alone for most of their visit. To address concerns most parents have of missing critical information as they relinquish responsibility to the young adult, it is helpful to have a list of questions for the young adult patient ask at the visit (or let the parents ask separately after the visit but generally with the patient present). They should also understand that once their child turns 18, Health Insurance Portability and Accountability Act (HIPAA) regulations come into play, and the parent cannot obtain medical information unless the patient provides approval. This becomes an issue as parents often call the adult clinic asking for results and medication refills, appointments, and management decisions/plans.

Pediatric Team (Age 17–18)

At this stage, the pediatric team should prepare for the final clinic visits prior to transfer of care. The pediatric healthcare team should remind the patient and the parents that at age 18, patients have the right to make their own decisions. The pediatric team should help identify potential adult IBD providers and encourage and facilitate an initial visit. Ideally, a transition clinic setup is optimal; however, few clinical centers/hospitals have one. A return visit after they have seen the adult provider may be helpful to discuss their experience and troubleshoot any remaining concerns. Plans for insurance coverage should be discussed with the patient and parents. Identifying any insurance coverage is important as this may impact who they may be able to see as they transition. A social worker, if available, should be consulted to further review and educate the young adult patient about medical insurance coverage. Understanding how to navigate the health-care system from a financial perspective is necessary, given the need to have ongoing coverage of medical care. The patient should be provided a summary of their medical history for school or work and obtain any consent for health information in order to provide to the new adult gastroenterologist. In addition, the team should complete a medical summary of the patient to provide to the adult provider. Hait and colleagues have suggested the following to be included in this letter (Table 61.2).

Table 61.2 Medical summary letter

Medical summary letter for transitioning IBD patients
Disease information: date of diagnosis, location, severity
Findings: labs, endoscopy, histology, radiology results, and dates
Medical therapies: dose, duration, adverse reactions, reasons for discontinuation
Surgical history
Psychosocial, developmental, and educational issues

Adapted from Hait et al. [44]

Before the last visit, the provider should ideally confirm that psychosocial needs are addressed to ease the transitioning process as well as any other potential barriers to transfer of care, including financial issues, attitudes, access, and family resistance. These needs can be met through the use of a multidisciplinary approach, involving a dietitian, social worker, and psychologist, when available. The medical team should discuss differences in the cultures of pediatric and adult medicine. It is important whenever possible to refer the patient in times of disease quiescence and social stability when the transition is most likely to be successful. This may occur at different ages for various patients. For those who attend college, the transfer may be after graduation and after a job is secured or graduate education has begun. For those who choose not to attend college, the transfer of care should occur when housing and employment arrangements are stabilized.

Adult Team (Age 18+)

The adult gastroenterologist's role in the early transition process is minimal as the patient only arrives to them at the end of this process around the age of 18; however, his/her role in accepting and facilitating transfer of care is a key. In general, the adult gastroenterologist should only accept the transfer after he or she has been given an adequate medical history of this patient from the pediatric provider. This will help provide the most optimal care as medications, and prior medical and surgical history will be important in ongoing medical care. Since the adult gastroenterologist can potentially have an even longer role in the patient's chronic care, the transi-

tion is crucial in establishing a physician–patient relationship that fosters independence as well as confidence, trust, and communication in both parties.

The adult gastroenterologist's role is to continue to foster this independence with the patient. The patient should continue to be the main focus and should be seen independently from the parents, especially if over-concerned parents tend to drive the visit interactions. At this time, legal implications of health care can also play a role. The patient is solely responsible for their medical information. It will be up to him or her to decide if, and to what extent, the parents should be involved. HIPAA regulations will come into play as parents, once used to obtaining and providing information, now legally do not have a role without the patient's consent. The adult gastroenterologist and the adult care team (nurses, medical assistants) should be aware of this when parents of transitioned patients call for information. However, if the transition process is successful, the patients will contact the office themselves for medical information.

The adult gastroenterologist should acknowledge the parents and work jointly to continue to allow for the patient to remain independent and communicate any issues they have at the first visit. There should be mutual understanding of everyone's role. Since the parents have been a key player in their child's chronic illness, it is understandable the parents will have concerns and questions, as well as some resistance toward the transition. However, with the understanding and acknowledgement that the adult gastroenterologist's goal is to provide optimal care for the patient, then the family, patient, and physician can work together toward this shared goal.

The adult gastroenterologist should confirm the patient has established a relationship with an adult primary care physician, especially if the patient has been seeing a pediatrician for their general health care. Specialists often take on the role of "generalist" due to their frequent interaction related to IBD visits. However, obtaining a primary care provider (PCP) is important to provide optimal care regarding other illnesses such as general health care, immunizations, and screening for other diseases such as breast and prostate cancer and for preventive care for other diseases such as hyperlipidemia, diabetes, and hypertension.

The adult team should confirm that all relevant medical records are obtained, including any outstanding information that may still be needed. This may warrant a phone conversation with the pediatric health-care providers to include specific social history, developmental issues, and family dynamics that may not have been fully explained in the records. The importance of adherence to therapy should continue to be addressed at this time as well as any parental concerns. The adult provider should anticipate and answer any questions about smoking, alcohol, substance abuse, and sexuality as well as the psychosocial impacts their disease may have. They should also educate the patient regarding the adult chronic care model.

Monitoring the Process

Some system should be established to monitor both the teaching of the above skills and what has been learned and retained. Although there is no single validated transition readiness tool for use in pediatric IBD, prior publicans have utilized such transition tools as the Transition Readiness Assessment Questionnaire (TRAQ) and the Smooth Transition to Adulthood with Treatment (STARx) transition readiness questionnaire for this purpose [53, 54]. This can also be accomplished through pop-up messages on an electronic medical record, where objectives and follow-up learning must be recorded by date, or a special form could be kept in the patient's chart to check off each set once taught and then mastered. The patient could also be given a copy of this checklist so they know what the entire skill set contains. A member of the health-care team should be dedicated to documenting this process to ensure patients are making progress in becoming independent. Having set questions at follow-up visits to document what has been learned is also important. Typical questions that patients might be expected to answer at a follow-up visit are as follows: (1) Can you describe your disease? (2) What are your symptoms of IBD? (3) What situations should you avoid? (4) When should you call or see the doctor? (5) What is your doctor's or nurse's phone number? (6) Did you make this appointment? (7) Have you called in one of your prescriptions for refill? (8) What health records have you collected (i.e., endoscopy reports; laboratory test results)? (9) Who is your insurance carrier? Before final transition, time should be set up to do a final review of their competence in all areas, and then when the patient is ready, preparations can be made to transition care to an adult provider. At this point, the patient should already be taking care of his or her health issues, and a successful outcome for transition is likely.

Conclusion

The transition process can be a challenging time period for adolescents living with IBD as they move toward adulthood. However, a successful transition can be implemented if steps are taken early in the process with the combined effort from the patient, the parents/guardians, and the pediatric gastroenterology team. The key is to provide sufficient and early training around the process so that the young adult patient, their family, and their providers can progress through the

process together ensuring adequate time to adapt and prepare for a successful transition and graduation to adult gastroenterology care. A dynamic and supportive process will help young adult IBD patients effectively self-manage their health-care needs and become independent young adults who can manage their own complex medical needs.

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